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REGULATORY REQUIREMENTS FOR MANUFACTURING AND APPROVAL OF HERBAL PRODUCTS IN INDIA AND G-8 COUNTRIES

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ABSTRACT

The regulatory requirements for the manufacturing and approval of herbal products in India and G-8 countries emphasize ensuring product safety, efficacy, and quality through distinct frameworks. In India, herbal products are regulated under the AYUSH Ministry, adhering to traditional medicine systems like Ayurveda, Unani, and Siddha, with requirements for GMP compliance, quality standards, and preclinical studies. Conversely, G-8 countries, including the US, EU member states, and others, classify herbal products as dietary supplements, traditional medicines, or pharmaceuticals, each requiring adherence to stringent guidelines such as the FDA or EMA standards. These include GMP certification, scientific validation of claims, and toxicological studies. Despite differences, the global market for herbal products is growing, necessitating manufacturers to navigate regulatory complexities to meet international compliance standards.

KEYWORDS: Herbal products, G-8 countries, Ayurveda, Unani, and Siddha

INTRODUCTION[1-5]

Herbal medicines are being used in India since Vedic age and it has been documented in Rigveda. It has been mentioned in Charak Samhita. Initially herbs have been used by the people traditionally from their experience and gradually a group of experts evolves who were called as apothecaries. Herbal medicines are also used since long back in other different countries like China. In India herbal medicines are being used in Ayurveda, Siddha, Unani & Homoeopahiic system of medicines. Ayurvedic system is being practiced since 6000 B.C.,

Chinese herbal medicines is being practiced since 5000 B.C. whereas the modern system of medicines started since 1800 A.D.

Interest on herbal products has been increasing since last few decades not only in underdeveloped and developing countries, but also in the developed countries. A large number of big pharma companies started to redirect their business strategy by investing large amount of finance in research and manufacturing of herbal medicines. Some Govt. institutions are also emphasizing on research on herbal medicines.

Herbal medicine has a Global market of US$ 80 - 100 billion (Gohil and Patel, 2007) and this market is expected to reach US$2500 billion by the year 2010 and US$ 5 trillion by the year 2050 according to the World Bank report. The Indian herbal drug market is about $ 1 billion and the export of herbal crude extract is about $ 80 million. (Mukherjee, 2001). We have about 7800 manufacturing units engaged in manufacturing of herbal drugs in India, which are consuming 200 tons of herbs annually.

Initially there was no regulation for controlling the quality of herbal medicines and the practitioners relied on their experience on proper identification of the plant. Gradually some regulation developed and the first organized regulation on quality is the Drugs and Cosmetics Act 1940 and Drugs and Cosmetic Rules 1945. This act initially prescribed the standards of Ayurvedic, Siddha and Unani medicines and laid down rules and regulation on manufacturing.

Standards of Drugs as per existing legislature of India[6-7]

Standards of medicines are prescribed in the Drugs and Cosmetic Act 1940 and individual monographs has been prescribed in the respective Pharmacopoeias. Recently the Govt. of India has published 4 volumes of Ayurvedic Pharmacopoeia encompassing standards of 326 drugs, which is grossly inadequate in comparison to the number of herbs used in the Ayurvedic system of medicines. A positive step has been taken in this direction by publishing of the Herbal Pharmacopoeias, having standards of 52 drugs (IDMA, 2002).

Unfortunately, neither the herbal products nor the herbal Pharmacopoeias have any statutory standing in our country (Govt. of India, 2005). That there are many herbal products in the market though it is difficult to categorize these products as per the Drugs and Cosmetics Acts

& Rules. Some herbal drugs are also marketed as food or nutritional supplements, with medicinal claims.

Keeping this problem in mind, status of herbal products was surveyed through different sources including Pharmacopoeias of different countries (WHO, 1998; WHO 2001; WHO, 2005).

