Good Manufacturing Practices For Premises And Materials

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:

- Human and veterinary products
- Medical devices
- Processed food

Usually see "cGMP" – where c = current, to emphasize that the expectations are dynamic. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

These regulations, which have the force of law, require that manufacturers, processors, and packagers of drugs, medical devices, some food, and blood take protective steps to ensure that their products are safe, pure, and effective.

Require a quality approach to manufacturing, enabling companies to minimize or eliminate instances of contamination, mix-ups, and errors.

Protects the consumer from purchasing a product, which is not effective or even dangerous. GMP regulations address issues including recordkeeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling.

In short, GMP makes the difference between nearly right and exactly right.

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PART I

Good Manufacturing Practices For Premises And Materials

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 the risk of contamination from the external environment.

Any factory, 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 the risk of mix-ups.
- To avoid contamination.
- Designed to avoid entry of pests, birds, rodents, etc. The interior surface should
  be smooth and free from crakes
- The production and dispensing area shall be well lightened, ventilated, and may have a proper air handling system.
- Proper drainage system as specified for various categories of products.
- The walls and floors of mfg. the area shall be free from cracks and open

- joints to permit easy and effective cleaning.

1.3. Water system

There shall be a validated system for the 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 record maintained by the licensee.

1.4. Disposal of waste

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

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.

4. Quality control area

Quality control laboratories shall be independent of the production areas.
Separate areas shall provide each for Physico-chemical, biological, microbiological, or radioisotope 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 a regular supply of water of appropriate quality for cleaning and testing purposes.

5. Personnel

The manufacture and testing shall be conducted under er 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 & responsibilities assigned to them.

6. Health, clothing, and sanitation of workers

Before 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 product,s or those of particular risk.
- Need for special protective clothing.
- Personnel should not move between areas producing different products.
- Garments need to clean.

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Health examinations:

On recruitment for direct operators, repeated regularly.

Training: – Check Induction training for new operators including 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.

7. Manufacturing operations & controls

- All manufacturing operations shall be performed by trained personnel under the direct supervision of approved technical staff approved by the licensing Authority. All the materials & containers used in mfg. the process shall be conspicuously labeled with
    - Name of product
    - Batch number and batch size
    - Stages of manufacture
- Products not prepared under aseptic conditions 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 products by proper air–handling system, pressure differential, segregation, and status labeling and cleaning. Proper records and SOPs thereof shall be maintained.

8. Sanitation in manufacturing premises

- Manufacturing premises shall be Cleaned and maintained according to validated cleaning procedures.
- Manufacturing areas shall not be used as storage or thoroughfare.
- A Routine sanitation program shall draw up and observed.

- The area shall well lighten the production area, particularly where visual online controls are carried out.

9. Raw materials

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

All materials shall store under appropriate storage conditions & follow the **'first in/first expiry'–'first out' rule.**

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

There shall be an 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 the shelf life of the formulation product shall not exceed that of the 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.

10. EQUIPMENT

- Equipment shall be located, designed, constructed, adapted, and maintained to suit the operations to carry out. The layout and design of the equipment shall aim to minimize the risk of errors and permit effective cleaning and maintenance to avoid cross-contamination, build-up of dust or dirt, and in general any adverse effect on the quality of the 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
- 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.

11. Documentation and records

- It is an essential part of the Quality assurance system. As such, shall be Related to all aspects of GMP.
- It aims to define the specification for all materials, methods of mfg. and control, to ensure that all personnel concerned with the manufacturer know the information necessary to decide whether 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.
- A 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. Pharmaceutical products are traceable. Records and associated SOP shall be retained for at least one year after the expiry date of the finished product.

12. Labels and other printed materials

- Necessary for identification of the drugs and their use.
- Printed in bright colors and legible manner.

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- 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 the QC department
- Record of receipt and use of all material shall be maintained.

