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Square Pharmaceuticals PLC. Bangladesh: In-Plant Training Report

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Square Pharmaceuticals PLC. Bangladesh

In-Plant Training Report

Submitted to

Mehdi Bin Samad

Lecturer

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Submitted by:

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Course Title: Pharmaceutical Industrial Training

Course Code: PHA407

Section: 09

Submission Date: May 19, 2026

Semester: Spring 2025

Department of Pharmacy

Independent University, Bangladesh

Declaration

It is hereby declared that,

The internship Report Submitted by my original work while completing the degree at Independent University, Bangladesh. The report does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing. The report does not contain material that has been accepted or submitted, for any other degree or diploma at a university or other institution.

I have acknowledged all of the main sources of help.

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Sincerely

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SQUARE PHARMACEUTICALS PLC.

CERTIFICATE

PRESENTED TO

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DEPARTMENT OF PHARMACY
SCHOOL OF PHARMACY AND PUBLIC HEALTH
INDEPENDENT UNIVERSITY, BANGLADESH
HAS SUCCESSFULLY COMPLETED THE TRAINING ON

INDUSTRIAL TRAINING

HELD AT SQUARE PHARMACEUTICALS PLC., DHAKA UNIT, KALIAKOIR, GAZIPUR
FROM 22ND DECEMBER 2025 TO 06TH JANUARY 2026

PRESENTED THIS ON: 11TH JANUARY 2026

AGM, Administration, HRD

Executive Director, Technical Operations

Acknowledgement

At the beginning of this report, we gratefully acknowledge the Almighty Allah, for granting us the opportunity to complete our industrial training and bring this report to successful completion.

We would like to express our sincere gratitude to Square Pharmaceuticals PLC. for providing us the opportunity to complete our in-plant training at their esteemed organization and for organizing a well-structured and informative program. Throughout our industrial training, we gained practical exposure to various departments, including Human Resources (HR), Research and Development (R&D), Production Planning & scheduling (PPS), Material Management and Inventory Control (MMIC), Warehouse, Production, and Quality Assurance. The professionalism, commitment, and dedication displayed by every member of the organization were truly inspiring. We sincerely appreciate the guidance and cooperation of the officers and personnel of various departments.

We would like to express our heartfelt thanks to our respected teachers and departmental authorities for their continuous guidance, supervision, and encouragement throughout the training period. Their academic support played a significant role in making this training meaningful and successfully.

Finally, we acknowledge the cooperation and teamwork of our fellow trainees, which contributed to the smooth completion of the training. This in-plant training has been a valuable learning experience and will be beneficial for our future professional careers.

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Md. Rafiqul Islam, Executive, HR

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Mahfuz Enam, Senior Executive, Production

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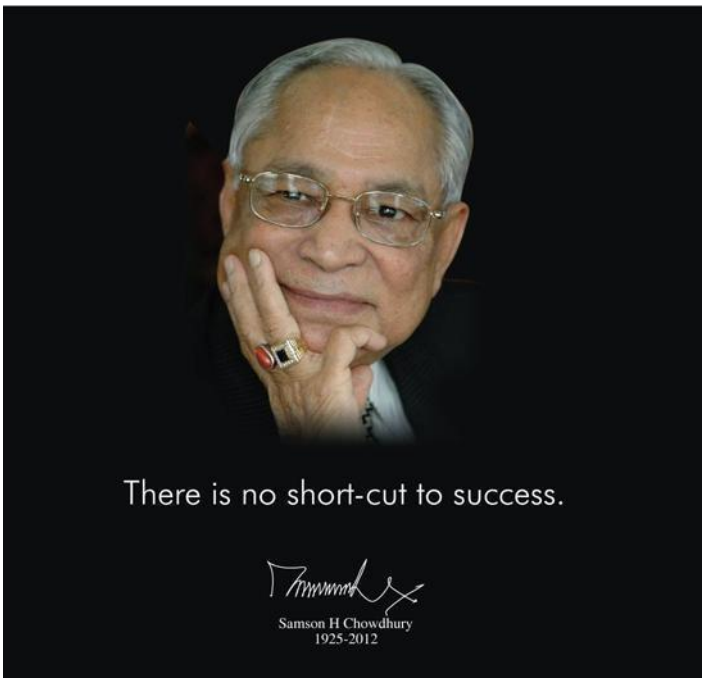
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Shopon Kumar, Senior Executive, QA

MD. Sohanur Rahman, Senior Executive, QA

Sabbir Ahmed, Senior Executive, QA



"The relentless pursuit for excellence; the urge to never stand still, to never slow down, and to never stop thinking."

Samson H Chowdhury, Founder Chairman, SQUARE (1925-2012)

Samson H. Chowdhury was one of the most successful industrialists and business magnates of Bangladesh's history. He was the chairman of Square Pharmaceuticals. He was a paramount personality of his time in ingenious drive, unprecedented ideas, business management, and human resource development. With his innovation, leadership, and perseverance, he built a business empire from the ground up. He started his business with a small village pharmacy in Pabna in 1952 and, over the span of six decades, built the Square Group, one of the largest and most diversified conglomerates in the country.

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1. Abbreviations

API – Active Pharmaceutical Ingredient
ARD – Analytical Research & Development
BMR – Batch Manufacturing Record
BP – British pharmacopoeia
BPR – Batch Packaging Record
CHQ – Corporate Headquarters
COA – Certificate of Analysis
CPP – Critical Process Parameter
CQA – Critical Quality Attribute
cGMP – Current Good Manufacturing Practice
DC – Direct Compression
DGDA – Directorate General of Drug Administration
DT – Disintegration Time
EOP – Equipment Operating Procedure
FDA – Food and Drug Administration
FBD – Fluidized Bed Dryer
FD – Formulation Development
GC – Gas Chromatography
GLP – Good Laboratory Practice
GMP – Good Manufacturing Practice
GPB – General Production Building
HPLC – High Performance Liquid Chromatography
HRD – Human Resource Department
HRIS – Human Resource Information System
HVAC – Heating, Ventilation and Air Conditioning
IMD – International Marketing Department
IPQC – In-Process Quality Control
IPC – In-Process Control
KPI – Key Performance Indicator
KRA – Key Result Area
LC – Letter of Credit
LOD – Loss on Drying
LOD/LOQ – Limit of Detection / Limit of Quantification
MDP – Management Development Program
MMIC – Material Management and Inventory Control
MOA – Method of Analysis
MOQ – Minimum Order Quantity
MSDS – Material Safety Data Sheet
PMD – Product Management Department
PMS – Packaging Material Specification
PMSA – Post-Marketing Surveillance Activity
PO – Purchase Order
PPS – Production Planning & Scheduling
PR – Purchase Requisition
PV – Process Validation
QA – Quality Assurance
QC – Quality Control
QIR – Quality Incident Report
QO – Quality Operation
R&D – Research and Development
RLD – Reference Listed Drug
RM – Raw Material
SCM – Supply Chain Management
SOP – Standard Operating Procedure
TDS – Technical Data Sheet
SAP – Systems, Applications and Products in Data Processing

2. Objectives of In-Plant Training

Over the last four years, we have studied several courses, both theoretical and practical, as part of our curriculum. But of course, the scope of learning about the pharmaceutical industry is limited in university settings. So, for the purpose of watching and learning about how the pharmaceutical industry functions, we took up the opportunity here, and our objectives for this training are as follows:

- To understand how our theoretical and practical knowledge relate to each other
- To know how each department works together
- To understand the importance of SOP and GMP
- To learn about the future opportunities within the industry
- To learn about documentation and its importance in the industry
- To learn how HRD coordinates with other departments
- To get a general idea about their current and upcoming projects

3. Introduction

Square Pharmaceuticals Company started its journey back in 1958 under the leadership of Samson H Chowdhury in Pabna. In all these decades, Square Pharmaceuticals PLC. has been the best amongst all the national and multinational companies since 1985. Square Pharmaceuticals PLC. has 14 cGMP manufacturing units. Square Unit in Pabna was the first manufacturing facility with a production of 3 billion tablets and capsules, 25 million tubes, 146 million liquid bottles, and 47 million ampoule injections. Square Pharmaceuticals PLC. is the largest pharmaceutical company in Bangladesh. With the slogan, “At SQUARE, we share, we care, and we go beyond together”. SQUARE Pharma's consolidated net turnover during the year 2024-2025 was BDT 76.29 billion (US$ 621.75 million) a growth rate of about 8.83%. Market share about 17.41% and having around 15,934 employees across the country and abroad. Square Company is associated with over 1,17,100 pharmacies around and growing each year. Around 86% of doctors recommend Square Pharmaceuticals PLC. products. Being the pioneer in the pharmaceutical sector, Bangladesh exports pharmaceutical products to 46 countries worldwide and has an operational manufacturing unit in Kenya as well, the first to develop a manufacturing plant outside the country. Square Pharmaceuticals strives to provide top-quality healthcare products at the lowest cost possible for the people in Bangladesh. The market capitalization of SQUARE Pharma is around BDT 185.18 billion (US $1.51 billion), which places it 1 in ranking in the pharmaceuticals sector

4. Milestones of Square Pharmaceuticals

Year	Achievement
1958	Square Pharma launched as a partnership firm.
1964	Converted to a Private Limited Company.
1974	Entered technical collaboration with Janssen Pharmaceutical, Belgium.
1982	Signed licensing agreement with F. Hoffmann-La Roche Ltd., Switzerland.
1985	Achieved top position in Bangladesh's pharmaceutical market.
1987	Became a pioneer in pharmaceutical export from Bangladesh.
1991	Became a Public Limited Company.
1998	Won the National Export Trophy for exporting pharmaceuticals.
2001	US FDA/UK MCA standard new pharmaceutical factory goes into operation
2004	Signing of agreement with ROVIPHARM.
2005	Opened new State-of-the-Art Square Cephalosporins Ltd.
2007	Dhaka Unit received UK MHRA approval.
2008	The new SVPO (Small Volume Parenteral and Ophthalmic) plant started in Dhaka.
2015	Achieved US FDA pre-approval.
2018	Established East African plant in Nairobi.
2021	Received special recognition from Large Taxpayer Unit and Green Factory Award.
2022	Won the National Productivity & Quality Excellence Award from the Ministry of Industries.
2023	Honored as Top Taxpayer with Tax Card in Pharmaceuticals by the National Board of Revenue (NBR).

5. Units of Square Pharmaceuticals PLC

Square Pharmaceuticals PLC has two units in Bangladesh. There are the Dhaka Unit and the Pabna Unit. The Dhaka unit is located at Kaliakoir, Gazipur, and the Pabna unit is in Pabna

Dhaka Unit

The Dhaka Unit is about 50 km away in the north of the capital city. Bovis Lend Lease, UK designed this plant. This is a state-of-the-art manufacturing facility for oral solid dosage forms and all facilities have been developed meeting the requirements of cGMP CFR 21. Dhaka Unit started its operation at the end of 2002.

In the year 2002, the representative of UNICEF, Copenhagen, audited Dhaka Unit facility and enlisted this plant for their global supply. Besides UNICEF audit, in 2003, David Begg Associates, an UK based consulting company also audited this facility and recognized that this plant fulfills the requirement of MHRA (United Kingdom Medicines and Healthcare Products Regulatory Agency).



Fig 1. Drone image of Square Pharmaceuticals PLC. Dhaka Unit

Solid Dosage Unit-1 (GPB): General Production Building (GPB) is the main production unit of the Dhaka plant, which started operation in 2002. This unit is primarily used for large-scale manufacturing and packaging of tablets and capsules. It supports bulk production with standard GMP compliance and plays a key role in meeting regular market demand.

Solid Dosage Unit-2: Solid Dosage Unit-2 was established in 2014 to meet the increasing demand for pharmaceutical products. It has a production capacity of 8000 million tablets and 2000 million capsules per year at full utilization. The unit is designed as a vertically structured steel building and is fully compliant with international GMP and regulatory guidelines. The layout was developed jointly by international consultants and the Square project team.

Cephalosporins Unit: This is a dedicated and self-contained manufacturing facility designed to prevent cross-contamination. Cephalosporins are highly sensitizing antibiotics; therefore, separate facilities are essential to avoid serious medical hazards. This unit ensures product safety, regulatory compliance, and patient protection.

Small Volume Parenteral & Ophthalmic Unit: Square Pharmaceuticals operates a state-of-the-art ophthalmic manufacturing plant at Kaliakoir, Gazipur. The facility is built according to US FDA and UK MHRA cGMP standards. It uses advanced Blow-Fill-Seal (BFS) technology, which maintains a sterile and aseptic environment. The plant was designed by Telstar S.A. (Spain), and the BFS machines were supplied by Weiler Engineering (USA).

Insulin Unit: Square established a modern Insulin Manufacturing Unit to ensure high product quality and sterility. The cleanroom infrastructure and utilities were developed by Tpro (Telster Projects), Spain, a global expert in turnkey cleanroom solutions. The unit is equipped with formulation and holding vessels, autoclaves, and CIP/SIP systems for bulk insulin production. Filling operations are carried out using IMA-MAC monoblock aseptic machines from Italy, enabling washing, depyrogenation, filling, stoppering, and capping in a single integrated process.

Facilities commissioned in a factory at the Kaliakoir site:

- 2001 – General Production Building
- 2005 – Cephalosporin Facility
- 2007 – Small Volume Parenteral and Ophthalmic
- 2009 – Insulin and Metered Dose Inhaler
- 2013 – Formulations Unit
- 2025 – Sterile Facility (FU6)

All these plants are designed and commissioned to meet by cGMP (Current Good Manufacturing Practices) requirements to meet the excellence in quality.

6. Human Resource Department (HRD)

The Human Resources (HR) Department is a vital part of any organization, responsible for managing and optimizing the workforce, which is often considered the company's most important asset.

