

**REGULATORY REQUIREMENT FOR SUBMISSION OF HERBAL
DRUG PRODUCT IN INDIA, USA AND EUROPEAN MARKET****Mathew George^{1*}, Lincy Joseph², Mahendra Kuril³, Kanaka V.S.⁴**¹Department of Pharmacology, Pushpagiri College of Pharmacy, Thiruvalla, 689107, Kerala.²Department of Pharmaceutical Chemistry, Pushpagiri College of Pharmacy, Thiruvalla,
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Pharmacology, Pushpagiri
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The present work has been done to facilitate the registration and regulation of herbal medicines by establishing the foundation for a harmonized regulatory standard to meet the common demands of the region. It is obvious that there are some dossier and GMP requirements for the registration of herbal drugs, nutritional supplements and OTC drug products in the regulated market as well as in less regulated market. After comparing the regulatory status of India, USA and European market, it was found out to make some suggestions for India, based on regulated markets. In European countries there is a system with well defined guidelines for the herbal products but in case of India and USA these products are treated like other medicinal products. At

last it was concluded that the system that is currently involved in India need to be further upgraded to require registration of individual drugs with specified quality control, safety and efficacy standards.

KEYWORDS: GMP, WHO, OTC drug.**INTRODUCTION**

Herbal medicinal products defined as 'any medicinal product exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations'. The world

health organization (WHO) estimates that 4 billion people, 80% of the world population, presently use herbal medicine for some aspects of primary health care. Major pharmaceutical companies are currently conducting extensive research on plant materials for their potential medicinal value.^[8,9]

The legal situation regarding herbal preparations varies from country to country. Herbal medicines have been included in the International Conference on Drug Regulatory Authorities (ICDRA) since fourth conference in 1986. A WHO consultation in Munich, Germany, June 1991, drafted guidelines to define basic criteria for the evaluation of safety, quality and efficacy for general use by the 6th ICDRA in Ottawa, October 1991. In, 1994, the WHO Regional Office for the Eastern Mediterranean published Guidelines for the formulation of natural policy on herbal medicines. The aim of such policies was to develop regulatory status and to ensure safety, efficacy of these herbal medicines.^[11]

Each country defines medicinal plants or herbs in different ways and they have adopted different approaches for their licensing, dispensing, manufacturing and trading. In India, the provisions applicable for the Ayurvedic products are according to Drugs & Cosmetics Act 1940, and corresponding Rules 1945. And for herbal products, the provisions are those that apply on allopathic medicines. For the registration of nutritional supplements India has adopted the Prevention of Food Adulteration Act (PFA Act) 1954 and Rules 1955.^[10,21]

In European Union, the regulatory status for herbal preparation is quite different. According to Council Directive 65/65/EEC, herbal preparations are not considered as medicinal products if they are intended to be used as food, cosmetics etc. The Council Directive 65/65/EEC establishes that proof of quality, safety and efficacy is a precondition for delivering a marketing authorization for a medicinal product. In UK, if the amount of vitamins and minerals in the food supplement is within Recommended Dietary Allowance (RDA), then it regarded as food with no medicinal claims.^[11,12,13]

While in case of US, no separate regulation for herbal products is permitted. Botanical preparation used as a dietary supplement, are regulated under DSHEA. And botanical preparation used as a food, are regulated under FD&C Act. For the registration of nutritional supplement in US, safety, nutritional support statements, nutrition information labeling etc. should be considered.^[3]

MATERIALS AND METHODS

Regulatory requirement for registration of herbal drug products in India:

The provisions have been made as follows, that is Schedule M (GMP for allopathic medicines) is followed for herbal products and Schedule T (GMP for herbal medicinal products) is followed for ayurvedic products.^[4]

Standards of ayurvedic drugs.

Table no: 1

Sl. No.	Class of drugs	Standards to be compiled with
1.	Single drugs included in Ayurvedic Pharmacopoeia	The standards for identity, purity and strength as given in the editions of Ayurvedic Pharmacopoeia of India for the time being in force.
2.	Asavas and Arishtas	The upper limit of alcohol as self generated alcohol should not exceed 12% v/v excepting those that are otherwise notified by the Central government from time to time.

