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GMP IN PHARMACEUTICAL MANUFACTURING: CURRENT BEST PRACTICES

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ABSTRACT
Good Manufacturing Practices (GMP) play a pivotal role in ensuring the production of high-quality pharmaceutical products that are safe, effective, and consistent. This publication provides an overview of the current best practices in pharmaceutical manufacturing, emphasizing the key principles of GMP and their application in the production environment. It examines the critical components of GMP, including personnel training, facility design, equipment maintenance, raw material control, and quality assurance systems, all of which are essential for maintaining compliance with regulatory standards. The paper also highlights the importance of risk management, validation processes, and continuous improvement in meeting evolving industry demands and ensuring consumer safety. With the increasing complexity of pharmaceutical products and manufacturing technologies, this publication discusses emerging trends and challenges in GMP, focusing on the integration of modern technologies such as automation, data integrity, and advanced quality systems.

KEYWORDS: Good Manufacturing Practice, GMP, Pharmaceutical Inspection, Food and Drug Administration.

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 of 20 pages, and was reissue third impression in 1972, with the addition of a 2-page appendix on sterile medicinal products. The color 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.

The Medicines and Healthcare products regulatory Agency (MHRA) has published new edition of the Orange Guide in 2007. In United States, the first GMP regulations were issued in 1963 and described the GMP to be followed in the manufacture, packaging, and storage of finished pharmaceutical products. GMP regulations were developed by the US FDA and issued the United States CFR Chapter 21 in 1978. The regulation was similar in concept to the Orange Guide, but enforceable by law whereas the UK guide as an advisory. US congress passed the Federal Ani-tempering Act in 1983, making it a crime to tamper with packaged consumer products.

In the 1980, US FDA began publishing series of guidance documents that have a major effect on our interpretation of current GMP (cGMP). A “Guide to Inspection of Computerized Systems in Drug Processing” was published in 1983 and “Guideline on General Principles of Process Validation” was published in 1987. March 1997, The US FDA issued 21 CFR Part 11 which dealt with the use of electronic records and signatures. In 2000, US FDA introduced a guidance document on the incorporation of risk management into device development.[1]

2. OBJECTIVE

- **Prevent Contamination:** Minimize risks of product contamination from personnel, environment, or equipment.
- **Maintain Quality Control:** Ensure consistent product quality through validated processes, equipment, and materials.
- **Protect Consumers:** Guarantee that products are safe, effective, and meet intended specifications.

- **Promote Accountability:** Establish clear documentation and traceability for production and quality assurance processes.
- **Encourage Continuous Improvement:** Facilitate regular review and improvement of manufacturing processes and systems.

3. DEFINITION

GMP is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standard appropriate to their intended use and as required by the marketing authorization. Good Manufacturing Practices (GMPs) are regulations that describe the methods, equipment, facilities, and controls required for producing.[2]

4. GENERAL REQUIREMENTS

4.1. Location and Surroundings

The factory buildings for mfg. of drugs shall be so situated or shall have such measures as.

- To avoid risk of contamination from external environment.
- Any factory, which produces obnoxious odors, fumes, dust, smoke, chemical or biological emissions.

4.2. Building and Premises

The building should be designed in such a way that permits mfg. operations in hygienic conditions.

- Compatible with other mfg. operations.
- Adequately provided with working space.
- To avoid risk of mix-ups.
- To avoid contamination.
- Designed to avoid entry of pests, birds, rodents etc. Interior surface should be smooth and free from crakes
- The production and dispensing area shall be well lightened, ventilated, and may have proper air handling system.
- Proper drainage system as specified for various categories of products.
- The walls and floors of mfg. area shall be free from cracks and open joints to permit easy and effective cleaning

4.3. Water System

- There shall be validated system for treatment of water to render it potable.
- Potable water should be used to perform all the operations except cleaning and washing.

