Ministry of Health of the Russian Federation
Volgograd State Medical University

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GENERAL PHARMACEUTICAL CHEMISTRY

Good manufacturing practice for medicinal products (GMP).

Lesson 11

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Discipline

GENERAL PHARMACEUTICAL CHEMISTRY

LESSON №11 Good manufacturing practice for medicinal products (GMP).	Good manufacturing practice for medicinal products (GMP). Main Components and Principles of GMP. Regulations and Standards. Guidelines and Basic Concepts of GMP.

QUESTIONS FOR THE LESSON

1. What is GMP?
2. What is the difference between GMP and CGMP?
3. What are the 5 main components of good manufacturing practice?
4. What are the 10 principles of GMP?
5. What are GMP regulations?
6. What are GMP standards?
7. Guidelines and basic concepts of GMP
8. How to comply with guidelines of GMP
9. USA GMP regulations
10. EU/UK GMP requirements
11. International GMPs

WHAT IS GMP?

GMP is an international standard that defines the rules and regulations that ensure the quality of the production process at all stages, including storage and testing of products. The GMP standard includes a number of indicators that must be complied with by a product manufacturer.

GMP is probably the most widespread quality system followed across the pharmaceutical industry as a whole. GMP compliance is a requirement within the R&D environment for the manufacture and testing of clinical trial materials (both drug product and API) and for commercial manufacture and testing of these materials for human and animal consumption. R&D facilities performing these operations may be subject to audit for compliance to GMP; commercial facilities will be audited by the appropriate regulatory authority, possibly without prior warning.

GMPs examine and cover every aspect of the manufacturing process to guard against any risks that can be catastrophic for products, such as cross-contamination, adulteration, and mislabeling. Some areas that can influence the safety and quality of products that GMP guideline and regulation address are the following :

- ✓ Quality management
- ✓ Sanitation and hygiene
- ✓ Building and facilities
- ✓ Equipment
- ✓ Raw materials
- ✓ Personnel
- ✓ Validation and qualification
- ✓ Complaints
- ✓ Documentation and recordkeeping
- ✓ Inspections & quality audits

WHAT IS THE DIFFERENCE BETWEEN GMP AND CGMP?

Good Manufacturing Practices (GMP) and current Good Manufacturing Practices (cGMP) are, in most cases, interchangeable. GMP is the basic regulation promulgated by the US Food and Drug Administration (FDA) under the authority of the Federal Food, Drug, and Cosmetic Act to ensure that manufacturers are taking proactive steps to guarantee their products are safe and effective. cGMP, on the other hand, was implemented by the FDA to ensure continuous improvement in the approach of manufacturers to product quality. It implies a constant commitment to the highest available quality standards through the use of up-to-date systems and technologies.

WHAT ARE THE 5 MAIN COMPONENTS OF GOOD MANUFACTURING PRACTICE?

It is paramount to the manufacturing industry to regulate GMP in the workplace to ensure consistent quality and safety of products. Focusing on the following 5 P's of GMP helps comply with strict standards throughout the entire production process.

People

All employees are expected to strictly adhere to manufacturing processes and regulations. A current GMP training must be undertaken by all employees to fully understand their roles and responsibilities. Assessing their performance helps boost their productivity, efficiency, and competency.

Products

All products must undergo constant testing, comparison, and quality assurance before distributing to consumers. Manufacturers should ensure that primary materials including raw products and other components have clear specifications at every phase of production. The standard method must be observed for packing, testing, and allocating sample products.

Processes

Processes should be properly documented, clear, consistent, and distributed to all employees. Regular evaluation should be conducted to ensure all employees are complying with the current processes and are meeting the required standards of the organization.

Procedures

A procedure is a set of guidelines for undertaking a critical process or part of a process to achieve a consistent result. It must be laid out to all employees and followed consistently. Any deviation from the standard procedure should be reported immediately and investigated.

Premises

Premises should promote cleanliness at all times to avoid cross-contamination, accidents, or even fatalities. All equipment should be placed or stored properly and calibrated regularly to ensure they are fit for the purpose of producing consistent results to prevent the risk of equipment failure.

WHAT ARE THE 10 PRINCIPLES OF GMP?

