CHAPTER - 6

PHARMACEUTICAL INDUSTRY AND BASIC CONCEPTS

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6.1 INTRODUCTION

Pharmaceutical manufacturing

- Pharmaceutical manufacturing is the process of **industrial-scale synthesis** of pharmaceutical drugs as part of the pharmaceutical industry.
- The process of drug manufacturing can be broken down into a **series of unit operations**, such as milling, granulation, coating, tablet pressing, and others.

6.2 PHARMACEUTICAL MANUFACTURING PLANT

- **Pharmaceutical Manufacturing Plant** is the place where manufacturing of the pharmaceutical products takes place.
- The pharmaceutical manufacturing plant is responsible for producing pharmaceutical products in large scale that follows testing for quality and purity of the product.
- It also **includes** batch integrity testing, quality assurance, calibration, validation and facility maintenance.

6.2.1 Structure of Pharmaceutical Manufacturing Plant

- Pharmaceutical manufacturing plants are typically designed with a **cleanroom environment** that prevents contamination of the products.
- The facility is **divided into different areas** such as production areas, packaging areas, quality control areas, and storage areas.
- The **basic structure of a pharmaceutical manufacturing plant** is designed to meet the requirements of Good Manufacturing Practices (GMP) and to ensure that the products produced are safe and effective for human use.
- The basic structure of pharmaceutical plant in shown is fig 6.1