4.4. Disposal of Waste

- The disposal of sewage and effluents shall be in conformity with the requirements of Environment Pollution Control Board.
- All bio-medical waste shall be destroyed as per the provisions of Bio-Medical Waste Rules, 1996.
- Record shall be maintained.
- Provision shall be made for proper storage of waste materials.

4.5. Warehousing Area

- Adequate areas for proper warehousing of various categories of materials and products.
- Designed and adapted to ensure good storage conditions.
- Quarantine area shall be clearly demarcated and restricted to authorized persons.
- Separate sampling area for active raw materials and excipients.

4.6. Production Area

- Designed to allow the production preferably in uni-flow and with logical sequence of operations.
- Separate mfg. facilities shall be provided for the mfg. of contamination causing and potent products such as.
  - β-lactam, sex hormones and cyto-toxic substance.
  - Service lines shall be Well designed and constructed, shall be identified by colours. Direction of flow shall be marked.

4.7. Ancillary Area

- Rest and refreshment rooms shall be separate from other areas.
- Facility for changing, storing clothes and for washing and toilet purpose shall be easily accessible and adequate.
- Areas for housing animals shall be isolated and maintained as prescribed in rule 150- C (3) of D & C Rules, 1945.

4.8. Quality Control Area

- Quality control laboratories shall be independent of the production areas. Separate areas shall be provided each for physico-chemical, biological, micribiological or radio –isotope analysis.
- Adequate space shall be provided to avoid mix-ups and cross contamination.
- The design of the laboratory shall take into account the suitability of construction materials and ventilation.
- Separate air handling units and radioisotopes testing areas. The laboratory shall be provided with regular supply of water of appropriate quality for cleaning and testing purposes.

4.9. Personnel

- The manufacture and testing shall be conducted under direct supervision of qualified technical staff.
- Personnel for QA & QC shall be qualified and experienced.
- No. of personnel employed shall be adequate and in direct proportion to the workload.
- Personnel in production and QC lab. shall receive training appropriate to the duties & responsibility assigned to them.

4.10. 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 effect.
- Prior to employment, all personnel shall undergo medical examination including eye examination, and shall be free from tuberculosis, skin and other communicable or contagious diseases.[3]

4.11. Plant Construction and Design

An enclosed building must be used for food processing. There should be sufficient space within the building for staff, equipment, and the storage of materials. Aisles between equipment and materials should be provided so that movement is easy and unobstructed, and cleaning is easily performed (USPHS, 2005). Precautions to prevent contamination within the building must be taken, for instance through the separation of operations so that the food processing operation occurs in isolated stages that correspond to physical locations within the facility. Ideally, raw materials and adjuncts enter the process near the receiving area, movethrough preparation, process, and packaging areas, and proceed to storage. All effort must be made to prevent finished product from coming into contact with unprocessed product and raw materials, since doing so may contaminate the finished product.[4]

5. 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 Figure 1.

Fig 1: Components of Good Manufacturing Practice.

Indian schedule M for GMP and requirements of premises, plant and equipment for pharmaceutical products. Part I includes general requirements, Warehousing area, Production area, Quality control area, Personnel, Ancillary area, Health, clothing and sanitation of workers, Manufacturing operations and controls, etc. Part I-A to part I-E mentions about the specific requirements for manufacture of different products and Part I-F mentions about the specific requirements of premises, plant and materials for manufacture of active pharmaceutical ingredients (bulk drugs). Part II describes the Requirement of plant and equipments for various dosage forms.[5]

Fig 2: Consolidated Components of Good Manufacturing Practices.

6. GOOD MANUFACTURING PRACTICES (GMP) GUIDELINES

GMP guidelines provide guidance for manufacturing testing and quality assurance in order to ensure that a food or drug product is safe for human consumption. GMP guidelines are not prescriptive instructions on how to manufacture products. They are series of general principles that must be observed during manufacturing.

