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GOOD MANUFACTURING PRACTICE (GMP) FOR PHARMACEUTICAL PRODUCTS

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ABSTRACT

A **Good manufacturing practice (GMP)** is a part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMP guidelines provide minimum requirements for pharmaceutical or a food product manufacturer must meet to assure that the products are of high quality and do not pose any risk to the consumer or public.

Keywords *- Good Manufacturing Practice, GMP, Pharmaceutical Inspection, Food and Drug, Administration, Pharmaceutical Product, Guidelines.*

1. INTRODUCTION

The term GMP was introduced to regulate manufacturing and packaging operations in the pharmaceutical industry. The Medicine Inspector of the Department of Health and Social Security of England, in consultation with other interested bodies compiled the guide to GMP also known as the Orange Guide. The first edition of the guide was published in 1971, the manufacturing of drug carried out under the Medicines Act. It was a relatively light volume of20 pages, and was reissue third impression in 1972, with the addition of a 2-page appendix on sterile medicinal products. The colour of its cover, it known as the Orange Guide. The second edition (52 pages, including five appendices) was published in 1977. The third edition (110 pages, five appendices) was published in 1983.

What is GMP?

Good manufacturing practice (GMP) comprises that part of quality assurance aimed at ensuring that a product is consistently manufactured to a quality appropriated to its intended use. GMP requires that the manufacturing process is fully defined before it is initiated and that all necessary facilities are provided. In practice, this means that personnel must be adequately trained, suitable premises and equipment used, correct materials used, approved procedures adopted, suitable and transport facilities available and appropriate records made.

Why it is required?

The Good Manufacturing Practices are prescribed to ensure that:

1. Raw materials used in the manufacture of pharmaceuticals are authentic, of prescribed quality and are free from contamination.
2. The manufacturing process is as has been prescribed to maintain the standards.
3. Adequate quality control measures are adopted and
4. The manufactured drug which is released for sale has the prescribed quality.
5. 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.

World Health Organization (WHO) GMP:

WHO **defines "good manufacturing practice has that part of quality assurance which assures that products are consistently produced and controlled to the quality standards appropriate to their indented use and as required by the marketing authorization?"**

GMP covers all aspects of the manufacturing process: defined manufacturing processes; critical manufacturing steps; suitable premises, storage, transport; qualified and trained production and quality control personnel; adequate laboratory facilities; approved written procedures and instructions; records to show all steps of defined procedures have been taken; full traceability of a product through batch rewards and distribution records and systems for recall and investigation of complaints.

2. COMPONENTS OF GMP

GMP requires that the manufacturing process is fully defined before being initiated and all the necessary facilities are provided. In practice, personnel must be adequately trained, suitable premises and equipment used, correct materials used, approved procedures adopted, suitable storage and transport facilities available, and appropriate records made. The essential components of GMP are summarized in below

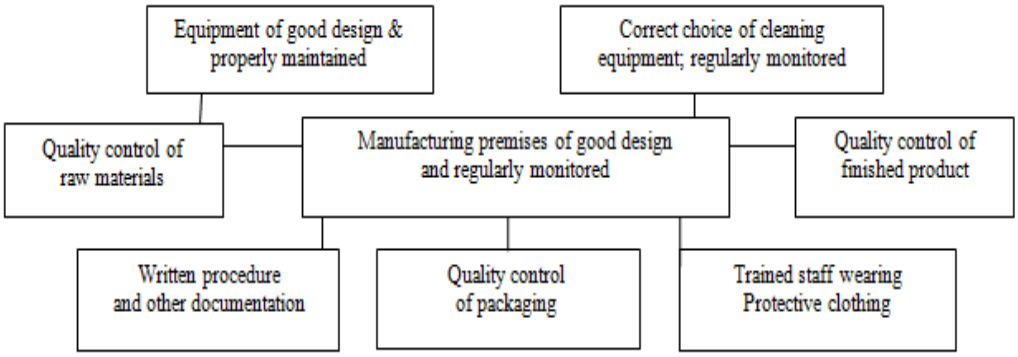

Fig.1. Components of Good Manufacturing Practice

3. GMP REQUIREMENTS FOR PREMISES AND MATERIALS FOR PHARMACEUTICAL PRODUCTS

1. GENERAL REQUIREMENTS:

1.1. Location and Surroundings: factory building(s) for manufacture of drugs shall be so situated and shall have such measures as to avoid risk of contamination from external environment including open sewage, drain, public lavatory or any factory which produces disagreeable or obnoxious, odour, fumes, excessive soot, dust, smoke, chemical or biological emissions.