13. 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 to ensure 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 the finished product is correctly processed and checked before release
  - .Ensure products are released after review by the authorized person
  - Provide storage and distribution
  - Organize self-inspection

14. 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**.**

- Ensures that a company's 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 are 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 programs
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 the self-inspection process with a quality audit. A quality audit consists of an 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 an outside or independent specialist or a team designed by management for this purpose. Such audits may also be conducted by suppliers and contractors.
Three types:

1. Internal audit
2. External audit
3. Regulatory audit

15. QUALITY CONTROL SYSTEM

- Quality control shall be concerned with sampling, specification, testing, documentation, and release procedures.
- The department as a whole shall have other duties such as establishing, evaluating, validating, and implementing all Quality control procedures and methods.
- All the batches were released after the certification of the QC department.
- Maintain reference/retained sample from each batch.
- The area of the quality control laboratory may be divided into chemical, instrumentation, microbiological and biological testing.
- An adequate area having the required storage conditions shall provide for keeping references samples. The quality control department shall evaluate, maintain, and store reference samples.
- There shall be authorized and dated specifications for all materials, products, reagents.

- The quality control department shall conduct stability studies of the products to ensure and assign their shelf life at the prescribed conditions of storage. All records of such studies shall be maintained.
- The in-charge of Quality Assurance shall investigate all product complaints thereof shall be maintained
- All instruments shall be calibrated and testing procedures validated before these are adopted for routine testing. Periodical calibration of instruments and validation of procedures shall be carried out.
- Pharmacopeias, reference standards, reference spectra, other references materials, and technical books, as required, shall be available in the quality control laboratory of the licensee.

16. Specifications

- For raw material & packaging material.
- For product containers & closures.
- For in-process & bulk products.
- For finished product.
- For the preparation of containers & closures.

17. Master formula records: -

Related to –

- All mfg. procedures for each product.
- Batch size to manufacture.

Includes:-

- Name of product with reference code.
- Patent & proprietary name with a generic name.
- Description of the dosage form.

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- Name, quantity & reference no. Of all starting material.
- A statement of expected final yield & the principal equipment to be used.
- Detailed SOP with the time taken for each step.
- Requirements for storage conditions of the products, containers, labeling
- Packaging detail and specimen labels.

18. Packaging records:-

There shall be Authorized packaging instructions for each product, pack size & type that include;

- Name of product with other description.
- The volume of product in the final container.
- Complete list of all the packaging materials with.
- Quantities size & type.
- Description of packaging operations.
- Detail of in-process control

19. Batch packaging record: -

- A batch packaging record shall be kept for each batch or part batch processed. It shall base on the relevant parts of packaging instructions, and the method of preparation of such records shall be designed to avoid transcription error.
- Before any packaging operation begins, checks are 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.

20. BATCH PROCESSING RECORDS:-

There shall be Batch processing Record for each product. It shall base on the parts of the currently approved master formula.

Before any processing begins, the check shall be performed and

recorded to ensure that the equipment and workstation are clear of previous products, documents or materials not required for the planned process removed and that equip0ment is clean and suitable for use.

During processing, the following information shall be recorded at the time each action is taken. The records shall be dated and signed by the person responsible for the processing operations:

- Name 0f the product
- No. of the batch being manufactured
- Date and time of commencement
- Initials of the operator of the different significant steps of production and where appropriate, of the person who checked each of these operations.
- Batch no.
- Equipment used.
- Records of the IPQC.
- Amount of then product obtained at different and critical stages of manufacture.

  Special problems.

21. **Standard operating procedures (SOP), and Records, Regarding**.

22.1 Receipt of material

Includes –

- Written SOP for receipt of raw, primary & printed packaging materials.
- Written SOP for the internal labeling, quarantine & storage of various materials.
- SOPs for related instruments & equipment.

22.2. Sampling

Includes –

- SOP for the method of sampling.
- SOP for equipment to use.
- Precautions to avoid contamination.
- Instruction for qty. & pooling of samples.
- Specific precautions for the sampling of sterile or hazardous materials

22.3. Batch numbering

SOPs

- Describe the detail of batch numbering set up for each batch of intermediate, bulk, or finished product.
- Applied to a processing stage & the respective packaging stage.
- Include the date of allocation, product identity & batch size.

22.4 Testing: -

There shall be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to use, the tests performed shall be recorded.

22. 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 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 marketed.

23. Reprocessing and recording: -

- Where the processing is necessary, written procedures shall be established and approved by the Quality assurance Department that shall specify the condition and limitations of repeating chemical reactions. Such reprocessing shall be validated.