The Key Functions of the Human Resources Department of SQUARE Pharmaceuticals PLC:

SQUARE Pharmaceuticals PLC is the foremost corporate entity and the top company in the country, supported by a substantial workforce managed by the Human Resources Department.



i. Recruitment and Selection

The recruitment function of Human Resource Management (HRM) involves identifying job requirements, attracting qualified candidates, and selecting suitable individuals for employment. The process begins when a vacant position arises or a new role is created. Recruitment advertisements are published on the company website and external platforms such as BD Jobs. Interested candidates should submit their CVs, which will be initially screened by HR. Shortlisted applicants are required to appear in a written examination. Candidates who pass the written test face the first viva, followed by a second viva for further evaluation.

After successful completion of the interviews, background verification is conducted for security purposes, followed by a medical examination. Finally, the most suitable candidate is selected and formally appointed to the position.

ii. Training and Development

Responsible for ensuring the learning and development program of –

- **Orientation:**
  Newly appointed employees receive Level-1 orientation training, which covers basic organizational knowledge, workplace do's and don'ts. After successfully passing the Level-1 assessment, employees proceed to Level-2 training and gain knowledge about the SOPs, EOPs, and information related to their assigned department. Upon completion and passing of the Level-2 examination, they are awarded a Certificate of Competence, which authorizes them to sign official documents.
- **GMP Training:**
  Training is provided on Good Manufacturing Practice (GMP) guidelines to ensure proper compliance with quality, safety, hygiene, and regulatory standards in pharmaceutical operations.
- **EDP and MDP:**
  Employee Development Programs (EDP) and Management Development Programs (MDP) are conducted to enhance professional skills, leadership abilities, and career growth of employees.
- **In-Plant Training (for Students):**
  A structured and detailed training plan is designed for trainees to ensure maximum learning exposure and meaningful industrial experience.
- **Hands-On Training (of CHQ):**
  Practical, department-specific training is provided to newly recruited employees to develop technical skills and ensure effective performance in their designated roles.

iii. Performance Management

- Salary increments are performance-based and evaluated through structured appraisal systems:
- KRA and KPI-based evaluation for executive-level employees and above, conducted every quarter.
- Performance Management System (PMS) for non-executive permanent employees, assessed quarterly.
- PMS for daily outsourced employees, conducted yearly.

iv. Visit, Protocol, and Audit Management

- Organizing and co-coordinating all types of visits and protocols at the Dhaka Unit.
- Protocols of High Officials
- Visit of delegates
- Doctor, MPO, and student visit
- Logistic support for audit management

v. General Services

- Providing general services to employees for smooth production and employee satisfaction.
- Canteen

- Transport
- Laundry
- Guesthouse and exclusive quarters
- Gardening
- Housekeeping
- Reception and dispatch, stationery store, waste management, etc.
- Providing 24-hour medical services for all employees at the plant

vi. Safety, Security, and Administration

- Taking care of security, safety, administrative issues, and different licenses as a business partner.
- Security of the asset and the whole plant
- Safety issues, including fire
- Personnel Administration for high productivity
- License (Trade, Factory, Acid, Fire, Environment)
- Industrial Relations

vii. HRIS

- Managing SAP HR modules:
- Personnel Administration
- Time Management
- Payroll for Daily Outsourced Employees

viii. Organizational Development

- The initiatives for organizational development on a limited scale –
- Policy Making
- HR Process development
- Exit and stay interview for HR reports and improvement actions
- Employee Satisfaction Survey

ix. Talent Management

Talent management focuses on identifying, developing, and retaining high-potential employees to build future leadership within the organization. Various initiatives are undertaken to nurture young talents and prepare them for higher responsibilities.

- **Identification of Talents:**
  Potential employees are identified through performance evaluations, skill assessments, and leadership potential indicators.
- **Rewards:**
  High-performing employees are recognized and rewarded to encourage motivation, retention, and continued excellence.
- **Mentoring:**
  Experienced professionals provide guidance and support to young talents, helping them develop technical expertise and professional confidence.
- **Leadership Training:**

Structured leadership development programs are conducted to enhance decision-making, communication, and managerial skills.

x. Maintaining good employee relations for smooth operations.

Maintaining positive employee relations is essential for ensuring a harmonious workplace and uninterrupted organizational operations.

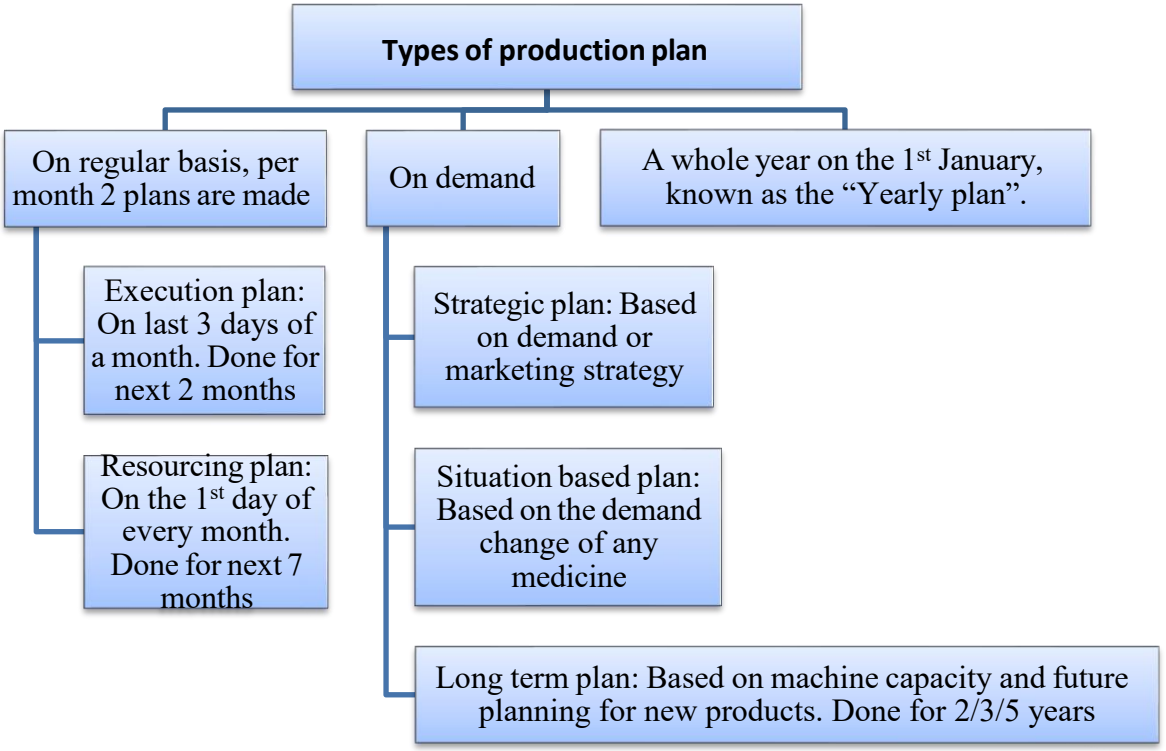
- **Employee Relations:**
  Open communication and fair workplace policies help build trust and cooperation between management and employees.
- **Counseling:**
  Counseling services are provided to support employees in managing work-related stress, personal challenges, and career development.
- **Employee Engagement:**
  Engagement activities, feedback mechanisms, and participative decision-making improve morale and job satisfaction.
- **Welfare:**
  Employee welfare initiatives focus on health, safety, and well-being, contributing to a supportive and productive work environment.

7. Production Planning & Scheduling (PPS) Department

PPS, or Production Planning & Scheduling, serves as a crucial link between the Sales/Marketing department and various factory departments. It plays a pivotal role in coordinating and aligning activities to ensure a seamless flow of operations.

Responsibilities:

- Planning and coordination among the manufacturing and all departments.
- Execution of plan.
- As a supply coordinator.



Key Considerations of the Production Plan:

- **Rolling Sales Forecasts:** Sales predictions over a specific period.
- **Opening Stock:** Current stock levels in the warehouse, depot (as national stock), and work in process.
- **Order demand:** Includes physician samples, institutional, and export supply orders.
- **Product Movement and Sale Nature:** Understanding how products move and sell in the market.
- **Sterility Characteristics (if needed):** Ensuring products meet sterility requirements.
- **Buffer/Safety Stock:** Maintaining safety stock levels to prevent shortages.

- **Materials Availability:** Ensuring raw materials are available.
- **Machine Capacity:** Evaluating and planning for machine utilization and capacity.
- **Other Resources:** Ensuring other essential resources for production are available.

Types of product supply:

- **Commercial supply:** PMD gives forecast of the product (70-80% of forecast matches with actual demand).
- **Export supply:** 30 to 40% of forecast matches with actual orders demand (Packaging is different based on the tender).
- **Institutional supply-Customer:** Defense, medical college, hospitals, UNICEF etc.
- **Physician sample supply:** Customers are doctors (marketing strategy).

8. Material Management and Inventory Control (MMIC) Department

MMIC deals with planning, purchasing, storing, controlling, and using materials properly to support smooth production. It includes:

i. Material Management

- Material Management ensures that required materials are available for production at the right time.
- Planning the quantity of raw and packing materials needed for production.
- Vendor selection and coordination with approved suppliers.
- Planning and supplying materials for new products.
- Ensuring materials meet the QC and QA specifications.

ii. Inventory Control

- Inventory Control focuses on proper storage and utilization of materials.
- Maintaining optimum stock levels to avoid oversharing and shortages.
- Monitoring buffer stock and lead time.
- Obsolete material (materials that are no longer in use) management.

Aim of and MMIC:

- To ensure the right quantity of materials.
- To ensure the right quality of materials.
- To receive materials at the right time.
- To release materials at the right time.
- To maintain a reserve stock to avoid a stock-out.
- To stabilize fluctuation in material consumption.
- To ensure maximum use of materials before expiry.

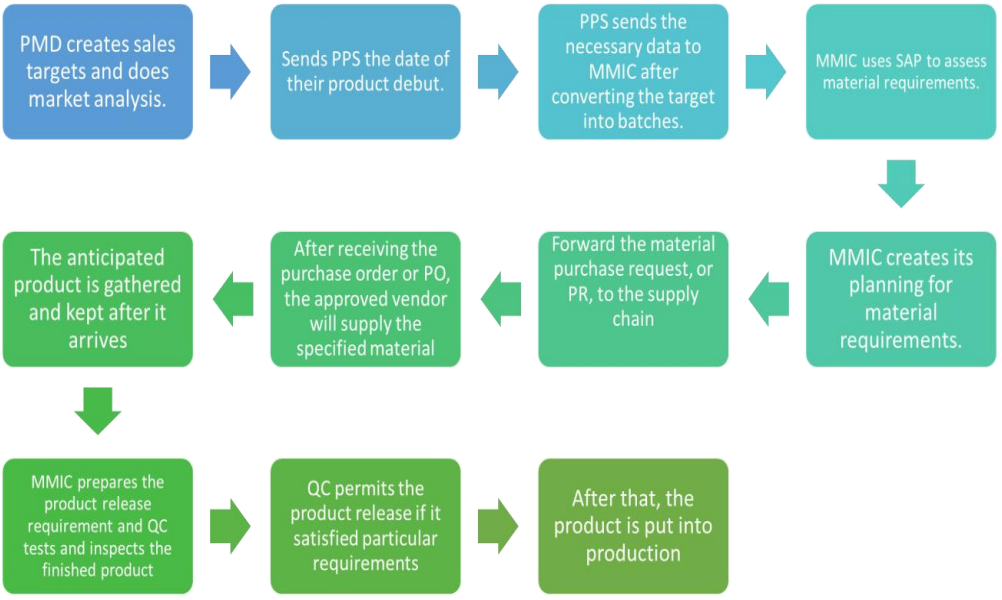


Figure: Flow chart represents the coordination of PPS and MMIC

9. Warehouse

A warehouse is a controlled area designed to receive, store, control, and issue raw materials, packaging materials, intermediates, and finished products while maintaining quality, safety, traceability, and compliance with GMP.

Types of warehouses:

There are **14** warehouses in the Dhaka unit of SQUARE Pharmaceuticals PLC.

- **6 raw material warehouses** (GPB, FU2, FU3, FU5, FU6, Cephalosporin- each having one)**:** They store raw materials needed for production and primary packaging materials.
- **6 finished goods warehouses** (GPB, FU2, FU3, FU5, FU6, Cephalosporin- each having one)**:** They hold finished products and packaging materials.
- **1 common warehouse:** Stores a mix of different materials and products as needed and secondary packaging materials.
- **1 solvent store:** Contains solvents.

Areas of warehouse

i. Unloading Bay:
- Handling unloaded materials.
- Conducting material inspections.
- Vendor approval is required before proceeding.
- Security is checked
- Cleaning of incoming materials

ii. Marshaling Area:
- Weight is checked and Cleaning received materials with vacuum cleaner.
- Transferring materials to the quarantine area.

iii. Quarantine Area:
- Stores raw materials and packaging until sampling procedure is performed by QC.
- Attaching a quarantine label at marshalling area and materials are covered with yellow net at finished goods warehouse.
- Materials stay here until they receive a "Passed Label" from QC.

iv. Passed Area:
- Approved materials are transferred to this area.

v. Damage Area:
- Materials that fail QC tests receive a hold tag and then rejected tag.
- Rejected materials are stored until disposal decisions are made.

vi. Cold storage:

- Cold Room: 2-8°C temperature.
- Cool Room: 8-15°C temperature.
- General Room Temperature: 15-25°C and RH: 40-65%.

Work procedure of warehouse

Forecast by PMD
↓
Planning by PPS according to the forecast
↓
SCM (selects vendor and orders material)
↓
Material is transferred by ship, air or by road
↓
Receiving materials are validated by SAP software
↓
QC takes sample for testing and materials are transferred to quarantine area
↓
QC approval
↓
Materials are transferred to passed area
↓
Production area
↓
Primary packaging
↓
Secondary packaging
↓
Finished product
↓
Finished goods warehouse
↓
Distribution center

Handling of existing materials

While waiting for distribution, the materials are retested 1st week of every month (Quarantine area) by QC
↓
Quarantine area materials are given an orange label first, then yellow label.
↓
If they are passed, materials are moved to Passed area and a green label is attached

Determination of receiving and departure time of materials

- **FIFO: First In, First Out**

Materials that are received first are issued first, regardless of expiry date; this is termed as "FIFO".

