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Regulatory Status of Herbal Products



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ABSTRACT

Regulation over the world the herbal products implemented under different classifications, some of which are, Natural health products, over the counter medicines, prescription medicines, Supplements, Traditional herbal medicines, Complimentary medicines, etc. Committee of EMA, Committee for Herbal Medicinal Products (HMPC), is to develop the regulations for safety, nonclinical studies, clinical, quality, and efficacy. Traditional herbal medicines registration scheme (THMRS) has been recently introduced by Medicines and Healthcare Products Regulatory Agency (MHRA- UK). However it was believed herbal medicines are completely safe but as per WHO all herbs are not at safe, providing their citizen the best product is the responsibility of every government. A review of the regulatory status of herbal medicines across the globe is given in the present article.



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INTRODUCTION

Herbal Medicines: These include herbs, herbal preparations, herbal materials, and finished herbal products.³

Herbs: Herbs include crude plant material that is flowers, fruit, seeds, leaves, wood, roots, rhizomes or other plant parts.³

Herbal Materials: Herbal materials are the plants or parts of medicinal plants. They include herbs, gums, fixed oils, fresh juices, resins essential oils and dry powders of herbs.³

Herbal Preparations: These are the starting method of finished herbal products and may include powdered herbal materials, or extracts, or oils, expressed juices and extract of herbal materials. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.¹

Finished Herbal Products or Herbal Medicinal Products: Medicinal products as active substances for herbal drug preparations. They consist of herbal preparations made up of one or more herbs. They may contain excipients along with the active ingredients. In few countries, herbal medicines may be by tradition or natural organic or inorganic active ingredients, which are not of plant origin.¹

REGULATORY STATUS

1. EUROPEAN UNION

The Committee on Herbal Medicinal Products on behalf of the EMA gives scientific opinions on herbal products and its preparations, along with information on uses and safe conditions for the maintenance and use of the product. This gives companies and national competent authorities a clear reference point when preparing or assessing an application for marketing authorization or registration of herbal medicinal products in EU Member States.²

Herbal medicinal products, marketing authorization granted under the European Directive 2001/83/EC based on quality, safety and efficacy tests and experimentations results. Definition traditional herbal medicine, provisions for a community list of herbal substances and community herbal monographs and simplified registration procedure are the main features of Directive 2001/83/EC. The HMPC which is part of the EMA was established

under regulation (EC) No 726/2004 and European Directive 2004/24/EC in September 2004. European Directive 2004/24/EC simplifies the registration procedure for herbal drugs as many companies face a lot of difficulties in fulfilling the requirements of Directive 2001/83/EC particularly about the efficacy of traditional herbal medicinal products. The evaluation of medicinal products, simplification of registration, authorization of herbal medicinal products, the establishment of the list of herbal substances and preparations and Community herbal monographs are some important tasks performed by the HMPC. The quality requirements for herbal substances and products are provided in HMPC Monographs of European Pharmacopoeia.³

Registration Process in European Countries⁴

1. The application holder shall be recognized in the Community.
2. For traditional-use registration, the applicant shall apply to the competent authority of the Member State concerned.
3. The application shall be accompanied by
 - (a) The particulars and documents
 - (i) The results of the pharmaceutical tests.
 - (ii) The summary of product characteristics.
 - (iii) In the case of combinations, the information referred to relating to the combination as such; if the individual active ingredients are not sufficiently known, the data shall also relate to the individual active ingredients.
 - (b) Any authorization or registration obtained by the applicant in another Member State, or in a third country, to place the medicinal product on the market, and details of any decision to decline the grant whether in the Community or a third country.
 - (c) Bibliographical to the outcome of a corresponding product has been in medicinal use for about 30 years from the date of the application, including 15 years within the Community. At the request of the Member State where the application for traditional-use registration has been submitted, the HMPC shall put together an opinion on the adequacy of the evidence of

the long term use of the product. The Member State shall submit the required documentation for the reference;

(d) A bibliographic review of safety data with an expert report, and if required by the authority, the data required to verify for assessing the safety of the medicinal product. Where the product has been used in the Community for less than 15 years but is eligible for simplified registration. The Committee shall consider whether the other criteria for a simplified registration are fully complied with. If the Agency considers it possible, it shall create a Community herbal monograph which shall be taken into account by the Member State when taking its final decision.

