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Good Manufacturing Practices: A pathway towards quality ASU medicines

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Abstract

Ayurvedic medicines are being used from time immemorial for prevention and cure of human beings, therefore the efficacy and safety of these medicines is undoubted. However, the quality of these drugs is still a challenge as far as international norms are concerned.1,2 Few ayurvedic herbo-mineral medicines have been banned in western countries and many surveys have reported the adulteration of herbal medicines. Herbal drugs contain numerous groups of compounds in complex matrices in which no single active constituent is responsible for the overall efficacy. This creates a problem in establishing quality control standards and standardization of herbal drugs1. Good manufacturing practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the production of adulterated and substandard medicines. GMP covers all aspects of production: - from the starting materials, premises and equipment to the training and personal hygiene of staff. GMP is the guidelines which, - governs the production, distribution and supply of the drug. These days, there is an increased concern for heavy metal toxicity with ayurvedic medicines. GMP also covers batch manufacturing records, distribution records and records of market complaints. Thus it ensures proper pharmacovigilance of ayurvedic medicines. It essential to produce high-quality and standardized medicines if we want global acceptance of Ayurvedic medicines which can be achieved by proper education and enforcement of GMP.

Keywords GMP, Quality, Ayurvedic medicines

INTRODUCTION

In ancient times, the raw materials (particularly herbs) were collected by experienced assistants under the guidance of the physicians (*Vaidyas*). Preparation of medicines was done by the assistants themselves in a small pharmacy attached to their clinic. In other words the preparation of the medicines was done under the vigilant physician. These days the same process i.e., production of medicines is done by pharmaceutical companies. In recent years, there has been a huge increase in the demand of Ayurvedic medicines in India as well as abroad. This increased demand was met by producing medicines at large scale by pharmaceutical/Ayurvedic companies. With increased production of quality medicines there is increased production of

substandard low-quality medicines by these companies. To get more profit, they adulterate and adopt shortcut methods to prepare classical medicines and thus these medicines become substandard.

Many questions are now being raised by the scientific and non scientific community of the world regarding the documentation of safety and efficacy of Ayurvedic Medicines. Hence, to control the manufacturing of Ayurvedic Medicines, Government of India has made the GMP mandatory for all units since June 23th 2002. GMP's are described in Schedule T of Drug and Cosmetic Act under rule 155-B of Drugs and Cosmetics Rule, 1945 with Latest Gazette Notification GSR 560 (E) dated: 7th March, 2003. [3,5] It is applicable to whole of the country with effect from 23rd June, 2000 for new A.S.U. Manufacturing units. Units registered prior to 23rd June 2000 are given 2 years time to comply. Request for G.M P. certificate is made on Plain Paper. G.M.P. certificate is given in Form 26 E-I (under Rule 155 -B) for a period of 5 years (G.S.R. 376(E) dated 3rd May, 2010). Earlier it was for three years. Supplementary guidelines for manufacturing of rasaushadhis have also been added by G.S.R. 157(E) and corrigendum G.S.R. 338(E).[3]

OBJECTIVES

- The manufacturing processes have been described to maintain standard.
- Raw materials used by manufacturers are authentic, of prescribed quality and free from contamination.
- Adequate quality control measures are adopted during processing of drugs.
- The manufactured drug which is released for sale should be of accepted quality.
- To achieve the objectives listed above, each licensee shall evolve methodology and procedures for following the prescribed process of manufacture of drugs which should be documented as a manual and kept for reference and inspection.

COMPONENTS OF G.M.P.

The manufacturing plant should have adequate space for: manufacturing process areas, quality control section, finished goods store, receiving and storing raw material office, office for rejected goods / drugs store.

Location and surroundings

- No open sewage
- No drainage coming from public areas & pubic lavatory
- No factory fume, smoke and dust

Buildings

- Hygienic conditioned.
- No cobwebs/insects/rodents.
- Adequate light & ventilation.
- Premises used for manufacturing, processing, packaging and labelling should be in conformity with the provisions of Factory Act.
- Logical placement of equipment to avoid risk of mixing, cross contamination and risk of omission of a control step.
- Interior surface should be smooth, easy for cleaning and disinfection.
- Flooring should be smooth and even so as not to permit retention or accumulation of dust or waste products.
- Fire safety measures
- Separate space for drying

Proper drainage system

- Proper sanitary fittings and electrical fixtures for safety furnace
- *bhatti* section should be covered with tin roof
- proper ventilation/chimney in factory prevention of flies and dust in factory premises
- proper fire safety measures/ exits should be installed.

Disposal of Waste

- In the manufacturing section and laboratories the waste water and residues which might be prejudicial to the work as well as public health shall be disposed of after suitable treatment as per guideline of pollution control.
- Containers Cleaning: Adequate arrangement for washing, cleaning & drying of containers.

Stores

It should provide adequate space for stores of different type of material such as raw material, packing material and finished products. Store should have proper ventilation and should be free from dampness.

