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Nitin Verma

School of Pharmacy and Emerging
Science (SPES), Baddi University of
Emerging Science and Technology,
Makhunmajara, Baddi, Distt-Solan,
H. P. 173205, India.

Herbal Medicines: Regulation and Practice in Europe, United States and India

Nitin Verma**ABSTRACT**

The present review deals with practice and regulation of herbal medicines in Europe, United States (US) and India. Herbal medicines are widely used for treatment of human ailments in various systems of medicines like Ayurvedic, Homeopathic, Sidha, Unani and other regional systems of medicines. Herbal drug products classification vary from country to country, some categories include functional foods, dietary supplements and traditional medicines. Critical problem in the evaluation of herbal drug products is that these are complex mixtures of constituents and the constituents responsible for the therapeutics effects are unknown which also complicates the stability of these products. A detailed literature survey for regulations of herbal drug products in Europe, US and India was performed to identify recently introduced changes in regulations or newly introduced regulations compliance with the regulatory bodies. Committee for Herbal Medicinal Products (HMPC), Committee of European Medicines Agency (EMA) is developing guidelines for quality, nonclinical studies, clinical efficacy and safety. Traditional herbal medicines registration scheme (THMRS) has been recently introduced by Medicines and Healthcare Products Regulatory Agency (MHRA, UK). US FDA has issued draft guidance for Industry on "Complementary and Alternative Medicine Products and Their Regulation". Drugs and Cosmetics Rules have been amended recently to control the quality, safety and efficacy of herbal drug products in India. It has been found that regulations for herbal drug products in Europe and United States are more stringent than in India which has been reflected by some reports of safety issues of Indian herbal drug.

Keywords: Herbal drug, efficacy, regulations, practices, quality, safety.

1. Introduction

Anemia Herbal medicines are "plant-derived materials or products with therapeutic or other human health benefits which contain either raw or processed ingredients from one or more plants" [1]. As per WHO definition, there are three kinds of herbal medicines: raw plant materials, processed plant materials and medicinal herbal products. The earliest recorded evidence of herbal medicine use in Indian, Chinese, Egyptian, Greek, Roman and Syrian texts dates back to about 5000 years. The classical Indian texts on herbal medicines include Rigveda, Athurveda, Charak Samhita and Sushruta Samhita. Herbal medicines are used by practitioners of traditional system of medicines across the globe due to their well-established and widely acknowledged use. The well accepted and accumulated experience of many practitioners and patients over an extended period of time make herbal medicines more popular. Furthermore, the use of herbal medicine is generally and currently regarded as safe. Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness [2]. Some traditional medicine systems are Indigenous Medicine existent in the region either recognised or ethnic as in Chinese medicine, Indian Ayurveda, Arabic Unani medicine, African & Latin American practices. In some Asian and African countries, 80% of the population depends on traditional medicine for primary health care [3]. Herbal medicines are also gaining popularity among developed countries like US, Europe etc through via several CAM approaches. New drug molecules from the plants have been isolated for the treatment of various infectious and chronic conditions e.g. new antimalarial drugs were developed from the discovery and isolation of artemisinin from *Artemisia annua* L.

Correspondence:**Nitin Verma**

School of Pharmacy and Emerging
Science (SPES), Baddi University of
Emerging Science and Technology,
Makhunmajara, Baddi, Distt-Solan,
H. P. 173205, India

