Report On

Industrial Training at Sanofi Bangladesh Limited.

By

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An internship report submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

Department of Pharmacy
Brac University
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Declaration

It is hereby declared that

1. The internship report submitted is my/our own original work while completing degree at Brac University.
2. 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.
3. The report does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

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Letter of Transmittal

Professor Dr. Eva Rahman Kabir

Chairperson,

Department of Pharmacy

Brac University

66 Mohakhali, Dhaka-1212

Subject: Submission of the Industrial Training Report Titled “Industrial Training at Sanofi Bangladesh Limited.”

Dear Madam,

It is an immense pleasure for us to submit to you the industrial training report titled “Industrial Training at Sanofi Bangladesh Limited.” Our main incentive was to prepare this report according to your guidelines and in accordance with your directions. We hope that we have done a satisfactory job considering our level of experiences and capabilities and have been able to relate the fundamental things with realistic applications.

Moreover, we are extremely thankful for the opportunity that you gave us to express my ability and we intently hope that you will like the work that we have done.

Sincerely yours,

Fariha Bushra
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Department of Pharmacy
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Non-Disclosure Agreement

This agreement is made and entered into by and between Sanofi Bangladesh Limited and the undersigned students at Brac University.

Acknowledgement

We would like to begin by thanking Almighty Allah who enabled us to complete this in-plant training successfully. However, this would not have been possible without the help of some respective individuals acknowledged below.

First of all, we are immensely grateful and indebted towards Mr. Muin Uddin Mazumder, Managing Director, Sanofi Bangladesh Ltd, Tongi IA, for giving us this opportunity to complete our In-plant training at a multinational pharmaceutical company like Sanofi Bangladesh Ltd. Secondly, we would like to thank Mr. Aminul Islam, Head of Plant HR and Mr. Ishtiaq Ahmed, Head of Manufacturing for their support and cooperation throughout the training period. We would also like to express our deepest appreciation to our In-plant training Coordinator Ms. Beronika Halder, Assistant Manager Site Office Coordination for her guidance and support throughout. Lastly, we want to acknowledge all the department heads, executives and working bodies of this site, for their valuable insights that helped us write this report.

Last but not the least, we would like show our gratitude, honor and unremitting respect and thank Dr. Eva Rahman Kabir, Professor and Chairperson, Department of Pharmacy of Brac University and Dr. Hasina Yasmin, Academic co-ordinator, Department of Pharmacy, Brac University, for giving us scope, support and opportunity to over past our in-plant training.

Executive Summary

This industrial training report is based on our experience throughout the training and our academic learning. It had been a tremendous opportunity to experience the work of different sectors of a multinational pharmaceutical organization. Firstly, the report discusses about the history of Sanofi Bangladesh Limited. Then the report discusses about the products they are manufacturing. Lastly, the working processes of different sectors in Sanofi Bangladesh Limited were briefly discussed.

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List of Acronyms

BMR	Batch Manufacturing Record
BPR	Batch Packaging Record
HRM	Human Resources Management
RM	Raw Materials
GMP	Good Manufacturing Practice
SOP	Standard Operating Procedure
PO	Purchase Order
OEB	Occupational Exposure Band
HSE	Health Safety and Environment
LAF	Laminar Air Flow
QC	Quality Control
QA	Quality Assurance
QS	Quality System
PTW	Portable Water
WFI	Water for injection
LAL	Limulus Amoebocyte Lysate
HVAC	Heat Ventilation Practice

Chapter 1

Introduction

1.1 Sanofi Bangladesh Limited

The pharmaceutical industry is one of Bangladesh's most promising fields. The 1982 drug ordinance coordinated the entire business in such a good course, to the point that in the late years Bangladesh is practically independent in delivering drug. The multinational organizations with a superior quality suggestion keep on offering new items. Being one of the main multinational pharmaceutical organizations working in Bangladesh, Sanofi Bangladesh Limited is applying its best push. Sanofi is a global pioneer in pharmaceutical companies. It is a French multinational pharmaceutical company and the global headquarter is situated in Paris, France.

Sanofi is involved in not only the manufacture and sale of prescription drugs and non-prescription products, but also in research and innovation. Sanofi is committed to customers, employees and more importantly patients.

In Bangladesh, Sanofi has been operating since 1958, in order to bring world-class treatment options at the doorstep of patients. Our vision is to be the most admired and best-in-class healthcare partner enhancing the quality of life through prevention, cure and innovation, with commitment towards society and environment. To uphold the pledge, products of global standard are produced at Tongi plant, following strict GMP (Good Manufacturing Practices) standards and maintaining international storage facilities. Sanofi Bangladesh Limited has a wide range of products with a broad array of names such as Pevisone, Flagyl, Sefrad, Fimoxyl, Xerosec etc. Sensitive and high-tech products like vaccines, insulin and chemotherapeutic drugs are imported directly from France, USA, UK and Germany.

Vision:

“To be the most admired and best-in-class healthcare partner enhancing the quality of life through prevention, cure and innovation with commitment towards society and environment”.

Mission:

Develop and master the best supplier network to deliver Sanofi’s strategic, ethical and operational objective.