1. Create Standard Operating Procedures (SOPs)
2. Enforce / Implement SOPs and work instructions
3. Document procedures and processes
4. Validate the effectiveness of SOPs
5. Design and use working systems
6. Maintain systems, facilities, and equipment
7. Develop job competence of workers
8. Prevent contamination through cleanliness
9. Prioritize quality and integrate into workflow
10. Conduct GMP audits regularly

REGULATIONS

GMP regulations are mandated by manufacturers' respective national government to regulate the production, verification, and validation of manufactured products and ensure that they are effective and safe for market distribution.

For example, in the United States, GMP is enforced by the US FDA through Current Good Manufacturing Practices (CGMP) which cover a broader range of industries such as cosmetics, food, medical devices, and prescription drugs. The FDA conducts facility inspections to assess if a manufacturing company complies with CGMP regulations. If any serious violations are found during the inspection, FDA recalls all products, which is problematic for manufacturers in terms of both profit and business operations.

The quality of manufactured products is highly regulated as it can pose negative health risks to consumers and even the environment. Poor hygiene, temperature-

control, cross-contamination, and adulteration in any step of the manufacturing process are some examples of how a manufactured product that doesn't follow GMP regulations can bring fatal consequences to consumers.

STANDARDS

GMP standards are developed to enhance the safety of manufactured products, especially pharmaceutical goods, and to ensure consumers get the highest quality possible. Adherence to GMP standards not only positively impacts the reputation of manufacturing companies but also reduces batch recalls and negative reports from consumers. Below are 4 measures you can follow to uphold GMP standards:

Quality team

A team of skilled workers that focus on improving current manufacturing procedures and complying with GMP. Members perform quality assessments on operations to identify problems and develop appropriate corrective measures. Part of the team's responsibility also be performing scheduled monitoring of instruments, equipment, processes, and staff skills.

Validation

Validation is the documented act of demonstrating instruments, processes, and activities that are regularly used or done. This is done to check if they function according to expectations. GMP can involve a number of things to be validated, but it's good to focus on the following processes:

- ✓ Process validation
- ✓ Cleaning and sanitation validation
- ✓ Computer system validation
- ✓ Analytical method validation

Surprise Audits

A surprise audit every now and then can help gain a more accurate insight into what goes on in the facility. Identify real root causes of non-compliance and take action before it progresses into a larger issue.

Compliance Training

Providing compliance training to staff is the best way to ensure compliance with GMP standards. All employees should receive training on recordkeeping,

sanitation, proper equipment handling, and labeling, and SOPs to minimize errors and maintain compliance.

GUIDELINES AND BASIC CONCEPTS

GMP guidelines are a set of principles that help manufacturers implement an effective manufacturing process and ensure that quality is built into the organization and the processes involved. GMP guidelines are customarily flexible, with countries having their own legislation to comply with local GMP guidelines and principles. But almost all regulations are derived from the basic concept and guidelines which are:

Quality management

The principle of quality management is to ensure that manufactured products are fit for their intended use, comply with requirements and does not place consumers at risk due to inadequate safety, quality, or efficacy measures. To achieve this quality objective, quality assurance, good manufacturing practices, quality control, and quality risk management should be comprehensively and correctly implemented.

Quality assurance

The system of quality assurance aims to ensure that manufactured products are designed and developed in a way that meets the requirements for Good Manufacturing Practice.

Good Manufacturing Practice for Products

As a part of quality assurance, good manufacturing practice is concerned with production and quality control. It aims to mitigate the risks that are inherent in the production process. Its basic requirements according to WHO's Good Manufacturing Practices for Pharmaceuticals state the following:

- All manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications and/or marketing authorization;
- Critical steps of manufacturing processes and significant changes to the process are validated;
- All necessary facilities for GMP are provided including i. appropriately qualified and trained personnel; ii. adequate premises and space; iii. suitable equipment and services; iv. correct materials, containers, and labels; v. approved procedures and instructions;

- Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
- Operators are trained to carry out procedures correctly;
- Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product were as expected. Any significant deviations are fully recorded and investigated;
- Records of manufacture including distribution which enable the complete history of a batch to be traced are retained in a comprehensible and accessible form;
- The distribution (wholesaling) of the products minimizes any risk to their quality;
- A system is available to recall any batch of product, from sale or supply;
- Complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures are taken in respect of the defective products and to prevent re-occurrence

Quality control

Quality control is a part of Good Manufacturing Practice that focuses on sampling, specification, and testing. It checks the organization, documentation, and release procedures to ensure that products go through the required tests before being released for sale or supply.