Fig 6.1: Basic Structure of Pharmaceutical Plant

- Pharmaceutical Company Hierarchy

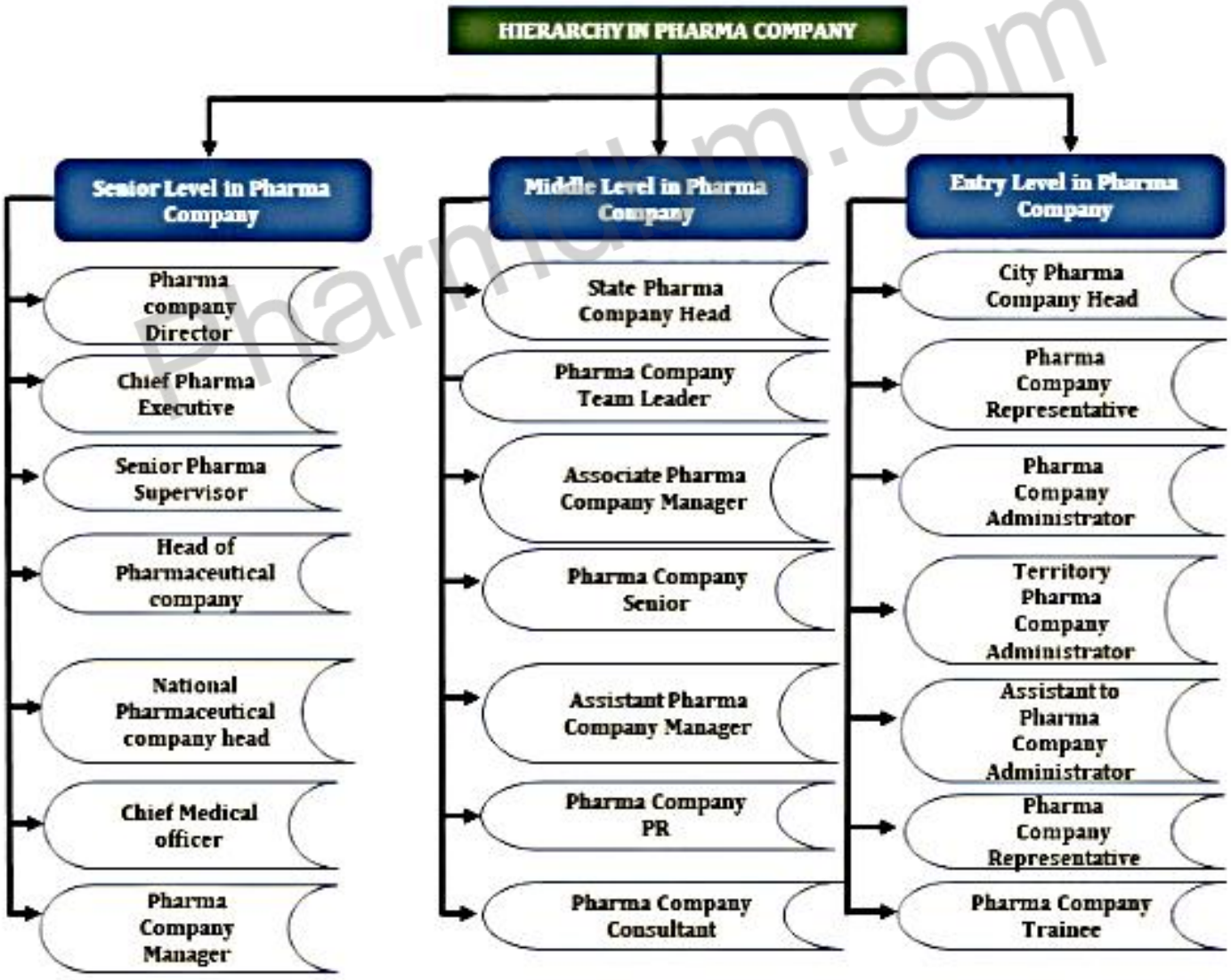

Fig 6.2: Pharmaceutical Plant Hierarchy

1. **Senior level in pharma company**
   - This level in pharma company is responsible for overall management and operation of the organization and also to **maintain the financial issue** in the industry.
2. **Middle level in Pharma company**
   - The personnel in this level work under the guidance of senior executives.
   - They also **supervise the entry level people** about the organization and make sure that the operations continue smoothly.
3. **Entry level in Pharma company**
   - The personnel in this level are responsible to carry day to day task and functions.
   - These are not much experienced people.