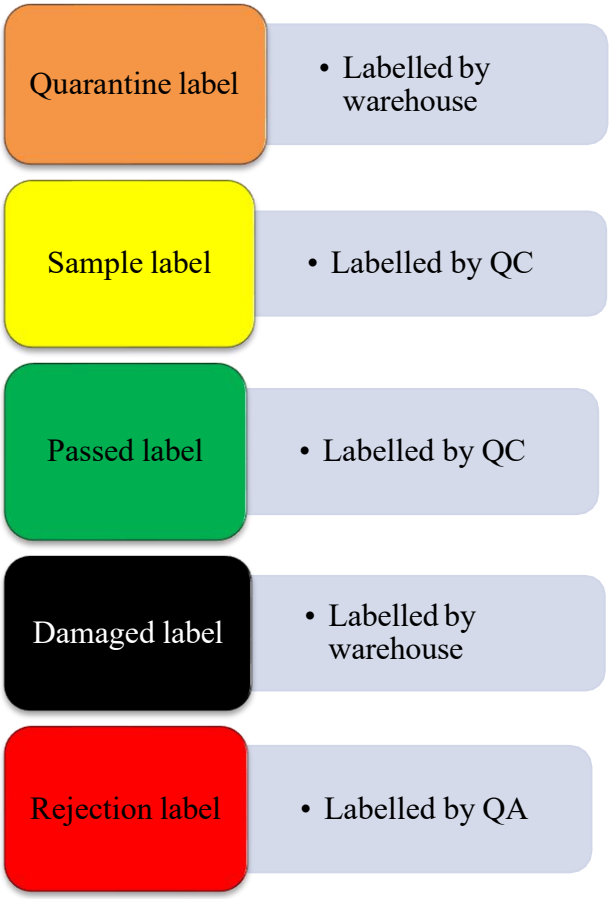
- **FEFO: First Expiry, First Out**

FEFO refers to materials with the earliest expiry date are issued first, even if received later.

Damaged material handling

Material unloaded in unloading bay
↓
Segregation
↓
Damaged material found
↓
Warehouse informs to QA
↓
QA samples and checks the material
↓
Damaged label is given to the products
↓
Damaged materials transferred to Damaged area
↓
A rejection form is raised
↓
The form is signed and approved by manager and director
↓
Product is labeled Rejection and it is informed to government VAT officers and supplier
↓
The materials are checked and confirmed by the government VAT officers
↓
Materials are discarded and burned in front of the government VAT officers
↓
The given VAT is returned by the government

Labeling name and color designation in the warehouse:



Utilities and Equipment in warehouse:

i. **HVAC system:** HVAC (Heating, Ventilation, and Air Conditioning) is a technology that provides thermal comfort and acceptable indoor air quality. It is a crucial system in both residential and commercial buildings, ensuring a comfortable and healthy environment

ii. **Pallet:** A pallet is a flat, portable platform used for stacking, storing, transporting, and handling goods and materials. It provides a stable base that allows for efficient movement and storage of goods using forklifts, pallet jacks, and other material handling equipment.

iii. **Forklift:** A forklift is a powered industrial truck used to lift, move, and transport materials over short distances. Forklifts are essential equipment in warehouses, distribution centers, manufacturing plants, and various other industrial settings.

iv. **Rack:** Warehouse racks are essential storage solutions designed to maximize space utilization, improve organization, and facilitate efficient material handling. They come in various types and configurations to meet different storage needs, enhancing the overall efficiency and safety of warehouse operations.

v. **Trolley (Hand & Power trolley):** Trolleys are versatile material handling devices used in various industries, warehouses, retail environments, and construction sites to

transport goods, equipment, and materials efficiently. They come in two primary types: hand trolleys, which are manually operated, and power trolleys, which are electrically or mechanically powered.

vi. **Reach Truck:** A Reach Truck is a specialized type of forklift commonly used in warehouses and distribution centers for narrow aisle operations and high stacking of palletized loads. It is designed to operate in confined spaces and to lift loads to significant heights, making it ideal for maximizing vertical storage space in warehouses.

vii. **Label counting machine:** Counts the labels automatically.

Environmental monitoring system (EMS):

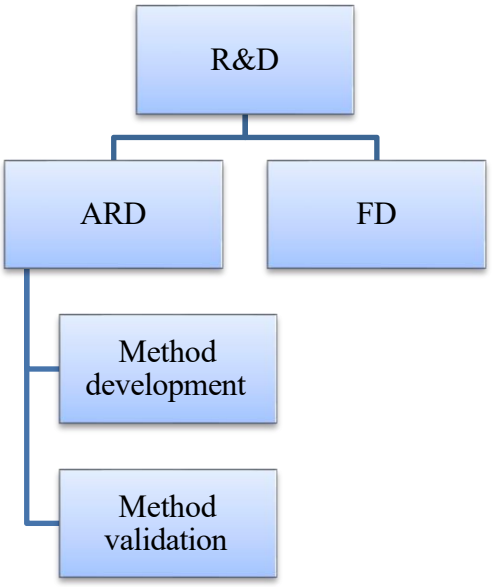
An environmental monitoring system in a warehouse ensures optimal storage conditions by using sensors to track temperature, humidity. EMS sensor notifies personnel of warehouse and engineering department for any deviations from set parameters. The system integrates with HVAC controls to automatically maintain desired conditions. Monitoring software provides real-time data, analytics, and reporting to ensure regulatory compliance and optimal inventory management.

10. Research & Development Department (R&D)

The R&D department is involved in a series of methodical processes aimed at discovering, developing, and bringing new medications to market.

Key functions of R&D involve:

- Conduct research as well as develop new medications.
- Enhance the quality of already existing products.
- Ensure efficiency, safety and legal adherence.
- Establish the manufacturing process and resolving manufacturing related problem
- Establish Recipe, Annexure, Master Formula, BMR and BPR for a product
- Select material and technique for packaging
- Conduct stability study and estimate product shelf life



Formulation Development (FD)

The Formulation Development wing at Square Pharmaceuticals PLC. works with a dedicated manufacturing facility that primarily formulates new products or reformulates existing products, contributing to the company's global success of the company by working as the backbone. The FD unit includes a dispensing unit, a blending and milling unit, a drying unit, an IPC room, a packing room, a lyophilizing room, and a stability chamber.

New Product Development

The needs and concepts that came from the research phase serve as guidelines for building the new product itself at this stage of the process. All applicable regulatory criteria as well as product standards must be met by the newly formed product.

The systematic workflow of FD is demonstrated below:

Product proposal from Marketing department
(IMD sends proposal for US market and ROW while PMD sends domestic market proposal)
↓
Literature review
(Checking of literature review RLD study and MSDS of API to evaluate the required machineries or process involved in the manufacturing or proposed product)
↓
Technical feasibility study
(the document is sent to ARD, FD, QC & Production department)
↓
Comments of different departments are collected and sent to the headquarter
↓
If **headquarter approves** that document, procurement of raw materials, excipient and packaging material is done
↓
Technical literature review
↓
Requisition of raw material
↓
Pre-formulation study
↓
Manufacturing process development
↓
Trial process
(Trial batch, process optimization, process validation batch, stability batch)

Trial and error process

Trial and error are the initial stage of process development in the pharmaceutical industry, where different formulations, materials, and processing conditions are experimentally tested to identify a workable manufacturing process. During this stage, various combinations of excipients, equipment settings, and operating parameters are tried to understand their effects on product quality and process performance. The primary aim of trial and error is to gain basic process understanding, eliminate unsuitable conditions, and select preliminary process parameters that can be further refined during process optimization.

Process Optimization

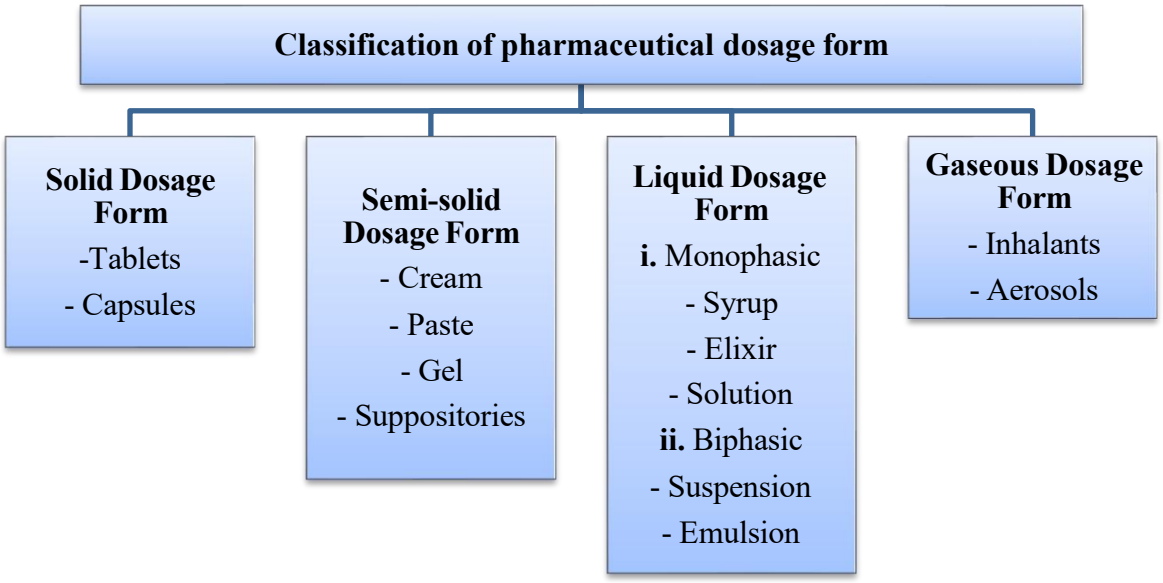
Process optimization is a planned and systematic activity carried out according to approved procedures to improve an existing manufacturing process without compromising product quality. It involves the identification, evaluation, and adjustment of critical process parameters

(CPPs) and Critical Quality Attributes to achieve consistent product quality, improved process efficiency, higher yield, and reduced variability.

Process Validation

Process validation is a documented and systematic approach that provides a high degree of assurance that a pharmaceutical manufacturing process is capable of consistently producing a product that meets its predetermined specifications and critical quality attributes. It is carried out according to an approved validation protocol, where all critical process parameters are identified, monitored, and controlled. As a standard practice, process validation is performed using three consecutive commercial-scale validation batches to demonstrate process consistency and reproducibility. During these batches, in-process controls and finished product tests are conducted, and the results are evaluated against predefined acceptance criteria. Any deviations observed during validation are properly investigated and documented. Upon successful completion of all three validation batches, a validation report is prepared and approved by the Quality Assurance department, confirming that the process is robust, under control, and suitable for routine commercial production**.**

Classification of Dosage Form:



- **Solid Dosage Form**

Solid dosage forms are pharmaceutical preparations in which the active pharmaceutical ingredient (API) is present in a solid state, commonly formulated as tablets, capsules, powders, or granules. They represent the most widely used dosage forms in the pharmaceutical industry due to their high stability, ease of manufacturing, accurate dosing, and cost-effectiveness. The

solid dosage formulation involves dispensing, sieving, granulation, compression, and coating processes.

Processes Involved in Solid Dosage Form:

i. Tablet

In Square Pharmaceuticals PLC. Tablet is produced by using three methods: dry granulation (also known as Roller Compaction), wet granulation and direct compression. The choice of granulation method is a critical decision that pharmaceutical manufacturers must make to ensure the quality and efficacy of their products.

Wet Granulation:

Wet granulation is a method that involves the addition of a liquid binding phase to a powder bed. This process allows for the uniform distribution of Active Pharmaceutical Ingredients (API), resulting in better content uniformity, improved flowability, and minimized tableting deficiencies. It is highly effective in enhancing the dissolution rate of poorly soluble drugs.

The wet granulation process includes the following steps:

At first **weighing and dispensing** activities are done where transferring specific amounts of powder or liquid raw materials from the bulk container and into smaller units that will be dispensed in specific quantities for batch manufacture.

↓

Then **sieving** is done to deagglomerate the particles, remove large lumps, and helps to maintain uniformity in both the shape and size of particles.

↓

The dry ingredients are mixed, which is known as **dry mixing.**

↓

Then a solvent introduction or pouring into the dry mixture of API and excipients and thus **wet mixing** is done.
Its CPP is impeller speed, chopper speed, binder solution addition time and CQA is dissolution and granules flowability.

↓

Once the wet milling process is complete, these granules are ready for **drying** to remove the excess water content and the **LOD** (Loss on Drying) value is also observed carefully to reach an optimum moisture content to get desired granules.

↓

Sizing or milling of dried granules

↓

Lubrication and final blending.

↓

Then the **compression** step involves the use of pressure to get a solid dosage form in a uniform shape with adequate API and excipient content as per requirement.

↓

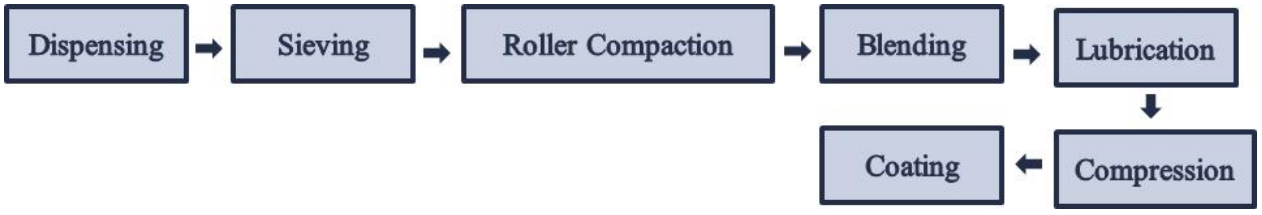
Lastly, depending on the drug's nature and the type of release (immediate, extended, or delayed) **coating method** is conducted.
CPP is pan speed and pan safety. CQA is the identification and modification in drug release from
↓
Packaging

Dry Granulation:

In dry granulation formation of granules occur without using any liquid binder solution and also drying is not necessary which makes the process ideal for moisture and heat sensitive substances It is faster than wet granulation and preferred choice when direct compression is not applicable.