Email: nitin.verma@baddiuniv.ac.in**Tel:** 01795-247353

Herbal medicines generates handsome revenue worldwide which has driven counterfeit, poor quality, or adulterated herbal products entry in international markets leading to serious patient safety issues. Safety, effectiveness and quality tests to herbal medicines are limited due to their complex nature, authentication issues and lack of appropriate standardization. The safety, effectiveness and quality of finished herbal medicine products depend on the quality of their source materials, which can include hundreds of natural constituents, and how elements are processed while manufacturing them. In one study it was found that one-fifth of both US-manufactured and Indian-manufactured Ayurvedic medicines purchased via the Internet were found to contain detectable lead, mercury, or arsenic ^[4]. The popular belief for herbal medicine is that because medicines are herbal (natural) or traditional they are safe (or carry no risk for harm). Scientifically it has been proven that herbal medicines and their practices can cause harmful, adverse reactions if the product or therapy is of poor quality, or it is taken inappropriately or in conjunction with other medicines. Increased patient awareness about safe usage, training, collaboration and communication among providers of herbal and traditional and other medicines is considered necessary for patient health and safety.

Countries have their own set of laws and regulations for herbal medicines and traditional medicines. W H O recommends that each country or area should adopt a regulatory system to manage the appropriate use of herbal medicines. Adopting a regulatory mechanism has always helped in ensuring that herbal medicines have acceptable quality, safety and efficacy. The WHO Guidelines for the assessment of herbal medicines may be consulted when assessment processes for herbal medicines are being prepared ^[5]. The W H O guidelines on good agricultural and collection practices for medicinal plants are intended for national regulatory bodies and offer advice on cultivation and collection methods, site selection, climate and soil considerations and the correct identification of seeds and plants ^[6].

These guidelines also offer guidance on post-harvest operations such as labeling and legal components including national and regional laws on quality standards, patent status and benefits sharing. It is not a binding guideline for any country, but it is a model or a sort of checklist which they can use to make their own national regulations. Protocols on safety, efficacy, standardization and documentation of herbal medicines have also been published by IUPAC subcommittee on biomolecular chemistry ^[7].

1.1 Regulation & Practices

1.1.1. European Regulations and Guidelines

Herbal medicinal products fall within the scope of the European Directive 2001/83/EC that foresees marketing of each medicinal product and requires an ad hoc authorisation to be granted on the basis of results of tests and experimentations concerning quality, safety and efficacy. The main features of Directive 2001/EC are traditional herbal medicine definition, simplified registration procedure, provisions for community herbal monographs and community list of herbal substances and preparations and establishment of the Committee for Herbal Medicinal Products (HMPC). European Directive 2004/24/EC on traditional herbal medicinal products has brought forward specifically in recognition of the position that for many herbal medicines it was difficult for companies to meet the full requirements for a marketing authorisation, particularly in relation to efficacy, as are required

under Directive 2001/83/EC. The Directive 2004/24/EC has established a HMPC which is part of the EMA, the European Agency responsible for the evaluation of medicinal products and to carry out tasks concerning the simplified registration and authorization of herbal medicinal products. CHMP establish Community herbal monographs and list herbal substances and preparations.

Monographs in European Pharmacopoeia provide the quality requirements for herbal substances and preparations. HMPC has also addressed general quality matters in several guidance documents concerning to non-clinical, quality, clinical efficacy and safety issues. The HMPC is responsible for identifying the priority herbal substances/preparations/combinations to be covered by a monograph or a list entry. Herbal substances proposed for assessment can be found in an inventory and herbal substances under assessment can be found in a priority list. As per directive the definitions of herbal medicinal product, herbal drug substances and herbal preparations are as follows:

1.1.1.1. Herbal substances

All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

1.1.1.2. Herbal preparations

Preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates. Medicinal products containing herbal substances/preparations must fall within one of the following three categories to reach the market (<http://www.ema.europa.eu>):

1. A product can be classified under traditional medicinal use provisions (traditional use) accepted on the basis of sufficient safety data and plausible efficacy: the product is granted a traditional use registration (simplified registration procedure) by a Member State,
2. A product can be classified under well-established medicinal use provisions (well-established use). This is demonstrated with sufficient safety and efficacy data. As a result the product is granted a marketing authorisation usually by a Member State or by the European Medicines Agency under certain conditions. (While both classification have specific requirements, both regulatory paths involve the assessment of mostly bibliographic safety and efficacy data, which are usually combined, for well-established use products, with product specific data.)
3. A product can be authorised after evaluation of a marketing authorisation application consisting of only "product-specific safety and efficacy data" (full dossier). As a result the product is granted a marketing authorisation by a Member State or by the Agency via the centralised procedure if all requirements are met.

