Review Article

A Comparative Study: Good Manufacturing Practice (GMP) Requirements for Herbal Products: INDIA & EUROPE

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ABSTRACT

The Present study deals with a brief overview of the GMP requirements for herbal products manufactured in India & Europe. Herbal medicine have always played an important role in the primary health care therefore should be manufactured under Good Manufacturing Practice (GMP) to ensure the quality & safety of the finished product. It is necessary to know the differences in the requirements of guidelines given by India & Europe. These guidelines focus on general requirements for quality assurance & quality control in manufacturing of herbal medicinal products. These guidelines will promote & improve the quality of herbal medicines & reduce the poor quality of herbal medicines. When these guidelines were compared, certain similarities & differences were observed.

Keywords: Indian GMP, Schedule T, Europe GMP.

INTRODUCTION

GMP

GMP "is that part of quality assurance which ensures that product are consistently produced & controlled to the quality standards appropriate to their intended use & as required by marketing authorization"(WHO 2004).

GMP guidelines represent minimal standards that are necessary condition for marketing authorization. Drugs are considered to be adulterated, if GMPs are not met. GMP standard are, however, only guidelines & alternative processes & control mechanisms can be used under the condition that equivalent assurance is attained.[1]

Guideline

WHO Supplementary guidelines for the manufacture of herbal medicinal products were issued in 1996. Good Manufacturing Practice guidelines covering herbal medicines, were developed by several WHO Member States, and the European Union revision of the present supplementary guidelines was decided.

The supplementary guidelines are to provide general and minimum technical requirements for quality assurance and control in manufacturing herbal medicinal products as a reference to WHO Member States. Each Member State should develop their own national GMP for manufacturing herbal medicines according to the country's actual situation.

These guidelines deal with herbal medicinal products exclusively. No combination of herbals with animals, chemicals and other substances is covered.[2]

Committee for Herbal Medicinal Products (HMPC) Committee of European Medicines Agency (EMA) is developing guidelines for quality, nonclinical studies, clinical efficacy and safety.[3]

In Europe, the 'Traditional Herbal Medicinal Products Directive' (THMPD), also known as the EC Directive 2004/24/EC is an attempt by the European Commission to further regulates the market for traditional herbal medicines.[4]

In India, at present, schedule T essentially describes the scope & statutory requirements under Drug & Cosmetics Act for the manufacture of herbal medicinal products. This Schedule covers bare minimum requirements for herbal drug manufacturing & quality control.[5]

Importance of GMP

Unlike conventional pharmaceutical products, which are usually produced from synthetic materials by means of reproducible manufacturing techniques and procedures, herbal medicines are mainly prepared from materials of herbal origin, which are often obtained from varied geographical and/or commercial sources.

In addition, they may vary in composition and properties. Furthermore, the procedures and techniques used in the manufacture and quality control of herbal medicines are often substantially different from those employed for conventional pharmaceutical products.

Because of the inherent complexity of naturally grown medicinal plants and the often variable nature of cultivated ones, the examples of contamination with toxic medicinal plants and/ or plant parts and the number and small quantity of defined active ingredients, the production and primary processing has a direct influence on the quality of herbal medicines.

For this reason, application of GMPs in the manufacture of herbal medicines is an essential tool to assure their quality.[6]

Herbal medicine

Herbal medicines must be now manufactured under Good Manufacturing Practice (GMP) to ensure the quality of the finished product and also demonstrate safety.[7] Herbal medicine have always played an important role in the primary healthcare in developing countries.[8] This is primarily because of the general belief that herbal drugs are without any side effects besides being cheap and locally available. According to the World Health Organization (WHO), the use of herbal remedies throughout the world exceeds that of the conventional drugs by two to three times.[9]

Herbal medicines have been widely utilized as effective remedies for the prevention & treatment of multiple health conditions for centuries by almost every known culture. Herbal medicines have been used since the beginning of human history. There are four basic systems known for herbal medicines: Traditional Chinese, Traditional Indian (Ayurvedic), Western, and Traditional Arab & therefore herbal medicines play an increasingly important role in healthcare and their use at the hope of tackling diseases is widespread.[10]

Many people are choosing to plant based medicines or products to improve their health conditions or as curative substance either alone or in combination with others. In India, approximately 70% of modern drug are discovered from natural resources and number of other synthetic analogues have been prepared from prototype compounds isolated from plants.[11] India is the largest producer of medicinal herbs and approximately called the botanical garden of the world.[12]