Conditions for the grant or renewal of a license: conditions are as follows,

- The manufacturing of Ayurvedic drugs should be carried out in premises and under hygienic conditions as specified in Schedule T.
- The manufacturing should be conducted under the supervision of competent technical staff consisting of at least one person, who is a whole time employee and who possesses the qualifications as per Act.
- The licensee should maintain batch manufacturing record, distribution record and records of market complaints for each batch.

Regulatory requirement for registration of nutritional supplements in India:

There is no separate requirement for nutritional supplement in India. Nutritional supplement consider as a Food for special dietary uses and follow the Prevention of Food Adulteration Act (PFA Act) 1954 and Rules 1955.^[2]

Food and safety standard act of India 2006: this act may be called the food safety and standard act 2006, passed by Government of India in August 24, 2006 for food.

Food safety and standards authority of India: this is to exercise the powers conferred on and to perform the functions assigned to it.

General provisions applicable as articles of food: The provisions that are made for articles of food. Those are as follows:

Section 19: no article of food shall contain any food additive or processing aid unless it is in accordance with the provisions of the act and regulations.

Section 20: no article of food shall contain any contaminant, naturally occurring toxic food

Section 21: no article of food shall contain insecticides or pesticides residues, antibiotic and solvent residues etc.

Section 22: no person shall manufacture, distribute or import any novel food irradiated food, proprietary foods and such other articles of food which the central government may notify in the behalf.

Section 23: no person shall manufacture, distribute, sell or deliver any packaged food products which are not marked and labeled in the manner specified by regulations.^[5]

Section 24: no advertisement shall be made of any food which is misleading or deceiving or contravenes the provisions of the act.

Section 26: every food business operator shall ensure that articles of food safety, the requirements of the act and rules made there under at all stages of production, processing , import distribution and sale under this control.

Section 27: the manufacturer or packer of an article of food shall be liable for such article of food if it does not meet the requirements of the act and rules.

Section 31: no person shall commence or carry on any food business except under a license.

Regulatory requirement for registration of herbal drug products in E.U.

There are three regulatory routes.

1. Unlicensed herbal remedies: these are supplied under Section 12 (2) of the Medicines Act do not require a consultation.
2. Registered traditional herbal medicines: according to traditional herbal medicines registration scheme (THMRS), products registered under this need to meet specific standards of safety and quality.
3. Licensed herbal medicines: these should be required to demonstrate safety, quality and efficacy and be accompanied by necessary safe information. And should have a Product License (PL) number on the packaging.^[11,12]

Traditional Herbal Medicines Registration Scheme (THMRS)

The provisions for traditional herbal medicinal products are according to directive 2001/83/EC, amendment by 2004/24/EC and 2004/27/EC. In order to obtain a product registration, there is need to submit a registration dossier based on Common Technical

Document (CTD) format. The dossier needs to include all the necessary physico-chemical, biological and microbiological tests. The Summary of Product Characteristics (SPC) should be developed with necessary information from experts providing evidence on safety and traditional use.^[14] Control tests and analytical procedures on herbal medicinal product should be validated according to ICH guidelines. Stability of herbal preparation and other substances present in the herbal preparation should be demonstrated.^[15,16]

Storage condition for the active substance for stability studies in general case

Table no: 2

Study	Storage condition	Minimum time period covered by data at submission
Long term	25 ⁰ C±2 ⁰ C/60% RH±5% RH	6 months
Intermediate	30 ⁰ C±2 ⁰ C/65% RH±5% RH	6 months
Accelerated	40 ⁰ C±2 ⁰ C/75%RH±5%RH	6 months

Storage condition for the active substance intended for storage in refrigerator

Table no: 3

Study	Storage condition	Minimum time period covered by data at submission
Long term	5 ⁰ C±3 ⁰ C	6months
Accelerated	25 ⁰ C±2 ⁰ C/60% RH±5% RH	6months

GMP requirement: It provides specific guidelines for storage area, production area, equipment, specification for starting materials, processing instructions and quality control.