6.2.2 Layout of Pharmaceutical Manufacturing Plant

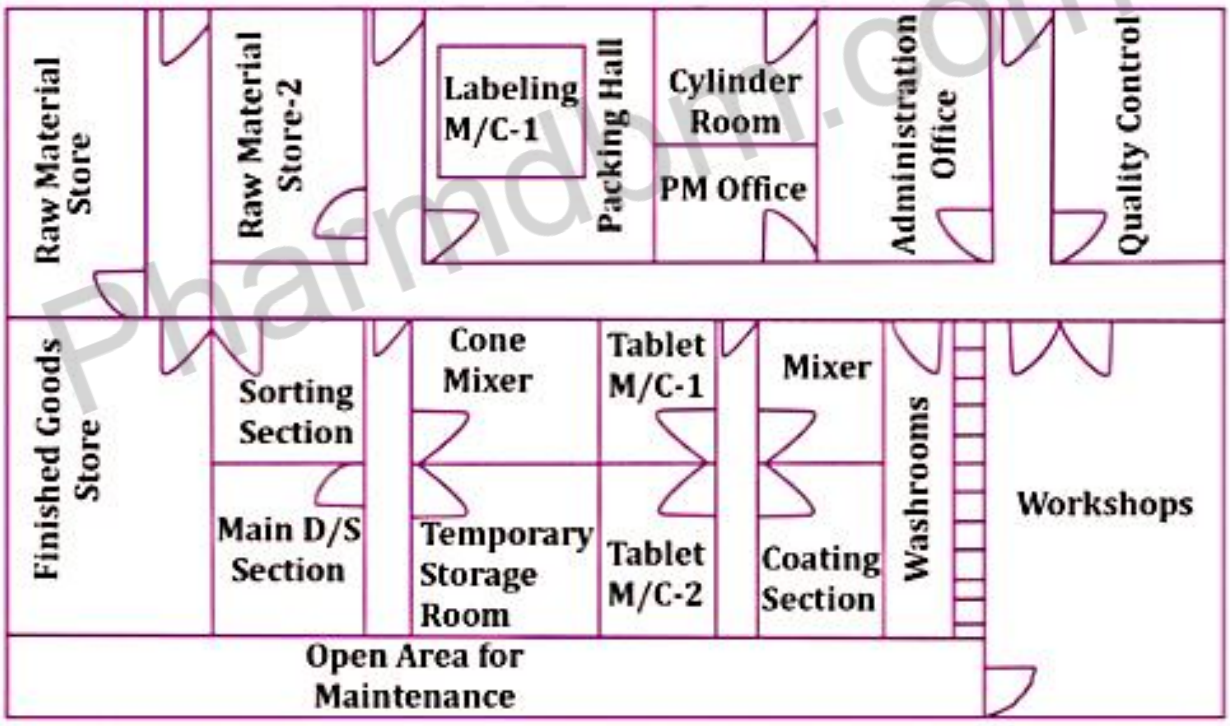

Fig 6.3: Layout of Pharmaceutical Manufacturing Plant

The manufacturing plant consist of the following

❖ **Raw material storage:** This area is used for the storage of raw materials that are used in the manufacturing process.

- **Formulation area:** This area is responsible for formulating the active pharmaceutical ingredients (APIs) into the final product. It may include areas such as granulation, compression, coating, and packaging.
- **Quality control area:** This area is responsible for ensuring that the products meet the quality standards. It may include areas such as chemical analysis, microbiology, and stability testing.
- **Packaging area:** This area is responsible for packaging the final product into different forms such as tablets, capsules, and injections.
- **Utility areas:** These areas are responsible for providing the necessary utilities for the manufacturing process, such as water, air, and electricity.

➢ **Characterstics of Pharmaceutical plant layout**

- It should provide adequate space for the machines, materials, storage, and other services needed for the production of pharmaceutical products.
- It should **facilitate smooth and continuous flow** of materials from one area to another without any delays or interruptions.
- It **should incorporate adequate** health, safety, and security features such as fire extinguishers, emergency exits, first aid boxes, etc.

➢ **Advantages of Pharmaceutical plant layout**

- It makes the **best use of the available floor space** for production operations.
- It **incorporates adequate** health, safety, and security features such as fire extinguishers, emergency exits, first aid boxes, etc.
- It **allows effective** supervision, coordination, and control of the production processes by the staff.

6.2.3 Sections Of Pharmaceutical Manufacturing Plant

The sections of a pharmaceutical manufacturing plant are as follows:

1. **Security office**: The **Security Office** in the pharmaceutical industry is a crucial component responsible for safeguarding personnel, assets, information, and the overall security of the facility. For this pharmaceutical plant employs 'Safety Officers' as specified in Factory Act.

2. **Vehicle Parking: Vehicle parking in the pharmaceutical industry** is a significant aspect of facility management, ensuring the organized and secure parking of vehicles for employees, visitors, and service personnel.

3. **Power Backup:** Power backup is a critical aspect in the pharmaceutical industry, where the reliability of electricity supply is essential for various processes and operations.
4. **Administrative Block:** **"Administrative Block"** typically refers to an area or section within a pharmaceutical facility that is dedicated to administrative functions and activities. It consists of finance, pantry and crockery storage.

5. **Production Block:** In the pharmaceutical industry, a **"Production Block" refers to** a specific area or building within a pharmaceutical facility dedicated to the manufacturing and production of pharmaceutical products. This block typically houses various units, equipment, and facilities required for the production of pharmaceutical drugs.

6. **Utility service Department:** The Utility Services Department in the pharmaceutical industry **plays a pivotal role** in ensuring the availability, reliability, and efficient operation of various utility services required for pharmaceutical manufacturing processes.

7. **Scrap Yard:** The concept of a scrap yard is more related to facilities that **handle the recycling and processing of various materials**, often found in end-of-life vehicles, appliances, and other consumer goods. In the pharmaceutical industry, there are specific processes and practices related to waste management, recycling, and disposal of materials.