Most individual herbal medicinal products are licensed nationally by member states, the process for licensing and information on herbal substances and, preparations is harmonised across the European Union. In United Kingdom, to get a product registered, companies have to submit a dossier to the Medicines and Healthcare products Regulatory Agency (MHRA) demonstrating that it meets the requirements of quality, safety and patient information as per the Traditional Herbal Registration Scheme (THRS). Minor claims are permitted on the basis of evidence of traditional usage. Irrespective of the regulatory pathway to access the market, the quality of the herbal medicinal product must always be demonstrated. Community herbal monographs prepared by the Committee on Herbal Medicinal Products (HMPC) at the Agency are relevant for the traditional use registration as well as the well-established use marketing authorisation.

A Community herbal monograph comprises the scientific opinion of the Committee on Herbal Medicinal Products (HMPC) on safety and efficacy data concerning a herbal substance and its preparations intended for medicinal use. The HMPC evaluates scientifically all available information including non-clinical and clinical data but also documented long-standing use and experience in the Community. Community monographs are divided into two columns: well-established use (marketing authorisation) and traditional use (simplified registration). Well-established use section describes the safety and efficacy data while traditional use section is accepted on the basis of sufficient safety data and plausible efficacy. A final Community monograph can be used in application reference material by a marketing authorisation applicant (well-established use part) and by a traditional use registration applicant (traditional use part). In contrast to the Community herbal monographs, the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products is legally binding to applicants and competent authorities in the Member States in so far as:

- An applicant will not be required to provide evidence of the safe and traditional use of a medicinal product for which he seeks a traditional use registration if he demonstrates that the proposed product and related claims in the application comply with the information contained in the Community list.
- Competent authorities will not have the opportunity to require additional data to assess the safety and the traditional use of the product.

The Community list is developed gradually through 'list entries'. When a draft list entry for a given herbal substance or preparation has been produced by the Committee, it is released for public consultation on this website for a period of three months. The list entry is then finalised by the Committee on Herbal Medicinal Products (HMPC) from a scientific point of view, before being submitted for approval by the European Commission. Following this approval, the Commission Decision amending the Community list is published by the European Commission.

A list entry document contains:

- The scientific and botanical name, and the common name in all EU languages;
- What is it used for (the indication);
- The specified strength and the posology;
- The route of administration and;
- any other information necessary for the safe use of the herbal substance or preparation used as an ingredient of a

traditional herbal medicinal product, including warnings, precautions and contraindications.

The format, procedure, template, and SOP for preparation and revision of community monographs and community list entries have been made available on the website of EMEA. The Committee on Herbal Medicinal Products (HMPC) has developed procedure to invite the public to submit scientific data on herbal substances and preparations. The provided information may then be used by the Committee in the development of Community monographs and to Community list entries. Scientific contributions in response to a call for the submission of scientific data can be provided to the Agency in electronic format (e-mail or CD-ROM) or paper format (two copies by post or fax) during the 2-month period following the publication date. Finalized community monographs as well as monographs under preparation have also been made available on EMEA website.

Community pharmaceutical legislation has created a binding Community mechanism which may be invoked in so called referrals. These referrals lead to an opinion from which the Commission issues a single decision addressed to all Member States which is reported for information to the applicant(s) or marketing authorisation holder(s). In addition to these referrals according to Articles 29, 30, 31, and 35 and 36 of Directive 2001/83/EC, Community pharmaceutical legislation has also created a mechanism by which Member States may refer certain matters of THMP to the HMPC of the Agency, but which does not lead to a binding Community procedure. These situations are foreseen in:

1. Article 16c (1)(c) of Directive 2001/83/EC ("Adequacy of evidence of the long standing use referral");
2. Article 16c (4) of Directive 2001/83/EC ("Traditional use less than 15 years referral").