In dry granulation, at first weighing and dispensing activities are done where transferring specific amounts of powder or liquid raw materials from the bulk container and into smaller units that will be dispensed in specific quantities for batch manufacture. Then sieving is done to deagglomerate the particles, remove large lumps, and help maintain uniformity in both the shape and size of particles. Then Roller Compactors are used to force fine powders between two counter rotating rolls and presses the raw materials into a solid compact (flakes, sheets, strips). Then these particles are homogenously mixed through blending. Then lubricant is used to reduce the friction, therefore ejection force, between tablet and die wall. Then the compression step involves the use of Pressure to get a solid dosage form in a uniform shape with adequate API and excipient content as per requirement. During compression, In-Process (IP) tests are conducted which involve individual weight, hardness, disintegration time, identification, friability, and thickness determination. Lastly, depending on the drug's nature and the type of release (immediate, extended, or delayed) coating method is conducted where an essentially dry, outer layer of coating material is applied to the surface of a dosage form that will help in identification purpose and modification in drug release from the dosage form.

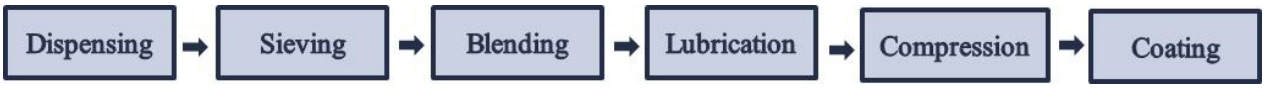
The dry granulation process includes the following steps:



Direct Compression:

Direct compression is a popular choice because it provides the shortest, most effective, and least complex way to produce tablets. The manufacturer can blend an API with the excipient and the lubricant, followed by compression, which makes the product easy to process. No additional processing steps are required. Moisture or heat sensitive ingredients, which would be contraindicated in wet granulation, can also be used in this type of process.

The direct compression process includes the following steps:



In direct compression, at first weighing and dispensing activities are done where transferring specific amounts of powder or liquid raw materials from the bulk container and into smaller units that will be dispensed in specific quantities for batch manufacture. CPP of sieving is the sieve screen size CQA is the flow of granules, remove large lumps, and help maintain uniformity in both the shape and size of particles.

Then these particles are homogenously mixed through blending. CPP of blending is the blending speed and blending time. CQA is blending uniformity. During blending, 10-point assay is done.

Then lubricant is used to reduce the friction, therefore ejection force, between tablet and die wall.

Then the compression step involves the use of Pressure to get a solid dosage form in a uniform shape with adequate API and excipient content as per requirement. CPP of compression is filling depth, feeder speed and CQA is disintegration, dissolution, friability, hardness etc.

Lastly, depending on the drug's nature and the type of release (immediate, extended, or delayed) coating method is conducted where an essentially dry, outer layer of coating material is applied to the surface of a dosage form that will help in identification purpose and modification in drug release from the dosage form.

ii. Capsule:

At first, capsule shell size is determined. The larger the number, the smaller the shell size is.

Then stability tests are done for both the capsule shell and the filling materials.

The report is sent to DGDA. If DGDA approves the sterility report, then the recipe is submitted, and if it is approved NRx is prepared including the brand name, ingredients, and packaging size.

- **Liquid Dosage Form:**

Liquid dosage forms are pharmaceutical preparations in which the active ingredient is dissolved, suspended, or emulsified in a suitable liquid vehicle for oral, topical, or parenteral administration**.** Example: solution, suspension, syrup, elixir.A few types of liquid preparations are formulated at this Dhaka Unit, including injectable preparations, Ophthalmic products and nasal sprays.

- **Gaseous Dosage Form:**

i. Pressurized Metered Dose Inhaler (pMDI):

pMDI are the most used inhaler worldwide. Here aerosol is created when a valve is opened (usually by pressing down the propellant canister) allowing liquid propellant to spray out of a canister.

The drug is usually contained in small particles suspended in the liquid propellant. The propellants in pMDI use hydrofluoroalkanes (HFAs) which do not result in ozone depletion. At room temperature and pressure these are gases, but they are readily liquefied by decreasing temperature and increasing pressure.

Advantages of pMDI:

- Precise dose delivery
- Rapid onset of action
- Minimal systemic side effects

In general, the manufacture of aerosol products takes place in two stages,

- Manufacture of concentrate
- Addition of propellant

Leak test and Aerodynamic Particle Size Distribution (APSD) are essential quality control tests for Metered Dose Inhalers (MDIs). The leak test is performed to ensure the integrity of the canister–valve system and to confirm that there is no loss of propellant or formulation APSD testing, on the other hand, evaluates the distribution of aerosol particles based on their aerodynamic diameter to predict lung deposition.

ii. Insulin:

Insulin is a peptide hormone essential for regulating blood glucose, and its production in pharmaceutical R&D involves cloning the human insulin gene into microbial or mammalian cells, followed by small-scale fermentation, purification, and testing. During formulation, insulin molecules can assemble into hexamers, which are more stable and allow controlled release, especially in long-acting insulin. R&D also focuses on developing short-acting insulin for rapid glucose control and long-acting insulin for sustained regulation, while optimizing formulations for stability, potency, and effectiveness.

Note: Due to safety restrictions, we were not permitted to observe the liquid and pMDI sections during our in-plant training.

Stability Studies:

Thermal Cycling Conditions:

Conditions	Temperature	Relative Humidity	Time Duration (Month)
Accelerated	40 °± 2 ° C	75 ± 5%	6
Intermediate	30 ° ± 2 °C	65 ± 5 %	6
Long Term	25 °± 2 °C	60 ± 5%	12
	30 °± 2 °C	65 ± 5%	

Stress Study: The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions. Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved. Stress testing is likely to be carried out on a single batch of the drug substance. It should include the effect of temperatures (in 10°C increments (e.g., 50°C, 60°C, etc.) above that for accelerated testing), humidity (e.g., 75% RH or greater) where appropriate, oxidation, and photolysis on the drug substance. The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension.

Photostability Study: This is done to check the light sensitivity of the product in 200UV and 1600 IR wavelengths.

Lyophilization Study: Lyophilization works on the principle of sublimation, where water is removed from a frozen product by direct conversion of ice into vapour under reduced pressure without passing through the liquid phase.

Compatibility Study: Here it is observed if the liquid formulation maintains its stability and efficacy even after running through different parts of the machine.

Instruments Observed in FD:

i. For Solid Dosage Form:

Instrument Name	Manufacturer Name
Blender	ERWEKA
Fluid Bed Dryer	ACG
Fluid Bed Processor	ACG
Rapid Mixing Granulator	NR Narong Group
Rotary Tablet Press	Pharm Tech Korea, ERWEKA

ii. For Liquid Dosage Form:

Instrument Name	Manufacturer Name
Balance	Mettler Toledo
Homogenizer	Silverson
Overhead stirrer	IKA Eurostar digital
Magnetic Stirrer	DAIHAN Scientific
Lyophilizer	Telstar Lyobeta 15
pH Meter	Mettler Toledo

Analytical Research and Development (ARD)

Analytical Research and Development (ARD) is a core functional unit within the pharmaceutical industry that ensures the quality, safety, efficacy, and regulatory compliance of pharmaceutical products throughout their lifecycle. ARD is responsible for the development, optimization, validation, transfer, and application of analytical methods used to evaluate active pharmaceutical ingredients (APIs), excipients, intermediates, and finished dosage forms.

ARD Laboratory Structure

The Analytical Research and Development department typically consists of four specialized laboratories, each supporting distinct analytical activities:

- **Instrument Laboratory**

Houses advanced analytical instruments used for qualitative and quantitative analysis.

- **Wet Chemistry Laboratory**

Focuses on classical chemical analysis such as titrations, pH analysis, and reagent-based testing.

- **High-Performance Liquid Chromatography (HPLC) Laboratory**

Dedicated to chromatographic analysis for assay, impurity profiling, and stability studies.

- **Validation Laboratory**

Responsible for method validation, method transfer, system suitability testing, and robustness studies in accordance with regulatory guidelines.

Workflow of ARD:

Developed formulation by FD
↓
Development of analytical method by ARD for drug analysis
↓
Selection of drug analysis technique (HPLC, GC etc)
↓
Determines drug stability under various conditions and ensures shelf-life
↓
Validation of analytical method according to ICH/USP/FDA guidelines
↓
Transfer of analytical methods to QC

Purpose of drug analysis:

- Assay testing
- Detection and estimation of impurities
- Checking of content uniformity
- Dissolution testing
- Methods are optimized to ensure specificity, sensitivity, precision, and accuracy, making them suitable for routine QC and regulatory submission.

Assay:

A quantitative measurement of the amount or potency of an API in a sample expressed as a percentage of the labelled amount. For example- a tablet labelled to contain 500mg of paracetamol might be assayed to confirm it contains more or less deviation of 5mg.

Content uniformity:

Content Uniformity is a critical quality control test used to ensure that every individual dosage unit (like a tablet or capsule) in a batch contains the exact amount of active pharmaceutical ingredient (API) intended.

Acceptance Criteria: Acceptance Value (AV) is calculated from the mean and standard deviation of the individual test results. Generally, the API content in each unit should fall within a specific range of the label claim (e.g., 85% to 115%).

Weight variation:

A weight variation test for tablets is a crucial quality control method checking if individual tablet weights in a batch are uniform, ensuring consistent drug dosage, safety, and efficacy by comparing each tablet's weight to the average, following pharmacopoeia (like USP) limits for acceptable deviation (e.g., max 2 tablets outside limits, none more than twice the limit) to guarantee uniformity of mass for patient dosing.

Acceptance limit:

Weight of tablets as per USP	Deviation allowed	Weight of tablets as per BP
130mg or less	10%	80 mg or less
130-324 mg	7.5%	80-250 mg
More than 324 mg	5%	More than 250 mg

Method validation

Method validation is the process which demonstrates that an analytical procedure is suitable for its intended purpose.

Types of Method validation

- **Analytical method validation:** Confirms that an analytical method produces reliable and reproducible results for the active drug, or dosage forms.
- **Cleaning Method Validation:** Confirms that cleaning method detected and quantify the trace amounts of residues with precisely and accurately.

Significance of method validation

- Ensures reproducibility of the result.
- Confirms method suitability in specific conditions.
- Reduces risk of failure by identifying limitations or potential interferences before scaling up production.

Core part of method validation

- **Accuracy**: How close the measured value is to the true value.
- **Precision**: Reproducibility of results under the same conditions (intra- and inter-day). Precision is typically classified into three main types:
- **Repeatability:** Repeatability refers to the variation when the same analyst performs the method multiple times on the same sample under identical conditions within a short period.
- Purpose: Measures short-term consistency of the method.
- **Intermediate Precision:** Intermediate precision refers to the variation observed when the method is performed within the same lab but under slightly different conditions (different analysts, instruments, or days).
- Purpose: Shows method reliability under normal operational variations in the lab
- **Reproducibility:** Reproducibility is how consistent a method is when done in different labs, by different people, using different equipment.
- Purpose: Demonstrates method's robustness and suitability for use across multiple labs.
- **Robustness**: The method's reliability under small deliberate variations in conditions.
- **Specificity/Selectivity**: Ability to measure the analyte without interference from other components.
- **Linearity**: The method's response is directly proportional to the analyte concentration within a given range.
- **Limit of Detection (LOD)**: The lowest amount of analyte that can be detected.

- **Limit of Quantitation (LOQ)**: The lowest amount of analyte that can be quantitatively measured with acceptable precision and accuracy.
- **System suitability:** System suitability is a set of tests performed on an analytical system to ensure that it is working properly and can produce reliable and valid results before analyzing samples

Quality Control Support

- Validated analytical methods by ARD are transferred to QC for routine application.
- Routine batch testing is done to ensure batch-to-batch consistency.

Instruments Used in ARD

Instrument	Brand / Model	Application
High-Performance Liquid Chromatography (HPLC)	Waters	Assay, impurity profiling, stability studies
Liquid Chromatography–Mass Spectrometry (LC–MS/MS)	Triple Quadrupole MS	Trace-level impurity and metabolite analysis
Dissolution Tester	ERWEKA, Pharmatest	Drug release and dissolution profiling
Sonicator	SONICLEAN	Sample preparation and dissolution
pH Meter	Metrohm	pH measurement and buffer preparation
Drying Oven	Venticell	Drying samples and stability studies
UV–Visible Spectrophotometer	Shimadzu	Quantitative analysis and method development

- **HPLC**

It is a powerful analytical technique used to separate, identify, and quantify components in a mixture. HPLC separates compounds based on their interactions with:

- Stationary phase (usually a solid column packed with silica or polymer particles)
- Mobile phase (a liquid solvent or mixture that moves through the column)

- Compounds interact differently with the stationary phase, causing them to elute at different times, called retention times.

Components of HPLC

- Solvent Reservoirs – contain the mobile phase.
- Pump – pushes the mobile phase through the column at high pressure.
- Injector – introduces the sample into the mobile phase.
- Column – where separation occurs.
- Detector – identifies and quantifies the compounds (common types: UV, fluorescence, refractive index).
- Data System – records the detector signal, giving a chromatogram.

How HPLC works

Step 1: Sample Introduction

The sample mixture is dissolved in a suitable solvent. A small volume of this sample is injected into the HPLC system via the injector.

Step 2: Mobile Phase Transport

The pump pushes the mobile phase (solvent) through the column at high pressure. The mobile phase carries the sample molecules along the column.

Step 3: Separation in the Column

The column contains the stationary phase. Each component of the sample interacts differently with the stationary phase

Step 4: Detection

After leaving the column, the separated molecules pass through a detector.

Common detectors:

- UV-vis detector – measures absorbance of UV light. Wavelength 190-400nm.
- PDA detector – PDA (Photodiode Array) detector is a multi-wavelength UV-Vis detector. It measures absorbance at one wavelength at a time, a PDA can measure absorbance simultaneously across a wide range of wavelengths (typically 190–800 nm).
- Refractive index detector – detects changes in refractive index.