1.2. Buildings and Premises: The building(s) used for the factory shall be designed, constructed, adapted and maintained to suit the manufacturing operations so as to permit production of drugs under hygienic conditions. They shall conform to the conditions laid down in the Factories Act, 1948 (63 of 1948). The premises used for manufacturing, processing, warehousing, packaging, labelling and testing purposes shall be –

1) Compatible with other drug manufacturing operations that may be carried out in the same or adjacent area / section;

2) Adequately provided with working space to allow orderly and logical placement of equipment, materials and movement of personnel so as to

1.3. Water System: The water used in manufacture shall be pure and of potable quality. Adequate provision of water for washing the premises shall be made.

1.4 Disposal of waste: From the manufacturing sections and laboratories the waste water and the residues which might be prejudicial to the workers or public health shall be disposed off after suitable treatment as per guidelines of pollution control authorities to render them harmless.

2. WAREHOUSING AREA: Adequate areas shall be designed to allow sufficient and orderly warehousing of various categories of materials and products like starting and packaging materials, intermediates, bulk and finished products, products in quarantine, released, rejected, returned or recalled, machine and equipment spare parts and change items. Where quarantine status is ensured by warehousing in separate earmarked areas in the same warehouse or store, these areas shall be clearly demarcated. Any system replacing the physical quarantine, shall give equivalent assurance of segregation. Access to these areas shall be restricted to authorized persons

3. PRODUCTION AREA: The production area shall be designed to allow the production preferably in uni-flow and with logical sequence of operations. In order to avoid the risk of cross-contamination; separate dedicated and self-contained facilities shall be made available for the production of sensitive pharmaceutical products like penicillin or biological preparations with live micro-organisms. Separate dedicated facilities shall be provided for the manufacture of contamination causing and potent products such as Beta lactum, Sex Hormones and Cyto-toxic substances.

4. ANCILLARY AREAS: Rest and refreshment rooms shall be separate from other areas. These areas shall not lead directly to the manufacturing and storage areas. Facilities for changing, storing clothes and for washing and toilet purposes shall be easily accessible and adequate for the number of users. Toilets, separate for males and females, shall not be directly connected with production or storage areas. There shall be written instructions for cleaning and disinfection for such areas.

5. QUALITY CONTROL AREA: Quality Control Laboratories shall be independent of the production areas. Separate areas shall be provided each for physio-chemical, biological, microbiological or radio-isotope analysis. Separate instrument room with adequate area shall be provided for sensitive and sophisticated instruments employed for analysis. Quality Control Laboratories shall be designed appropriately for the operations to be carried out in them. Adequate space shall be provided to avoid mix-ups and cross-contamination. Sufficient and suitable storage space shall be provided for test samples, retained samples, reference standards, reagents and records.

6. PERSONNEL: The manufacture shall be conducted under the direct supervision of competent technical staff with prescribed qualifications and practical experience in the relevant dosage form and / or active pharmaceutical products. The head of the Quality Control Laboratory shall be independent of the manufacturing unit. The testing shall be conducted under the direct supervision of competent technical staff who shall be whole time employees of the licensee.

7. HEALTH, CLOTHING AND SANITATION OF WORKERS: The personnel handling Beta-lactum antibiotics shall be tested for Penicillin sensitivity before employment and those handling sex hormones, cytotoxic substances and other potent drugs shall be periodically examined for adverse effects. These personnel should be moved out of these sections (except in dedicated facilities), by rotation, as a health safeguard.

8. MANUFACTURING OPERATIONS AND CONTROLS: All manufacturing operations shall be carried out under the supervision of technical staff approved by the Licensing Authority. Each critical step in the process relating to the selection, weighing and measuring of raw material addition during various stages shall be performed by trained personnel under the direct personal supervision of approved technical staff. The contents of all vessels and containers used in manufacture and storage during the various manufacturing stages shall be conspicuously labelled with the name of the product, batch no., batch size and stage of manufacture. Each label should be initialed and dated by the authorized technical staff.