These referrals to the HMPC lead to an opinion and also in some cases the Article 16c (4) referrals may lead to a monograph which Member States shall take into account.

1.1.2. United States of America Regulations

In United States, the term complementary/alternative medicines (CAM) are most commonly used for traditional medicine systems. "Complementary medicine" refers to use of CAM together with conventional medicine, such as using acupuncture, in addition to usual care to help lessen pain. Most use of CAM by Americans is complementary (National Center for Complementary and Alternative Medicine (<http://nccam.nih.gov>)). 'Alternative medicine' refers to use of CAM in place of conventional medicine. "Integrative medicine" (also called integrated medicine) refers to a practice that combines both conventional and CAM treatments for which there is evidence of safety and effectiveness. CAM practices are often grouped into broad categories, such as natural products, mind-body medicine, and manipulative and body-based practices. Although these categories are not formally defined, they are useful for discussing CAM practices. Some CAM practices may fit into more than one category. Practices of traditional healers can also be considered a form of CAM. Traditional healers use methods based on indigenous theories, beliefs, and experiences handed down from generation to generation.

FDA in its draft guidance "Guidance for industry on complementary and alternative medicine products and regulation by the food and their regulation by the food and drug administration" clarified different categories of Complimentary

Alternative Medicines (CAM) products into cosmetic; device; dietary supplement; drug, as well as "new drug" and "new animal drug;" food; and food additive. These statutory definitions cover some CAM products. It was also clarified neither the FDA Act nor the Public Health Service Act exempts CAM products from regulation. The draft guideline was later withdrawn after recommendations of several agencies including The American Herbal Products Association (AHPA).

FDA's Center for Drug Evaluation and Research (CDER) Guidance for Botanical Drug Products differentiates between those botanical drugs that could be marketed as Over-The-Counter (OTC) and those that would require New Drug Application (NDA). The document also provides guidance for navigating the new drug route, including discussions of the possibility of lesser demand for certain information for botanicals with an established history of use. Waiver for related toxicology studies or bridging studies may be considered by FDA on case to case basis^[8]. Botanical new drugs are entitled to a waiver for preclinical pharmacology/toxicology studies in support of an initial clinical trial under IND, contingent on previous human experience^[9]. This guidance addresses all botanical drug products (in all dosage forms) that are regulated under the Act, except those also regulated under section 351 of the Public Health Service Act (42 U.S.C. 262).

Botanical products are finished, labeled products that contain vegetable matter as ingredients. A botanical drug product may be marketed in the United States under (1) an OTC drug monograph or (2) an approved NDA or ANDA. A botanical product that has been marketed in the United States for a material time and to a material extent for a specific OTC drug indication may be eligible for inclusion in an OTC drug monograph codified in 21 CFR parts 331-358. The manufacturer would need to submit a petition in accordance with 21 CFR 10.30 to amend the monograph to add the botanical substance as a new active ingredient.

When a final OTC drug monograph is published for a specific use of a botanical drug, any person may market a product containing the same substance and for the same use, provided the labeling and other active ingredients (if present) are in accord with all relevant monographs and other applicable regulations. In contrast, when a product is approved under an NDA, the approval is specific to the drug product that is the subject of the application (the applicant's drug product), and the applicant may be eligible for marketing exclusivity for either 5 years (if it is a new chemical entity) or 3 years from the time of approval, even in the absence of patent protection. A new botanical drug (containing multiple chemical constituents) may qualify as a new chemical entity under § 314.108 (a). If a product qualifies as a new chemical entity, during the period of exclusivity, FDA will not approve, or in some cases even review, certain competitor products unless the second sponsor conducts all studies necessary to demonstrate the safety and effectiveness of its product and submits a 505(b) (1) application. Therefore, if a person wishing to market a botanical drug product that is not included in an existing OTC drug monograph desires marketing exclusivity for the product, the person should seek approval of an NDA rather than petition the Agency to amend a monograph. Attachment A contains a schematic showing different regulatory approaches that can be taken for marketing botanical drug products in the United States, including OTC drug monograph and NDA procedures. GACP (Good Agriculture and Collection Practices) guideline was published by AHPA and American Herbal Pharmacopoeia to develop quality control standards for the manufacture of herbal supplements and botanical medicines, as