In some countries herbal products are considered as drugs, e. g. China, UK, Canada, Germany, etc. while some countries do not grant herbal products, the status of drugs e.g., USA, Netherlands etc. They consider it as nutritional supplements and have framed definite legislation for it e. g. USA (Marwick, 1995).

In India there are some gray areas in case of status of herbal drugs (Table –I) and there exists no definite policies about food supplements. Recently Govt. of India has published Food Safety act to resolve this problem (Govt. of India, 2006). As per the experts this said act has not been implemented and failed to resolve the problem.

Sometimes mere mentioning of a drug in some textbooks is considered sufficient as per existing legislature, whereas the texts are not properly defined (Govt. of India, 2005).

Table – 1: Standard of Herbal Drugs as per Indian legislation.

System of Medicine	Standard
Modern Drugs	The second schedule of Drugs & Cosmetics Act.
Homeopathic Drugs	The second schedule of Drugs & Cosmetics Act.
Ayurvedic, Siddha & Unani Drugs	Rule 168 of Drugs & Cosmetics Act.
Herbal	?

Standards of Ayurvedic Drugs[8-10]

Standards required to be complied with in manufacturing for sale or distribution of Ayurvedic, Siddha and Unani Drugs are laid down in Drugs & Cosmetics Rules, which are given in the table below.

Table 2: Standards of Ayurvedic, Siddha and Unani drugs as per D & C Rules.

Sl. No.	Class of Drugs	Standards to be complied 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 Aristas	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.

Till date, only four volumes of Ayurvedic Pharmacopoeia having monographs of about 326 herbs have been published, which is quite inadequate with respect to the huge number of herbs used in the Ayurvedic system of medicines (IDMA, 2002). Mere mentioning of preparation method in a list of 57 texts, are sufficient for manufacturing such Ayurvedic drugs. All of these books are old texts except the Ayurvedic Formulary of India (Part I) & Ayurvedic Pharmacopoeia of India. There is ample scope of misuse of this provision, as 55 books out of 57 are not properly defined in the legislature.

The monographs cover only a few parameters, which are considered to be quite inadequate for standardization (Govt. of India, 1990; Govt. of India, 1999; Govt. of India, 2001; Govt. of India, 2004). Monographs of herbs in British Herbal Pharmacopoeia prescribe chemical characterization involving TLC, GC & PC electrophoresis, whereas no such modern methods are required in the Ayurvedic Pharmacopoeia. Minimum pharmacological characterization is required, which is quite inadequate, compared to characterization specified by other Pharmacopoeias.

No standards for combination products are prescribed in statute, except Asavas and Aristas. Only alcohol content of these two products is given in D & C Act.

Standards of Siddha Drugs

As per the Drugs Act, simply mentioning of manufacturing process in a list of 30 books allows production of Siddha Drugs. Amongst these 30 books, 29 are old texts and Siddha Formulary of India (Part I) is the only book published by the Govt. of India recently.

Standards of Unani Tibb System of Drugs

As per the Drugs Act mere mentioning of manufacturing process in a list of 13 books allows production of Unani & Tibb drugs. Amongst these 13 books, 12 are old texts and the only modern book is National Formulary of Unani Medicine (Part I) published by Govt. of India.

Schedule T for Good Manufacturing practice

To manufacture good quality Ayurvedic, Siddha and Unani medicines Good Manufacturing practices have been made mandatory by incorporation of revised Schedule T in the year of 2003 (Govt. of India, 2005). Important features of Schedule T are as follows.

i) Raw materials to be used in manufacture of medicines must be authentic, of prescribed quality and free from contamination.

ii) Manufacturing process is as prescribed to maintain the standard.

iii) Adequate quality control measures to be adopted.

iv) Drugs released for sale shall be of acceptable quality.

v) To achieve the objectives listed above, the firm is required to maintain the following conditions stringently-

A) Well designed factory premises with sufficient space required to be provided.

B) Proper machineries require to be provided.