A. Raw materials stores

- Raw material store should have appropriate containers which would protect the quality of raw materials and prevent from contamination or rodents and insect infestation.
- Suitable cabins for raw material of Metallic origin, Mineral origin. Animal origin, Fresh herbs, Dry herbs or plant parts, Excipients, Volatile oils/perfumes and Flavours, Plants extracts, Exudates/Resins etc.
- Each container used for raw material storage should be properly identified with the label

which indicates name of the raw material, source of supply and will also clearly state the status of raw material such as 'UNDER TEST' or 'APPROVED' or 'REJECTED'.

- Label of raw material should clearly indicate Batch No or Lot No, and date of receipt of the consignment.
- All raw materials must be sampled and tested either by the in-house quality control technical person or by laboratories approved by the Government and should be used only on approval after verifying.
- Records of the receipt, testing and approval or rejection should be maintained.

B. Packing Materials

All packing materials such as bottles, jars, capsules etc. should be stored properly. All container and closure lids should be properly cleaned and dried before packing the products.

C. Finished Goods Stores

- The finished goods transferred from the production area after proper packaging should be stored in proper shelves within an area marked "Quarantine".
- After the quality control laboratory: and the experts have checked the correctness of finished goods with reference to its packing/labelling as well as the finished product quality described, the goods are moved to Approved Finished Goods Stock area. Only approved finished goods should be dispatched as per marketing requirements.
- Distribution records should be maintained as required.
- Specific storage conditions should be provided for special drugs.

Working Space

- The manufacturing area shall provide adequate space (manufacture and quality control) for orderly placement of equipment and material used in any of the operations.
- Facilities for easy and safe working, facilities to minimize or eliminate mixing up of the drugs should be provided to prevent cross contamination of one drug by another drug that is manufactured, stored or handled in the same premises. (Table-1)

Health, Clothing, Sanitation and Hygiene of Workers

- Workers should be free from contagious diseases.
- Workers should use proper uniform suitable to work.
- Hands should be covered with cloth or synthetic covering.

- Personal cleanliness, clean towel, soap, scrubbing brushes, separate lavatories for men and women and facility for changing of clothes and cupboards to keep clothes/belongings should be maintained.

Medical Services

- Annual medical check-up of all employees should be done to ensure freedom from infectious diseases.
- First-Aid facility should be available. Health record of all the employees should be maintained.

Machinery and Equipments

- Equipment should be according to the size of operation and nature of product manufactured.
- Suitable machinery manually operated, semi-automatic or automatic should be available in the manufacturing unit. These may include machines for use in the process of manufacture such as crushing, grinding, powdering, boiling, mashing, burning, roasting, filtering, drying, filling, labelling and packing etc.
- To ensure ease in movement of workers and orderliness in operations a suitably adequate space will be ensured between two machines or rows of machines. These Equipments have to be properly installed and maintained with proper cleaning.
- Proper standard operational procedures (SOPs) for cleaning, maintaining and performance of every machine should be laid down.

Table 1 Space requirement for manufacture of ASU medicines

S. No.	Category of Medicine	Minimum Space Required
1.	Anjana/Pisti	100 sq. ft.
2.	Churna/Nasya/Manjan/Lepa/ Kwatha Churna	200 sq. ft.
3.	Pills/Vati/Gutika/Mathirai	100 sq. ft.
4.	Kupi pakva/Ksara/ Parpati	100 sq. ft.
5.	Kupi pakva/ Ksara/ Parpati/ Satva	150 sq. ft.
6.	Kajal	100 sq. ft.
7	Capsules	100 sq. ft.
8.	Ointment/Marham Pasi	100 sq. ft.
9.	Pak/Avaleh/Khand/Modaklla kayam	100 sq. ft,
10.	Panaka / Syrup/ Pravahi Kwathi Manapaku	150 sq. ft.
11.	Asava/Arishta	200 sq. ft.
12.	Sura	100 sq. ft.
13.	Arka/ Tinir	100 sq. ft.
14.	Taila/Ghrita/Ney	100 sq. ft.
15.	Aschyotan/Netra Malham/Panir	100 sq. ft.
16.	Pisti/ Grinding area	100 sq. ft.
17.	Powdering area for Raw drugs of plant origin	200 sq. ft.
18.	Kupi pakwa/ Kshar/ Parpati/ Bhasma/ Satwa/ Sindur	150 sq. ft.

Batch Manufacturing Records

- Manufacturer should maintain batch manufacturing record of every manufacturer.
- List of raw materials used, quantity obtained from the store, tests conducted

during the various stages of manufacture like taste, colour, physical characteristics and chemical tests as may be necessary.

Distribution Records

Records of sale and distribution of each batch of Ayurveda, Siddha and Unani Drugs should be maintained in order to facilitate prompt and complete recall of the batch, if necessary.