9. SANITATION IN THE MANUFACTURING PREMISES: The manufacturing premises shall be cleaned and maintained in an orderly manner, so that it is free from accumulated waste, dust, debris and other similar material. A validated cleaning procedure shall be maintained. The manufacturing areas shall not be used for storage of materials, except for the material being processed. It shall not be used as a general thoroughfare. A routine sanitation program shall be drawn up and observed, which shall be properly recorded and which shall indicate –

a) Specific areas to be cleaned and cleaning intervals;
b) Cleaning procedure to be followed, including equipment and materials to be used for cleaning
c) Personnel assigned to and responsible for the cleaning operation.

10. RAW MATERIALS: All raw materials procured for manufacturing will be stored in the raw materials store. The manufacture based on the experience and the characteristics of theparticular raw material used in Ayurveda, Siddha and Unani system shall decide the use of appropriate containers which would protect the quality of the raw material as well as prevent it from damage due to dampness, microbiological contamination or rodent and insect infestation, etc. If certain raw materials require such controlled environmental conditions, the raw materials stores may be sub-divided with proper enclosures to provide such conditions by suitable cabinization. While designing such containers, cabins or areas in the raw materials store, care may be taken to handle the following different categories of raw materials: Raw materials in the storage area shall be appropriately labelled. Labels shall be clearly marked with the following information:

a) designated name of the product and the internal code reference, where applicable, and analytical reference number;
b) manufacturer's name, address and batch number;
c) the status of the contents (e.g., quarantine, under test, released, approved, rejected);

11. EQUIPMENT: Equipment shall be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of the equipment shall aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products. Each equipment shall be provided with a log book, wherever necessary.

12. DOCUMENTATION AND RECORDS: Documentation is an essential part of the Quality assurance system and, as such, shall be related to all aspects of Good Manufacturing Practices (GMP). Its aim is to define the specifications for all materials, method of manufacture and control, to ensure that all personnel concerned with manufacture know the information necessary to decide whether or not to release a batch of a drug for sale and to provide an audit trail that shall permit investigation of the history of any suspected defective batch.

13. LABELS AND OTHER PRINTED MATERIALS: Labels are absolutely necessary for identification of the drugs and their use. The printing shall be done in bright colours and in a legible manner. The label shall carry all the prescribed details about the product. All containers and equipment shall bear appropriate labels. Different colour coded labels shall be used to indicate the status of a product (for example: under test, approved, passed, rejected). To avoid chance of mix-up in printed packaging materials, product leaflets, relating to different products, shall be stored separately. Prior to release, all labels for containers, cartons and boxes and all circulars, inserts and leaflets shall be examined by the Quality Control Department of the licensee.

14. QUALITY ASSURANCE: This is a wide-ranging concept concerning all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that products are of the quality required for their intended use; The system of quality assurance appropriate to the manufacture of pharmaceutical products shall ensure that the pharmaceutical products are not released for sale or supplied before authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the label claim and any other provisions relevant to production, control and release of pharmaceutical products.

15. SELF INSPECTION AND QUALITY AUDIT: It may be useful to constitute a self-inspection team supplemented with a quality audit procedure for assessment of all or part of a system with the specific purpose of improving it.To evaluate the manufacturer's compliance with GMP in all aspects of production and quality control, concept of self-inspection shall be followed. The manufacturer shall constitute a team of independent, experienced, qualified persons from within or outside the company, who can audit objectively the implementation of methodology and procedures evolved. The procedure for self-inspection shall be documented indicating self-inspection results, evaluation, conclusions and recommended corrective actions with effective follow up program. The recommendations for corrective action shall be adopted.Written instructions for self-inspection shall be drawn up which shall include the following:

a) Premises including personnel facilities.
b) Maintenance of buildings and equipment.
c) Storage of starting materials and finished products.
d) Equipment.
e) Production and in-process controls.
f) Quality control.
g) Documentation.
h) Sanitation and hygiene.
i) Validation and revalidation programmes.
j) Calibration of instruments or measurement systems.
k) Recall procedures.
l) Complaints management.
m) Labels control.
n) Results of previous self-inspections and any corrective steps taken.