The detector sends a signal to a computer, producing a chromatogram:

Peaks on the chromatogram = individual compounds.

Retention time = time a compound takes to pass through the column.

Peak area = quantity of the compound.

Step 5: Analysis

By comparing retention times with standards, compounds can be identified

By measuring peak areas, the amount of each compound can be quantified.

HPLC peak:

Tailing

In ideal HPLC analysis, chromatographic peaks should be symmetric and Gaussian. A tailing peak, by contrast, is asymmetric with a prolonged slope on the trailing side (right side). Tailing can affect the accuracy of peak integration, decrease resolution, and lead to poor reproducibility.

Acceptance Limit:

$Tf \leq 2.0$ (USP / ICH practice

Ideal peak → $Tf = 1.0$

Theoretical Plate in HPLC

The theoretical plate is a measure of column efficiency in HPLC. It indicates how well a column can separate compounds. The higher the number of plates, the better the separation.

Resolution in HPLC (Rs)

Resolution in HPLC describes how well two adjacent peaks are separated from each other in a chromatogram. It is one of the most important parameters for method performance and system suitability. Resolution in HPLC is the measure of separation between two adjacent peaks, and a value of $Rs \geq 1.5$ indicates baseline separation.

- **Gas chromatography**

Gas Chromatography (GC) is an analytical technique used to separate, identify, and quantify volatile compounds in a mixture. GC uses a gas as the mobile phase instead of a liquid. Separation is based on distribution between a stationary phase and a mobile gas phase.

Components that interact more with the stationary phase travel slowly.

Components that interact less travel faster.

This results in different retention times for each compound.

Components of a Gas Chromatograph

- Carrier Gas (Mobile Phase): Inert gases like helium, nitrogen, or hydrogen.
- Constant flow carries sample through the column.
- Injector: Introduces the vaporized sample into the column. Often heated to vaporize the sample instantly.
- Column: Usually a coiled tube inside an oven. Contains stationary phase: solid particles or liquid coated on solid support. Can be packed column or capillary column.
- Oven: Maintains controlled temperature to optimize separation.
- Detector: Measures the eluted compounds. Common types:
  Flame Ionization Detector (FID) – detects organic compounds.
  Thermal Conductivity Detector (TCD) – detects all compounds, less sensitive.
  Electron Capture Detector (ECD) – very sensitive for halogenated compounds.

Data System: Records signal as a chromatogram: peaks vs. retention time.

- **Ion Chromatography**

Ion Chromatography (IC) is a type of liquid chromatography used to separate and analyze ions (anions and cations) in a sample. Separation is based on ionic interactions between charged analytes and a charged stationary phase (ion-exchange resin).

Components with stronger interaction with the stationary phase elute later, while those with weaker interactions elute earlier.

A suppressor is often used to reduce the background conductivity of the eluent, making detection more sensitive.

Components of Ion Chromatography

- Pump – Moves the eluent (mobile phase) through the column.
- Injector – Introduces the sample into the flow.
- Ion-Exchange Column – Contains resin beads with charged groups:
- Cation-exchange column → separates positively charged ions (Na^+, Ca^{2+}).
- Anion-exchange column → separates negatively charged ions (Cl^-, NO_3^-).
- Suppressor – Reduces eluent conductivity to improve detection sensitivity.
- Detector – Usually conductivity detector, sometimes UV or amperometry.
- Data System – Produces chromatogram: peaks vs. retention time.

- **UPLC**

UPLC stands for Ultra-Performance Liquid Chromatography. It's an advanced form of HPLC that provides faster, higher resolution, and more sensitive analysis.

Uses smaller particle size columns (<2 µm) and higher pressures than traditional HPLC.

Same basic principle as HPLC: separation occurs due to differences in interaction with the stationary phase and mobile phase.

Components of UPLC:

- Solvent Reservoirs – Mobile phase.
- High-Pressure Pump – Can handle much higher pressures than HPLC pumps.
- Injector – Introduces sample into the mobile phase.
- UPLC Column – Packed with sub-2 µm particles.
- Detector – UV, PDA, or mass spectrometry (MS).
- Data System – Records chromatogram and calculates results.

- **AAS**

AAS is based on the principle that free atoms in the ground state absorb light at a specific wavelength characteristic of that element.

When a solution containing metal, ions is atomized (converted into free atoms), these atoms absorb radiation emitted from a hollow cathode lamp specific to that metal. The amount of light absorbed is directly proportional to the concentration of the element in the sample (Beer–Lambert law).

- **Dissolution**

The dissolution test is a critical quality control test used in the pharmaceutical industry to measure the rate and extent to which a drug substance is released from a tablet (or other dosage form) into a liquid medium under standardized, in vitro conditions. This test is essential for ensuring batch-to-batch consistency, product stability, and predicting the drug's performance and bioavailability in the body.

Testing Process

The test involves placing a specified number of tablets (typically 6) into a dissolution apparatus containing a precisely defined volume and type of dissolution medium at a constant temperature of 37 ± 0.5°C (To simulate physiological conditions).

Dissolution medium (Adjusted to a specific pH, typically between 1.2 and 6.8) is warmed to the required temperature.

The tablet is introduced into the apparatus, and the stirring mechanism is started at a specified speed (RPM).

Samples of the medium are withdrawn at predetermined time intervals, filtered, and analyzed (commonly using UV-vis spectroscopy or High-Performance Liquid Chromatography - HPLC) to determine the concentration of the dissolved drug.

The results expressed as a percentage of the labeled drug content dissolved over time, are compared against official acceptance criteria set by regulatory bodies like the U.S. Pharmacopeia (USP).

Types of Apparatus

Paddle Method: Tablets or capsules are placed in vessel with paddle stirring the medium.

Basket Method: Tablets or capsules are placed in wire mesh basket, rotated in dissolution medium.

Types of Dissolution Medium

- Purified water
- HCl
- Sodium Lauryl Sulfate - SLS
- Buffer

11. Production Department

The Production Department is the backbone of pharmaceutical manufacturing, responsible for converting approved raw materials into safe, effective, and high-quality finished products in compliance with GMP requirements. This department operates through well-defined, validated processes, strict documentation practices and close coordination with QA, QC, Warehouse, Engineering and Planning to achieve batch integrity, cost control and uninterrupted supply while maintaining patient safety as the highest priority.

The production department has six units:

- Formulation unit 1(General production unit)
- Formulation unit 2 (Small Volume Parenteral and Ophthalmic Unit)
- Formulation unit 3 (Insulin Unit and Metered Dose Inhaler)
- Formulation unit 5 (Largest solid dosage unit)
- Cephalosporin unit
- Formulation unit 6 (Standby for Operational Start-up)

The production unit visit was scheduled for four days at Formulation unit 5. The first three days were dedicated to the manufacturing section, while the final day focused exclusively on the packaging section.

Main functions of Production Department:

- Management of day-to-day production activity.
- Conduct and follow daily, weekly & monthly production plan and implement accordingly Maintain Good Manufacturing Practice (cGMP) in all operations of the section.
- Maintenance of Control Charts, Receipt, Return, Usage and Reconciliation of materials and proper storage and delivery of Intermediate and Finished bulks, maintaining good housekeeping.
- Utilize efficiently manpower, machinery and materials to improve productivity.
- Prepare and update Batch Manufacturing Records (BMR), Batch Packaging Records (BPR), Standard Operating Procedure (SOP) and other documents.
- Coordinate with warehouse, QA, QC & Engineering department to ensure smooth production.
- Organize training on SOP, basic GMP and Machine operation & cleaning.

Formulation unit 5

This production unit was established in 2014 with the objective of manufacturing pharmaceutical solid dosage forms. At full capacity utilization, the facility has an annual

production capacity of 8,000 million tablets and 2,000 million capsules. The production floor is located on the second floor of the building. Production area is subdivided into two area –

- Manufacturing area
- Packaging area

The manufacturing area is equipped with a GMP-compliant HVAC system to control temperature, humidity, and air quality. Although the general manufacturing area is class D, Dispensing is carried out in a class C dispensing booth.

Function of differential air pressure:

- Cleanroom differential air pressure is maintained through a pressure cascade to:
- Prevent entry of contaminants into critical production areas.
- Minimize risk of cross-contamination between adjacent areas.
- Maintain cleanroom integrity in compliance with GMP requirements.
- Protects product quality and operator safety.

Tablet manufacturing overview:

Materials received from warehouse
↓
Pre-dispensing
↓
Dispensing
↓
Post-dispensing
↓
Sieving (In case of direct compression materials goes to Blending step)
↓
Granulation (wet granulation, dry granulation)
↓
Blending
↓
Compression
↓
Coating (if it is coated tablet)
↓
Primary packaging
↓
Secondary packaging
↓
Finished product goes to warehouse

Dispensing:

Dispensing refers to the process of weighing, measuring and issuing raw materials or packaging materials from the warehouse to production according to an approved Batch Manufacturing Record (BMR). The dispensing area is subdivided into 3 major area:

1. Pre-Dispensing Area:

The pre-dispensing area is used for preparation and checking before actual weighing of raw materials. Works in the Pre-dispensing Area:

- Receipt of materials from warehouse with approved requisition.
- Verification of raw materials (Material name, code, batch no. and quantity checked)
- Preparation of dispensing containers.

2. Dispensing Booth:

The dispensing area is where accurate weighing of API and excipients is performed according to BMR. There are 6 dispensing booths in FU5, where 6&7 no is used for dispensing API separately and the rest of them are used for Excipients.

Dispensing is performed in a Class C dispensing booth and three types of weights- tare weight, gross weight, and net weight- are considered during the dispensing operation to ensure accuracy and traceability. Works in the dispensing Area:

- Balance verification and calibration.
- Material verification (Cross-checked with BMR and dispensing slip)
- Weighing of raw materials.
- Labelling of dispensed materials (Product name, batch no., material name, quantity, date)
- Documentation (Dispensing record filled and signed)
- Deviation handling (Any over/under-weighing reported to QA)

3. Post-Dispensing Area:

Post-dispensing area is used for temporary storage and controlled transfer of dispensed materials. Works in Post-Dispensing Area:

- Holding of dispensed materials (Materials kept in closed, labelled containers)
- Status labelling (“Dispensed” or “Under Process” labels applied)
- Segregation (Different batches kept separately.)
- Transfer to manufacturing area (Issued as per production order)

Critical Process Parameters (CPP) for Dispensing:

- Calibration Status
- Balance Capacity
- Material Identification
- Line/ Area clearance

Critical Quality Attributes (CQA):

- Correct material identity
- Correct weight/quantity

Sieving:

Sieving refers to the process of separating powder particles based on size using a sieve or mesh.

Purpose:

- Uniform particle size
- Remove lumps and foreign particles.

In the manufacturing facility, four designated sieving booths equipped with Russell and COSMEC sieves along with X-ray detection systems for sieve integrity checking; are allocated for dry granulation and direct compression operations; however, sieving required for wet granulation is conducted inside the wet granulation chamber to maintain process control and prevent cross-contamination.

CPPs:

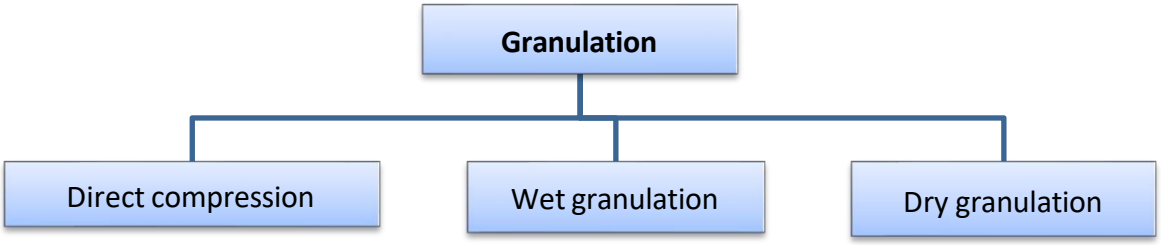
- Sieve size
- Sieving time
- Sieving method
- Material quantity

CQAs:

- Uniform particle size
- No lumps
- Good flow property

Granulation:

Granulation is a unit operation in which fine powder particles are converted into larger, free-flowing, and compressible agglomerates. On the manufacturing floor, three types of granulations are performed:



i. Wet granulation:

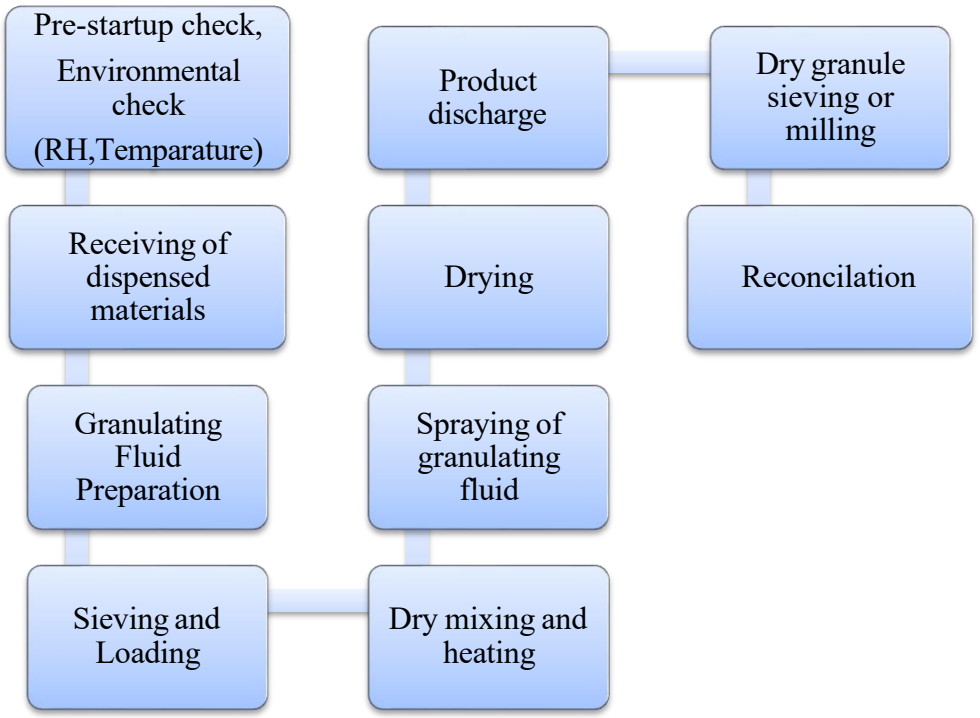
Wet granulation is the process of converting powder blends into granules using a binder solution to enhance flow, uniformity, and compressibility.