1.2 History of Sanofi

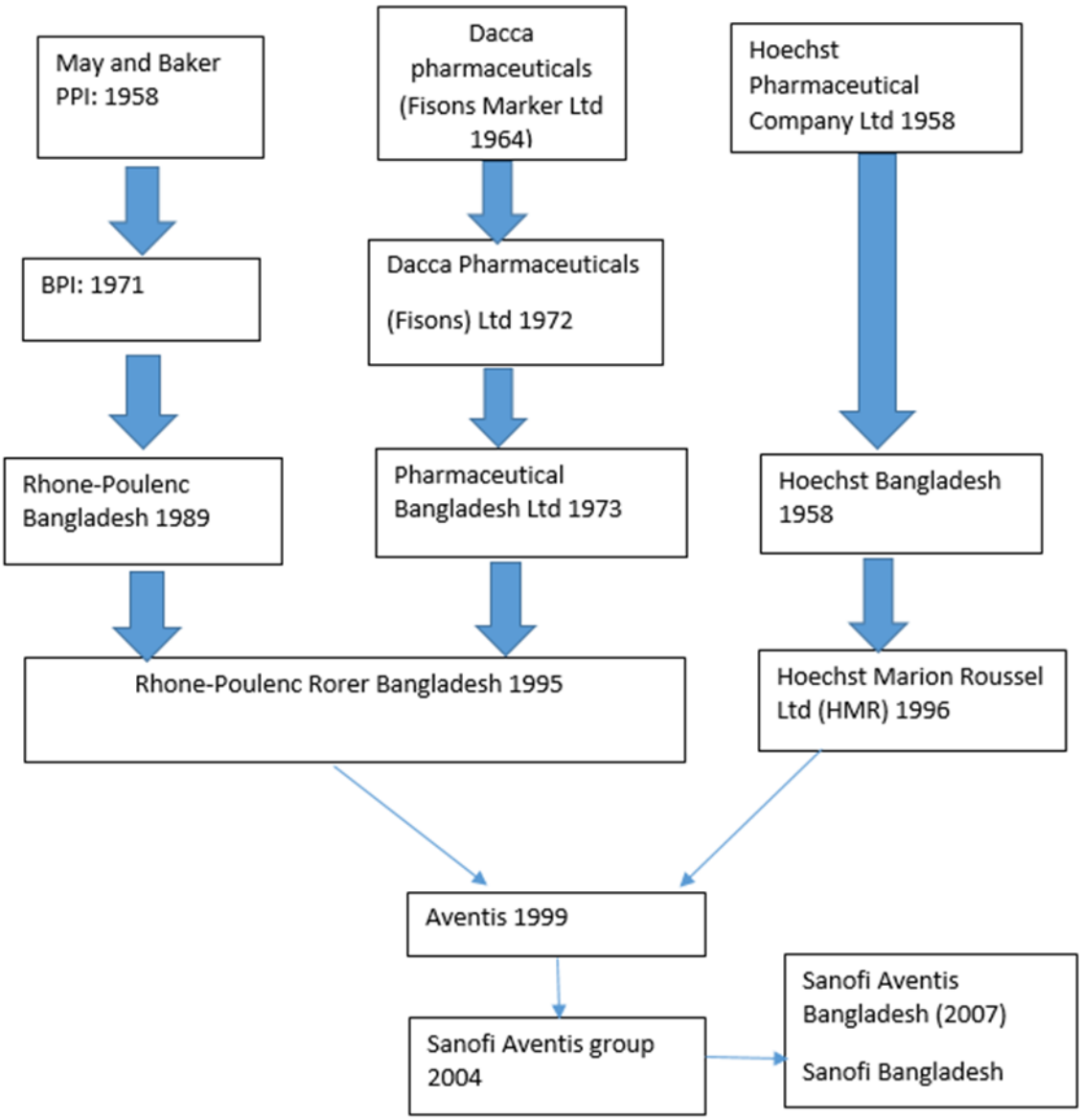


Figure 1: History of Sanofi Bangladesh Limited

Chapter 2

Human Resources

Human resources describe the people who make up the workforce of an organization, industry, business sector, or economy. The term human resources were first coined in the 1960s when the value of labor relations began to garner attention and when notions such as motivation, organizational behavior, and selection assessments began to take shape. It is the department or support programs accountable for the recruitment and recruiting of staff, the screening of candidates, the production and monitoring of expertise, the implementation of benefits and adherence with relevant governmental regulations.

Human Resource Departments are the entities organizations form to organize people, reporting relationships, and work in a way that best supports the accomplishment of the organization's goals. The definition of human resource management emphasizes the sphere of influence to encompass 'the strategic approach to manpower management in an organization'. On the other hand, HRM is the organizational function that deals with issues to people such as compensation, hiring, performance management, organization development, benefits and disputes, employee motivation, communication, administration and training. Examples of core qualities of HR management are extensive knowledge of the industry, effective. Human resources department has two wings: human resource and administration as well as security.

2.1 Function of Human Resources department

Table 1: Function of HR department

Human resources	Administration	Security
Recruitment	Canteen management	Building security
Performance management	Employee transport	People protection
Talent management	Laundry and dress management	Crisis management
Training & management	Site up keep	Product protection
Industrial & public relation	Visitor management	Cyber and info protection
Salary and wage administration	Regular attendance	Business protection
Legal activities	OT recording & payment	
Regular HR reporting	Service book and leave management	
Orientation- New employee	Licenses management	
Organize in-plant training	Property and salvage management	
Employee grievance handling	Out sources management	
Event management		

Chapter 3

Good Manufacturing Practices (GMP)

GMP is that part of Quality assurance which ensures that the products are consistently manufactured and controlled to the Quality standards appropriate to their intended use. GMP is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production than cannot be eliminated through testing the final product.