4. The competent authorities of the Member States shall notify the applicant, the Commission and any competent authority that requests it, of any decision they take to refuse traditional-use registration and the reasons for the refusal. The list shall contain, about each herbal substance, the indication, the specified strength, and the posology, the route of administration and any other information necessary for the safety aspects of the herbal product.

Medicinal products with herbal substances should be under any of the three categories to reach the market;

→ A product can be classified under traditional medicinal use provisions (traditional use) accepted based on sufficient safety data and plausible efficacy: the product is granted a traditional use registration by a Member State,

→ 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 decided on a marketing authorization by a Member State or by the EMA under certain conditions.

United States of America:

Herbs are classified as dietary supplements by the Dietary Supplement Health and Education Act (DSHEA) of 1994 in the US. This law defines supplements quite broadly as "anything that supplements the diet." Supplements, therefore, include vitamins, minerals, herbs, amino acids, enzymes, organ tissues, metabolites, extracts, or concentrates.¹

In the US, the term complementary medicines are commonly used for traditional medicine systems. "Complementary medicine" refers to the CAM together with conventional medicine, 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' references to the use of CAM for conventional medicine. "Integrated medicine" refers to a practice that combines both conventional and CAM treatments in which there is a sign of safety and effectiveness. Traditional healers use methods based on indigenous theories, beliefs, and experiences handed down from generation to generation.⁵

Herbal Drug Products are differentiated in two categories first is those marketed as Over-the-counter (OTC) and second are those that require New Drug Application (NDA) by guidance for herbal drug products given by FDA's Center for Drug Evaluation and Research (CDER). Herbal drugs of the well-known history of use and people, not demands for certain information from them the guidance document provides new drug route navigation such as discussions of the possibility of lesser demand for information by the public. FDA may consider toxicology studies or associating studies related waiver on a case to case basis. Under IND to support an initial clinical trial a waiver is entitled to new herbal drugs based on preclinical pharmacology/toxicology studies, depending on the earlier human experience. Except for those herbal drug products regulated under section 351 of the Public Health Service Act (42 U.S.C. 262), all herbal drug products are regulated under the act addressed by this guidance.⁶

Herbal products containing plant material as ingredients are called finished or labeled products. In the United States, herbal drug products may be marketed under an approved NDA or ANDA or an OTC drug monograph. The FDA regulation 21 CFR parts 331-358 stated if an herbal product has been marketed for a long period for a specific OTC drug indication may be eligible for inclusion in an OTC drug monograph. If the manufacturer wants to amend the monograph for the inclusion of an herbal substance as a new active constituent must submit a petition by 21 CFR 10.30.⁶

When an OTC drug is distributed for a specific use of a botanical drug, then any person can market a product with 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 may be suitable 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. Good Agriculture and Collection Practices regulations were published by AHPA and American Herbal Pharmacopoeia to develop quality control standards for the manufacture of herbal supplements, as needed to ensure the 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. The combination has been proven successful in reducing quality and safety issues from herbal products. More and more practitioners are also moving away from traditional knowledge to evidence-based medicines.⁷

Indian Regulation

In India, all the officially recognized health systems viz. Ayurveda, Siddha, Yoga, Homeopathy, Unani and Naturopathy except Allopathy have a major share of herbal drug products. In India, herbal drugs are regulated by Research Councils (ICMR and CSIR) Department of AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homoeopathy), Drugs and Cosmetics Act 1940 (Amendment) and IMCC (Central Council of Indian Medicine) Act. Drug Controller General of India (DCGI's) regulations must be followed in case of herbal medicinal plants and remedies required to be incorporated into a modern system. According to the 1964 amendment of Drugs and Cosmetics Act 1940, all "Ayurvedic, Siddha or Unani" medicines specified in the Schedule First those are proposed for the diagnosis, prevention and treatment of disease in human beings or animals and

developed under the procedures described in the books of Ayurvedic, Siddha and Unani systems of health. Some degree of controls provided by the 1964 amendment, for example, over the manufacturing of drugs which is performed by a qualified person under given hygienic conditions using unadulterated raw materials and all ingredients are labeled properly. The Ministry of Health and Family Welfare (Department of Health) established Pharmacopoeial Laboratory for Indian Medicine (PLIM) in Ghaziabad to overwhelm the difficulty comes in implementation of the 1964 amendment of the FD&C Act. PLIM comprises the Drug Depot, the Drug Standardization, and Testing Unit and the Herbarium and Reference Museum. Indian systems of health were also described in Pharmacopoeias.⁸