C) Quality control laboratory require to be provided with required instrumentations and well qualified personnel.

D) Shall evolve methodology and procedures for following the prescribed process of manufacture.

E) Which should be properly documented and kept for reference and inspection.

Standards of Homoeopathic Medicines

Standard of Homoeopathic medicines has been prescribed in Second schedule of the Drugs and Cosmetics Act, 1940, which is given in Table-III.

Table 3: Standards of Homoeopathic Medicines as per Drugs & Cosmetics Act.

Sl. No	Class of Drug	Standard to be complied with
1.	Drugs included in the Homoeopathic Pharmacopoeia of India	Standards of identity, purity and strength specified in the edition of the Homoeopathic Pharmacopoeia of India for the time being and such standards as may be prescribed.
2.	Drugs not included in the Homoeopathic Pharmacopoeia of India but which are included in the Homoeopathic Pharmacopoeia of the United States of America or the United Kingdom or the German Homoeopathic Pharmacopoeia.	Standards of identity, purity and strength prescribed for the drugs in the edition of such Pharmacopoeia for the time being in which they are given and such other standards as may be prescribed.
3.	Drugs not included in the Homoeopathic Pharmacopoeia of India or the Homoeopathic Pharmacopoeia of the United States of	The formula or list of ingredients displayed in the prescribed manner on the label of the container and such other

	America or the United Kingdom or the German Homoeopathic Pharmacopoeia.	standards as may be prescribed by the Central Government.

In addition to this, three more parameters are required to be controlled for mother tincture, which are- identification of crude drugs, total solids & alcohol content.

For the first category presently, we have eight volumes of Pharmacopoeia prescribing the monographs including identity, purity and strength of several raw materials (Govt. of India, 1971). But no standard for finished product was included till publication of fifth volume in the year of 1987. Sixth and eighth volume included standard of a few finished products of Mother Tinctures & Mother solutions (Govt. of India, 2000). Standards include a few preliminary criteria like pH, wt. per ml, alcohol percentage, γ max and identification, which are considered inadequate for proper quality control at this age when sophisticated techniques like HPTLC are easily available.

Schedule M1: In order to ensure proper quality of Homoeopathic medicines manufacture, Schedule M1 was introduced in 1987 specifying requirement of technical staff, manufacturing plants, testing equipment etc.(Govt. of India, 2005). Experts feel that this is quite inadequate in this age of science.

Recently Government of India has taken an initiative to implement Good Manufacturing Practices (GMP) and a guideline has already been published, which is effective from 2nd October 2008. This guideline is more detailed and prescribed minimum requirement of manufacturing areas, equipments, minimum qualification required for the personnel engaged in manufacturing and quality control, documents to be maintained etc. for manufacturing quality medicines.

Patent Protection to be exploited fully[11-13]

Despite possessing huge natural wealth, India has not shown promising performance in the field of the thriving $ 80 - 100 billion global herbal market. A few countries - China, Russia, Europe, Japan and even USA have marched ahead with numerous international patents on medicinal plants.

If India can fully exploit its natural resources, skilled manpower and potential traditional knowledge and couple them with its technical prowess, she can march ahead to compete with global players by partly substituting costly modern medicines with modern herbal drugs. If

she can concentrate her efforts to develop her heritage herbal products and processes it seriously, it will be hard to hold back her progress (Mandal and Mandal, 1999).

It is unfortunate that some of the Indian products have been patented by different companies which are being used in India since a long time like- Neem, Amla, Kurchi, Sarpagandha, Calendula, Sankhapushpi, Jamun, Anar, Bagbherenda, Karela. Fortunately, Government of India has taken initiative to challenge the patent granted on turmeric to an US University and as a result U.S. patent (No. 5,401,504) on the use of turmeric (Curcuma longa L., Zingiberaceae) for healing was invalidated because it was not a novel invention. This is an encouraging victory for Indian activists campaigning to protect indigenous wisdom. Under World Trade Organisation (WTO) rules, patents are provided for inventions that qualify for their novelty, non-obviousness, and utility. The turmeric patent failed to satisfy the criteria of novelty as turmeric paste has been used to treat wounds and stomach infections for centuries by Indians. The turmeric patent was just one of the hundreds that the developed countries have claimed by ignoring indigenous and existing knowledge.

