Good manufacturing Practice

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GOOD MANUFACTURING PRACTICE (GMP): AN OVERVIEW

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❖ 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 record keeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling.

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

❖ Why GMP?

- Final testing of the product cannot ensure the Quality efficiency and safety.
- Final testing may always not detect contamination, error, etc.
- Conformance to the predetermined specification.
- To minimize contamination eg:- microbial contamination.
- To eliminate error.
- To produce product of consistent quality.

- Government requirement.
- Ensure quality product.
- Reduce rejects, recalls.
- Satisfied customers.
- Company image and reputation.

❖ CODE OF FEDERAL REGULATIONS (CFR):

- It is the Portion of FDA.
- The collection of final regulations published in the federal register (daily published records of proposed rules, final rules, meeting notices, etc.
- Divided into 50 titles.
- Current regulations of GMP appear in part **210 (title 21) of code of federal regulations** published by **USFDA.**

❖ EVOLUITON OF GMP

- 1963: - first GMP publication –USA
- 1971: -first revision
- 1978: - Major revision
- Current regulation of GMP appear in part 210 (title 21) of code of federal regulations published by USFDA

❖ MAIN RISKS WITHOUT GMP:

- Unexpected contamination of products, causing damage to health or even death.
- Incorrect labels on containers, which could mean that patients receive the wrong medicine.
- Insufficient or too much active ingredient, resulting in ineffective treatment or adverse effects.

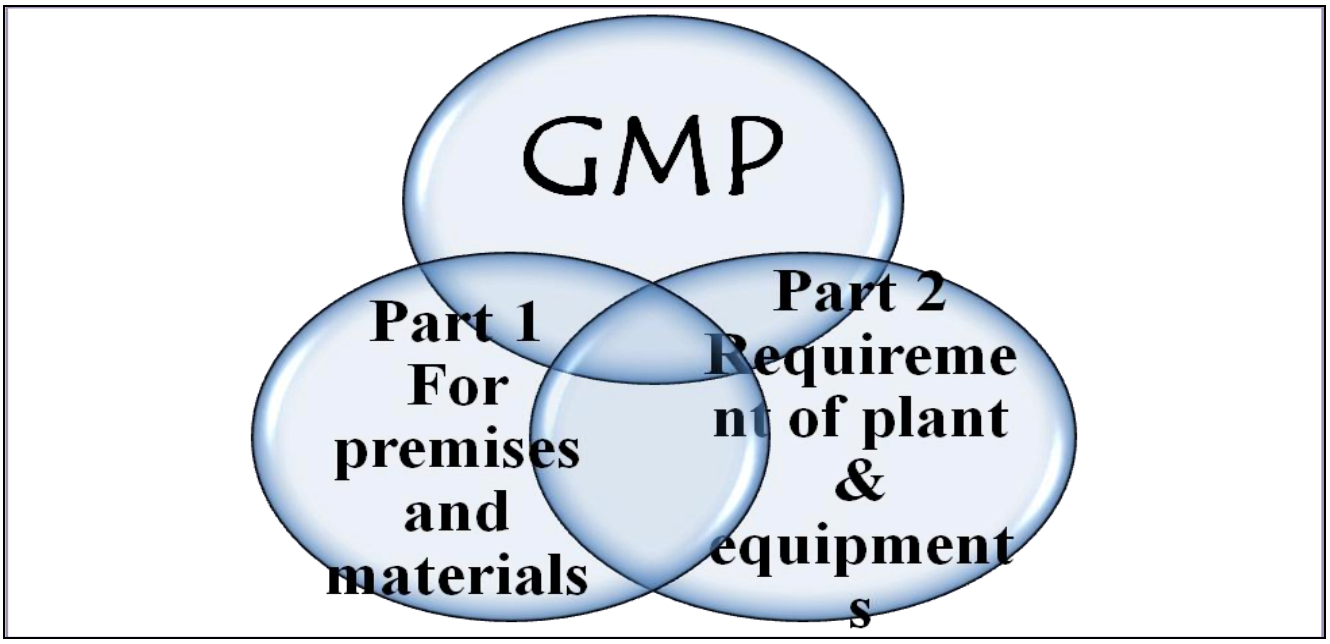
❖ WHY GMP IS IMPORTANT?

- Government requirement
- Ensure quality product
- Reduce rejects, recalls
- Satisfied customers
- Maintain manufacturing consistency
- Company image and reputation

❖ PRINCIPLES OF GMP:

- Design and construct the facilities and equipments properly
- Follow written procedures and Instructions
- Document work
- Validate work
- Monitor facilities and equipment
- Write step by step operating procedures and work on instructions
- Design ,develop and demonstrate job competence
- Protect against contamination
- Control components and product related processes
- Conduct planned and periodic audits

❖ PARTS OF GMP:



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 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 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;
    - 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. 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.seprate 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.

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-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.

- ***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 ands equipment .It allow dry, clean and orderly placement of stored materials and products, wherever necessary ,under controlled temp.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 beRelated 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 associate d 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 colours 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 mad 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
- .Ensure products are released after review by authorized person
- Provide storage and distribution
- Organize self-inspection

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**.**

- 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 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.
Basically three types:

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

16. QUALITY CONTROL SYSTEM

- Quality control shall be concerned with sampling, specification, testing, documentation, and release procedures.
- It is not confined to laboratory operations but shall be involved in all decisions concerning the quality of the product.
- The department as a whole shall have other duties such as to establish, evaluate, validate and implement all Quality control procedure and methods.
- All the batches released after certification of 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.
- Adequate area having the required storage conditions shall be provided for keeping references samples. The quality control department shall evaluate, maintain and storage 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 instrument and validation of procedures shall be carried out.
- Pharmacopoeias, reference standard, reference spectra, other references materials and technical books, as required , shall be available in the quality control laboratory of the licensee.