Product information: Labeling and package leaflet should be in English and meet requirements of article 54 to 65 of Directive 2001/83/EC. Applicant is required to submit bibliographic or expert evidence that the product has been in medicinal use throughout a period of 30 years preceding the date of application. Each product requires a separate registration. Advertising of traditional herbal medicines fall within the THMRS, articles of 86 to 99 of Directive 2001/83/EC.^[14,15]

Advertising: Advertising and promotion of traditional herbal medicines that fall within the THMRS must meet the requirements of Articles 86 to 99 of Directive 2001/83/EC as amended.

Regulatory requirement for registration of nutritional supplements in European Union.

In UK, most vitamins, minerals and supplements are controlled under Food Standard Agency (FSA). Food supplements are regulated as food if the amount of vitamins or minerals in the supplement is within the recommended dietary allowance. No medicinal claims are permitted. The product must be safe and labeled according to the Food Labeling Regulations 1996. Supplement labels must express their nutrient content in terms of EU Recommended Daily Allowances (RDA).^[13]

Regulatory requirement for registration of herbal drug products in US.

For a new botanical drug FDA regulations require NDA for marketing submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act. Regulatory management of botanical drug products is the same as non-botanical drug products and is based on 21 CFR 312, 314 and the Act.^[17]

In US, botanical drugs can be marketed under approved new drug application (NDA) and over the counter (OTC) monograph. For a botanical drug to be included in an OTC monograph there must be published data establishing general recognition of safety and effectiveness. In 1938, the Food, Drug and Cosmetic Act (FDC Act) required proof of safety and submission of a new drug application (NDA) for new drugs.^[6]

The Federal Food, Drug and Cosmetic Act of 1938 (FDC Act) amended governs the marketing and sale of food, drugs and cosmetics in interstate commerce in US.

Herbal product regulation: Section 4 of the Dietary Supplement Health and Education Act of 1994 (DSHEA) established that the burden of proof for safety lies with the Federal Food and Drug Administration (FDA). FDA is having many of controls over the marketing of these products. Dietary supplement ingredients that were first marketed in US after 15th October 1994 are defined by Section 8 of DSHEA as new dietary ingredients. DSHEA requires the manufacturer to submit all evidence at least 75 days before the product enters interstate commerce. FDA may prohibit the marketing if they are not satisfied with the evidences.

Scientific standards required for herbal product: Section 485C of DSHEA mandated the establishment of an office of dietary supplement within the national institutes of health. Under DSHEA, this office was mandated to

1. conduct and coordinate scientific research

2. collect and compile results of scientific research and
3. Serve as the principal advisor to other government agencies on issues relating to dietary supplements.

FDA issued a final rule clarifying the requirements for dietary supplements. However, a manufacturer must not notify FDA about structure/ function claim within the first 30 days of **Advertising of herbal products:** It is governed by the Federal Trade Commission Act and Federal Trade Commission's criteria for support of food advertising claims. Wholesale distribution of herbal products is governed by DSHEA.

Health claims: The Nutrition and Education Act of 1990 (NLEA) established the procedures for approving health claims for food. It requires "significant scientific agreement" before a health claim is permitted on a food label.^[7]

Regulatory requirement for registration of nutritional supplements in USA.

The Dietary Supplement Health and Education Act 1994 (DSHEA) amends the adulteration provisions of the FD &C Act. A dietary supplement must be safe and should not present a significant or unreasonable risk of illness or injury. The label of the supplement should bear the identification as "dietary supplement".^[8]

Format for the supplement fact: These are the statements of nutritional support that provide useful information to consumer. It should be truthful. The supplement fact must be enclosed in a box by using hairlines. The title must be larger in size and bold.

cGMP rule for dietary supplement : This rule establishes cGMP necessary for activities related to manufacturing , packaging, labeling dietary supplements to ensure the quality.

Use of DSHEA disclaimer in advertising.

Under DSHEA, all statements must be accompanied by a two part disclaimer on the product label: that the statement has not been evaluated by FDA and that the product is not intended to diagnose, treat, cure or prevent any disease.