Machine observed in wet granulation:

Names	Country of origin	Number of machines
1. COSMEC 60L	Italy	1
2. COSMEC 400L	Italy	1
3. COSMEC 800L	Italy	1
4.GLATT 1500L	India	1
5. FBE-ACG 1300L	India	2

We observed six chambers of the wet granulation process: four chambers equipped with Rapid Mixer Granulator (RMG) and Fluid Bed Dryer (FBD) systems such as Glatt and COSMEC, and the remaining two chambers equipped with FBE 1300L fluid-bed systems.

Workflow:



There is a slight difference in the working procedures of FBE 1300L and RMG + FBD systems, mainly in the way granulation and drying are performed, though both achieve the same end goal of producing uniform, dried granules. In RMG + FBD systems, dry and wet mixing occurs in the Rapid Mixer Granulator (RMG), and the wet mass is then transferred to the Fluid Bed Dryer (FBD) for drying; whereas in FBE 1300L, both mixing and drying occur simultaneously within the same fluid-bed unit.

CPPs:

- Binder concentration & type
- Mixing time in RMG or FBE
- Impeller and chopper speed (RMG)
- Inlet air temperature & drying time (FBD / FBE)
- Fluidization air velocity (FBD / FBE)

CQAs:

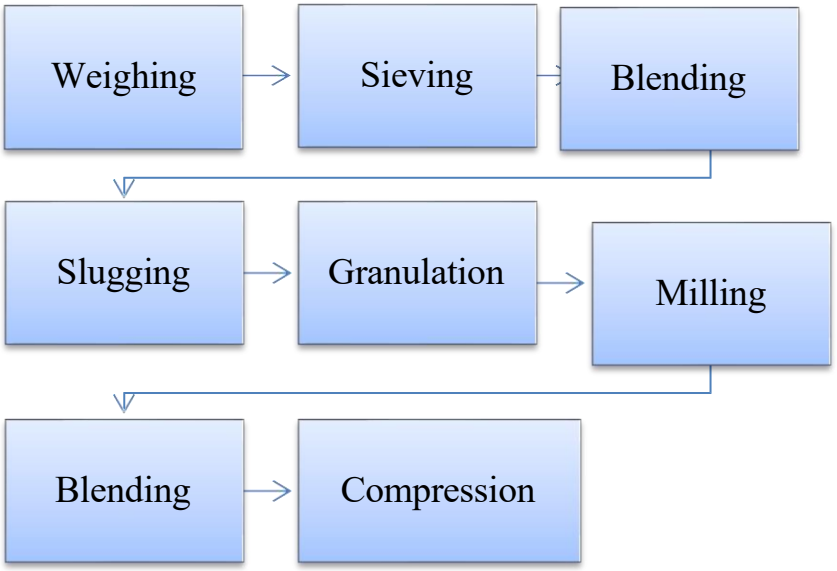
- Moisture content / Loss on Drying (LOD)
- Granule size distribution
- Flow property (angle of repose, compressibility index)
- Density / Bulk & tapped density

- Content uniformity
- Hardness of granules

ii. Dry granulation:

Dry granulation is a pharmaceutical process in which powders are compacted into granules without using any liquid binder, suitable for moisture- or heat-sensitive drugs.

Process flow of dry granulation:



CPPs:

- Roller compaction pressure/force
- Roller speed/feed rate
- Milling speed and sieve size
- Blend uniformity before compaction

CQAs:

- Granule size and size distribution
- Moisture content / LOD
- Flow properties

Blending

Blending is a critical unit operation in tablet production that ensures the uniform distribution of active pharmaceutical ingredients (API) and excipients, directly impacting both product quality and content uniformity.

The equipment used for blending is:

Instrument name	Capacity	Origin
MATCON	1000 kg(max)	Italy
Cos-Mec	1000 kg(max)	Italy

The blender accommodates inputs from three prior manufacturing operations-

- Wet granulation
- Dry granulation
- After sieving in case of direct compression

Blending procedure:

Pre-startup check
↓
Environment check
↓
instruments calibration
↓
IBC is attached with blender
↓
Blending (without lubricants for specific time and RPM according to BMR)
↓
Blending (with lubricants)
↓
Reconciliation

CPP:

- Blending time
- Blending RPM

CQA:

- Content uniformity
- Flow properties

Compression:

Compression process is the mechanical operation of converting a uniform blend of powders or granules into solid dosage forms (tablets) by applying controlled force between punches and dies, ensuring consistent weight, hardness, content uniformity, and structural integrity.

Instruments used in compression stage:

Machine Name	Number of Station	Country Of Origin	Number Of Machine
FETTE P2020	Single station	China	1
FETTE 1200i	Single station	Germany	1
FETTE P3030	Double station	China	1
FETTE 3200i	Double Station	Germany	2
FETTE 2200i	Single station	China	1
KORSCH XL 400	Single Station	Germany	1
Eco press (Veterinary)	Single Station	India	1

Tablet Tooling:

Tablet tooling refers to the set of punches and dies used in tablet compression machines to shape and size tablets during the manufacturing process.

Components of tablet tooling:

- **Punches**
  Upper punches
  Lower punches
- **Dies**

Types of tablet tooling:

Tablet tooling is categorized based on the punch-die configuration, which influences tablet shape, compression, and ejection. The standard classifications are:

- B type tooling
- D type tooling
- DB type tooling
- DD type tooling

Compression Procedure:

Pre-startup check
↓
Environment check
↓
Instruments calibration
↓
Tablet tooling
↓
Mount the IBC on the discharge station above compression room
↓
Operation
↓
Reconciliation

CPP:

- Compression force
- Precompression force
- Turret speed

CQA:

- Content uniformity
- Friability
- Weight uniformity
- Dissolution and disintegration
- Hardness

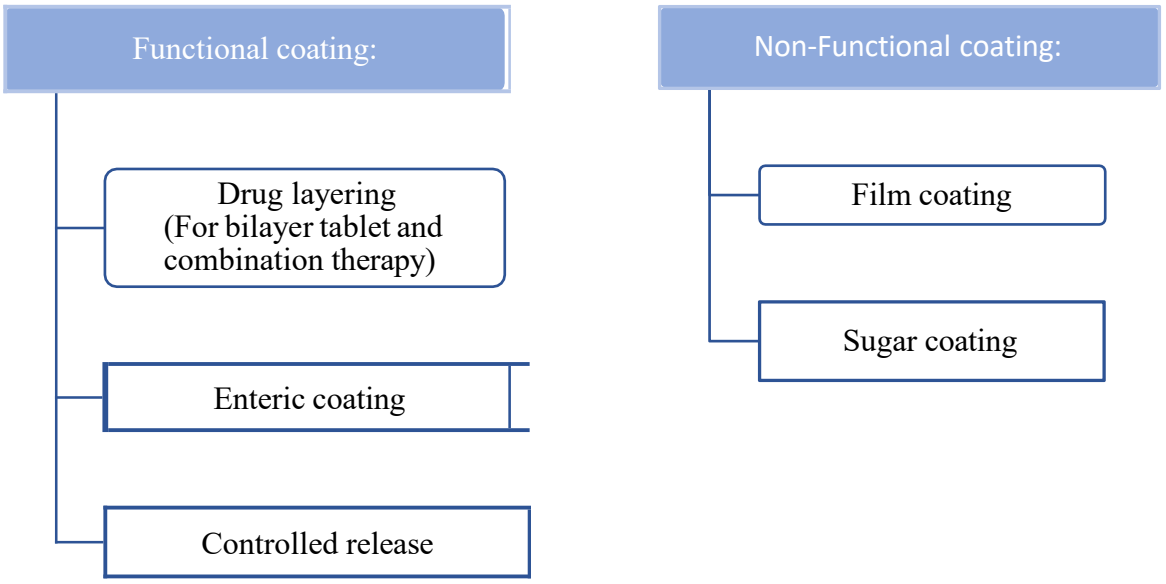
Coating:

Coating is the process of applying a thin, uniform layer of coating material over the solid dosage form (tablet, capsule or pellets) to improve the appearance, protect the drug, mask taste or odor, to control release and enhance stability.

Coating material:

A coating material is a substance, or a combination of substances applied as a thin layer over the surface of a solid dosage form (tablet, capsule or pellets). Example: **Opadry** (White, blue, yellow, pink, orange, brown).

Types of coating:



Instruments used in coating:

Instrument name	Origin (Country)	Capacity (KG)	Spray gun (Number)	Type of coating	Drying method	Ongoing coating
PAM GLATT GCS 700	Germany	630	6	Enteric, color, film	Steam	Calboral-DX 600 mg tablet
PAM GLATT GCS 175	Germany	120	4	Color, film	Steam	Deprex 10 mg tablet
NR coater FC 31	Thailand	25	1	Color, film	Heat	Vori 50 mg tablet
ACG SC 700	India	630	6	Enteric, color, film	Steam	Calboplex tablet

ACG SC 1000	India	700	8	Color, film	Steam	Calbo 500 mg tablet
GANS coater 1500	India	120	3	Color, film	Steam	Lorno 8 mg tablet

Suspension preparation of coating material:

Area clearance by both production and QA
↓
Weighing of purified water
↓
Taking coating material (Opadry) from the pre-dispense area
↓
Weight checking of the coating material according to BMR
↓
Vortex mixing of purified water and slowly add the coating material
↓
Mix well as per BMR
↓
Validated material: Use within the validated time
Non-validated or new material: Use within 24 hours
↓
If not used, deviation must be raised to QA

Workflow of coating:

Area clearance by both production and QA
↓
Mechanical setting and product setting
↓
Coating suspension preparation
↓
Suspension transfer to the coating room
↓
Connecting suspension vessel with the peristaltic pump system of the coating machine
↓
Prewarm the coating pan
↓
Load the core tablets into the coating machine → Take initial weight of the core tablets
↓
PRE-JOG
↓
Coating condition setup as per BMR
↓
Spraying of coating material onto the core tablets using air pressure
Atomization air pressure- For spraying

Compressure air- For suspention transfer
Pattern air- For spreading
↓
Drying
↓
Cooling
↓
IPC (In Process Control)
↓
Reconciliation
↓
QC test
↓
QA comments and approval

End point of coating:

According to BMR, the below parameters are checked to determine the end point of coating.

- Weight gain due to coating
- Appearance
- Solution level

IPQC of coating:

i. **By production department:**
   - **After every 30 minutes:**
     - Appearane
     - Weight of 20 tablets
     - Pan speed check
     - Inlet temperature (For drying) check
     - Temperature adjust
     - Atomic air pressure check
     - Spray pump check
     - Liquid spraying flow and speed check
     - Checking differential pressure of the pan
   - **Before and after coating:**
     - Weight difference of 100 tablets due to coating.

ii. **By QA department:**
   - **Before and after coating:**
     - Weight difference of 20 tablets due to coating.

Encapsulation (For capsules):

Encapsulation is the pharmaceutical process of enclosing a measured dose of drug substance (API and excipients) inside a hard or soft gelatin capsule to produce a solid oral dosage form for accurate dosing, protection, and ease of administration.

Instruments used in encapsulation:

Instrument name	Origin (Country)	Segment	Magazine	Filling station	Filling pins in each station	Filling pressure (Bar)	Ongoing encapsulation
MG2-G140	Italy	-	-	48	1	6	Flugal 200 mg capsule
Harro höfliger	Germany	12	12+12	6	24	6	-
Sejong 100	South Korea	12	7+7	6	14	6	B-50 Forte capsule
Sejong 150	South Korea	12	10+10	6	20	6	-

Different sized tools are used to prepare capsules of 0 to size 4.

Here, 0 represents the largest capsule and 4 represents smallest capsule.

Workflow of encapsulation:

MG2-G140 automatic capsule filling machine:

Elevator contains the capsule shells

↓

Shells are sorted by rolling tubes → Defected shells are separated

↓

Caps are moved to upper part and bodies are moved to lower part

↓

Capsule shells are filled through suction

↓

Filled capsules are locked and discharged

↓

Ejected capsules are polished by a polisher

↓

Polished capsules are passed through a metal detector to detect if any capsule contain metal residues or not

Sejong 100 automatic capsule filling machine:

Elevator contains the capsule shells

↓

Shells are sorted by rolling tubes → Defected shells are separated

↓

Caps are moved to upper part and bodies are moved to lower part

↓

Capsule shells are filled by tamping method

↓

Filled capsules are locked and discharged

↓

Ejected capsules are polished by a polisher

↓

Polished capsules are passed through a metal detector to detect if any capsule contain metal residues or not

Tamping method:

Each station has 14 pins and fills the capsules from the bottom to the top. Station 1 fills the lowest part of the capsule shells. Station 2,3,4 fills the middle part one after another and station 5 fills the topmost part of the capsule shells. Station 6 ejects the capsules.

Packaging

Packaging is the science, art and technology of enclosing or protecting products for distribution, storage, sale, and use. Pharmaceutical packaging can be defined as the economical means of providing presentation, protection, identification, information, convenience compliance, integrity, and stability of the product.

Types of packaging

i. Primary Packaging

Primary packaging is the first level of packaging that comes in direct contact with the drug. It protects the product from moisture, light, air, and contamination and maintains stability. Ex: (Blister and Strip Packaging)

Modes of Primary Packaging Available in FU5

- Blister (tablets, capsules)
- Strip (tablets, capsules)
- HDPE bottles (PFS)

- Bottle filling line for tablets
- There are 12 packaging machines in this department. 9 for blister packaging, 1 for strip packaging and 1 for PFS & 1 is tablet and capsules filling machine.

- **Blister Packaging**

Blister packaging consists of a formed plastic cavity sealed with aluminum foil. It protects individual doses and improves patient compliance.