6.2.4 Activities Of Pharmaceutical Manufacturing Plant

The **proper activities of Pharmaceutical Manufacturing Plant** are necessary to provide the right medicine to the right patient at right time. These includes the following:

1. **Raw Material Procurement:** Raw materials are procured from approved vendors and are subjected to quality testing before use. It involves researching, selecting, ordering, and paying for raw materials required for a business.
2. **Production:** The production process is carried out in accordance with standard operating procedures (SOPs) to ensure consistency and quality.

3. **Quality Assurance:** Quality assurance is a process that ensures products, services, or processes meet or exceed established quality standards.

4. **Quality Control:** Quality control activities are carried out throughout the manufacturing process to ensure that the products meet the quality standards.

5. **Packaging:** The final product is packaged into different forms such as tablets, capsules, and injections.

6. **Storage:** The raw materials, intermediates, and finished products are stored in a controlled environment to ensure their stability.

7. **Cleaning and Maintenance:** Cleaning and maintenance are essential activities in the pharmaceutical industry, as they ensure the quality, safety, and efficacy of the products and processes. Cleaning and maintenance involve the removal of visible and microscopic contaminants from equipment, utensils, surfaces, and personnel by using appropriate methods, materials, and schedules.

8. **Pharmaceutical Distribution:** Pharmaceutical distribution is the process of delivering pharmaceutical products from the manufacturers to the end users, such as pharmacies, hospitals, clinics, or consumers.

9. **Patient Assistance Programs:** Patient assistance programs (PAPs) are initiatives that pharmaceutical companies carry out to manage and support patients throughout their treatment journey.

6.3 QUALITY CONTROL (QC)

- Quality Control (QC) is a **procedure or set of procedures** intended to ensure that a manufactured product adheres to a defined set of quality criteria or meet the requirement of the customer.

- Quality control is used to **verify that pre-determined quality standards** are being met through quality inspections and reviews which detect poor quality, and identify, non-conformance with those standards.

6.3.1 Objectives of Quality control

The objective of the quality control is-

- To decide about the **standard of quality of a product** that is easily acceptable to the customer and at the same time this standard should be economical to maintain.

- To take various steps to solve any kind of deviations in the quality of the product during manufacturing.
- To increase the operational efficiency of the organization by improving quality of raw material, equipments etc.

6.3.2 Functions of Quality control department

The function of the quality control is-

- To suggest method and ways to prevent the manufacturing difficulties.
- To find out the points where the control is breaking down and to investigate the causes of it.

6.3.3 Concepts of Quality control

- Quality control involves the **installation of system** and **establishment of quality standard** to ensure and maintain the standard of the product.

➢ Steps in Quality control

1. **Establishing quality standard:** Quality standards are maintained in terms of size, design, durability, appearance etc. on the basis of customer requirement.
2. **Selecting the manufacturing process:** The selection of the step determines the specific output of the required specifications.
3. **Development of measurement techniques:** This step is required to check that whether the production conforms to the set specification or not.
4. **Monitoring product quality:** It helps in periodically checking of end product to check the alteration in the set quality standard and find the location of such alteration.

➢ Techniques of Quality control

1.Inspection

It involves periodic checking and measuring before, during and after the production process. It can be done in two ways:

a. Centralized inspection: Centralized inspection in the **pharmaceutical industry refers** to the practice of conducting inspections and assessments of pharmaceutical manufacturing facilities, processes, and products by a central regulatory authority or organization.

- The aim is to **ensure compliance with regulatory standards**, guidelines, and good manufacturing practices (GMP).

b. Floor inspection: Floor inspection in the pharmaceutical industry refers to the examination and assessment of the manufacturing floor or production area where pharmaceutical products are processed and manufactured.

Advantages of Inspection

- Inspection plays a crucial role in the pharmaceutical industry, contributing to the overall quality and compliance of pharmaceutical products.
- Inspection helps guarantee the safety of pharmaceutical products for consumers.