needed to ensure availability of products having a high degree of safety and effectiveness. Recent developments in the analytical techniques and standardization of herbal drug products have led the scientists to integrate evidence based medicines and traditional knowledge^[10]. The integration has been proven successful in reducing quality and safety issues from herbal drug products. More and more practitioners are also moving away from traditional knowledge to evidence based medicines.

1.1.2.2. Indian Regulations

Herbal drug products constitute a major share of all the officially recognized systems of health in India *viz.* Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy, except Allopathy. IMCC (Central Council of Indian Medicine) Act, Research Councils (ICMR and CSIR), Department of AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy) & Drugs and Cosmetics Act 1940 (Amendment) regulates herbal medicines in India. Herbal remedies and medicinal plants to be incorporated in modern system (Allopathic) must follow Drug Controller General of India (DCGI's) regulations.

As per Drugs and Cosmetics Act 1940 amended in 1964, "Ayurvedic, Siddha or Unani drug" includes all medicines intended for internal or external use for or in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, and manufactured exclusively in accordance with the formulae described in, the authoritative books of Ayurvedic, Siddha and Unani (Tibb) systems of medicine, specified in the First Schedule^[11]. The amendment provided for a limited set of controls over like manufacturing under prescribed hygienic conditions under the super vision of a qualified person, use of genuine raw materials and labeling of all the ingredients used. To overcome the difficulty of implementing the amendment of the Act, the Pharmacopoeial Laboratory for Indian Medicine (PLIM) was established in Ghaziabad by the Ministry of Health and Family Welfare (Department of Health). PLIM houses the Drug Standardization and Testing Unit, the Drug Depot, and the Herbarium and Reference Museum. Pharmacopoeias were also made available for each of the Indian system of medicine.

Indian system of registration of herbal medicinal products has provision in each state via state drug licensing authority of Ayurvedic, Sidha and Unani drugs. Recent amendments in Drugs and Cosmetics (First Amendment) Rules 2008 has introduced Schedule TA for record of utilization of raw materials by Ayurvedic or Sidha or Unani licensed manufacturing units. Drugs and Cosmetics (Second Amendment) Rules 2008 permitted the use of excipients given in Indian Pharmacopoeia or Bureau of Indian Standards Act 1986 or Prevention of Food Adulteration Act 1954 and Food Products Order for use in Ayurvedic Sidha and Unani drugs.

GCP guidelines published by ICMR also pertain to traditional drugs (Kumar NK, 2006). According to these guidelines traditional herbal medicines have been classified into three groups:^[12]

1. Traditional Herbal drugs as per Classical text, regular use and prescribed pharmacopoeia – reverse pharmacology approach
2. Traditional formulations for a new indication/new process/new combination/new herbal or plant based NCE – acute, subacute and chronic toxicity data to be generated (Schedule Y of Drugs & Cosmetics Act, 1940).
3. Formulations – GMP compliant Standardization.

Department of AYUSH, ICMR and CSIR work together to achieve safe, effective AYUSH products for the identified diseases and to develop new drugs. AYUSH objectives are to control drug quality, laying down pharmacopoeial standards, overseeing working of Pharmacopoeial Laboratory of Indian Medicines (PLIM), partnership with the Quality Council of India (QCI) and to oversee functioning of Indian Medicine Pharmaceutical Company Limited (IMPCL). AYUSH also controls enforcement of Good Manufacturing Practices (GMP), setting up of common facilities following the Cluster approach and implementing the scheme for Drug Quality Control. With the advent of IPR regime, AYUSH department has also started digitalization of traditional medicinal formulations, knowledge & manuscripts and documentation and promotion of local health traditions.