3.1 Importance of Good Manufacturing Practices

GMP prevents errors that cannot be eliminated through quality control of the finished product. Without GMP it is impossible to be sure that every unit of a medicine is of the same quality as the units of medicine tested in the laboratory.

GMP should be implemented to ensure that-

- The manufactured drugs are safe and providing intended therapeutic effect.
- The drugs do not contain any toxicity and thus free of any health hazard.
- The proper maintenance of GMP enhance the export opportunity.

3.2 Key aspects of GMP

- All manufacturing processes are clearly defined in it.
- Qualification and validation are performed according to the instruction of GMP.
- All necessary information is provided, including

    - Qualified and trained personnel
    - Adequate premises and space
    - Suitable equipment and services
    - Approved procedure and instructions
    - Suitable storage and transportation
    - Appropriate material, container and label

- Adequate personnel, laboratory, equipment for in process quality control

- A system is available to recall any batch of products from sale or supply
- All the steps should be documented in logbook written in cleared and unambiguous language.

3.3 Rules of GMP

- Design and construct the facilities and equipment's properly.
- Following written procedures and instructions.
- Monitoring who does what
- Keep step by step records
- Train and develop stuffs
- Practice good hygiene
- Maintain facilities and equipment
- Control components and product related process
- Perform regular audits.

3.4 Aim of GMP

- To ensure consistency of the product
- To avoid contamination and cross contamination
- To ensure that the product conforms to its specified quality, it is safe for usage and the product will produce desired effect

GMP also ensures that the manufacturing facilities are staying up to the mark or not. In manufacturing area there are three separate units:

1. Non-Antibiotic Area
2. Penicillin Unit
3. Cephalosporin Unit

Non-Antibiotic area is also divided into three different divisions. They are:

1. Solid dosage form
2. Semisolid dosage Form
3. Sterile products.

Chapter 4

Health Safety and Environment

A health safety and environment (HSE) management system has been established in Sanofi Bangladesh Limited. It covers all Sanofi operations carried out at any locations in factories, offices and warehouse. This system is designed to ensure health and safety of each employee working at Sanofi, to develop safe industrial processes, and to limit the environmental impacts of Sanofi activities and products.

Objectives of HSE:

- Actions taken
- Application of HSE policy
- To eliminate the health, safety and environmental risks
- Develop initiatives to fertilize HSE within all activities and pro-actively contribute to continuous improvement
- Monitor performance

HSE Management System:

The structure of HSE Management System is based on the "Plan-Operate-Monitor-Improve" structure. This is equivalent to the management approach plan-do-check-act

Figure 2: The structure of HSE Management System

Plan: A risk-based approach is developed to enable the establishment of comprehensive objectives and plans to improve management of risks and compliance to applicable regulations and conformance to internal requirements.

Operate: Operational controls, procedures and processes are implemented to ensure safe work practices and effective control of risks.

Monitor: HSE results are monitored on an ongoing basis to measure the performances against targets. Audit is performed to evaluate the system effectiveness.

Improve: Regular management reviews are performed.

HSE Missions:

In compliance with Sanofi commitments as defined in its code of ethics, the main mission of the global HSE team are:

1. Define and implement action plans, documents, processes, method, tools to prevent and limit HSE risks and impacts.
2. Ensure that current and emerging scientific, technical, and regulatory issues are captured and communicated.
3. Point out significant HSE risk.
4. Participate to merger and acquisition operations as well as assessment of environmental risks and management of risks directly retained or indirectly retained regarding given guarantee.
5. Support all sites and organizations in each business and along all the value chain (Engineering, Procurement, suppliers and etc) to carry out plans to achieve continuous HSE progress.
6. Strengthen the HSE network and job family by developing core expertise and competencies as HSE Management System.

HSE Management System:

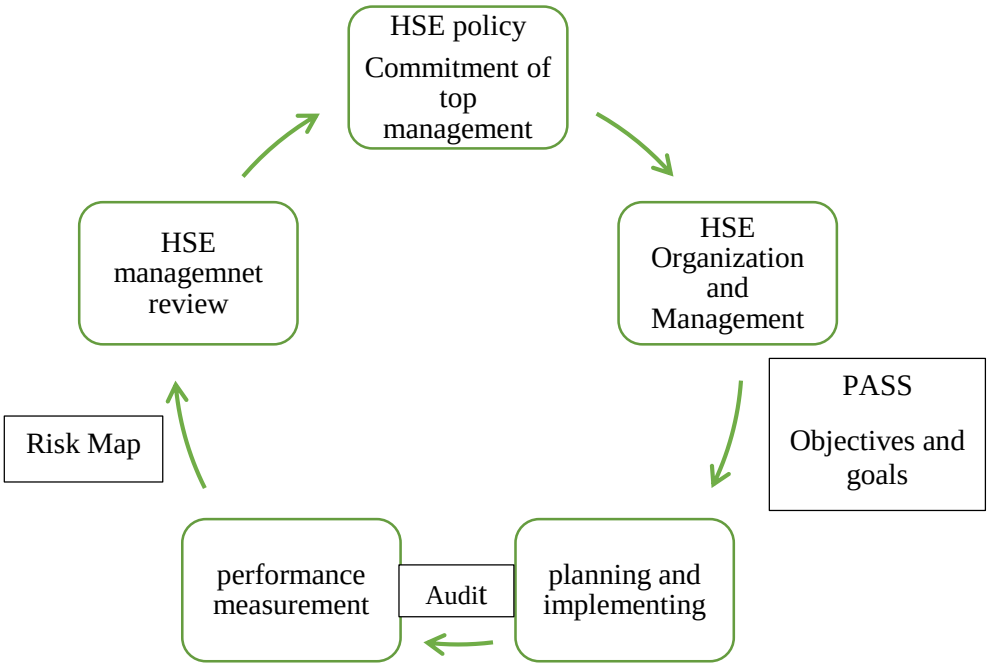


Figure 3: HSE Management System

HSE Management Tool:

1. Policy
2. Documentation
3. Governance
4. Organization and Resources

Some key activities of HSE:

1. PASS Annual HSE action
2. Training Program
3. Internal HSE audit and inspection
4. Risk assessment
5. Evaluation of compliance
6. Emergency Management
7. Waste Management
8. Health Awareness

4.1 Risk identification, Management and Operating Control

The process for risk identification and management is a pillar to the global Health, Safety and Environment Management System. Its Main purpose is to identify hazard and risks, assessing their likelihood and potential effects establish a global risk mapping and implement risk mitigation measures, for process safety, occupational hygiene and environment.

Appropriate controls are identified and implemented following the hierarchy of risk control strategy in order, eliminate, substitute, technical measure and engineering controls, organizational measure, personal protective equipment

Risk assessments are reviewed annually or at each significant change and are consolidated yearly in a risk matrix.

Chapter 5

Procurement

Procurement is act of buying goods, services from outside external sources. More precisely, it means acquiring supplies through purchase. Generally, it deals with cost, quality and delivery. To run a company smoothly, procurement plays essential role. In case of a Pharmaceutical industry, it is indispensable as purchasing is involved in the initial step to produce a drug i.e. from raw material buying issue to equipment and machinery buying steps.

Function:

- **Sourcing:**
  Suitable supplier and vendors are identified.
- **Negotiating:**
  Price is compared with the corporate and competitor benchmarking is another good form of negotiation. In Sanofi Bangladesh there are two teams for this process. They are in India and China. It is called LCM (Low Cost Market Team).
- **Purchase order:**
  After collecting the PO, communication with supplier is maintained until materials are received.
- **Shipment purchase order follow-up:**
  Follow up above mentioned process i.e. from sources of purchasing, negotiation and following up of purchase order. Shipment dates are adjusted and maintained.
- **Issue of Purchase Orders**
- **Maintenance of Purchase Records**
- **Follow up of Purchase Order for Delivery in Time**
- **Maintenance of Vendor Performance Records**

5.1 Procurement domain:

Table 2: Procurement domain

Marketing & Sales	**Common Spend**	**COGS & Distribution**	**Manufacturing CAPEX & Maintenance**	**Scientific & Clinical**
1. Promotional Items	1. Fleet & Travel	1. Raw Materials Secondary Manufacturing	1. CAPEX	1. Clinical
2. Market Research	2. Energy & Waste	2. Raw Materials Chemistry, Biotechnology & Vaccines	2. Spare parts & Maintenance	2. Lab. Equipment & Supplies
3. Communication Agencies, Events & Media	3. IT & ETMS	3. Packaging & Devices		3. Research Materials & Subcontracting
	4. Real Estate & Site Services	4. Supply Chain, Subcontracting & Licenses		
	5. Consulting, HR & Insurance			