In order to prevent grant of patents based on Indian traditional knowledge, Government of India has undertaken an ambitious project of creating a Traditional Knowledge Digital Library (TKDL). This is a joint venture of the Council of Scientific Research and Central Council for Research in Ayurveda & Siddha. This project is intended to cover about 35,000 formulations available in 14 classical texts of Ayurveda to convert the information in to patent compatible format. The work has been initiated with a co-operative set up of 30 Ayurveda experts, 5 information Technology experts and 2 Patent examiners. The digital library will include all details in digital format about international patent classification, traditional research classification, Ayurveda terminology, concepts, definitions, classical formulations, doses, disease conditions and references to documents.

Steps to be taken to improve the existing efforts of standardization[14-16]

Control on quality of raw materials: Quality of medicines of herbal origin mainly depends on quality of raw materials. Presently, a major part of the raw materials are procured from wild origin, which have almost no control on parameters of cultivation or collection etc. Controlled cultivation could be a parameter of the quality control. If Good Cultivation Practice & Good Harvesting Practices are developed and implemented raw materials of good quality can be ensured. European Guidelines for Good Agricultural Practice (G.A.P.) of Medicinal and Aromatic Plants, Good Agricultural and Collection Practice for Medicinal

Plants (GACP), Japan, Good Agricultural Practice for Traditional Chinese Medicinal Materials, People's Republic of China etc. have been published for this purpose. Recently World Health Organization has also published Good Agricultural & Collection Practice (GACP) which may be practiced in case of Cultivation and collection of Medicinal plants (20).

Research for developing quality control methods[17-20]: It is a fact that quality control of herbal drugs is not developing sufficiently, especially for combination products. Research on developing standardization methods involving modern instrumentation is urgently required. Though a few attempts have already been made, more emphasis is required in this area. Monographs of more plants require to be incorporated in the existing Ayurvedic Pharmacopoeia. More stringent specifications including use of sophisticated instruments are to be incorporated. Research & development of marker compounds & Metabolomics are order of the day, and stress must be laid in this area.

Clinical trial: In the third world countries like India, there is always a lack of enthusiasm noted for conduction of clinical trials, and there is a dearth of coordination and effort to translate and utilize the results of clinical trials within various working groups and professionals. While most modern clinicians and researchers believe in rigorous screening and clinical trials, most specialists in traditional medicine are convinced of 100 % efficacy of their drugs and consider clinical trials as redundant. This attitude is much more prevalent in India than in China, where institutes of traditional medicine have established their drugs on scientific basis rather than on the rationale of drug (Roy Chaudhury, 1994). For proper conduction of clinical trials, there is a requirement of experienced clinical pharmacists, pharmacologists, as well as experts in traditional system of medicines.

CONCLUSION

In the present study, the regulatory status of herbal drugs in India and G-8 countries has been unveiled from available sources of official documents. An attempt has been made to compare the regulatory status of herbal drugs in G-8 countries. Though the harmonization of regulations of herbal drugs across the globe is a herculean task, it becomes a crying need, as the study proposes. Some recommendations have also been made for bringing under the law of India so as to sharpen the statute and to ensure safety and acceptability of herbal as well as traditional drugs among G-8 countries. Recommendations are also developed from the study

to represent before proper authority to strengthen the existing regulatory mechanism for herbal as well as ASU drugs in India.