- Pharmaceutical manufacturing facilities must maintain clean and hygienic manufacturing area.
- Controlled environmental conditions in order to prevent cross contamination of drug product from adulterants that may render the product unsafe for human consumption.
- Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.
- Any change to the manufacturing processes is evaluated. Changes that have an impact on quality of the drug are validated as necessary.
- Instructions and procedures are written in clear and unambiguous language. (Good Documentation Practice)
- The distribution of the food or drugs minimizes any risk to their quality.
- A system is available for recalling any batch from sale or supply.
- Complaints about marketed products are examined, the cause of quality defects are investigated, and appropriate measures are taken with respect to the defective products and to prevent recurrence.[6]

7. MANUFACTURING CONTROL:

The basis for controlled manufacture requires that operating procedures are capable of producing products that conform to defined specifications, taking into account any defined raw material, process, or packaging tolerances.

- **Operating Procedures:** Written operating procedures and instructions are essential and form part of the QA system. These procedures should define what is to be done, when, how, and by whom and should include all ancillary activities and precautions. They should be clearly written, should be easy to understand, and should place emphasis on issues that may affect both product quality and operational efficiency. Training must ensure that operatives understand the operating instructions.

- **Preproduction Checks:** Before processing, authorized personnel should check the processing area and plant for cleanliness, availability of the necessary materials, and that packages and labels are correct for the product specification. The accuracy of equipment settings for process monitoring and must be assessed and any final adjustments should be made during the first few minutes of production. Any intermediate or final product prepared before the establishment of correct steady-state conditions must be excluded from the finished product.

- **Process Control:** Effective process control requires a hazard and risk assessment of that process, coupled with the continuous monitoring of critical control points. The concept of this approach is increasingly being applied also to the quality, health and safety, and environmental assessment of processes operating in the context of GMP. Data generated by continuous monitoring of process conditions or inspection and analysis should ideally be analyzed using appropriate statistical process control procedures, in order to identify and monitor trends**.**

- **Pest Control:** All food manufacturers should either use a specialist pest control organization or provide employees with specialist training. The most effective approach to pest control is good housekeeping. Items, such as ingredients, packaging, and equipment, must always be stored on raised platforms and never be less than 50cm from a wall. Only approved substances may be used for pest control; extreme care must be taken to avoid cross-contamination of foods and materials likely to be exposed to them. Approved bait boxes should be sited so as not to interfere with manufacturing activities.[7]

8. SANITATION AND HYGIENE IN FOOD PROCESSING INDUSRTY:

Sanitation and hygiene of personnel, premises, equipment/apparatus and production materials and containers should be practiced to avoid contamination of the manufacturing of products.

- **Personnel Hygiene:** Personnel involved in food production must be healthy, undergo regular medical examinations, and comply with current vaccination requirements. Anyone with a communicable disease, illness, or visible open lesions must report it immediately and avoid handling food, packaging, or related materials. Clean and protective attire appropriate to duties is mandatory, and smoking, eating, or drinking in production and storage areas is prohibited. Strict personal hygiene, including handwashing before work, after breaks, and post-restroom use, is required.

- **Premises Hygiene**
  - Every food industry should have adequate washing and well ventilated toilet facilities for all employees, workers and security
  - The toilet, drinking water and food canteen for employees should be provided and separated from the production area to avoid any contaminations.
  - To storage and keep the clothing and personal belongings suitable locker facilities should be provided at appropriate location to all employees.

- Waste material should be regularly collected in suitable receptacles for removal to collection points outside the production area.
- The use of rodenticides, insecticides, fumigating agents and sanitizing materials in cleaning and killing rodents, insects, fungus and microbes must not contaminate equipment, raw materials, packaging materials, in-process materials or finished products.

- **Equipment and Apparatus Hygiene:** Equipment and utensils should be kept clean and hygienic condition. Now days, vacuum or wet cleaning methods are preferred. In cleaning process compressed air and brushes should be used with care and avoided if possible, as they increase the risk of product contamination. Always SOP must be followed for cleaning and sanitizing of major machines.