16. QUALITY CONTROL SYSTEM: Quality control shall be concerned with sampling, specifications, testing, documentation, release procedures which ensure that the necessary and relevant tests are actually carried and that the materials are not released for use, nor products released for sale or supply until their quality has been judged to be satisfactory. It is not confined to laboratory operations but shall be involved in all decisions concerning the quality of the product. It shall be ensured that all quality control arrangements are effectively and reliably carried out. The department as a whole shall have other duties such as to establish, evaluate, validate and implement all Quality Control Procedures and methods.

17. SPECIFICATION:

1) For Raw materials and Packaging materials
2) For Product Containers and Closures
3) For in-process and bulk products.
4) For Finished Products.
5) For preparation of containers and closures.

18. MASTER FORMULA RECORDS: There shall be Master Formula records relating to all manufacturing procedures for each product and batch size to be manufactured. These shall be prepared and endorsed by the competent technical staff i.e., head of production and quality control.

19. PACKAGING RECORDS: There shall be authorised packaging instructions for each product, pack size and type. These shall include or have a reference to the following: - **1.** name of the product. **2.** description of the dosage form, strength and composition. **3.** the pack size expressed in terms of the number or doses, weight or volume of the product in the final container. **4.** complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material. **5.** reprocessing of the relevant printed packaging materials and specimens indicating where batch number and expiry date of the product have been applied. **6.** special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before the operations begin. **7.** description of the packaging operation, including any significant subsidiary operations and equipment to be used. **8.** details of in-process controls with instructions for sampling and acceptance.

20. BATCH PACKAGING RECORDS: A batch packaging record shall be kept for each batch or part batch processed. It shall be based on the relevant parts of the packaging instructions, and the method of preparation of such records shall be designed to avoid transcription errors. Before any

packaging operations begins, checks shall be made and recorded that the equipment and the work stations are clear of the previous products, documents or materials not required for the planned packaging operations, and that the equipment is clean and suitable for use.

21. BATCH PROCESSING RECORDS: There shall be Batch Processing Record for each product. It shall be based on the relevant parts of the currently approved Master Formula. The method of preparation of such records included in the Master Formula shall be designed to avoid transcription errors. Before starting of any process inspect all the manufacturing area and ensure that the equipment and work station are clear of previous products. This should be documented and recorded. During processing, the following information shall be recorded at the time each action is taken and the record shall be dated and signed by the person responsible for the processing operations.

22. STANDARD OPERATING PROCEDURES (SOPS) AND RECORDS, REGARDING:

1) Receipt of Materials
2) Sampling
3) Batch Numbering
4) Testing
5) Records of analysis

23. REFERENCE SAMPLES: Each lot of every active ingredient, in a quantity sufficient to carry out all the tests, except sterility and pyrogens/Bacterial Endotoxin Test, shall be retained for a period of 3 months after the date of expiry of the last batch produced from that active ingredient. Samples of finished formulations shall be stored in the same or simulated containers in which the drug has been actually marketed.

24. DISTRIBUTION RECORDS: Records of sale and distribution of each batch of Ayurveda, Siddha and Unani Drugs shall be maintained in order to facilitate prompt and complete recall of the batch, if necessary. The duration of record keeping should be the date of expiry of the batch, Certain categories medicines, do not have expiry date, in contrast their efficacy increases with the passage of time. Hence, records need to be maintained up to 5 years of the exhausting of stock.

4. SUMMARY AND CONCLUSIONS

The Good Manufacturing Process (GMP) is a production and testing practice that helps to ensure/ maintain the quality and purity of the pharmaceutical product depends on the condition maintained during the manufacturing process. GMP concept strictly adhere to stringent specifications followed during the manufacturing process. This assures the quality of the final product. Hence GMP is very essential to provide quality products and thereby preventing the market entry for counter fit drug. Many countries have legislated that pharmaceutical companies must follow GMP procedures, and have created their own GMP guidelines that correspond with their legislation. Basic concepts of all of these guidelines remain more or less similar to the ultimate goals of safeguarding the health of the patient as well as producing good quality medicines. Quality objective can be achieved only through careful planning and implementation of QA system and practical implementation of GMP. The effective implementation of GMP requires extensive care and knowledge about the different components of GMP that should be incorporated form the inception of the manufacturing building and product development till the production.

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