Blister packs are classified mainly based on the method of forming and the materials used:

Cold-Formed Blister (Alu–Alu Blister)

Cold-formed blisters are made by mechanical forming of aluminum laminate without heat. Both base and lidding are aluminum-based.

Thermoformed Blister (Alu-PVC Blister) or (Alu-PVDC)

Thermoformed blisters are prepared by heating plastic films (PVC, PVDC) and forming cavities. The filled cavities are sealed with aluminum foil.

Types of Instruments Used for Blister Packaging in FU5

Instrument name	Origin	Number of instruments
Heino Ilsmann 250	Germany	2
Heino Ilsmann 300	Germany	1
Hoong-A HM 400P	Korea	3
Hoong-A HM 600P	Korea	1
Hoong-A Minister V6	Korea	1
IMA blister pack	Italy	1
NOACK blister pack (inactive)	Italy	1

Process of Blister packaging

Tablets are loaded into the hopper.

↓

The hopper supplies tablets continuously to the feeding system by gravity or vibration.

↓

PVC / PVDC / Alu-PVC film is unwound from the roll.

↓

The film passes through heating plates.

↓

Heated film is formed into blister cavities using vacuum or pressure (forming mold).

↓

Tablets move from hopper to filling disk / channel.

↓

Tablets are guided and dropped into formed blister pockets.

↓

Sensors ensure correct tablet count (missing tablet rejection if any).

↓

Aluminum foil is unwound and placed over the filled blister.

↓

Heat and pressure are applied by sealing rollers/plates.

↓

Blister cavities are sealed tightly with aluminum foil.

↓

Sealed blister passes through cooling zone.

↓

Visual or automatic inspection for defects (empty pocket, improper seal).

↓

Continuous blister web enters the cutting unit.

↓

Blisters are cut into strips or cards of required size.

↓

Finished blister packs are collected in trays or conveyed to secondary packaging.

De-blistering

De-blistering is the process of removing tablets or capsules from blister packs in a controlled and systematic way, usually for quality control, reworking or inspection purposes.

- **Strip Packaging**

Strip packaging involves sealing tablets or capsules between two aluminum foils. It provides excellent protection from moisture and air.

Types of Instruments Used for Strip Packaging

Instrument name	Origin	Number	Ongoing packaging
SOLPAC	Korea	1	B-50 Forte Capsule

Process of Strip Packaging:

Capsules are loaded into the hopper.
↓
Capsules move downward by gravity/vibration to the feeding system.
↓
Capsules pass through channels
↓
Ensures one capsule per pocket and proper alignment.
↓
The upper foil and lower foil rolls of the strip packaging material are unwound
↓
Capsules are placed between the two foils at fixed intervals.
↓
Synchronization ensures accurate capsule positioning.
↓
Upper and lower foils are sealed together using heat and pressure.
↓
Capsules get enclosed in individual strip pockets.
↓
Sealed strip passes through cutting knives.
↓
Continuous strip is cut into required lengths
↓
Finished strip packs are collected in trays or sent to secondary packaging.

- **Packaging of Powder for Suspension**

Powder for suspension is a dry mixture intended to be reconstituted with water before use. Packaging is designed to protect the product from moisture, contamination, and loss of potency.

Types of Instruments Used for Powder for Suspension (PFS)

Instrument Model	Origin	Number	Ongoing packaging
CVC PFS filling line	Taiwan	1	Eromycin PD 60ml

Process of filling PFS:

Clean, dry glass or HDPE bottles are fed through unscrambler/conveyor.
↓
Bottles are oriented properly for further processing.
↓
Bottles are cleaned using compressed air.
↓
Removes dust and foreign particles.
↓
Bottles pass through drying tunnel or air drying zone.

↓

Dry powder is filled using filling system.

↓

Ensures accurate weight of powder in each bottle.

↓

Fill weight check at regular intervals.

↓

Ensures uniformity and compliance with specifications.

↓

Inner plug (LDPE) is inserted to protect powder.

↓

Screw cap is applied.

↓

Bottles checked for leakage (manual method).

↓

Bottles are labeled

↓

Batch, Mfg & Exp dates

↓

Bottles packed into cartons

↓

Measuring cup/spoon inserted

Packaging for Tablets Filling in Bottles

Instrument name	Origin	Number	Ongoing packaging
COUNTEC	Korea	1	Rex Tablet

Parameters to be checked for Blister/Strip Packs:

- Product name
- Cutting
- Embossing of batch no. & expire date is legible
- Perforation
- Correct printing
- Empty/torn/Dented pocket shift to operate the machine.

In-Process Check During Primary Packaging-

Leak Test:

Performed to ensure the integrity of the primary packaging (such as blisters and strips) by detecting any leakage. This test confirms that the package is properly sealed, preventing contamination, moisture ingress, or loss of product potency.

Appearance:
Visual inspection of the packaged product to verify the correctness of fill, sealing, labelling, and overall presentation. It ensures the absence of defects such as cracks, dents, improper sealing, discoloration, or foreign matter.

Camera Test:

Automated vision systems are used to inspect each unit for defects such as missing tablets, incorrect count, faulty sealing, misalignment, or printing errors. This test enhances accuracy and consistency while minimizing human error during high-speed packaging operations.

ii. Secondary Packaging

Secondary packaging encloses the primary package and provides identification, labeling. It also helps in branding and handling. Ex: (Inner Carton).

Components of Secondary Packaging

- Labels
- Leaflets
- Ancillary components like droppers, measuring cups, spoons
- Boxes
- Cartons-
- Inner cartons
- Shipper cartons
- Master cartons

Process of secondary packaging

The product is placed on a conveyor belt
↓
Visual inspection of the product
↓
Insertion of additional materials
↓
The packs are placed in an inner carton
↓
A batch code is printed on inner carton
↓
Inner carton is placed in a shipper carton
↓
Shipper carton is labelled and signed
↓
The weight of the shipper carton is measured
↓
Transferred to Master carton

12. Quality Control (QC)

Quality Control (QC) is a critical component of pharmaceutical manufacturing that involves the inspection, testing and verification of products and materials to ensure compliance with predefined quality standards. QC ensures that all starting materials, including raw materials (RM), excipients and packaging materials, comply with the approved specifications before being released for production.

Each QC laboratory is divided into four functional wings:

- Raw Material Testing
- Finished Product Testing
- Stability Studies
- Packaging Material Testing

QC Testing Parameters

Several analytical and physical tests are performed by QC to determine product quality. Common parameters include:

- **Appearance:**
  Visual inspection for color, uniformity, and absence of foreign particles.
- **Solubility:**
  Determines the solubility profile of a substance in specific solvents, ensuring consistency with pharmacopeial standards.
- **Melting Point:**
  Used to confirm identity and purity of raw materials; impurities usually lower or broaden the melting point range.
- **Particle Size:**
  Influences dissolution rate, bioavailability, and uniformity of dosage forms.
- **Loss on Drying (LOD):**
  Measures moisture or volatile content, which affects stability and shelf life.
- **Moisture Content:**
  Ensures the material does not exceed acceptable moisture limits that could cause degradation or microbial growth.

These tests collectively confirm identity, purity, strength, and quality of pharmaceutical materials.

Instruments Used in Quality Control

QC laboratories are equipped with advanced analytical instruments, including:

- **HPLC (High-Performance Liquid Chromatography):** Quantitative analysis of active ingredients and impurities.
- **IR / Raman Spectroscopy:** Identification of raw materials and excipients.
- **Sieve Shaker:** Particle size distribution analysis.
- **UV-visible Spectrophotometer:** Assay and content uniformity testing.
- **Gas Chromatography (GC):** Detection of volatile impurities and residual solvents.
- **Atomic Absorption Spectroscopy (AAS):** Trace metal analysis.
- **Density Meter:** Measurement of liquid density for formulation consistency.
- **Melting Point Apparatus:** Identity and purity confirmation.
- **Particle Size Analyzer:** Ensures uniform particle size distribution.
- **Refractometer:** Measures refractive index to assess purity and concentration.
- **Polarimeter:** Determines optical rotation of chiral substances.
- **Water Bath & Ultrasonic Bath:** Sample preparation and dissolution.
- **Moisture Analyzer & LOD Apparatus:** Determines moisture content to ensure stability.

Each instrument contributes to ensuring product safety, efficacy, and consistency.

Chemical Reference Substances (CRS)

Chemical Reference Substances (CRS) are used for identification and standardization purposes. Due to their high cost, working standards are prepared through proper dilution and validation to serve as alternatives, ensuring accuracy while maintaining cost efficiency.

Functions of QC:

i. Sampling and Material Control

During sampling, QC personnel attach sampled labels to materials undergoing testing.

MMIC (Materials Management and Inventory Control) supplies raw materials along with Goods Receipt (GR), Certificate of Analysis (CoA), and documentation.

ARD (Analytical Research & Development) provides approved specifications and test methods.

Untested materials are discarded if not tested within 7 days, while tested and approved materials are labeled as “Passed” and must be used within 60 days.

Sampling Methods

- **Raw Materials (RM):**

Tested both individually and as composite samples to ensure uniformity. Individual identification tests are confirmed using IR spectroscopy.

- **Excipients:**

For large consignments, random sampling is performed using the √(n+1) method.

ii. Process Validation and Batch Testing

At every manufacturing stage, QC performs tests and provides approval before proceeding to the next step or commercial production.

iii. Finished Product Testing

In-Process Control (IPC) tests are conducted on the production floor, while QC evaluates bulk products against predefined specifications. QC determines compliance with specifications but does not authorize batch release.

iv. Microbiological Testing

For vitamin and sterile products, microbiological testing is mandatory to ensure product safety.

v. Packaging Material Quality Control

Both primary and secondary packaging materials undergo strict QC testing. Parameters such as identity, integrity, dimensional accuracy and compatibility are evaluated to ensure product protection, stability and compliance with regulatory standards.

13. Quality Assurance

Quality Assurance (QA) is the systematic process of ensuring that pharmaceutical products are consistently produced, controlled, and documented according to predefined quality standards, regulatory requirements, and Good Manufacturing Practices (GMP), so that they are safe, effective, and of acceptable quality.

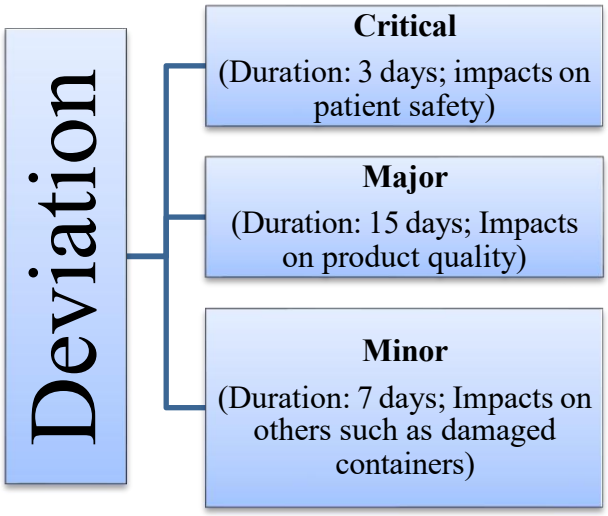
To find a root cause, QA follows the "6M method":

i. Man: QP, gowning
ii. Material: Potency, quarantine label, pass label, product label
iii. Machine: Instrument calibration
iv. Method: SOP, EOP
v. Measurement: Operational logbook
vi. Milieu (Mother nature): Environment, HVAC system

If all these are done properly, then cleaning pass is given. Validated cleaning is done by following MST (Manufacturing Science and technology). The aim of cleaning is to prevent physical, chemical, and microbial contamination.

Deviation

Any operation carried out in the pharmaceutical sector requires adherence to SOP. Deviation occurs when there is a fault with the SOP or specification. Deviation is basically departure from the standard. QIR needs to be ready for any harm or inaccuracy that may arise when the work is being done. In both situations, the materials are returned. to the storage facility. To find the issue, an investigating team is assembled. It follows a plan when conducting its investigation. It creates a report by going over the historical data. Finally, a determination is made regarding the applicability of the SOP. It is rejected if it is not.



The working procedure of QA is divided into 2 sections, such as:

- Operational QA or IPQA
- Documentational QA

Operational QA or In-Process Quality Assurance (IPQA)

IPQA involves monitoring of the manufacturing process on the production floor to ensure that the products meet the quality standards. It is done to detect problems at an early stage and reduce the rate of product failure.

Role of IPQA in the tablet production:

Before starting the production of a new product, QA checks these following steps to permit the production and ensure the product quality. After every complete cleaning, line clearance is done.

- **Dispensing**

Line clearance: Checks if the instruments are clean, ready to work and logbooks are prepared for entering data.

BOM check: Checks and ensures the bill of materials of the APIs and excipients that came from the warehouse. It is done in the pre dispensing area.

BMR check: At first, production checks the batch manufacturing record and then QA checks that. It is also done in the pre dispensing area.

- **Sieving**:

Line clearance: Done as before.

- **Granulation**:

Line clearance: Done as before.

Halogen moisture analyzer:

Checking of bubble point and logbook entry
↓
10 gm of tablet granules (Max 10.050gm) are kept in the apparatus
↓
LOD checking
↓
Time and % LOD input in logbook
↓
Printout is attached to the BMR

- **Blending:**

Line clearance: Done as before.

Waste handling is must in this step as the waste of one material should not mix with the other material.

- **Compression:**

Line clearance: Done as before.

Tests of IPQA: At the end of tablet compression, a sample batch is taken (For large tablets, 10 tablets are taken and for small tablets, 6.5 gm of tablets are taken as sample). These are done in the **IPC room.**

i. **Hardness & Thickness:**

Sample is taken as required and kept in the machine to measure their thickness and hardness at the same time.

Available instruments:

- SORTAX – 2 machines.
- ERWEKA – 2 machines.
- Pharmatron – 1 machine.

ii. **Friability:**

Sample is taken as required and kept in the machine for 4 minutes. The instrument is rotated at 25 RPM.