5.2 Purchasing process:

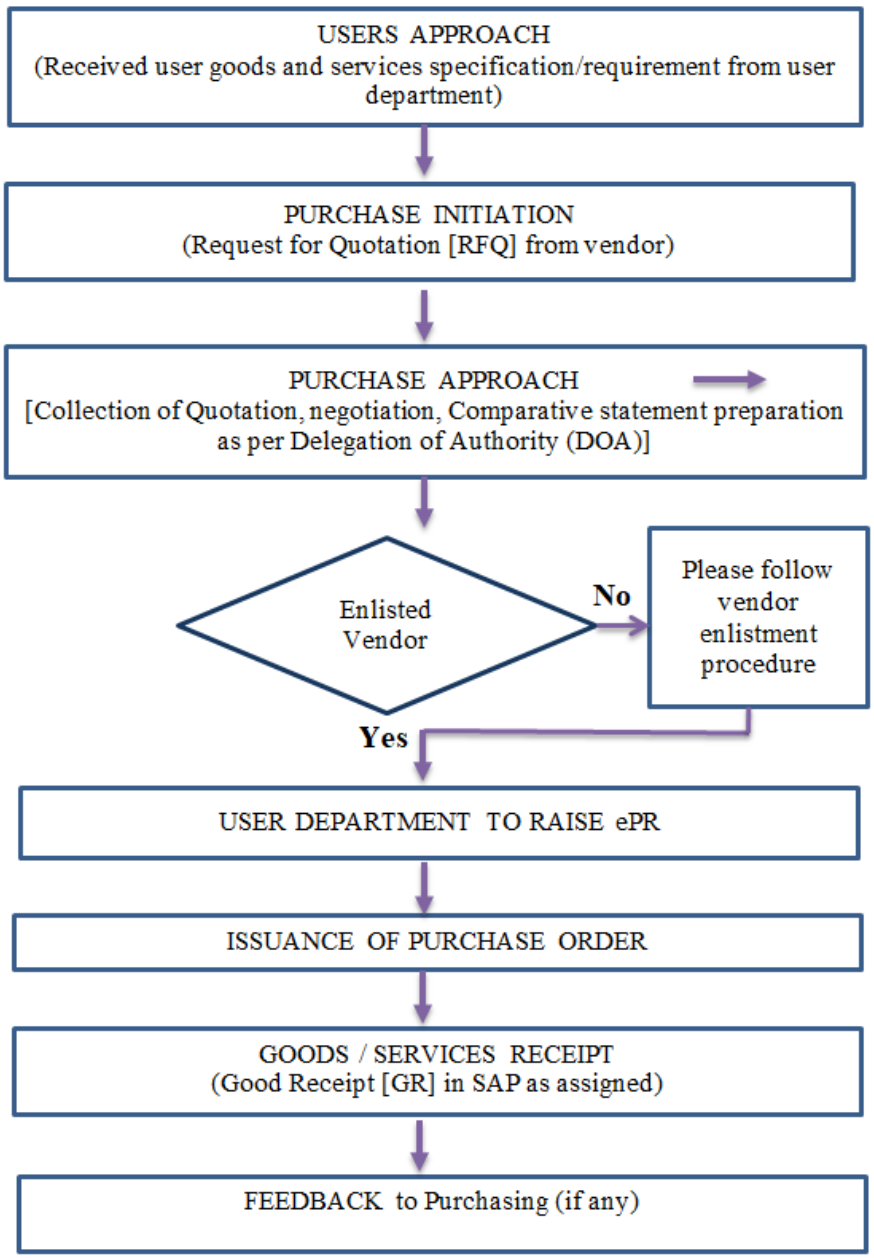


Figure 4: Work flow of Purchasing Process

5.3 Type of Purchase:

- COGS (Costs of Good Sold)-Raw materials and packaging
- Non- COGS

5.3.1 Work flow for purchasing department:

- **For COGS**

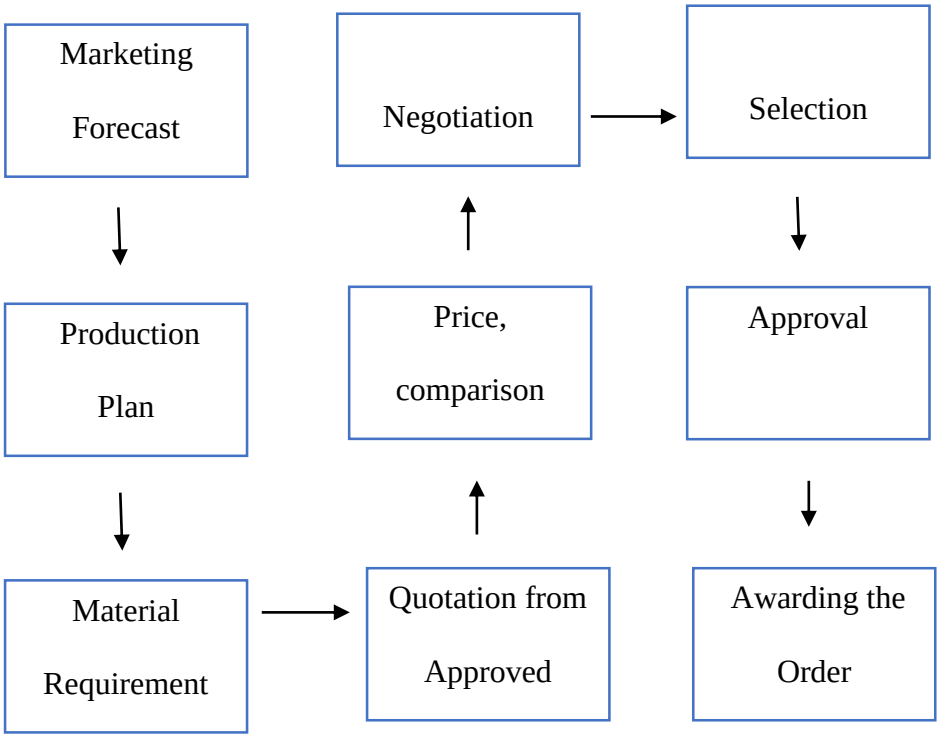


Figure 5: Work-flow of COGS

COGS Purchasing Process (Approved Import Source):

1. Formal Purchase Requisition received from Planning Department through SAP
2. Downloaded the PR in excel and prepare a file with the detail information on last Purchase status along with the Budget data.
3. RFQ submits through electronic mail communications to the respective approved sources to the LCM China/India Sanofi and also Third party.
4. Check the quotation with the previous data on pricing, Qty and the local drugs approval status on pricing, QTY and source validation status.
5. After completion of negotiation process prepare Comparative Statement (CS)

6. After receiving respective authority Approval on CS, issue PO in favor of respective approved Vendor and submits for respective authority approval.
7. After receiving the PO approval, organize all necessary documents for L/C establishment/Advance payment and submit to Commercial department
8. After receiving the L/C docs from Commercial we shared the PO and L/C copy to LCM China/India Sanofi or the third party (Vendor).
9. To maintain shipment deadline, do follow up with LCM China/India Sanofi and also third party for shipment update and reference shipping documents.
10. Shipping documents share to Commercial department to maintain the Clearance process
11. Completing the clearance process respective docs maintain to Archive