2. Statistical Quality control

Statistical quality control (SQC) is the application of statistical methods for the purpose of determining if a given component of production (input) is within acceptable statistical limits and if there is some result of production (output) that may be shown to be statistically acceptable to required specifications.

It is of two types

a. Process control: Process control in the pharmaceutical industry refers to the systematic and ongoing efforts to monitor, regulate, and optimize the various stages of pharmaceutical manufacturing to ensure the production of high-quality and safe medicinal products.

b. Acceptance sampling: Acceptance sampling in the pharmaceutical industry is a quality control method used to assess and make decisions about the quality of a batch or lot of products based on the inspection of a sample.

Advantages of Statistical Quality Control

- Statistical Quality Control relies on data analysis to make informed decisions about the quality of processes and products..
- Implementing Statistical Quality Control can lead to cost savings by

reducing the need for extensive testing and inspection.

6.4 QUALITY ASSURANCE (QA)

- **According to WHO**, quality assurance is a wide- ranging concept covering all matters that individually or collectively influence the quality of a product.
- With regard to pharmaceuticals, **Quality Assurance can be divided into major areas:** development, quality control, production, distribution, and inspection

6.4.1 Functions of Quality Assurance

- Stability testing and evaluation of shelf life of products
- Warehousing of finished products (Drug Products)
- Complaints and product recalls

6.4.2 Concept of Quality Assurance

- QA process has a defined cycle called as PDCA cycle.
- The phases of this cycle are Plan, Do, Check and Act.
- This process ensure that the process followed in the drug's development and manufacturing are evaluated and improved periodically

(a) Plan: It deals with **identification of the objectives** leading to a high-quality outcome, then determines and plans the processes that are required to deliver on those objectives.

(b) Do: In this process necessary changes are made in the developed process, product and services.

(c) Check: In this stage, **the developed product** and process are being checked either it meets the standard requirement or not.

(d) Act: In this phase, necessary action is taken to ensure the improvements in the product, process and service.

6.4.3 Quality Assurance Method

1. **Failure Testing:** Failure testing, also known as **reliability testing** or **stress testing**, is a quality assurance practice that involves subjecting a product or system to extreme conditions or stress levels to assessits

its performance under adverse circumstances. performance under adverse circumstances.

2. Statistical Process Control: Statistical Process Control (SPC) is a **quality assurance methodology** that uses statistical methods to monitor and control processes to ensure they operate consistently and produce products that meet predefined quality standards.

3. Total Quality Management: Total Quality Management (TQM) is a **comprehensive management philosophy** and approach that focuses on continuously improving the quality of products and processes throughout an organization.

6.4.4 Quality Management and Certification

A quality management system is a management technique used to communicate to employees what is required to **produce the desired quality of products** and services and to influence employee actions to complete tasks according to the quality specifications.

- **Purpose of Quality Management System**

1. Establishes a vision for the employees.
2. Builds motivation within the company.

6.4.5 Total Quality Management

- Total Quality Management is a management approach in which quality is emphasized in every aspect of the **business** and **organization.**
- **Its goals are** aimed at long-term development of quality products and services.

Table 6.1: Total Quality Management

TERMS	DESCRIPTION
TOTAL	Made up of the whole
QUALITY	Degree of excellence a product or service provides
MANAGEMENT	Act, art, or manner of planning, controlling and Directing. Therefore, TQM is the art of managing the whole to achieve excellence.

➢ Elements of TQM

1. Ethics

- **Ethics** is the discipline concerned with good and bad in any situation. It is a two-faceted subject represented by organizational and individual ethics.

2. Integrity

- **Integrity implies** honesty, morals, values, fairness, and adherence to the facts and sincerity. The characteristic is what customers expect and deserve to receive.

3. Trust

- Trust is a **by-product of integrity and ethical conduct**. Without trust, the framework of TQM cannot be built.
- It allows empowerment that encourages pride ownership and it encourages commitment.

5. Training

- Training the employees **require interpersonal skills**, the ability to function within teams, problem solving, decision making, job management performance analysis and improvement, business economics and technical skills.