Available instruments:

- ERWEKA – 2 machines.
  One is single chambered which is used for the tablets compressed in single station compressor.
  Another is double chambered which is used for the tablets compressed in a double-station compressor.

iii. Disintegration:

Checks the time of tablet disintegration in 18 ml purified water.

Available instruments:

- ELECTROLAB – 2 machines.
- ERWEKA – 1 machine.
  6 tablets are tested in single chambered disintegrator.
  12 tablets are tested in double chambered disintegrator.

iv. Coating:

v. Packaging:

BMR is checked by HMI (Human Machine Interface)

- **Primary packaging:**
- **Secondary packaging:**

- **Batch release:**

Only qualified persons (QP) can release a batch.

To be a QP, a person must have experience in QA and have GMP, SOP based training.

Role of IPQA in the capsule production:

The process is similar to "Role of IPQA in the tablet production"

Here, encapsulation is done instead of granulation, blending and compression.

Hold time study:

Checks if the materials and products are held within the determined time or not.

If the product is held for more time, then deviation is raised.

If any problem is raised during production, QA solves those using the **"6 M method"**.

Documentational QA

In pharmaceutical sector, it is believed that, "If it's not documented, it didn't happen". This shows the importance of documentation. Documentational QA ensures that what is written, approved, followed, recorded, reviewed, and archived in a pharmaceutical facility is accurate, traceable, complete, and compliant with the regulatory requirements.

Documentational QA works through QMS (Quality Management System):

The QMS tools are:

i. APQR (Annual Product Quality Report):

The QA department performs an Annual Product Quality Review Report (APQR), which is a last one-year review to verify the consistency of existing processes, appropriateness of current specifications, and requirement checks for process improvement for an existing product. As the name suggests, APQR is performed annually. This is a calendar as per rolling forecast.

The APQR report consists of:

- **Review of starting materials**- Review of details of API and excipient sources, batch numbering, QC batch results, vendor approval details, number of materials used, batch numbers used, supply chain traceability.
- **Review of critical IPC and finished product test result-** Review of processes of dispensing, granulation, blending, compression, coating, packaging; review of results of LOD, hardness, thickness, average weight. Data collection is carried out, histogram and trend- chart are made. Process capability (CpK) and percentage yield value determination based on 25 batch or minimum 10 batch.
- **Review of specification meeting failed batches**- Review of OOT and OOS data is carried out, review of batch rejection records, review of quality incident report and laboratory incident report is done. Deviation, reprocessing, and CAPA effectiveness reviewed.
- **Review of process or analytical process changes-** Process related changes and their details are reviewed. Analytical method and/or analytical specification changes and their details are reviewed.

Review of adequacy of product related CAPA- previous year CAPA review.

Process capability index- Compilation of process capability (CpK) values. CpK is the ability of a process to produce output within specification limit. The acceptance criterion for a capable process is CpK $\geq$1.33.

Review of previous APQR- previous year APQR review. Comparison of hardness, thickness, average weight, percentage yield, assay, DT, CpK values and details of previous year and current year APQR data.

Recommendation- After performing full APQR, any suggestions or solutions are included.

Conclusion- Processing parameters for APQR are reviewed.

Enclosure- Contains appendixes.

ii. QIR (Quality Investigation Report):

Quality incident report
↓
Root cause
↓
Capa
↓
Investigation
↓
Quality check
↓
Report

iii. OOS (Out of Specification):

A situation where a material, procedure, or product does not fulfill the requirements or criteria stated in its quality standards is referred to as being Out of Specification (OOS). This could involve any parameter that is essential to the quality of the product, such as potency, purity, stability, or any other feature. In the case that a specification is found during the handling of a pharmaceutical product that deviates from the specification provided in the documentation, QC will raise an OOS.

OOS investigations happen in two parts:

Phase-I

Phase-I investigation shall be carried out in two phases, Phase I (a) and Phase I (b):

Phase I (a) consists of a preliminary review, by the analyst, to determine whether there has been a clear and obvious root cause that caused the OOS.

Phase I (b) occurs after phase -I A has failed to identify a clear and obvious cause. This is a more detailed investigation by the analyst and supervisor. Here, a hypothetical root cause is taken under consideration and is investigated to determine the actual root cause.

Phase-II

Phase II is done when phase I fails to determine the actual root cause. The investigation consists of manufacturing investigation and laboratory investigation:

Manufacturing investigation- At first deviation is raised, then investigation is carried out by a specific team selected by QA, root cause is identified through 6M, CAPA is raised against root cause, report is prepared and submitted.

Laboratory Investigation- It is done if the manufacturing investigation does not reveal the actual root cause.

Separate studies are conducted, and the results are compared. Then the comparative results are validated.

If the results are same, the root cause is determined, CAPA is raised against that and report is submitted.

If the results are different, then no root cause is determined properly. Then a hypothetical root cause is considered by the experts and from that the root cause is determined. CAPA is raised against that root cause and the report is submitted.

QA additional laboratory testing shall include retesting a portion of the original sample is not sufficient for retesting. After finding a suspect and suspect analysis, hypothesis identification and find out the root cause, if the root cause cannot be found out the procedure is repeated.

iv. OOT (Out of Trend):

When observed data points deviate from the established trend or predicted range for a certain parameter, it is referred to as being "Out of Trend." Here atypical data are found. A parameter or collection of data points that deviates from the anticipated or previous trend is indicated by an out- of-trend result. It is also determined by the 6M method.

v. CC (Customer Complain):

It consists the problems related to distributed products and includes query management.

At first product is identified that it belongs to the company
↓
Representative sample is checked
↓
Investigation is done
↓
Feedback report is sent to the complainer
↓
If the complaint is valid, the batch is isolated (one in a billion)

Product Recall

Product recall occurs against a product complaint. When a product complaint comes, then QA verifies the complaint's validity. There are 3 classes of product recall-

- CLASS 1 – Immediate recall
  The product must be recalled within 24 hours
  DGDA must be notified about the Incident.
- CLASS 2 – Recall product
  DGDA can be notified or may not be notified
  The problem can be harmful, but not as much as class 1.
- CLASS 3 - Recall product
  Do not need to notify DGDA
  Minor problems

vi. CAPA (Corrective Action and Preventive Action):

If any incident occurs and an action is taken to rectify it, it is called corrective action.

To prevent the incident from repeating in future, the action taken is called preventive action.

CAPA can be raised from any site. If CAPA is not completed within time, timeline is extended with valid reasoning and justification by the responsible department. The justification should be scientific, calculative, specific, and accountable.

CAPA can be defined in two types according to the timeline. These are-

Short term CAPA- 90 days timeline. No report is needed.

Long term CAPA- More than 90 days. Monthly progress report is required.

vii. Quality Risk Management:

Risk is defined as the multiplication of the severity, probability, and detectability. QRM system assesses the risks involved in a process and then aims to mitigate them to reduce their probability. QRM outcome is always aimed towards ensuring that patient safety is prioritized. The risk is first identified and understood, what the risk is, what information is available regarding the risk. The QRM system can be categorized into the following:

Risk analysis: The degree of the risk is then analyzed. How severe is the risk, how likely it is to occur, etc. are observed and understood. It is sub divided into 2 sections: **Failure mode and solve process.**

Risk mitigation: Here CAPA is raised and process is validated by batch checking. If approved, date is determined, and work is done within time.

viii. Change management:

Change Control Request (CCR)

It is the system that manages changes that may affect product quality or the reproducibility of the process. A written procedure that describes the action to be taken if a change is proposed to facilities, materials, equipment and or processes used in the fabrication, packaging and testing of drugs that may affect the operation of the quality or support system. It is done through 6M method.

Change Control Requests are of three types (based on severity, probability, detectability)**:**

- Major
- Moderate
- Minor

Workflow of CCR:

Change identification
↓
CCR initiation
↓
Preliminary review by QA
↓
Change classification & impact assessment
↓
CCR review and approval

Change Document Request (CDR)

The change document request (CDR) process serves as the formal mechanism of initiating & controlling changes to critical documents by a company's QMS. Here no action is changed.

Workflow of CDR:

Change proposal of CDR to QA manager by any trained person to raise CDR
↓
Risk analysis
↓
Risk management by QRM
↓
Action plan
↓

Date selection to execute plan
↓
Work complete within time
↓
CDR controller approves the change

Rejection management:

- The products are excluded from the calculation because of:
- Failure to maintain quality
- Expired material
- Container integrity affected

Workflow of rejection:

Rejection form is raised (Including batch no and form no)
↓
Investigation
↓
QA approval
↓
EDTO (Executive Director Technical Operation) acknowledgement
↓
Destruction within 6 months

ix. Self-inspection (Audit):

It is conducted to reduce the risks of failure in actual audit. It is done by a lead auditor, a co-auditor, and a trainee auditor**.** It is of 2 types:

- For high-risk area, yearly 2 self-inspections are done.
- For low-risk area, yearly 1 self-inspection is done.

The auditee must be informed at least 15 days before the audit.

All these tools ensure the quality of the company.

x. Vendor Management

Vendor approach
↓
Vendor questionnaire
↓
Sourcing by TSD

↓

DQA

↓

Tracking number

↓

FD

↓

ARD (MOA, COA as per USP, BP)

↓

Initial Test

↓

R&D Trial

↓

Physical parameter by FD
Chemical analysis in ARD

↓

Stability chamber

↓

Manufacturing certificate

↓

GMP

↓

DGDA and these types of authorities

↓

MSDS

↓

Impurity profile

↓

Nitrosamine impurity and heavy metal impurity

↓

Residual solvent

↓

TSE, BSE, Stability data

↓

Assessment report from R&D

↓

QA approval

↓

CCR raise

↓

Qualify in the SAP

↓

Vendor approved by QA

↓

Supply Chain Management can buy from the vendor

↓

Provisionally approved list

↓

Successful Process Validation

↓

Included in approved list

Vendor Disqualification

Batch fail/OOS
↓
Inform
↓
Vendor check
↓
CAPA raise
↓
Consecutive 3 batch fail
↓
Disqualify

Requalify

Vendor requalify is done after every 3 years.

QC gives vendor ratings.

1= 100%

0.5-0.8 = Need to inform the vendor to improve their quality

<0.5 = Not good

Vendor Audit

Audit is done for -

- All API vendor
- Critical excipients
- Primary packaging
- Secondary packaging

Audit team is formed with at least one qualified person from QA and another qualified person from QC. For sterile product, audit team is formed with qualified personnel from QA and microbiology department.

Types of Audits

- Announced - On site audit

- Unannounced
- Remote - Only paper audit
- Third-party audit - Audit report from other company.

➢ **Archive**

An Archive is a controlled area used to systematically store and preserve GMP documents and records for a defined retention period

Significance of Archive

- Ensures traceability and accountability
- Support audits, inspections, investigations
- Enables deviation, OOS, and CAPA investigations
- Controls obsolete and superseded documents

Types of Documents stored in Archive

- All documents related to GMP except HR, accounted, finance related documents
- BMR
- QA documents e.g. QMS, deviation, CCR, CDR
- Packaging material documents
- QC raw data & reports
- Calibration & maintenance records
- Training records
- Warehouse & distribution records
- Obsolete documents
- Logbooks

Important terms related to Archive

- **Retention Time:**
  Retention Time is the predefined period for which a document, record, sample, or product must be retained and stored in a controlled manner to comply with regulatory requirements.
  Usually, Retention Time varies depending on purpose of the product.
  Documents related to CCR are kept for lifetime, QMS documents are kept for 6 years and all type of logbook for 5 years.

- **Obsolete Document:**

Obsolete documents are documents that are no longer in use, valid, or applicable for current operations, procedures, or regulatory compliance.

- **Controlled copy:**
  A controlled copy is an officially approved, current version of a document issued to authorized personnel for operation ensuring compliance

- **Uncontrolled copy:**
  An uncontrolled copy is a reference-only document that is not approved or controlled for GMP operations. It is normally for reading purposes

Archive workflow

Documents approved by QA
↓
Assign document name, number, batch number, date of archival, Retention period and index in logbook
↓
Transferred in Archive
↓
Stored

Disposal of Archive documents

After every 3-month archive documents are disposed.

Documents selected and proposal is given to QA
↓
QA manager approves
↓
Checked by authorized personnel in Archive room
↓
File from the shelf is taken
↓
Incineration label is placed on the file
↓
Documents disposed

Retrieval of documents from Archive

Documents requested and QA approves

↓

Logbook entry

↓

Documents can be kept for 1 month

↓

Return

14. Conclusion

The In-plant training experience at Square Pharmaceuticals PLC. has provided me an invaluable opportunity to bridge the gap between academic knowledge and real-world application. The training encompassed several critical departments: Human Resources (HR), Warehouse, Research and Development (R&D), Production, Quality Control (QC), Quality Assurance (QA). This comprehensive exposure has given me a holistic understanding of how the industry functions and the interdependencies between various departments. I have learned about the inevitable role of documentation, the importance of SOPs and GMP, and the collaborative efforts required to bring a pharmaceutical product from conception to market. This training has not only reinforced my academic knowledge but also equipped me with practical skills and a broader perspective on future opportunities within the industry. The experience has underscored the importance of continuous learning, adaptability, and teamwork in the dynamic and ever-evolving pharmaceutical field. The HR department plays a pivotal role in the pharmaceutical industry. During our training, I observed how HR manages recruitment, training, employee relations, and compliance with labor laws. The exposure to the ARD department provided me with an understanding of the analytical techniques used to ensure the quality and efficacy of pharmaceutical products. I learned about various analytical methods, such as chromatography, spectroscopy, and dissolution testing. During our training, I observed inventory management practices, including the use of advanced software systems for tracking and managing stock. I learned about the significance of proper storage conditions, inventory turnover, and the logistics involved in ensuring that products are delivered on time. We learned about the various stages of production, including dispensing, sieving, granulation, blending, compression, encapsulation and packaging. I also observed how production teams work closely with QC and QA to ensure that the products meet all necessary standards. My time in the QA department underscored the importance of Standard Operating Procedures (SOP) and Good Manufacturing Practices (GMP). Learned about the processes involved in quality control, including sampling, testing, and validation. QA ensures that all products are manufactured consistently and comply with all regulatory requirements.