# Design of Pharmaceutical Manufacturing Plant

**Learning Objectives:** Students will be able to:

1. Explain the principles and significance of Good Manufacturing Practices (GMP) in pharmaceutical manufacturing.
2. Demonstrate an understanding of fundamental concepts related to pharmaceutical facility design,
3. Evaluate sustainability practices within the pharmaceutical manufacturing industry and anticipate emerging trends and innovations that are shaping the future of the field.

**Table of Content:**

## 1. Introduction

Pharmaceutical plant design is essential for safe, efficient drug manufacturing. It covers facility planning, cleanroom design, equipment selection, and regulatory compliance. This knowledge is crucial for ensuring the quality and safety of medications while optimizing manufacturing efficiency and cost-effectiveness.

### 2. Major stages of pharmaceutical plant design

The major steps in designing a pharmaceutical manufacturing plant are as follows:

i. Define the scope of the project. This includes determining the type of products to be manufactured, the production capacity required, and the regulatory requirements that must be met.
ii. Select a site for the plant. The site must be large enough to accommodate the plant and its future growth. It must also be located in an area with adequate infrastructure and utilities.
iii. Develop a conceptual design. This includes developing a layout for the plant and identifying the major equipment and systems that will be required.
iv. Develop a detailed design. This includes developing detailed drawings and specifications for all aspects of the plant, including the layout, equipment, and systems.
v. Obtain regulatory approvals. Once the detailed design is complete, it must be submitted to the regulatory authorities for approval.
vi. Construct the plant. The plant is constructed in accordance with the approved design.
vii. Install and commission the equipment. The equipment is installed and commissioned in accordance with the manufacturer's instructions.
viii. Validate the plant. The plant must be validated to ensure that it can meet all applicable regulatory requirements.
ix. Start production. Once the plant is validated, production can begin.

## 3. GMP Compliance

Good Manufacturing Practices (GMPs) are regulations and guidelines that guarantee pharmaceutical product quality and safety. They oversee every aspect, from raw material sourcing to product packaging and distribution. GMPs aim to reduce contamination, errors, and quality issues, ensuring consistent and compliant pharmaceutical production.

Good Manufacturing Practices (GMP) cover the "5 Ps" of pharmaceutical manufacturing:

- People:
- Premises:
- Processes:
- Products:
- Procedures:

GMP contains four parts, with nine chapters in the first part, and 21 annexes:

Part I - Basic Requirements for Medicinal Products: This part focuses on the basic requirements for medicinal products in pharmaceutical manufacturing. It covers essential aspects to ensure product safety, quality, and efficacy.

- Chapter 1 - Pharmaceutical Quality System (into operation since 31 January 2013)
- Chapter 2 – Personnel (into operation since 16 February 2014)
- **Chapter 3 - Premise and Equipment** (into operation since 1 March 2015)
- Chapter 4 – Documentation (January 2011)
- Chapter 5 - Production (into operation since 1 March 2015)
- Chapter 6 - Quality Control (into operation since 1 October 2014)
- Chapter 7 - Outsourced activities (into operation since 31 January 2013)

- Chapter 8 - Complaints and Product Recall (into operation since 1 March 2015)
- Chapter 9 - Self Inspection

Part II - Basic Requirements for Active Substances used as Starting Materials
Part III - GMP related documents
Part IV - GMP requirements for Advanced Therapy Medicinal Products
Annexes
Glossary

## 4. Fundamentals of Facility Design

### A. Diagrams

The following diagrams are needed in the design of a pharmaceutical manufacturing plant:

- Site plan: This diagram shows the overall layout of the plant on the site, including the location of the buildings, roads, parking lots, and other facilities.
- Floor plans: These diagrams show the layout of each floor of the plant, including the location of the rooms, equipment, and other features.
- Block flow diagrams (BFD): BFD identifies major process operations and their relationships to each other
- Process flow diagrams (PFDs): PFD's are graphical representations of the manufacturing process based on manufacturing instructions
- Piping and instrumentation diagrams (P&IDs): These diagrams show the location and arrangement of the piping and instrumentation in the plant.
- Electrical diagrams: These diagrams show the location and arrangement of the electrical equipment in the plant.
- HVAC diagrams: These diagrams show the layout of the heating, ventilation, and air conditioning (HVAC) system in the plant.

In addition to these general diagrams, there may be other diagrams that are needed depending on the specific design of the plant. For example, there may be diagrams for specific equipment or systems, such as the cleanroom system or the wastewater treatment system.

### B. Facility Layout and Zoning

Facility layout and zoning are two of the most important aspects of pharmaceutical manufacturing plant design. The layout of a plant should optimize the flow of materials and personnel, while the zoning plan should ensure that different types of activities are conducted in areas that are appropriately designed and controlled to prevent cross-contamination.