Traditional Knowledge Digital Library (TKDL) (<http://www.tkdl.res.in>) is a database containing codified literature from Indian Systems of Medicine. TKDL contains more than 2.23 lakh formulations from the texts of traditional medicine systems of India viz. Ayurveda, Unani and Siddha. TKDL is a representative database of more than 1200 Ayurvedic, Yoga, Unani and Sidha formulations which provides information on traditional knowledge in English, German, French, Japanese and Spanish. TKDL is a collaborative project between Council of Scientific and Industrial Research (CSIR), Ministry of Science and Technology and Department of AYUSH, Ministry of Health and Family Welfare, and is being implemented at CSIR. TKDL gives legitimacy to the existing traditional knowledge and enables protection of such information from getting patented by the fly-by-night inventors acquiring patents on India's traditional knowledge systems. It will prevent misappropriation of Indian traditional knowledge, mainly by breaking the format and language barrier and making it accessible to patent examiners at International Patent Offices for the purpose of carrying out search and examination.

In 2009, AYUSH department in collaboration with QCI introduced certification scheme for AYUSH drug products. – There are concerns raised all the time about the quality of AYUSH products as regards their safety, efficacy and quality. In order to meet these concerns a new scheme of voluntary certification of AYUSH products has been started in collaboration with QCI.

The Ayush Certification is awarded at two levels. Ayush Standard Mark which is based on compliance to the domestic regulatory requirements; and Ayush Premium Mark which is based on either or both of the following options; Option A: Compliance to the GMP Requirements based on WHO Guidelines and Levels of contaminants as given in Certification Criteria document. Option B: Compliance to regulatory requirements of any importing country provided these are more stringent than Option A above. The certification to the above mentioned criteria shall be carried out by the CBs duly accredited for the certification scheme as per ISO/IEC Guide 65, by NABCB and/or recommended by QCI. Hyderabad-based Foodcert India (P) Ltd and Mumbai-based Bureau Veritas Certification (India) Pvt Ltd have thus become the approved certified bodies under the scheme^[13].

Several regulatory guidelines have been recently introduced. The National Medicinal Plants Board (NMPB), Department of AYUSH has prepared India specific guidelines on Good Agriculture Practices (GAPs) on the pattern of Good Agriculture and Field Collection Practices (GACPs) developed by the World Health Organization (WHO) for medicinal plants. In the preparation of this standard assistance has been taken from Good Agriculture and Field Collection Practices (GAFCPs) developed by the World

Health Organization (WHO) in 2003 and Good Agricultural Practices enunciated by the GLOBALGAP Secretariat which is being implemented in over 80 countries. The standard provides requirements for Good Field Collection Practices on different aspects for harvesting and post-harvest management of medicinal plants. Adoption of Organic and Good Agriculture & Collection practices is expected to lead better resource management by sensitizing farmers, growers and other stakeholders.

2. Conclusions

The legal status and the practice of use of herbal drug products vary significantly from one country to another thus making it difficult for the free circulation of such products. European regulations are most comprehensive among most of the global regulations for herbal medicinal products. FDA guidelines on botanical drug products established New Drug Application (NDA) route parallel closely the route followed for a synthetic new chemical entity. Indian regulations are also developing *vis a vis* to global regulations for herbal drug products. Indian regulations are still at nascent stage when compared to regulations of Europe and US. Harmonization of regulations, like that in European Countries could overcome the barrier for efficient trade as well as uniform standards for herbal medicinal products.

3. Conflict of Interest

There is no conflict of interest.

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