GOOD MANUFACTURING PRACTICES (GMP)

GMP is that part of Quality assurance which ensures that the products are consistently produced and controlled according to the Quality standards appropriate to their intended use. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

Good Manufacturing Practice is a set of regulations, codes, and guidelines for the manufacture of drug substances, drug products, medical devices, in vivo and in vitro diagnostic products, and foods.

A set of principles and procedures which, when followed by manufacturers for therapeutic goods, helps ensure that the products manufacture will have the required quality.

The 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors', otherwise known as the **'Orange Guide'** is published to help companies and individual personnel comply with GMP regulations that govern the international pharmaceutical industry.

WHY GMP IS IMPORTANT?

- A poor-quality medicine may contain toxic substances that have been unintentionally added or unexpected contamination of products.
- A medicine that contains insufficient or too much of active ingredient, resulting in ineffective treatment or adverse effects.
- Incorrect labels on products may lead to wrong usage of medicines by patients.

OBJECTIVES

- To assure quality of a product and finally the safety, wellbeing and protection of patient.
- To perform every operation with the objectives of maintaining the identity and integrity and products of effective production.
- To establish systems of control at all levels of manufacturing, right from the receipt of raw materials by continuous working, using correct equipment to dispatch finished goods from factory.
- cGMP is just a guideline, system and quality theme for compliance.
- It is just a way to build quality in a product.
- Improves productivity and minimizes rejection and mistakes.

1. GENERAL REQUIREMENTS

1.1. 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.

1.2. 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 cross 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.

1.3. 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.

The storage tanks shall be cleaned periodically and records maintained by the licensee.

1.4. 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.

2. 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

3. 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; Beta lactam, sex hormones and cyto-toxic substance.

Service lines shall be well designed and constructed, shall be identified by colors.

Direction of flow shall be marked.

4. ANCILLARY AREAS

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.

5. QUALITY CONTROL AREA

Quality control laboratories shall be independent of the production areas.

Separate areas shall be provided each for physico-chemical, biological, microbiological 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.

6. 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.

7. HEALTH, CLOTHING AND SANITATION OF WORKERS

The personnel handling beta-lactam 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.

Clothing: Protection of operator and product, highly potent products or those of particular risk. Need for special protective clothing. Personnel should not move between areas producing different products. Garments need to be cleaned.

Health examinations: On recruitment for direct operators, repeated on regular basis.

Training: Check Induction training for new operators includes basic personal hygiene training. Written procedures - to wash hands before entering a manufacturing area.

Illness: Staff with illness or open lesions should not handle starting materials, intermediates or finished products.

8. MANUFACTURING OPERATIONS & CONTROLS

All manufacturing operations shall be performed by trained personnel under direct supervision of approved technical staff approved by the licensing Authority.

All the materials & containers used in mfg. process shall be conspicuously labeled with Name of product, Batch number and batch size, Stages of manufacture

Products not prepared under aseptic condition are required to be free from pathogens like, Salmonella, Escherichia coli, Pyocyanea, etc.

The licensee shall prevent mix-up and cross-contaminations of drug materials and drug product by proper air –handling system, pressure differential, segregation, and status labeling and cleaning.

Proper records and SOPs thereof shall be maintained.

9. SANITATION IN MANUFACTURING PREMISES

Manufacturing premises shall be cleaned and maintained according to validated cleaning procedures.

Manufacturing areas shall not be use as storage or thoroughfare.

A Routine sanitation program shall be drawn up and observed.

Area shall be well lightened production area particularly where visual on-line controls carried out.

10. RAW MATERIALS

The licensee keep an inventory of all raw materials to be used at any stage of production of drugs and maintain records as per Schedule U.

All materials shall store under appropriate storage condition & follow ‘first in/ first expiry’ ‘first out’ rule.

Raw material from each batch checked for quality & appropriately labels the storage area.

There shall be adequate separate area for materials “under test”, “approved “, and “rejected” with arrangement and equipment.

It allows dry, clean and orderly placement of stored materials and products, wherever necessary, under controlled temperature and humidity.

Only raw materials which have been released by the quality control department and which are within their shelf- life shall be used.

It shall be ensured that shelf life of formulation product shall not exceed with that of active raw material used.

It shall be ensured that all the containers of raw materials are placed on the raised platforms/racks and not placed directly on the floor.

11. EQUIPMENTS

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 minimize 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 product.

Balance and other measuring equipment of an appropriate range, accuracy and precision shall be available in the raw material stores, production and in process control operation and these shall be calibrated and checked on a scheduled basis in accordance with SOP and record maintained.

To avoid accidental contamination, wherever possible, nontoxic/ edible grade lubricant shall be used and the equipment shall be maintained in a way that lubricants don't contaminate the products being produced.

Defective equipment shall be removed from production and quality control areas or appropriately labeled.

12. DOCUMENTATION AND RECORDS

It is the essential part of the Quality assurance system. as such, shall be related to all aspect of GMP.

Its aim is to define the specification for all materials, method of mfg. 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.

Documents shall be approved, signed and dated by appropriate and authorized persons.

Document designed, prepared, reviewed and controlled, wherever applicable, shall comply with these rules.

The records shall be made or completed at the time of each operation in such a way that all significant activities concerning the mfg. of pharmaceutical product are traceable.