Herbal production less in INDIA

India is a land of different people which have their own religion, beliefs & culture. Thus diverse medicinal system has developed in this region. Since ancient time, Indian society depends on traditional medicinal systems practiced. During British rule introduction of allopathic drug and neglecting Indian traditional medicine by British ruler are responsible for significant erosion of Indian traditional medicine. High progress in allopathic medicine and modern facilities also decreases the growth of traditional medicine. Still, about 70% rural populations of India are believed in traditional medicine for primary healthcare.[11]

	INDIA[13,14]	EUROPE[15-19]
Quality assurance in the manufacture of herbal	➢ The use of modern analytical techniques (especially high performance thin-layer chromatography (HPTLC), gas chromatography (GC), high performance liquid chromatography (HPLC), capillary electrophoresis (CE), mass spectrometry (MS) and atomic absorption (AA) to characterize herbal medicines, quality assurance also requires the control of starting materials, storage and processing.	➢ Herbal substances with regard to quality such as content of active principle, macroscopical and olfactory properties, limit values for microbial contamination, chemical residues and heavy metals etc., must be based on recognised regional and/or national specifications and should be laid down in written form.
Sanitation & hygiene	➢ Because of their origin, herbal materials may contain microbiological contaminants and to reduce contamination in general, a high level of sanitation and hygiene during manufacture is necessary. ➢ Water supply to the manufacturing unit should be monitored, and Waste from the manufacturing unit should be disposed of regularly so as to maintain a high standard of hygiene in the manufacturing area.	➢ During production process of herbal substance & their preparation there are chances of exposed to microbiological & other contaminants to reduce this contamination a high level of hygiene is maintained.
Qualification and validation	➢ Qualification of critical equipment, process validation and change control are important in the production of herbal medicines with unknown therapeutically active constituents & reproducibility of the production process is the main means for ensuring consistency of quality, efficacy and safety between batches. ➢ The written procedure should specify critical process steps and factors (such as extraction time, temperature and solvent purity) and acceptance criteria, as well as the type of validation to be conducted and the number of process runs.	➢ All qualification & validation activities related to facilities, equipment, utilities, process & product should be planned & should only be performed by suitably trained personnel. ➢ The key elements of the site qualification & validation programme should be clearly defined & documented in a validation master plan or equivalent document.
Complaints	➢ The person responsible for handling complaints and deciding on the measures to be taken have appropriate training and/or experience in the specific features of the quality control of herbal medicines.	➢ Appropriately trained & experienced personnel should be responsible for managing complaints & quality defect investigation & for deciding the

	➢ Two types of complaints: 1. Product quality complaints 2. Adverse reaction/ events. ➢ Product quality complaints may be due to faulty manufacture, product defects or deterioration as well as, adulteration of the herbal material. These complaints should be recorded in detail and the causes thoroughly investigated. ➢ The second type of complaint, reports of any adverse reaction/event should be entered in a separate register in accordance with national and international requirements. ➢ An investigation should be conducted to find out whether the adverse reaction is due to a quality problem and whether it is a new observation.	measures to be taken to manage any potential risks. ➢ Sufficient trained personnel & resources should be made available for handling, assessment, investigation & review of complaints. ➢ There should be written procedures describing the actions to be taken upon receipt of a complaints & all complaints should be documented.
Product Recalls	➢ The product recall procedure depends on national regulation & there should be standard operating procedure for storage & disposal of recalled products in a secure segregated area, complying with the requirements.	➢ There should be written procedure for any product recall & competent authorities should be informed in advance in cases where products are intended to be recalled. Recalled products should be identified & stored separately in a secure area, complying with the requirements.
Contract production and analysis	➢ The contract partner should have adequate premises and equipment for the production of herbal medicines according to GMP. ➢ Technical aspects of the contract should be drawn up by competent persons who have knowledge of specific characteristic of herbal medicines, including their production and quality control testing.	➢ All contract manufacturer should comply with GMP guide. Special consideration should be given to the prevention of cross contamination & to maintain traceability.
Self-inspection	➢ At least one member of the self-inspection team should possess a thorough knowledge of herbal medicines.	➢ Self-inspection should be conducted in an independent & detailed way by designated competent person. Independent audits by external experts may also be useful. All self-inspection should be recorded.
Training	➢ The personnel should have adequate training related to herbal & records of training should be maintained and periodic assessments of the effectiveness of training programmes should be made.	➢ Personnel should receive adequate botanical training before performing tasks that require this knowledge.
Personal hygiene	➢ Personnel entrusted with the handling of herbal materials, preparations and finished products should be required to have a high degree of personal hygiene and there should be training programs & their record. ➢ Personnel must be protected from contact with toxic irritants and potentially allergenic plant materials by means of adequate protective clothing ➢ They should wear suitable gloves, caps, masks, work suits and shoes throughout the whole procedure of manufacture.	➢ Personnel with handling of herbal substances should be required to have a high degree of personal hygiene and have received adequate training regarding their hygiene responsibilities. ➢ Personnel must be protected from contact with toxic or potentially allergenic medicinal Plants/herbal substances by means of adequate protective clothes.
Premises	Premises should be designed, located, constructed, adapted and maintained to suit the operations to be carried out. **1) <u>Storage areas</u>** ➢ Storage areas should be well organized with special attention should be paid to cleanliness and maintenance. ➢ Incoming fresh herbal materials should be stored between 2 °C and 8 °C, whereas frozen materials	**1) <u>Storage areas</u>** There should be separate storage area for herbal substance equipped in such a way as to give protection against the entry of insects or rodents. ➢ Different enclosed areas should be used to quarantine incoming and for the approved herbal substances. ➢ The storage area should be well aerated and the containers should be located in