***Facility Layout***

The goal of facility layout is to create a plant that is efficient and effective. There are a number of factors to consider when designing a facility layout, including:

- The flow of materials: raw materials, packaging materials, intermediate products, finished products, and waste related to pharmaceutical operations should flow through the plant in a logical and efficient manner.
- The flow of personnel: Personnel should also be able to move through the plant efficiently.
- The use of space: The plant should be designed to maximize the use of space.

There are five main types of pharmaceutical plant layouts

i. Product layout: all of the equipment and machinery necessary to produce a particular product is arranged in a sequential order, similar to an assembly line
ii. Process layout: similar equipment and machinery are grouped together, regardless of the product being produced
iii. Group or cellular layout: equipment and machinery are grouped together based on their function

iv. Fixed-position layout: In a fixed-position layout, the product being produced is too large or heavy to be moved, so the equipment and machinery are arranged around it
v. Combined layout: two or more of the above layouts are combined to create a layout that is tailored to the specific needs of the plant

***Zoning***

Production Area:
- Design production area to follow a logical order and ensure suitable cleanliness levels
- Keep equipment and materials organized in a manner that minimizes confusion and contamination
- Design packaging premises for each medicinal product separately
- Proper ventilation and air control facilities
- Sufficient lighting in production areas
- Provide adequate space for in-process control

Storage Area:
- Store products in conditions that ensure good storage, cleanliness, and proper temperature
- Design receiving and dispatch bays for protection against weather
- Store highly active materials in safe and secure areas
- Provide areas for quarantined, rejected, recalled, or returned products
- Pay special attention to the safe and secure storage of printed packaging materials
- Segregate rejected or recalled materials

Quality Control Area:
- Laboratories should be separated from production areas
- Laboratories for the control of biologicals, microbiologicals and radioisotopes need to be separate from each other
- Design laboratories to suit the operations to be carried out in them
- Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.
- Provide adequate suitable storage space for samples and records

Ancillary Area:
- Provide separate rest and refreshment rooms
- Provide adequate facilities for changing clothes, washing, and toilet purposes
- Design maintenance workshops far away from production areas
- Keep parts and tools that are stored in production areas in a separate room or locker

**C. Finishing materials**

Materials and Finishes are selected for suitability within every select environment in the facility; this table summarizes the materials commonly used for finishing of a pharmaceutical production plant.

| | Walls | Floors | Ceiling |
|---|---|---|---|
| Production area | Epoxy coved | Epoxy or terrazzo coved | Epoxy coved |
| Storage area | painted | Sealed hardened concrete | Suspended ceiling |
| Quality control area | Epoxy coved | Epoxy or terrazzo coved | Suspended ceiling |

## 5. Equipment Selection and Integration

### A. Criteria for Pharmaceutical Equipment Selection

The selection of pharmaceutical equipment is a critical decision that can have a significant impact on the quality, safety, and efficiency of the manufacturing process. There are a number of factors to consider when selecting pharmaceutical equipment, including:

- Process requirements: The equipment must be able to perform the required manufacturing processes to the required standards.
- Capacity: The equipment must have the capacity to produce the required volume of products.
- Accuracy and precision: The equipment must be able to produce products with the required accuracy and precision.
- Reproducibility: The equipment must be able to produce products with a consistent level of quality.
- Reliability and maintainability: The equipment must be reliable and easy to maintain.
- Cleanability and sterilizability: The equipment must be easy to clean and sterilize to prevent contamination.
- Cost: The equipment must be affordable and cost-effective to operate.
- Compliance with regulations: The equipment must comply with all applicable regulations, such as Good Manufacturing Practices (GMPs).

When selecting pharmaceutical equipment, it is important to consider all of the relevant factors and to choose equipment that is best suited for the specific needs of the manufacturing process.
Here are some additional tips for selecting pharmaceutical equipment:

- Get input from stakeholders:
- Compare different suppliers and models:
- Read reviews:
- Visit suppliers
- Get a warranty:

**Example:** A pharmaceutical company is developing a new drug product that is a liquid injectable solution. The company needs to select a mixing tank for the drug product. The following factors are considered when selecting the mixing tank:
The company researches different mixing tanks and compares the features and specifications of each tank. The company also gets quotes from multiple suppliers.
The company selects a mixing tank that has the following parameters:

- Volume: 1000 liters
- Mixing speed: 100-500 RPM
- Mixing time: 15-30 minutes
- Temperature control: 20-30 degrees Celsius
- Accuracy: +/- 1%
- Reproducibility: < 2% RSD
- Cleanability and sterilizability: The mixing tank is made of 316L stainless steel and is designed for easy cleaning and sterilization.
- Compliance: The mixing tank complies with all applicable GMPs regulations.

### B. Integration of Equipment into Manufacturing Processes

Equipment integration in manufacturing is the process of connecting and synchronizing machines and devices to function as a cohesive system, often achieved through automation, robotics, and AI.
The benefits of this integration include

- increased efficiency,

- reduced costs,
- improved quality,
- enhanced flexibility.