Records and associated SOP shall be retained for at least one year after the expiry date of the finished product.

13. LABELS AND OTHER PRINTED MATERIALS

Necessary for identification of the drugs and their use.

Printed in bright colors and legible manner.

All containers and equipment shall bear appropriate labels. Different color-coded labels can be used.

Printed packaging materials & leaflets shall be stored separately to avoid mix-up.

Packaging, labeling and release shall be done after approval of QC department

Record of receipt and use of all material shall be maintained.

14. QUALITY ASSURANCE

To understand key issues in quality assurance/ quality control. To understand specific requirements on organization, procedures, processes and resources. To develop actions to resolve current problems.

Principles of Quality Assurance

Wide-ranging concept: Covers 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 the products are of the quality required for the intended use. Quality Assurance incorporates GMP and also product design and development.

Requirements for QA Systems

- Ensure products are developed correctly.
- Identify managerial responsibilities.
- Provide SOPs for production and control.
- Organize supply and use of correct starting materials.
- Define controls for all stages of manufacture and packaging.
- Ensure finished product correctly processed and checked before release.
- Ensures products are released after review by authorized person
- Provide storage and distribution
- Organize self-inspection

15. SELF-INSPECTION AND QUALITY AUDIT:

Self-inspection:

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.

- Ensures that company Operations remain compliant with GMP.
- Assists in ensuring continuous quality improvement.
- Should cover all aspects of production and quality control which are designed to detect shortcomings in the implementation of GMP.
- Must recommend corrective action if shortcomings are observed and set a timetable for corrective action to be completed.
- Special occasions may demand additional self-inspections.

For example:

- Recalls
- Repeated rejections
- GMP inspections announced by the National Drug Regulatory Authority.

Written instructions for self-inspection include:

- Personnel
- Premises including personnel facilities
- Maintenance of buildings and equipment
- Storage of starting materials and finished Products
- Equipment

- Production and in-process controls
- Quality control
- Documentation
- Sanitation and hygiene
- Validation and revalidation programmes
- Calibration of instruments or measurement systems
- Recall procedures
- Complaints management
- Labels control
- Results of previous self-inspections and any corrective steps taken

Quality Audit:

It may be useful to supplement self-inspection process with a quality audit. A quality audit consists of examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialist or a team designed by a management for this purpose. Such audits may also be conducted to suppliers and contractors.

Three types:

1. Internal audit

2. External audit

3. Regulatory audit

Ten Principles of GMP

1. Design and construct the facilities and equipments properly

2. Follow written procedures and Instructions

3. Document work

4. Validate work

5. Monitor facilities and equipment

6. Write step by step operating procedures and work on instructions

7. Design, develop and demonstrate job competence

8. Protect against contamination

9. Control components and product related processes

10. Conduct planned and periodic audits

List of important documents in GMP

- SOP (Standard Operating Procedure)
- Specifications
- MFR (Master Formula Record)
- BMR (Batch Manufacturing Record)
- Manuals
- Master plans/ files
- Validation protocols
- Forms and Formats
- Records

COMMON PROBLEMS IN GMP EXECUTION:

1. Organization

- Lack of commitment
- Lack of resources for execution

2. Layout & Construction

- No quarantine area
- Insufficient environmental monitoring
- Cracked floor

3. Equipment:

- No calibration
- No performance check of balance before use
- Rusty Parts not kept improperly

4. Laboratory Testing:

- Poor reference standard keeping
- Poor data recording
- Reagent with no label

5. Documentation & Recording:

- No signature; no countercheck
- Improper correction made
- No written procedure
- Incomplete complaint record
- No up-to-date training records
- No document reviews

6. Labeling:

- Status not defined clearly

- Poor labeling control
- Release label not kept securely
- Inadequate reconciliation of batch label
- Defective equipment with no label

7. Validation:

- Insufficient validation
- Insufficient raw data
- No validation programmes

QA, GMP & QC inter-relationship

It is the sum total of the organized arrangements with the objective of ensuring that products will be of the quality required for their intended use QA

GMP Is that part of Quality Assurance aimed at ensuring that products are consistently manufactured to a quality appropriate to their intended use GMP

QC Is that part of GMP concerned with sampling, specification & testing, documentation & release procedures which ensure that the necessary & relevant tests are performed & the product is released for use only after ascertaining its quality

GMP Covers

- All aspects of production; **from the starting materials, premises and equipment to the training and personal hygiene** of staff.
- Detailed, written procedures are essential for each process that could affect the quality of the finished product.
- There must be systems to provide **documented proof** that correct procedures are consistently followed at each step in the manufacturing process - every time a product is made.

WHAT ARE cGMPs?

cGMP refers to the Current Good Manufacturing Practice regulations enforced by the US Food and Drug Administration (FDA).

cGMP provides for systems that **assure proper design, monitoring and control of manufacturing processes and facilities**.

Adherence to the cGMP regulations assures the identity, strength, quality and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations

Requirements of cGMP

- Organization and personnel
- Building and facilities
- Equipment
- Control of components
- Containers and closures
- Production and process control
- Packaging and labeling control
- Holding and distribution
- Records and reports
- Returned savaged drug products
- The inspection for compliance with GMP regulations
- Controlled substances safeguards