17. Specifications

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

18. Master formula records: -

Related to –

- All mfg. procedures for each product.
- Batch size to be manufactured.

Includes:-

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

19. Packaging records:-

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

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

20. Batch packaging record: -

- A batch packaging record shall be kept for each batch or part batch processed. It shall be based 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 be made and recorded that the equipments 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 parts of the currently approved master formula.

Before any processing begins, check shall be performed and recorded to ensure that the equipment and work station are clear of previous products, documents or materials not required for the planned process are removed and that equip0ment is clean an suitable for use.

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:

- Name po0f 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.
- Equipments used.
- Records of the IPQC.
- Amount of then product obtained at different and critical stages of manufacture.

- Special problems.

22.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 instrument & equipments.

22.2. *Sampling*

Includes –

- SOP for method of sampling.
- SOP for equipments to be used.
- Precautions to avoid contamination.
- Instruction for qty. & pooling of sample.
- Specific precautions for sampling of sterile or hazardous materials

22.3. *Batch numbering*

SOPs

- Describing the detail of batch numbering set up for each batch of intermediate, bulk or finished product.
- Applied to a processing stage & to the respective packaging stage.
- Include 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 b e used, the tests performed shall be recorded.

23. Reference samples: -

- Each lot of every active ingredient, in a quantiy 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. Reprocessing and recording: -

- Where 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 in to 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.

25. Distribution records: -

- Prior to distribution or dispatch of given batch of a drug, it shall be ensured that the batch has been duly tested, approved and released by the quality control personnel. 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.

26. 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 be validated, prospectively or retrospectively.
- When any new master formula or method of preparation is adopted, steps shall be taken 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 be validated.

27.PRODUCT RECALLS: -

- A prompt and effective recall system of defective products shall be devised for timely information of all concerned stockists, 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 be readily made available to the persons designated fore recalls.
- The effectiveness of the arrangements for recalls shall be evaluated from time to time.
- The recalled products shall be storded separately in a secured segregated area pending final decision on them.

28. 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.

29. SITE MASTR FILE:-

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

Containing specific and factual GMP about th 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: -
    - Description of the quality system and of the activities of t he quality control department. Procedure for the release of the finished products.

- Loan licence manufacture and licensee:-
    - Description of the way in which compliance of GMP by the loan licensee shall be assessed.

- Distribution, complaints and product recall
- Self-inspection
- Export of drugs: - it may be
    - Products exported to different countries.
    - Complaints and product recall, if any.

❖ DIFFERENT SUBPARTS OF PART I

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

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

The general requirements as given in part-I

Additional requirements are as following

- 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 manufacture of oral liquids (syrups, elixirs, emulsion, suspension)

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

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

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

The general requirements as given in part-I

Additional requirements are as following;

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

PART-II

Requirements of plant and equipment

Area requirements	**Basic installation**	**Ancillary Area**
1. External preparations	30 sq. m	10 sq. m
2. Oral liquid preparations	30 sq. m	10 sq. m
3. Tablets	80 sq. m	20 sq. m

Coating section	30 sq. m	10 sq. m
4. Powders	30 sq. m	-
5. Capsules	25 sq. m	10 sq. m
6. Surgical dressings	30 sq.	-
7. Ophthalmic preparations	25 sq. m	10 sq. m
8. Pessaries & suppositories	20 sq. m	-
9. Inhalers & vitrellae	20 sq. m	-
10. Repacking of drug & pharmaceutical chemicals	30 sq. m	-
11. Parenteral preparations		

11.1 In glass containers	150 sq. m	100 sq. m(svp) 150 sq. m (lvp)
11.2 In plastic containers	250 sq. m	150 sq. m 100 sq. m (lvp Packaging)

❖ **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. Labelling:

- Status not defined clearly
- Poor labelling 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

❖ How do GMPs of different countries compare?

- At a high level, GMPs of various nations are very similar most require things like:
  - Equipment and facilities being properly designed, maintained, and cleaned
  - Standard Operating Procedures (SOPs) be written and approved
  - An independent Quality unit (like Quality Control and/or Quality Assurance)
  - Well trained personnel and management
- The World Health Organization (WHO) version of GMP is used by pharmaceutical regulators and the pharmaceutical industry in over one hundred countries worldwide, primarily in the developing world.
- The European Union's GMP (EU-GMP) enforces more compliance requirements than the WHO GMP, as does the Food and Drug Administration's version in the US.
- Similar GMPs are used in other countries, with Australia, Canada, Japan, Singapore and others having highly developed/sophisticated GMP requirements.
- In the United Kingdom, the Medicines Act (1968) covers most aspects of GMP in what is commonly referred to as "The Orange Guide", because of the color of its cover, is officially known as *The Rules and Guidance for Pharmaceutical Manufacturers and Distributors*.

❖ Enforcement of GMP in Different countries

- GMPs are enforced in the United States by the FDA;
- Within the European Union, GMP inspections are performed by National Regulatory Agencies (e.g., GMP inspections are performed in the United Kingdom by the Medicines and Healthcare products Regulatory Agency (MHRA);
- In Australia by the Therapeutical Goods Administration (TGA);
- In India and Pakistan by the Ministry of Health

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