REFERENCES

1. Gohil, K.J., Patel, J.A. Herb-drug interactions: a review and study based on assessment of clinical case reports in literature. Indian J Pharmacol, 2007; 39: 129-139.
2. Govt. of India, Ministry of Health. Homoeopathic Pharmacopoeia of India, Vol. I. Delhi, The Controller of Publications, 1971.
3. Government of India, Ministry of Health and Family Welfare, Department of Indian System of Medicine & Homoeopathy. The Ayurvedic Pharmacopoeia of India, Part – I, Vol. I. The Controller of Publications, Delhi, 1990.
4. Government of India, Ministry of Health and Family Welfare, Department of Indian System of Medicine & Homoeopathy. The Ayurvedic Pharmacopoeia of India, Part – I, Vol. II. Delhi, The Controller of Publications, 1999.
5. Govt. of India, Ministry of Health and Family Welfare, Department of Indian System of Medicine & Homoeopathy. Homoeopathic Pharmacopoeia of India, Vol. 8. The Controller of Publications, Delhi, 2000.
6. Government of India, Ministry of Health and Family Welfare, Department of Indian System of Medicine & Homoeopathy. The Ayurvedic Pharmacopoeia of India, Part – I, Vol. III. The Controller of Publications, Delhi, 2001.
7. Government of India, Ministry of Health and Family Welfare, Department of Ayurveda, Yoga-Naturopathy, Unani, Siddha & Homoeopathy (AYUSH). The Ayurvedic Pharmacopoeia of India, Part – I, Vol. IV, The Controller of Publications, New Delhi, 2004.
8. Government of India, The Drugs and Cosmetics Act 1940 and The Drugs and Cosmetics Rules, 1945. Ministry of Health and Family Welfare, 2005.
9. Government of India. The Drugs and Cosmetics Act 1940 and The Drugs and Cosmetics Rules, 1945. Ministry of Health and Family Welfare, 2005; 405–413.
10. Government of India. The Drugs and Cosmetics Act 1940 and The Drugs and Cosmetics Rules, 1945. Ministry of Health and Family Welfare, 2005; 367–369.
11. Government of India. The Food Safety And Standards Act, 2006.
12. Brahmaiah Bonthagarala, Regulatory Requirements for Registration of Generic Drugs in "BRICS" Countries, International Journal of Pharmaceutical Science and Health Care, ISSN 2249 – 5738, November-December 2016; 6(6): 20-39.

13. Brahmaiah Bonthagarala, Current Regulatory Requirements for Registration of Medicines, Compilation and Submission of Dossier in Australian Therapeutic Goods Administration, International Journal of Advanced Scientific and Technical Research, ISSN 2249-9954, November-December 2016; 6(6): 144-157.
14. Brahmaiah Bonthagarala, Comparison of Regulatory Requirements for Generic Drugs Dossier Submission in United States and Canada, International Journal of Pharmaceutical Science and Health Care, ISSN 2249 – 5738, November-December 2016; 6(6): 1-19.
15. Brahmaiah Bonthagarala, Regulatory Requirements for Marketing of Generic Drugs in USA, International Journal of Pharmaceutical Research and Bio-Science, ISSN: 2277-8713, IJPRBS, 2017; 6(2): 178-195.
16. Brahmaiah Bonthagarala, Guidelines for bioavailability and bioequivalence studies: A Review, The Pharma Innovation Journal, 2018; 7(7): 661-666, ISSN (E): 2277- 7695.
17. Brahmaiah Bonthagarala *et al*, Generic Drug Registration and Regulatory Requirements in European Countries,World Journal of Pharmaceutical Research, 2018; 7(16): 800-815.
18. World Health Organization. Regulatory situation of herbal medicines: a world wide review (document WHO/TRM/98.1). Geneva, 1998.
19. World Health Organization. Legal status of traditional medicine and complementary / alternative medicine: a worldwide review (document WHO/EDM/TRM/2001.2). Geneva, (2001)
20. World Health Organization. WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants. World Health Organization, Geneva, 2003.