Record of Market Complaints

- Manufacturers should maintain a register to record of the complaints as well as corrective action initiated to prevent recurrence regarding the products. Once in a period of six months, the complaint records have to be sent to the licensing authority.
- Register should be available for inspection during any inspection of the premises. Reports of any adverse reaction resulting from the use of drugs should be maintained in separate register. These should be intimated to NPRC-ASU.

Quality Control

Every licensee is required to provide facility for quality control section in his own premises or through Government approved testing laboratory. The test shall be as per the Ayurveda, Siddha and Unani pharmacopoeia standard.

- There should be 150 sq. feet area for quality control section.
- For identification of raw drugs, reference books and reference samples should be maintained.
- Manufacturing record should be maintained for the various processes.
- To verify the finished products, controlled samples of finished products of each batch should be kept for 3 years.
- Keep record in establishing shelf life and storage requirements for the drugs.
- Manufacturers who are manufacturing patent/ proprietary ASU medicines shall provide their own specification and control references in respect of such formulated drugs.
- The record of specific method and procedure of preparation, that is, Bhavana, Mardana and Puta (earthen pits) and the record of every process carried out by the manufacturer shall be maintained.
- The standards for identity, purity and strength as given in respective pharmacopoeias of Ayurveda, Siddha and Unani systems of medicines published by Government of India shall be complied with.

- All raw materials will be monitored for fungal, bacterial contamination with a view to minimise such contamination.
- Quality control section will have Expert in Ayurveda or Siddha or Unani medicine, a Chemist and a Botanist (Pharmacognosist)

Requirement of Sterile Product

Manufacturing area for the production of sterile Ayurvedic product, separate enclosed area should be provided. This area should be aseptic, dust-free, moisture less and should have bacteria free air supply.

Precaution against contamination and mix

- Manufacturing operations should be carried out in a separate block of adequately isolated building or operating in an isolated area within the building.
- Use appropriate pressure differential in the process area.
- The germicidal efficiency of UV lamps shall be checked and recorded indicating the burning hours or checked using intensity.
- A suitable exhaust system should be provided. Designing laminar flow sterile air systems for sterile products should be provided.
- Individual containers of liquids and ophthalmic solutions shall be examined against black-white background fitted with diffused light after filling to ensure freedom from contamination with foreign suspended matter.
- Expert technical staff approved by the Licensing Authority shall check and compare actual yield against theoretical yield before final distribution of the batch.
- All process controls as required under master formula including room temperature, relative humidity, volume, filled, leakage and clarity shall be checked and recorded.

SUPPLEMENTARY GUIDELINES FOR MANUFACTURING OF RASAUSHADHIS

- Supplementary guidelines are to be provided for general and minimum technical requirements for quality assurance and control in manufacturing Rasaushadhis.
- These supplementary guidelines deal with Bhasmas, Sindur, Pishti, Kajjali, Khalviya Rasa, Kupi pakwa Rasayan, Parpati, Pottali, Satwa and Druti Kalpana.
- These guidelines need to establish the authenticity of raw drug, minerals and metals, in process validation and quality control parameters to ensure that these formulations are processed and prepared in

accordance with classical texts and for which safety measures are complied.

- Only those manufacturing units which have GMP for ASU drugs and supplementary certificate of Rasaushadhis are allowed to manufacture the same.
- Minimum Manufacturing space of 1200 square feet covered area is required for manufacturing herbal ASU Drugs. For manufacturing Rasaushadhies, separate minimum 1500 sq ft area is mandatory.

DISCUSSION

All Ayurvedic Samhitas have emphasized the importance of quality of medicines. Drug has been considered as an essential part of *Chikitsa Chatushpad.*[6] Ayurvedic literature is full of examples where methods of collection, processing, storage and packaging of drugs have been mentioned. These methods have been documented after a lot of research. Ayurvedic medicines give better results if these methodologies are adopted for preparing quality drugs.[1,2] GMP provides a strong base for ensuring preparation of quality medicines. These are the minimum requirements that need to be followed by Ayurvedic drug manufacturers. Compliance of Good Manufacturing Practices will increase the credibility of Ayurvedic medicines in general public and it will help in global acceptance and marketing of these medicines.

CONCLUSION

Government of India has made the GMP mandatory to manufacture quality formulations for Ayurvedic, Siddha and Unani drugs manufacturing units. Implementation of Good Manufacturing Practices in Ayurvedic pharmaceutical units will lead to manufacture of safe and efficacious medicines. GMP also validates the processes involved in Ayurvedic pharmaceutics. It also facilitates the functioning of regularity authority and enforcement personnel and ultimately ensures the safety of Ayurvedic, Siddha and Unani medicines.Sugandha Vacha i.e. *Alpinia galanga* is a common adulterant of Vacha (Acorus calamus). Macroscopic and microscopic detection is easy, reliable and cost effective tool for detection of this adulterant in medicinal plant materials. From the present study, it is clear that the adulterant, Alpinia galanga can be differentiated from the genuine drug, Acorus calamus, by macroscopic and microscopic studies.

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