Quality risk management

Quality risk management is a systematic process of assessing risks that can affect the quality of the product. According to its principles, quality risk management should ensure that:

- ✓ 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 and users;
- ✓ The level of effort, formality, and documentation of the quality risk management process is commensurate with the level of risk.

Sanitation and hygiene

Sanitation and hygiene are vital in every aspect of the manufacturing process. It covers anything that can cause contamination such as personnel, the premises, equipment, containers, and production materials. All potential sources of

contamination should be identified and eliminated with a comprehensive sanitation and hygiene program.

Building and facilities/premises

As a principle, the premises should be situated in an environment that is suitable for its operations and one that is free from risks of contamination of materials and products. The premises should also be designed to minimize errors in operations and should be easy to clean and maintain.

Equipment

Same with the premises, equipment should be designed, located, and maintained to function according to its intended use. Additionally, it should be cleaned and stored according to procedures. In the event of a defect or malfunction, it should be removed or labeled as defective.

Raw materials

All materials used for production should be stored properly according to the appropriate conditions which are set by the manufacturers. There should be a proper stock management system implemented to ensure that all incoming materials are correct and of high quality.

Personnel

The success of GMP compliance heavily relies on the people implementing it. For this reason, it is vital that all personnel are qualified and trained to do the job. They should be aware of the principles of GMP and receive continued training, hygiene instructions, and other tools relevant to their needs. Respective managers should be clear on job descriptions for each worker to avoid misunderstandings and reduce the risk of issues like overlapping responsibilities.

Validation and qualification

It is necessary to qualify systems, premises, and equipment if they are fit/ready for their intended use and validate if processes and procedures can repeatedly produce high-quality products. Critical steps in the manufacturing process should be verified to ensure that product quality is consistent and maintained at a high level. According to the WHO (World Health Organization), qualification and validation should establish and provide documentation stating that:

- ✓ the premises, supporting utilities, equipment, and processes have been designed in accordance with the requirements for GMP (design qualification or DQ)
- ✓ the premises, supporting utilities, and equipment have been built and installed in compliance with their design specifications (installation qualification or IQ);
- ✓ the premises, supporting utilities, and equipment operate in accordance with their design specifications (operational qualification or OQ); and a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation or PV, also called performance qualification or PQ)

Complaints

Handling complaints is also part of GMP, therefore all manufacturing companies should have a well-designed GMP complaint system. Ideal complaint handling should have a ready solution to provide for all contingencies.

Documentation and recordkeeping

Good documentation and record keeping are an essential part of the quality assurance system and are required in compliance with GMP requirements. Accurate recordkeeping can help managers and supervisors keep track of the historical record of manufacturing procedures and corrective measures implemented. Below are general requirements for documentation:

- ✓ Documents must be designed, prepared, reviewed, and distributed with care.
- ✓ Documents should be clear and legible.
- ✓ Documents must be approved, signed, and dated by appropriate and authorized personnel.
- ✓ Documents must have unambiguous contents such as title, nature, and purpose.
- ✓ Documents must be regularly reviewed and updated.
- ✓ Documents must not be handwritten.
- ✓ Any corrections made to a document or record must be signed or initialed and dated. The reason for the correction should also be recorded (where appropriate).
- ✓ Record each action taken for traceable activities such as manufacturing and control of products.