	should be stored below –18 °C. ➢ Herbal materials including raw herbal material should be kept in dry area & should be processed on "first in, first out" (FIFO) basis. **2) <u>Production areas</u>** ➢ There should be dedicated areas for production of herbal medicines & if it is not feasible, campaign manufacturing should be adopted. ➢ To facilitate cleaning and to avoid cross-contamination, adequate precautions should be taken during the sampling, weighing, mixing and processing of medicinal plants, e.g. by use of dust extraction and air-handling systems.	such a way so as to allow free circulation of air. ➢ Storage of herbal substances & preparations may require special conditions of humidity, temperature or light protection; these conditions should be provided and monitored. **2) <u>Production areas</u>** ➢ Whenever dust is generated special provision should be made during sampling, weighing, mixing & processing of herbal product. ➢ To facilitate cleaning and to avoid cross-contamination, as for example, dust extraction, dedicated premises, etc. should be used.
Equipment	➢ Processing of herbal materials may generate dust or microbiological contamination so effective cleaning of the equipment is important. ➢ Vacuum or wet-cleaning methods are preferred ➢ As a rule non wooden equipment should be used unless it is a requirement of traditional method of manufacture, where it is necessary to use traditional equipment (such as wooden implements, clay pots, pallets, hoppers, etc.), this should be dedicated.	➢ Equipment, filtering materials etc. used in the manufacturing process must be compatible with the extraction solvent, in order to prevent any release or undesirable absorption of substance that could affect the product.
Materials	➢ All incoming herbal materials should be quarantined and stored under appropriate condition. **<u>Reference samples & standards</u>** ➢ The reference standard for a herbal medicine may be a botanical sample. ➢ All reference standard should be stored under appropriate condition & their expiry date should be determined and indicated.	➢ The starting material should be as free as possible from pests and diseases in order to guarantee healthy plant growth. Where possible, species naturally resistant or tolerant to disease should preferably be used.
Documentation	**<u>General Principles</u>** ➢ Its aims are to define the specifications and procedures for all materials and methods of manufacture and control & to ensure that all personnel concerned with manufacture know what to do and when to do it. ➢ It ensures the availability of the data needed for validation, review and statistical analysis. **<u>Specification for starting material</u>** 1) Herbal materials Specifications for herbal materials should include the following information as appropriate: • The family and botanical name of the plant used. • Details of the source of the plant. • A description of the plant material based on visual (macroscopic) and microscopic examination. • Suitable identity tests including such as TLC or other chromatographic fingerprint for known active ingredient. A reference sample should be available for identification purposes. • Limit tests such as dry residue of liquids, ash value, water-soluble extractives, moisture/water content and loss on drying. ➢ If starting materials are official in any	**<u>Specifications for starting materials</u>** ➢ Documentation on audits of the herbal starting material suppliers carried out by, or on behalf of the herbal medicinal product manufacturer should be made available. ➢ The manufacturer should ensure that the suppliers of the herbal substance/preparation are in compliance with Good Agricultural and Collection Practice. a. Documentation for herbal substances should include: • The binomial scientific name of plant. • Details of the source of the plant • Which part(s) of the plant is/are used; • When a dried plant is used, the drying system should be specified; • Specific distinctive tests are required where an herbal substance is liable to be adulterated/ substituted. A reference authentic specimen should be available for identification purposes; • The water content for herbal substances, determined in accordance with the