5. Teamwork

- To become successful in business, teamwork is also a **key element of TQM**. With the use of teams, the business will receive quicker and better solutions to problems.

6. Leadership

- Leadership in TQM requires the manager to provide an **inspiring vision, make strategic directions** that are understood by all and to instill values that guide subordinates.

7. Communication

- It binds everything together.
- It acts as **a vital link** between all elements of TQM.

➢ **TQM Philosophy**

- TQM Focuses on identifying quality problem root causes.
- It involves the technical as well as people.

It consists of the following

1. **Focus on Customer:** It identifies and meet customer needs. It always stays tuned to changing needs, e.g. fashion styles
2. **Continuous Improvement:** It means continuous learning and problem solving, incremental improvement that occurs on a regular basis. e.g. Kaizen, 6 sigma's
3. **Employee Empowerment:** It is necessary to empower all employees for external and internal customers and involved them in quality initiatives.
4. **Team Approach:** Teams formed around processes of 8 to 10 people. They should meet weekly to analyze and solve problems.

6.4.6 Quality Audit

- Quality auditing is the **systematic**, **independent**, and **documented review** and evaluation of an organization's quality management system (QMS) to determine whether quality activities and results comply with a strategic arrangement that is effectively implemented and appropriate to achieve the objectives.

6.5 cGMP (CURRENT GOOD MANUFACTURING PRACTICE)

- cGMP refers to the **Current Good Manufacturing Practice regulations** enforced by the FDA. cGMP provides for systems that assure proper design, monitoring, and control of manufacturing processes and facilities.

- It's not only required to meet current Good Manufacturing Practices (cGMP) standards and regulatory requirements, but it's also what sets the most successful CDMOs and preventative.

6.5.1 Objectives

- Ensure that products are consistently manufactured and controlled to the specified quality.
- Concerned with all aspects of production and quality control. In the manufacture of cosmetic products, overall control and monitoring.

6.5.2 Testing

- Final testing of the product cannot ensure the **Quality efficiency and safety**.
- Final testing may always not detect errors.

6.5.3 GMP (Goods Manufacturing Practices)

- Good Manufacturing Practices is the aspect of quality assurance that **ensures that medicinal products** are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the product specification.

Principles of GMP:

- ✓ **Principle 1:** Defining and creating standard operating procedures (SOPs).
- ✓ **Principle 2:** This principle focuses on effectively following documents pertaining to work procedures.
- ✓ **Principle 3:** This principle works to examine problems or complaints regarding a product. It mandates documentation of work after completion, which also enables regulatory compliance.
- ✓ **Principle 4:** Validation is an essential step to progress ahead in the process. This principle involves creating documentary evidence that the techniques, processes, and production maintain the expected level of compliance during all the stages.

- ✓ **Principle 5:** Properly defining and designing equipment and construction facilities.
- ✓ **Principle 6:** Maintaining facilities and equipment.
- ✓ **Principle 7:** Each employee impacting the product quality should be trained. Basic GMP theory and practice, as well as role-related training, should be included in the training.
- ✓ **Principle 8:** Preventing contamination through cleanliness.
- ✓ **Principle 9:** This principle entails incorporating quality directly into all production phases by putting clearly defined controls in place and preserving accurate, timely records.
- ✓ **Principle 10:** It undertakes periodic audits to evaluate the efficacy of GMP compliance. Therefore, audits must be performed regularly to ensure that nothing is overlooked.

➢ **Components of GMP**

- GMP mainly consist of five components that is termed as **5P's** as given in fig 6.4

Fig 6.4: Components of GMP

6.6 INTRODUCTION TO CONCEPT OF CALIBRATION

- Calibration is the **standardization process** of an instrument based on an existing standard. It helps make the instrument set work in a required range while maintaining accuracy.
- Calibration must be performed according to approved **written procedures and the calibration records** must be maintained for a certain period of time.