In India, there is a provision to register herbal medicinal products in each state via state drug licensing authority. Recently Schedule TA (Rules 2008) has been introduced in the Drugs and Cosmetics Act (first amendment) for utilization of record of raw materials by licensed manufacturing units of Ayurvedic or Sidha or Unani medicines or products. By the second amendment (Drugs and Cosmetics Rules 2008) manufacturers of herbal drug products can use excipients mention in Indian Pharmacopoeia or Prevention of Food Adulteration Act 1954 or Bureau of Indian Standards Act 1986. The ICMR has also published GCP guidelines for traditional herbal drugs. These GCP guidelines have classified traditional herbal medicines into three groups⁹ :

1. Traditional Herbal drugs manufactured based on the study of regular use, Classical text, and prescribed pharmacopeia.
2. Traditional herbal formulations manufactured by a new process in new combinations using a new plant-based chemical entity for a new indication and toxicity data have been generated for acute, sub-acute and chronic toxicity.
3. Traditional herbal formulations based on GMP compliant Standardization.¹⁰

To develop safe, effective AYUSH products for a recognized disease organization such as ICMR, CSIR, and the Department of AYUSH work together.

Objectives of the Department of AYUSH are:

- To control drug quality.
- To establish pharmacopoeial standards.

- Supervising functioning of the Pharmacopoeial Laboratory of Indian Medicines (PLIM).
- Make interaction with the Quality Council of India (QCI).
- Supervising working of Indian Medicine Pharmaceutical Company Limited (IMPCL).
- AYUSH also works for the implementation of Good Manufacturing Practices (GMP)

Table No. 1: LEGISLATIVE FRAMEWORK FOR HERBAL DRUGS IN THE EU, US & INDIA¹⁰

Items	EU	US	India
Legislation	<ul style="list-style-type: none"> • CD 2001/83 (“basic” regulation) • CD 2003/63 of 25 June 2003 (Annex I, criteria) • CD 2004/24 (Traditional herbal medicinal products) • CD 2004/27 of 31 March 2004 (HMPC) 	The Dietary Supplement Health and Education Act (DSHEA) of 1994 <ul style="list-style-type: none"> • The FDA regulation 21 CFR parts 331-358 • The Public Health Service Act (42 U.S.C. 262) 	The Drugs and Cosmetics Act of 1940 amended 1964. <ul style="list-style-type: none"> • The Drugs and Cosmetics Rules 2008. • The Prevention of Food Adulteration Act 1954 • The Bureau of Indian Standards Act 1986.
Committee	Central European Authority with specified tasks. <ul style="list-style-type: none"> • Committees and Working Parties • Herbal Medicinal Products Committee – HMPC • Monographs and List Working Party – MLWP 	<ul style="list-style-type: none"> • Center for Drug Evaluation and Research (CDER). • National Center for Complementary and Alternative Medicine 	Research Councils (ICMR and CSIR) <ul style="list-style-type: none"> • Department of AYUSH

Africa Regulations:

WHO report recently as said that on the status of traditional medicine in Africa indicates the following:

- In 2000 only ten African countries had laws on the use of herbal products. By 2010 the figure was twenty countries.

- In 2000 only four African countries had a registration system of traditional doctors. By 2010 the figure was fifteen countries.
- In 2000 just one African country had issued a market authorization for traditional herbals. By 2010 the figure was twelve countries.
- Egypt wherever the herbal medicines are regulated and manufactured with licenses just like Europe. The protection of the intellectual properties of traditional healers has become a progressively important part of the regulatory situation. Eight countries, including South Africa, Ghana, and Nigeria, have national laws involving the IPR and traditional medicine. There is, however, a wide gap between the existence of the legislation and also the application of the law in systems of herbal preparation.¹¹

PHILIPPINES:

Regulatory System:

The Philippines defines Traditional Medicine (TM) as the totality of knowledge, skills, and practice of health care that can't be expressly explained in a scientific framework however its impact in maintaining health and care has been recognized by the society to be reflective of their culture, history and social consciousness. It uses numerous terms like herbal and/or traditional drugs, herbal medicine (HM), traditionally used herbal products and herbal supplements (HS) which include food supplements (FS). The guideline policies within the Philippines are categorized according to the type of product. Summary of the traditional and health supplement governing requirements in the Philippines. Criteria for safety, traditional use, scientific validity, and quality: To make sure the safety of TM and HS, the Philippine regulatory body needs to submit the technical data for safety and GMP certificate of the manufacturer for product registration. Pre-marketing Evaluation needs references to support safety. These may include monographs, pharmacopeias, and websites for TM; and websites for HS. Toxicity studies are required for their premarketing assessment. On the other hand, registration of TUHP needs along with the submission of technical data for safety, toxicity studies, and a list of references supporting it. However, there should be a documented traditional experience of the use of at least five decades. For all these products, the submission of technical data for effectiveness or claimed application is needed for product registration. Pre-marketing Evaluation of TM and HS in the Philippines involves verification of claims of raw material and finished product effectiveness. Additionally, TM should

undergo clinical trials. For TUHP, only verification of claims of the raw material effectiveness is required. In ensuring the product quality of TM and HS, technical data for quality and a GMP certificate should be submitted for product registration. Evaluation of formula, raw material, manufacturing processes, and finished product specifications are conducted before product marketing. Results of the following quality control parameters are required: stability study, determination of water content, disintegration time and microorganism count. The requirement for submission of technical data for quality is also applicable to TUHP. Post-marketing surveillance of herbal medicines Countries was 1st asked whether they had a PMS system for herbal products. If countries responded “yes”, the future question asked whether there’s a national system to monitor the adverse effects of herbal products. If such a system exists, the date of establishment was requested. Countries were requested to select all methods of sale employed on their territory from the following options:

- in pharmacy as prescription drugs;
- in pharmacy as OTC drugs;
- in special outlets;
- by licensed practitioners;
- no restrictions on selling herbal medicines;
- and other ways. If "other ways" were selected, a description was requested.



Market Importance of Herbal Medicines

The % of herbal medicines prescribed in medical treatment is always increasing. Several places have already succeeded in using 100% plant-based drugs which reduce the burden of the State's subsidy on medicines. Thousands of communities have achieved a certain percentage of herbal drugs to be used in treatment, as set by the MOH. The successful combination of modern and traditional medicine has given impetus to the gradual transformation of herbal medicine to facilitate handling and promote exports. Medicines are produced from plant extracts and purified products, and they are exported as finished or semi-finished products. All medicines prepared from medicinal plants can be used in Viet Nam as substitutes for Western drugs and Chinese herbs which, in former times, it has been more important.¹²

SUMMARY

The herbal drug is the use of herbs and medicinal plants which gives a better quality of life. Herbs are effective as drugs, but not with the side effects. They create a more potent, effective and efficient treatment to ensure a quicker therapeutic response. They contain more than one constituent which has different pharmacological effects and so it is necessary to check its quality and safety. Hence the study of the governing requirements of herbal products is essential to faster marketing approval.

Herbal medicines are gaining a huge demand day by day. Around the world, countries are becoming concern about the usage of herbal medicines. It is now known to control herbal medicine is required as herbs are not always safe. Major regulatory bodies around the world are developing new strategies to control the market. Regulatory bodies are concern about public safety. Many countries have developed a new research institute, some are revising national policy others have already developed. Above all, it has been understood that the requirement of post-marketing surveillance is highly important. In the myth over the safety of herbal medicine, this domain is always is neglected from the purview of pharmacovigilance. However, the importance of such things is now accepted today. Countries like India are in the growing stage of such development. AYUSH the Indian controlling authority has implemented many rules and laws but how far those laws and rules comply is a matter of investigation. Herbal products which are marketed are not having product leaflet none of them are clinically tested and GMP complied. To overcome all these problems public concern and development of public knowledge are highly required. The government must have to be more vigilant in online marketing. It is found practitioner is very much orthodox in herbal practicing so development in this domain is very much required.

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