Common methods for equipment integration include

- programmable logic controllers (PLCs), which control various devices,
- manufacturing execution systems (MES) that manage processes, track work orders, and optimize tasks.

AI plays a growing role by analyzing equipment data to enhance efficiency and quality.

## 6. Sustainability in Pharmaceutical Manufacturing

Green pharmaceutical manufacturing practices are those that aim to reduce the environmental impact of the pharmaceutical manufacturing process. This can be achieved by using renewable energy sources, reducing waste and emissions, and using sustainable materials.

Some examples of green pharmaceutical manufacturing practices include:

- Using renewable energy sources: Pharmaceutical companies can use renewable energy sources such as solar and wind power to power their manufacturing facilities. This can help to reduce greenhouse gas emissions and other pollutants.
- Reducing waste and emissions: Pharmaceutical companies can reduce waste and emissions by using more efficient manufacturing processes and by recycling and composting materials.
- Using sustainable materials: Pharmaceutical companies can use sustainable materials, such as recycled plastics and bio-based materials, in their packaging and manufacturing processes.

Here are some specific examples of how pharmaceutical companies are implementing green manufacturing practices:

- Pfizer has committed to using 100% renewable energy to power its operations by 2030.
- Eli Lilly has reduced its greenhouse gas emissions by 30% since 2010.
- GSK has reduced its water consumption by over 30% since 2010.
- Merck has diverted 90% of its waste from landfills.

## 7. Future Trends and Innovations

Emerging technologies are rapidly transforming the pharmaceutical manufacturing industry. These technologies are helping to improve the efficiency, quality, and sustainability of pharmaceutical manufacturing.

Here are some examples of emerging technologies in pharmaceutical manufacturing:

- Continuous manufacturing: Continuous manufacturing is a process in which raw materials are fed into a production line and products are continuously produced. Continuous manufacturing is more efficient than traditional batch manufacturing, and it can also help to improve product quality.
- 3D printing: 3D printing is being used to create custom medical devices, such as implants and prosthetics. 3D printing can also be used to create prototypes of new drugs and to manufacture small batches of drugs for clinical trials.
- Artificial intelligence (AI): AI is being used to improve the efficiency and quality of pharmaceutical manufacturing. For example, AI can be used to predict demand for products, optimize production schedules, and identify potential quality problems.
- Blockchain: Blockchain is a distributed ledger technology that can be used to track the movement of goods through the supply chain. This can help to ensure the authenticity and quality of pharmaceutical products.

## 8. Requirements for obtaining approval for the opening of a pharmaceutical manufacturing plant in Algeria

The application for approval to open a pharmaceutical manufacturing establishment requires the following documents:

i. A completed, dated, sealed, and signed application form for approval to open the pharmaceutical manufacturing establishment.
ii. Copies of the establishment's bylaws, specifying the pharmaceutical activity mentioned in the application.
iii. A copy of the business registry, indicating the activity code related to the application's purpose.
iv. Documentation for the technical director pharmacist.
v. Documentation for the assistant pharmacist.
vi. Proof of ownership or lease agreement with the current address of the manufacturing site in question.
vii. A layout plan of the entire pharmaceutical establishment at a 1/100 scale, detailing the layout of the premises.
viii. A plan specifying the placement of major equipment.
ix. A plan detailing air and water treatment systems.
x. Plans detailing the flow of personnel, raw materials, packaging materials, intermediate products, finished products, and waste related to pharmaceutical operations.
xi. Technical support for technology transfer agreements, if applicable.
xii. Subcontracting contracts, if applicable.
xiii. A list of pharmaceutical operations subject to outsourced activities and the conditions of execution, in the case of outsourcing.
xiv. Detailed configuration of the pharmaceutical establishment, including all locations for the production and storage of gases in fixed tanks or bottles, for medical gases.
xv. The designation of radiopharmaceutical drugs, their risk management approach, and radioprotection justification, along with proof of the technical director's competence in radioprotection and authorization from the atomic energy commission, for radiopharmaceutical drugs.
xvi. Copy(ies) of the prior approval for construction, in the case of constructing the pharmaceutical establishment.
xvii. The operating permit for a classified establishment issued by the competent environmental ministry services.
xviii. Compliance with safety standards established by civil defense services.
xix. Documentation regarding facility security conditions.
xx. Documentation regarding the security of pharmaceutical documentation.
xxi. Quality risk management procedure.
xxii. The projected organizational chart reflecting the pharmaceutical establishment's organization, including key responsibility positions, staff count, and qualifications.
xxiii. Proof of payment for the pharmaceutical establishment's expertise request fee.

The application should be submitted to the Department of Production, Industrial Development, Export Promotion, and Research in both electronic and paper formats.

## 9. Conclusion

In conclusion, the lesson on pharmaceutical plant design underscores the critical role of meticulous planning and compliance with regulations in ensuring the production of safe, effective and high-quality pharmaceuticals. It emphasizes the importance of facility layout and zoning, equipment selection, and integration to meet industry standards and safeguard patient well-being.

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