	pharmacopeia, reference to that pharmacopeia should be made & if starting material is comprises of genetically modified organism, it should comply with national or international regulations & label should indicate this information. **Finished herbal products** ➢ The control tests and specifications for the finished herbal product should be such as to allow the qualitative and quantitative determination of the main active constituents. **Processing instructions** ➢ The processing instructions should describe the different operations to performed on the plant material, such as drying, crushing, milling and sifting & also include the time , temperatures required in the drying process, and the methods to be used to control fragment or particle size. ➢ If the plant should be processed fresh, without drying, the reasons and criteria determining the use of fresh material should be stated ➢ For the production of processed extracts, the instructions should specify details of any vehicle, the durations and temperatures needed for extraction, and any concentration stages and methods that may be required. ➢ Any treatment, such as fumigation, used to reduce fungal or microbiological contamination and steps of blending should be documented	European • Pharmacopoeia. ➢ Any treatment used to reduce fungal/microbial contamination or other infestation should be documented. **Processing instructions** ➢ The processing instructions should describe the different operations carried out upon the herbal substance such as cleaning, drying, crushing and sifting, and include drying time and temperatures, and methods used to control cut size or particle size. ➢ There should be written instructions and records, which ensure that each container of herbal substance is carefully examined to detect any adulteration/substitution or presence of foreign matter. ➢ The processing instructions should also describe methods of removing foreign materials and procedures for cleaning/selection of plant material before the storage or the start of manufacturing of herbal substance. ➢ For the production of an herbal preparation, instructions should include details of solvent, time and temperature of extraction, details of any concentration stages and methods used.
Good practices in quality control	**General** ➢ The quality control of the herbal material, preparations and finished herbal products should have the necessary expertise to carry out identification tests and recognize adulteration, & establish their quality, but does not imply the control of every single constituent. **Sampling** ➢ Because herbal materials are different parts of the same plant and thus have an element of heterogeneity, sampling should be carried out with special care by personnel with the necessary expertise. **Testing** ➢ The identity and quality of herbal material, herbal preparations and of finished herbal products should be tested as described : ➢ There should be adequate facilities for testing of herbal materials & medicines. ➢ Herbal material, herbal preparations and finished herbal products can be categorized as follows: a. The active constituents are identified, and may be quantified as such; b. The former are not identified and/or not quantifiable, but marker substances can be quantified. ➢ Identification methods may be based on: • Physical and macroscopic • Chromatographic procedures (TLC, HPLC, HPTLC	**Sampling** ➢ Due to the fact that herbal substances are heterogeneous in nature, their sampling should be carried out with special care by personnel with particular expertise. ➢ A reference sample of the plant material is necessary, especially in those cases where the herbal substance is not described. ➢ Quality Control personnel should have particular expertise and experience in herbal substances, preparations and products in order to be able to carry out identification tests and recognise adulteration, the presence of fungal growth, non-uniformity within a delivery of crude material, etc. ➢ The identity and quality of herbal substances, preparations and products should be determined in accordance with the relevant current European guidance on quality and specifications of herbal medicinal products and traditional herbal medicinal products.

	or gas–liquid chromatography (GLC)), spectrometric techniques (UV-VIS), IR, nuclear magnetic resonance ➢ Where active constituents cannot be quantified, characteristic chromatograms and/or fingerprint chromatograms may be applicable. **Stability studies** ➢ If the expiry date for a herbal material or herbal preparation is given, some stability data to support the proposed shelf-life under the specified storage conditions should be available. ➢ The fingerprint methods used for the stability studies. ➢ Normally the first three production batches should be included in the stability-monitoring programme to confirm the expiry date. **Packaging materials and labeling** ➢ All packaging materials, such as bottles, container & closure should be thoroughly cleaned & dried & stored properly. ➢ There should be adequate information on the label to inform the users of the composition of the product, indications or actions, directions for use, cautions and adverse reactions if any, and the expiry date. ➢ The qualitative and quantitative particulars of the active ingredients in herbal materials and preparations should be expressed in the following ways: ➢ For herbal materials and preparations consisting powdered herbal materials: The quantity of the herbal material must be stated or, if constituents with known therapeutic activity are unidentified, the quantity of the herbal material/herbal preparation should be stated.	

CONCLUSION

Herbal products are generally considered as adulterated drugs but manufacturing as per GMP guidelines will definitely improve the quality, safety and efficacy of herbal products. India is a rich source of herbal medicines. So comparative study about these GMP guidelines will help the manufacturer in production of safe and effective herbal products in both the countries.

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