6.6.1 Advantages

Quality measuring system will help organization in the following ways:

- The error of an instrument is taken into account while using it and hence correct measurements are recorded and reported.
- Wherever possible, one can adjust or repair the instrument to minimize the error to the best extent.

6.6.2 Objectives

- **Calibration** brings out the nature and magnitude of error (if any) of testing measuring instruments.

6.6.3 Instrument Calibration

- All the testing and measuring instruments calibrated at a reputed institute or organization like RRSL, NC QC, etc. which has a **set of precise reference standard, instruments**.
- It should provide good, most accurate and reliable calibration services with due traceability. Some of them are built to provide following facilities:

6.7 VALIDATION

- Validation is an important part of **Analytical as well as Bio-Analytical Method.** The procedure involved in checking data or programs for correctness, compliance with standards and conformance with the requirement specifications.
- It is establishing documented evidence, which provides high degree assurance.

6.7.1 Importance of validation

The importance of validation is

- During the process the knowledge of process increases.
- It assures the repeatability of the process.

- It assures that the **product is continuously producing** according to the marketing authorization.

6.7.2 Method of validation

1. Identification
2. Quantitative tests for content or impurities
3. Limit tests for control of impurities

6.7.3 Guidelines of validation

- **ICH Q2A:** Text on validation of analytical procedures Definitions and Terminology (March 1995).
- **ICH Q2B:** Validation of analytical procedure: Methodology (June 1997).
- **FDA:** (Draft) Guidance for industry Analytical procedure and methods validation.

6.7.4 Types of validation

There are various types of Validation as given below:

1. **Equipment Validation:** Equipment validation is established documented set up that proves any equipment works correctly and leads to accepted and accurate results (predetermined result).

✓ **Design Qualification**

- It is a documented verification of design of the equipment and manufacturing facilities.
- The **main purpose of Design qualification** is to make sure that all the requirements for the systems should clearly defined at the start.

✓ **Installation Qualification**

- Installation qualification confirms that the **précised equipment** has been received and installed as per target and agreement in exact design.

✓ **Operational Qualification**

- Operational qualification **ensures that installed equipment/instrument** will function perfectly according to its operation specification in the mention environmental conditions.
- It also checks that the **equipment function perfectly to meet pre-assigned performance criteria** and ensure how the testing results are recorded.

2. **Method Validation:** Method Validation establishes documented evidence that the procedure adopted for a test is fit for the intended purpose in terms of quality, reliability and consistency of results.

   ✓ **New Method Development:** It established method used in a different laboratory, analysis of instrumentation. It demonstrates the equivalence between new and established method.

   ✓ **Objectives:** The objectives of this exercise are to consider appropriate validation characteristics to provide a sound overall knowledge of the capabilities of the analytical method.

   ✓ **Scope:** The scope covers analytical performance parameters.

3. **Facilities Validation**

   Facility validation **deals with establishing documented evidence** that provides a high degree of assurance that the manufacturing processes, including buildings, systems, and equipment consistently produce the desired results according to predetermined specifications.

4. **Cleaning Validation**

   Cleaning validation is a **procedure of establishing evidence** that cleaning processes for manufacturing equipment prevents product contamination.

5. **Computer system Validation**

   Validation of computerized systems is a documented process to ensure that a computerized system does exactly what it was designed to do in a consistent and reproducible way (suitability to use), **ensuring the integrity and security of data processing.**

6. Process Validation

It is establishing documented evidence, which provides **high degree assurance**, such as manufacturing of pharmaceutical dosage forms will consistently produce a product meeting its predetermined specification.