Inspections & quality audits

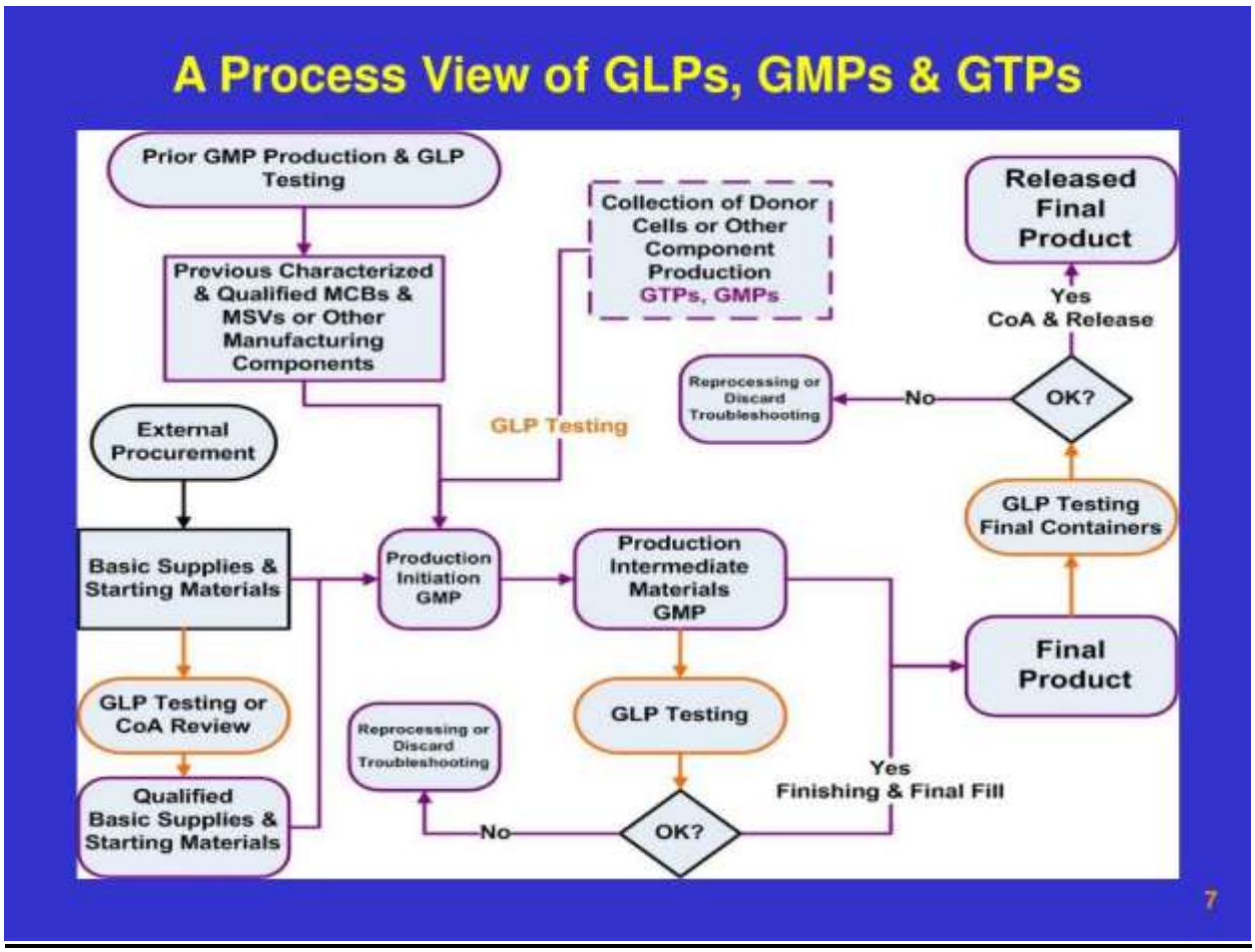
Inspections should be regularly performed to monitor if GMP is implemented and complied with. Document what areas need more work and provide corrective measures for continuous improvement. Quality audits are done to assess the quality systems implemented by the manufacturing company. GMP audit checklists can help companies comply with GMP guidelines set by regulatory authorities.

HOW TO COMPLY WITH GUIDELINES

GMP guidelines and regulations address different issues that can influence the safety and quality of a product. Meeting GMP or cGMP standards helps the organization comply with legislative orders, increase the quality of their products, improve customer satisfaction, increase sales, and earn a profitable return of investment.

Conducting GMP audits play a big part in assessing the compliance of the organization to manufacturing protocols and guidelines. Performing regular checks can minimize the risk of adulteration and misbrand. A GMP audit helps improve the overall performance of different systems including the following:

- Building and facilities
- Materials management
- Quality control systems
- Manufacturing
- Packaging and identification labeling
- Quality management systems
- Personnel and GMP training
- Purchasing
- Customer service



USA GMP REGULATIONS

The USA Food, Drugs and Cosmetics Act (FD&C Act) states that 'All drugs shall be manufactured, processed and packaged in accordance with current good manufacturing practice' . No distinction is drawn between the manufacture of drug products (secondary manufacture) and the manufacture of APIs (primary manufacture).