- **Sanitation Standard Operating Procedures (SSOP):** According to food regulations and orders the SSOP should include the general maintenance, list of substances used in cleaning and sanitizing, proper storage facility for toxic materials, good pest control system, proper sanitation of food-contact surfaces, sstorage and handling of clean portable equipment and utensilsand facility for disposalof rubbish materials.[8]

9. QUALITY CONTROL

Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

The basic requirements of Quality Control are that:

(i) Adequate facilities, trained personnel and approved procedures are available for sampling and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;

(ii) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by approved personnel and methods;

(iii) Test methods are validated;

(iv) Records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;

(v) The finished products contain active ingredients complying with the qualitative and quantitative composition of the Marketing Authorisation or Clinical Trial Authorisation, are of the purity required, and are enclosed within their proper containers and correctly labelled;

(vi) Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification;

(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations.

10. QUALITY RISK MANAGEMENT

Quality Risk Management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

The principles of Quality Risk Management are that:

(i) The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;

(ii) The level of effort, formality and documentation of the Quality Risk Management process is commensurate with the level of risk.[9]

11. DOCUMENTATION

Documentation is the key to operating a pharmaceutical company in compliance with GMP requirements. The system of documentation devised or adopted should have as its main objective to establish, monitor, and record "quality" for all aspects of the production and quality control. Several types of documents are needed to accomplish this.

11.1 Standard operating procedures, specifications and master formulae

Descriptive documents give instructions on how to perform a procedure or a study, or give a description of specifications. The instruction type documents are: standard operating procedures (SOP); protocols (for validation studies, stability studies, safety studies); and master formulae (manufacturing instructions). These kinds of documents provide the specific details defining the quality of incoming materials, the quality of the production environment, the quality of the production and control process, and the quality of the final product.

11.2 Forms for recording data

Another type of documentation is the form used for recording data as it is taken during the performance of tasks, tests, or events. These are forms (datasheets, or data record forms), reports, batch processing records, and equipment log books. These documents provide the evidence that the raw materials, facility environment, the pro duction process, and the final product consistently meet the established quality requirements.

11.3 Identification Numbers

There are also the identification systems or codes devised to number and track both information and documents. These are SOP numbers, equipment

numbers, form numbers, receiving codes, and batch/lot numbers. These numbering systems should be designed so that procedures, processes and materials can be traced throughout the data records.

11.4 Labels

Labelling systems are used to identify the status of the equipment or facility, restricted areas, and warning labels. These include raw material tags, quarantine labels, release labels, reject labels, labels to identify specific storage areas, biohazard or radioactive labels, restricted access labels, equipment "cleaned" or "waiting for cleaning" labels, process intermediate labels, and the final product labels. These permit the identification and tracking of materials, of the progress of a production process, and assurance of the proper functioning of equipment.[10]

12. EQUIPMENT

Equipment (mechanical, electronic, or automated) must be qualified as capable of performing its intended functions or operations before first use, and procedures for routine calibration and maintenance must be established and followed. Equipment needs to be designed and located to facilitate operations, cleaning, and maintenance, and equipment may require sanitization or sterilization to prevent contamination. The suitability of single-use disposable equipment for its use in processing may be determined by the use of a valid COA from the supplier in lieu of testing or examination by the outsourcing facility. In addition, the integrity of the packaging of the single-use disposable equipment should be verified upon receipt before use.[11]

13. CONCLUSION

Good Manufacturing Practices (GMP) continue to be the cornerstone of ensuring the safety, efficacy, and quality of pharmaceutical products. Adhering to GMP standards not only meets regulatory requirements but also fosters a culture of continuous improvement, minimizes risks, and ensures patient safety. The integration of emerging technologies, such as automation, artificial intelligence, and continuous monitoring systems, has significantly enhanced GMP compliance, providing real-time data to mitigate risks and improve manufacturing efficiency. Additionally, the adoption of risk-based approaches, Quality by Design (QbD), and environmental controls ensures that manufacturers meet stringent product quality standards.

As the pharmaceutical industry moves toward more personalized medicine and biotechnology-driven products, the future of GMP will likely incorporate more advanced technologies and increasingly stringent standards.

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