✓ Stages of Process Validation

The Process Validation has been divided into 3 different stages as given in fig 6.5

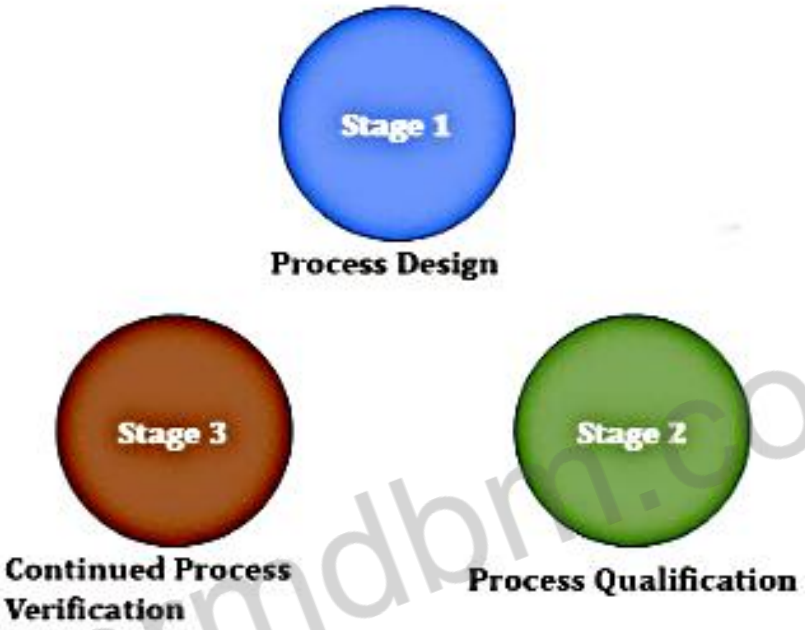

Fig 6.5: Stages of Process Validation

Stage 1: Process Design - This is the **research and development phase** and involves defining a process for manufacturing the product.

Stage 2: Process Qualification - This **stage evaluates/qualifies the process designed** earlier to ensure it can reproduce consistent and reliable levels of quality. It involves collecting and evaluating data on all aspects and stages of the manufacturing process.

Stage 3: Continued Process Verification - Continued Process Verification **involves ongoing validation** during production of the commercial product to ensure the process designed and qualified in the previous stages continues to deliver consistent quality.

✓ **Types of Process validation**

i. **Prospective Validation:** Validation conducted prior to the distribution of either a new product or product made under a revised manufacturing process.

ii. **Retrospective Validation:** Validation of a process for a product already in distribution based upon accumulated production and control data, or evidence, e.g., stability studies.

iii. **Concurrent Validation:** In process monitoring of critical processing steps and end product testing of current production.

6.7.5 Strategies of Validation

This optimization consists of defining and performing the **minimum number of verification and validation actions** but detecting the maximum number of errors/faults/defects and achieving the maximum level of confidence in the system.

These includes the following:

1. **Validation master plan:** A Validation Master Plan, also referred to as "VMP", outlines the principles involved in the qualification of a facility, defining the areas and systems to be validated, and provides a written program for achieving and maintaining a qualified facility.
2. **Validation report:** The validation report summarizes all validation results, gives recommendations for fixing errors and/or improving the overall quality of the speech corpus and gives an executive summary.
3. **Expert Evaluation:** Expert evaluation is a crucial step in the validation process of a study, particularly in fields such as research, scientific experiments, or industrial processes.

6.7.6 Department and Authority for Validation

There are different department and authority for validation

as given in Table 6.2.

Table 6.2: Department and authority for validation

DEPARTMENT/DESIGNATION	RESPONSIBILTY
Manager Production	Responsible for manufacturing of batches and review of protocol and report.
Manager QC	Responsible for analysis of sample collected
Executive QC	Responsible for samples collection and submission to QC
Manager Maintenance	Providing utilities and engineering support
Executive Production	Responsible for preparation of protocol and manufacturing of validation batches

6.7.7 Revalidation

- **Analytical methods require validation** whenever the conditions for which the methods have been developed change. **Revalidation of the analytical method** is required in the following circumstances:
- An existing method is modified to meet special requirements.
- Changes to the formulation composition of an agricultural and veterinary chemical product.
- Revalidation should be performed to **ensure that the analytical method** maintains its characteristics.
- The degree of revalidation depends on the nature of the change to a new dosage strength in a product.