It must be noted that the US regulations refer to current GMP. The regulations give the pharmaceutical manufacturer plenty of scope to interpret the requirements appropriately for his specific facility and process, but in doing this the regulations require the manufacturer to adopt best current practice. The onus is placed upon the manufacturer to keep current with what the industry is doing (best practice), with what the current interpretation of the regulations are, and what the US FDA's expectations are.

With the issue of the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline ICH Q7A – Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients in November 2000, that the worldwide pharmaceutical industry finally received detailed guidance for manufacture of APIs for both commercial and R&D purposes.

It is mandatory to have controls in the following areas:

Subpart A – General provisions

Subpart B – Organisation and personnel

Subpart C – Buildings and facilities

Subpart D – Equipment

Subpart E – Control of components and drug product containers and closures

Subpart F – Production and process controls

Subpart G – Packaging and labelling control

Subpart H – Holding and distribution

Subpart I – Laboratory controls

Subpart J – Records and reports

Subpart K – Returned and salvaged drug products

The areas of these regulations that will be most important for a pharmaceutical analyst will be:

Organisation and personnel – this includes the requirement to have a QC unit having responsibility and authority to approve and reject all components, drug product containers, closures, in-process materials, packaging materials, labelling and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. Further requirements cover laboratory facilities and the responsibility of the quality unit for approving or rejecting all materials, specifications and procedures. The responsibilities of the quality unit must be described in written procedures.

Records and reports – this part describes the key records that require to be retained. These include drug product component and container/closure records, labelling records, production records, production record review, laboratory records, distribution records and complaint files.

In conclusion, the USA cGMP regulations apply to interstate commerce within the USA and to any facility worldwide, that exports pharmaceutical materials (drug products, APIs, or components of these products) to the USA or, wishes to perform clinical trials in the USA. These facilities are open to inspection for cGMP compliance by US FDA inspectors and for those facilities found to be in non-compliance with these requirements the material will be deemed adulterated with respect to identity, strength, quality and purity. Products from these facilities will be refused entry for sell or use within the USA. Data from these facilities may not be accepted in support of regulatory filings.

EU/UK GMP REQUIREMENTS

Two European directives lay down the principles and guidelines for GMP in the EU, one for medicinal products for human use and the other for veterinary products. These directives have been incorporated in the national law of member states. The European Commission has issued nine volumes of the rules governing medicinal products in the EU. The latest edition was issued in 1998. Volume four covers GMP for medicinal products for human and veterinary use. These are now used as a basis for inspection by the various national regulatory authorities (e.g. Medicines Control Agency (MCA) in the UK).

The basic requirements are detailed under the following chapter headings:

Chapter 1: Quality assurance

Chapter 2: Personnel

Chapter 3: Premises and equipment

Chapter 4: Documentation

Chapter 5: Production

Chapter 6: Quality control

Chapter 7: Contract manufacture and analysis

Chapter 8: Complaints and recall

Chapter 9: Self-inspection

There are a further 14 Annexes:

Annex 1: Manufacture of sterile medicinal products

Annex 2: Manufacture of biological medicinal products for human use

Annex 3: Manufacture of radiopharmaceuticals

Annex 4: Manufacture of veterinary medicinal products other than immunologicals

Annex 5: Manufacture of immunological veterinary medicinal products

Annex 6: Manufacture of medicinal gases

Annex 7: Manufacture of herbal medicinal products

Annex 8: Sampling of starting and packaging materials

Annex 9: Manufacture of liquids, creams and ointments

Annex 10: Manufacture of pressurised metered dose aerosol preparations for inhalation

Annex 11: Computerised systems

Annex 12: Use of ionising radiation in the manufacture of medicinal products

Annex 13: Manufacture of investigational medicinal products

Annex 14: Manufacture of products derived from human blood or human plasma

INTERNATIONAL GMPS

A large number of those countries that have pharmaceutical industries, especially generic pharmaceutical manufacturers, have set up GMP QS based on USA requirements for the simple reason that the USA has the largest pharmaceutical market in the world. A large number of API manufacturers export to the USA and hence have required to comply with USA cGMP for pharmaceutical manufacture. The World Health Organisation (WHO) for a number of years has been very active in setting global GMP standards for both drug products and APIs.

GMPs represent a technical standard upon which is based the 'WHO Certification scheme on the quality of pharmaceutical products moving in international commerce'.