RESULTS AND DISCUSSION

Comparison of regulation for nutritional supplements, herbal and OTC drug products for different countries.

Table no: 4

Products	USA	UK	India
Nutritional supplements	DSHEA 1994	Food legislation of UK (Directive 2000/13/EC)	PFA Act 1954 and corresponding Rules 1955
OTC drug products	21 CFR 312, 314	Council directive 92/27/EEC	Drug and Cosmetics Act 1940 and corresponding Rules 1945
Herbal products	21 CFR 312, 314	2001/83/EC	Drug and Cosmetics Act 1940 and corresponding Rules 1945

Suggestion on regulation for registration of herbal drug products in India based on most regulated market.

Following are the suggestions on regulation for registration of Ayurvedic products in India,

- Control of excipients: Excipients added to the Ayurvedic preparations should be described. Information on the quality control and full details of manufacture, characterization, controls and safety data should be provided.
- Control of quality: Ayurvedic substances must be tested for microbiological quality and for residues of pesticides and fumigation agents. To implement Good Agricultural and Collection Practice (GACP), coordination agencies should be established.
- Safety requirements : data should be provided on the following
 - Acute toxicity
 - Long term toxicity
 - Organ targeted toxicity
 - Immunotoxicity
 - Embryo fetal and prenatal toxicity
 - Mutagenicity genotoxicity
 - Carcinogenicity
- Labeling requirements: labeling of the Ayurvedic products should contain:
 - Method and route of administration
 - The statement “ store out of the reach and sight of children”
 - Special warnings
 - Storage precautions
 - Duration of therapy
 - If intended for self medication, full instructions for use

- Registration requirements: The system need to be further upgraded to require registration of individual drugs with specified quality control, safety and efficacy standards. The imported herbal medicines must be registered and marketed in the countries of origin. It should meet the safety and efficacy of herbal medicines and should be submitted to drug authority.

CONCLUSION

The herbal products are treated differently in various countries. In European countries there is a system with well defined guidelines for the herbal products but in case of India and USA these products are treated like other medicinal products. By comparing the guidelines by selecting three different regions India, USA and European Union, it was concluded that the system that is currently involved in India need to be further upgraded to require registration of individual drugs with specified quality control, safety and efficacy standards.

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REFERENCES

1. Traditional Medicines and Modern Health Care. Progress report by the Director General. Geneva, World Health Organization, 31 October 1990.
2. The Prevention of Food Adulteration Act 1954 and Rules 1955, amended up to October, 2004, <http://mphfw.nic.in/pfa%20acts%20and%20rules.pdf>
3. Dietary Supplement Health and Education Act. 1994. Public Law 103-417.
4. The Drugs and Cosmetics Act, 1940& Rules 1945, Government of India, Ministry of health and family welfare, (As amended up to 30th June 2005), <http://www.cdco.nic.in/html/Drugs&CosmeticsAct.pdf>
5. The gazette of India, extraordinary, part II, section I, published by authority, Ministry of law and justice (legislative department), New Delhi, August 24, 2006; 1-46.
6. Federal Register. May 11, 1972; 37: 9464.
7. Nutrition Labeling and Education Act. 1990. Public Law 105-115.

8. http://www.holisticonline.com/Herbal-Med/hol_herb-intro.htm
9. <http://www.euromonitor.com>
10. http://www.indianmedicine.nic.in/html/acts/orders_%20D&C_%20Act.pdf
11. http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=659
12. http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=658
13. <http://emea.europa.eu.int>
14. [http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dID=1385&noSaveAs=o
&Rendition=WEB](http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dID=1385&noSaveAs=o&Rendition=WEB)
15. <http://www.emea.europa.eu/pdfs/human/pmf/2001-83-EC.pdf>
16. <http://www.emea.europa.eu/pdfs/human/qwp/012202en.pdf>
17. <http://www.cfsan.fda.gov/~dms/dslg-toc.html#toc>
18. <http://www.cfsan.fda.gov/~dms/dietsupp.html>