- If the product batch has to be reprocessed the procedure shall be authorized and recorded. An investigation shall be carried out into the causes necessitating reprocessed batch shall be subjected to stability evaluation.
- Recovery of product residue may be carried out, if permitted, in the master production and control records by incorporating it in subsequent batches of the product.

24. Distribution records: -

- Prior to distribution or dispatch of a given batch of a drug, it shall be ensured that the batch has been duly tested, approved, and released by the quality control personnel. A pre-dispatch inspection shall be performed on each consignment on a random basis to ensure that only the correct goods are dispatched.
- Records for distribution shall be maintained in a such manner that finished batch of a drug can be traced to the retail level to facilitate prompt and complete recall of the batch, if and when necessary.

25. Validation and Process validation: -

- Essential part of GMP and shall be conducted as per the pre–defined protocols.
- A written report summarizing recorded result and conclusions shall be prepared, documented and maintained.
- Shall be undergo periodic validation to ensure that they remain capable of achieving the intended results.
- Critical process shall validated, prospectively or retrospectively.
- When any new master formula or method of preparation adopted, steps shall take to demonstrate its suitability for routine processing.
- Significant changes to the mfg. Processes, including any change in equipment or materials that may affect product quality and/or the reproducibility of the process shall validated.

26.PRODUCT RECALLS: -

- A prompt and effective recall system of defective products shall devised

- for timely information of all concerned stockiest, wholesalers, suppliers, up to the retail level within the shortest period. The licensee may make use of both print and electronic media in this regard.
- The distribution records shall readily made available to the persons designated fore recalls.
- The effectiveness of the arrangements for recalls shall evaluated from time to time.
- The recalled products shall store separately in a secured segregated area pending final decision on them.

27. COMPLAINTS AND ADVERSE REACTIONS: -.

All complaints thereof concerning product quality shall be carefully reviewed and recorded according to written procedures. Each complaint shall be investigated
/evaluated by the designated personnel of the company and records of investigation and remedial action taken thereof shall be maintained.
Reports of serious adverse drug reactions resulting from the use of a drug along with comments and documents shall be forthwith reported to the concerned Licensing Authority.
There shall be written procedures describing the action to be taken, recall to be made of the defective product.

28. SITE MASTR FILE:-

The licensee shall prepare a succinct document in the form, of „**Site Master File** „

Containing specific and factual GMP about the production and /or control of pharmaceutical manufacturing preparations carried out at the licensed premises.
It shall contain the following

- General information
- Personnel
- Premises

- Equipment
- Sanitation
- Documentation
- Production
- Quality control: -

o Description of the quality system and the activities of the quality control department. Procedure for the release of the finished products.
- Loan license manufacture and licensee:-

o Description of how the compliance of GMP by the loan licensee shall be assessed.

- Distribution, complaints, and product recall
- Self-inspection
- Export of drugs: - it may be

o Products are exported to different countries.

o Complaints and product recall, if any.

DIFFERENT SUBPARTS OF PART I

PART IA*: Specific requirements for the manufacture of sterile products, parenteral preparations (small volume injectable and large volume parenteral), and sterile ophthalmic preparations.*

PART I B: Specific requirements for the manufacture of oral solid dosage forms (tablets and capsules)

The general requirements as given in part-I

Additional requirements are as follows

- General
- Sifting, mixing, and granulation
- Compression (tablets)

- Coating (tablets)
- Filling of hard gelatin capsules
- Printing (tablet and capsules)
- Packaging (Strip and blister)

PART IC: Specific requirements for the manufacture of oral liquids (syrups, elixirs, emulsion, suspension)

PART ID: Specific requirements for the manufacture of topical products i.e. external preparation (creams. Ointments, pastes, emulsions, lotions, solutions, dusting powders, and identical products.

PART IE: Specific requirements for the manufacture of metered-dose inhalers (MDI).

PART IF: Specific requirements of premises, plant, and materials for the manufacture of active pharmaceutical ingredients (BULK DRUGS).

The general requirements as given in part-I Additional requirements are as follows;

- Building and civil works
- Utility services
- Equipment design, size, and location
- In-process controls
- Product containers and closures

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 record
        - No document review

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 programme

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