- **For non-COGS**

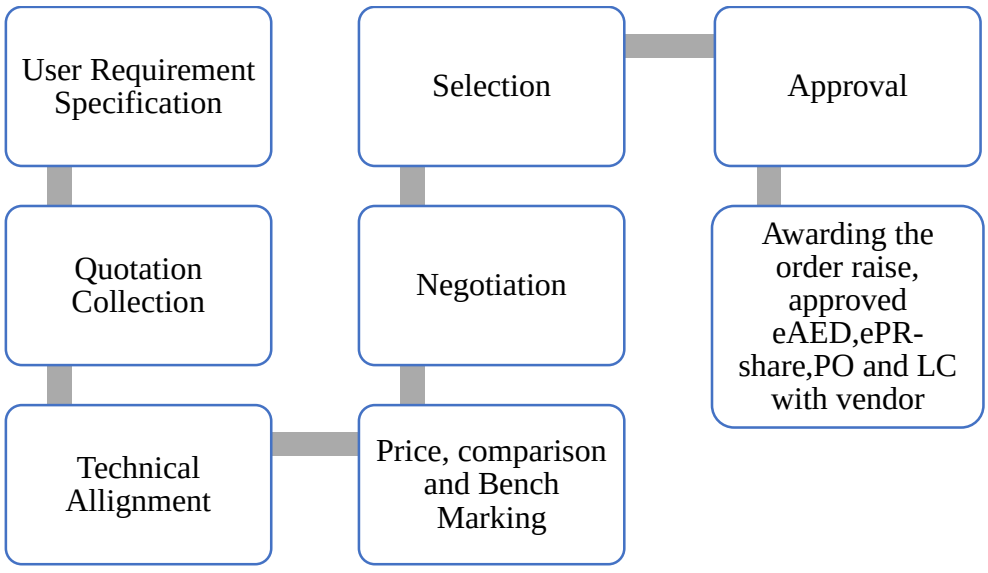


Figure 6: Work-flow of non-COGS

Non-COGS Purchasing Process (For Imported Sourcing):

1. Formal URS received from USER department/Project department
2. Selection of vendor group or sourcing
3. Request for quotation
4. Pre bid meeting (between vendor and USER department/Project department to clarify technical issues

5. Offer/ Quotation collection (Technical and financial offers separately)
6. Technical offer offered to user/ project department for technical evaluation and arrange technical evaluation, meeting with vendor
7. Negotiation meeting with vendor
8. Vendor selection (based on technical and financial negotiation)
9. Comparative statement preparation
10. Arrangement of approval of comparative statement as per financial delegation of authority
11. Request for AED
12. Request for ePR
13. ePR approval from purchasing and purchase order (PO) print through SAP
14. Arrangement of approval of PO as per financial delegation of authority
15. Sharing the PO with the vendor and request the proforma invoice.
16. Request for LC to commercial department
17. Sharing the LC with the vendor
18. Following up the shipment status
19. After shipment, sharing the shipping documents with the vendor
20. Arranging the installation and commission for CAPEX equipment
21. Archiving the purchasing documentation and reporting

Non-COGS Purchasing Process (For local sourcing):

1. Formal URS received from USER department/Project department
2. Selection of vendor group or sourcing
3. Request for quotation
4. Pre bid meeting (between vendor and USER department/Project department to clarify technical issues
5. Offer/ Quotation collection (Technical and financial offers separately)
6. Technical offer offered to user/ project department for technical evaluation and arrange technical evaluation, meeting with vendor
7. Negotiation meeting with vendor
8. Vendor selection (based on technical and financial negotiation)
9. Comparative statement preparation
10. Arrangement of approval of comparative statement as per financial delegation of authority

11. Request for AED and ePR
12. ePR approval from purchasing and purchase order (PO) print through SAP
13. Arrangement of approval of PO as per financial delegation of authority
14. Sharing the PO with the vendor
15. Following up the delivery status
16. Arranging the installation and commission for CAPEX equipment
17. Archiving the purchasing documentation and reporting

Chapter 6

Supply Chain Management

Plant supply chain has three departments:

- Planning
- Commercial
- Warehouse

6.1 Planning Department

Planning is the process of analyzing the current situation, assessing needs, establishing goals for the organization, setting objectives and determining the strategies, responsibilities and resources needed to achieve the goals.

Planning department deals with the planning of different process starting from the initial entries into the warehouse and until to the entries of the finished goods.

Key functions:

Planning department has some key functions to maintain. Such as:

- Production planning
- Material planning
- Inventory management
- Master data management
- Institutional order and export
- External manufacturing

Production planning:

Production planning is based on market forecast. There are two supply chain-

- Plant supply chain- which is under industrial operation
- Market supply chain- which is under commercial operation

The overall process goes through the following stages:

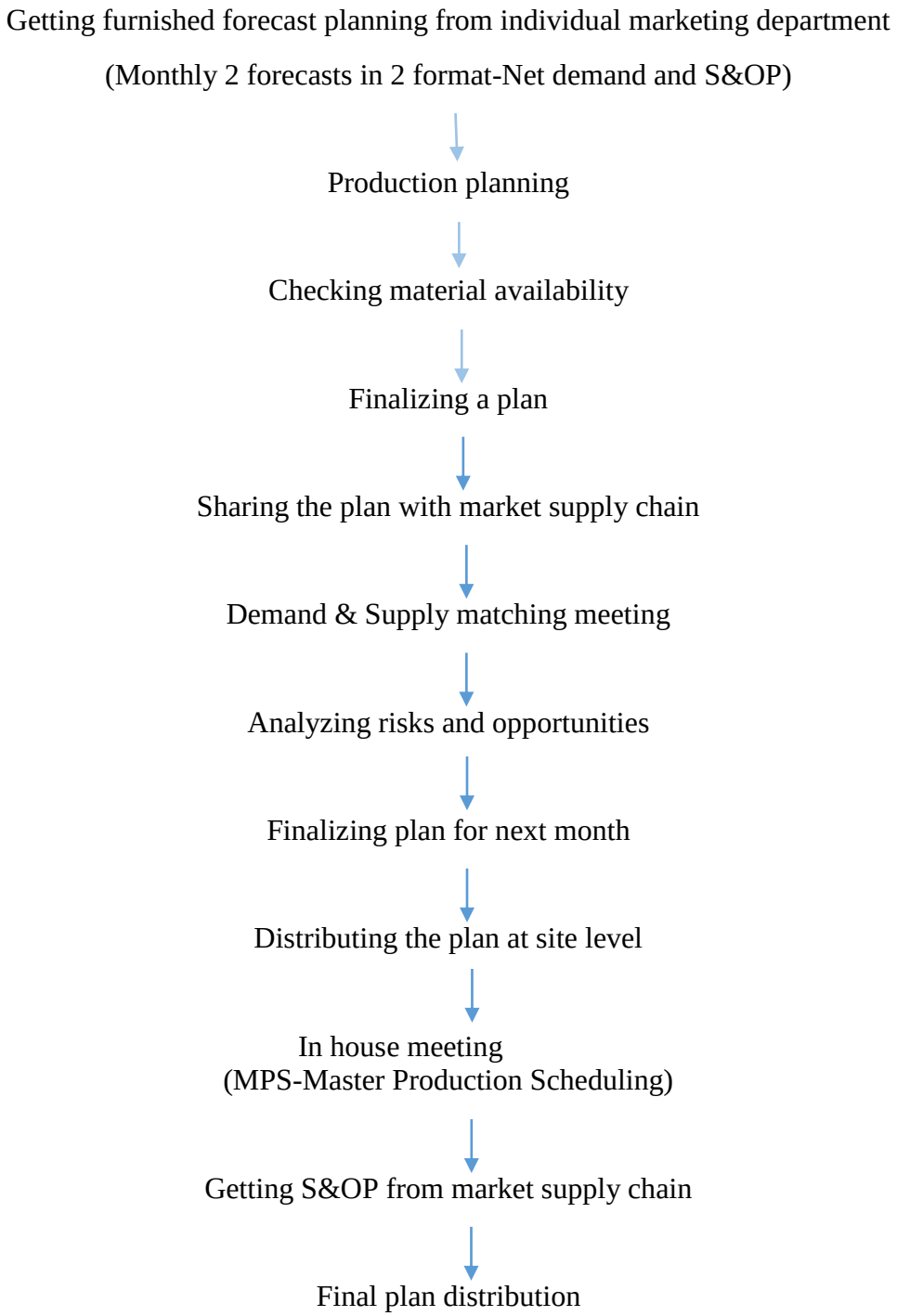


Figure 7: Production planning process

In case of planning for more than one-month S&OP for each month is needed. Using the safety coverage, onward production planning is done.

Safety coverage-

- Solid: 2 months
- Semi-solid:1.8 month
- Liquid:1.8 month
- Injectable:2.5 month

Material planning:

Material planning goes through the following stages:

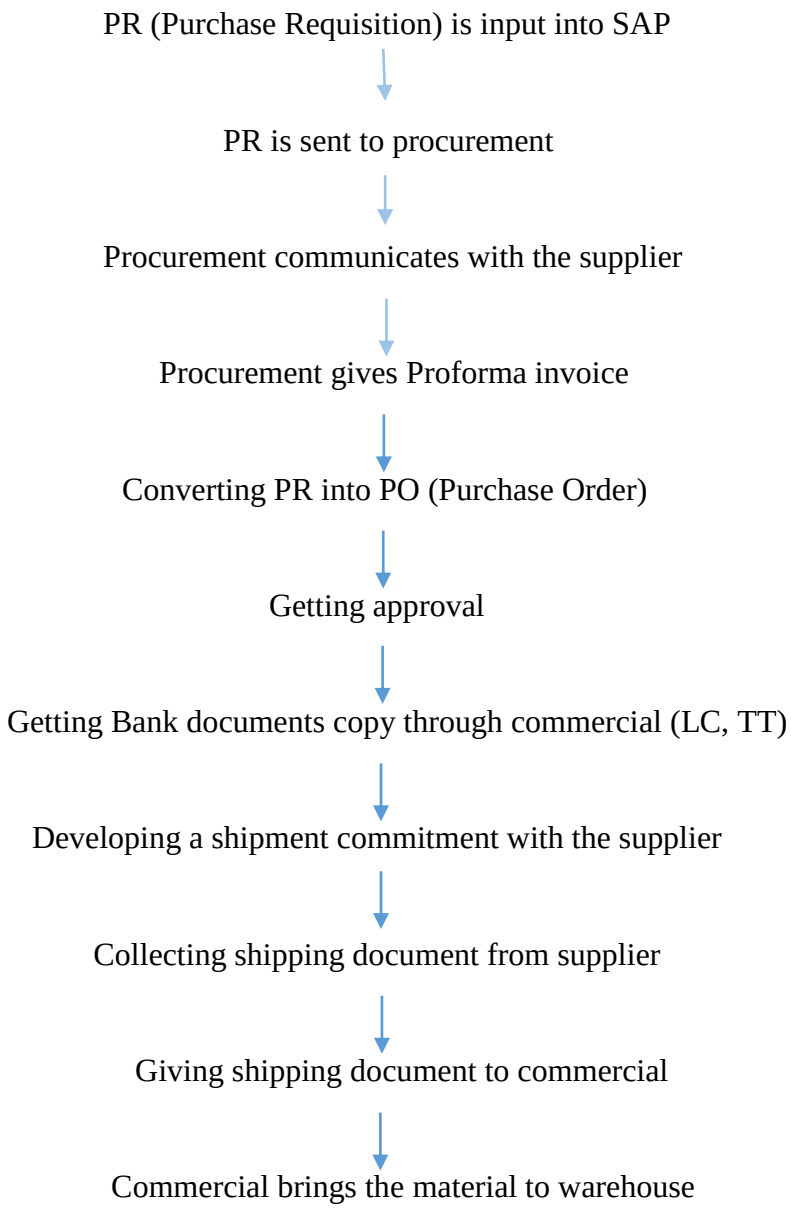


Figure 8: Stages of Material planning

Factors to be considered for material planning:

- Material lead time
- Mode of transport
- Source of supply
- Minimum order quantity (MOQ)
- Economic order quantity
- Fixed lot size
- Safety stock
- Bill of Material (BOM)
- Shelf life
- Expiry analysis

Inventory management:

The stock or item used to support production activities (maintenance, repair, operating supplies) and customer services (finished goods) is called inventory. Inventory can be managed by maintaining the following matters:

- Material classification-Inventory is classified based on material value. This is called ABC classification:
    1. Class A: Materials with 80% value
    2. Class B: Materials with 15% value
    3. Class C: Materials with 5% value

High value or class A materials are mainly focused. These materials are kept at optimum level.

- Item cost
- Carrying cost
- Ordering cost
- Stock out cost
- Capacity associated cost

Master data management:

Every time when a new product or material comes it has two codes:

- LMID-Local Material Identification Number (SAP)
- GMID-Global Material Identification Number

SAP has three modules:

- MM- Material Master Module. Here the information of material is given.
- WM- Warehouse Module
- PP-Production Planning

Institutional order and export:

Institutional orders are taken from several government and non-govt. organizations e.g. navy, army, hospitals, bank etc. In case of institutional order, customized packaging materials are used as per directions and requirements of respective organizations.

Sanofi Bangladesh also exports their products to Sri Lanka and Maldives. Flagyl tablet, Flagyl injection, Avomin, Stemetil.

External manufacturing:

Sanofi Bangladesh is involved in tolling out products as well. They usually toll out to Incepta Pharmaceuticals Ltd and toll in for Healthcare Pharmaceuticals Ltd, and Beximco Pharmaceuticals Ltd.

6.2 Commercial Department:

Commercial department particularly deals with the administration of revenue and expenses to generate a financial return. Commercial policies relate to the rules or practices defining ways of conducting the business and the standard terms controlling external relationships. Commercial Department mainly takes care of the import of materials from different approved vendor in different countries and it does import in both Industrial and Commercial bases. The job of a Commercial Manager is to help the company to maintain a consistent trajectory of growth, as well as avoiding obstacles that arise from a constantly shifting market. A Commercial Manager manages and oversees several teams, whose duties span a variety of departments within the organization.

The Commercial Department of Sanofi Bangladesh Limited is responsible for ensuring available material, finished goods, and machineries as requisition and demand in time.

Local Regulatory Authorities Required for the Commercial (Imports & Exports):

Almost all the Regulatory Authorities & officers related to Commercial jobs are located at Dhaka Regulatory Authorities and Offices for attaining regular jobs related to Imports and Customs:

- Directorate of Drugs Administration (two different Govt. offices and required two-way Correspondences)
- Directorate of Narcotic Control (four different Narcotics Control offices)
- Insurance Company.
- Finance Divisions (Head Office) for jobs like LC authorization, Bank Endorsement, Import duty etc.
- Banks
- Chief Controller of Import and Export.
- Suppliers/Indenters (for L/C advise, shipment follow up, shipping details and shipping documents)
- Various shipping lines/ Air Lines (for shipments/goods tracking at different ports/ and or in transit)
- C&F Agents (four different Customs stations Dhaka, ICD, Benapole and Chittagong)
- Commissioner of Customs (four different Customs stations Dhaka, ICD, Benapole and Chittagong)
- Local Transports/ carriers (Chittagong Sea port and Benapole Land port)

- BERC or Bangladesh Energy Regulatory Commission
- Surveyor

The activities of commercial department of Sanofi Bangladesh Limited are classified below:

1. Import related activities

- Obtaining prior import approval from DGDA (Directorate General of Drug Administration).
- Obtaining prior import permission (IP) or import authorization (IA) for narcotics control item from DGDA and Department of Narcotic Control for importation & production or sales.
- For each and every product, arranging Drug Administration clearance certification on document from DGDA and processing letter of credit (LC)/Invoice/Customs Clearance for all those things.
- Arrangement or execution of all imports, which is ensured by the use of LC/TT/CAD.
- If required, then executing each and every import under LC/LCA (Letter of Credit Authorization) and marine cargo policies for each and every shipment upon execution of shipments from overseas.
- Collecting and checking shipping documents during shipment.
- For customs clearance of imported goods, arranging bank endorsement/release of original shipping documents.
- Organizing customs clearing & forwarding jobs for all shipments upon arrival at ports/customs stations.
- Verifying all import duty and other taxes/bills through finance for customs clearance of all materials and supplies in time.
- Harmonizing with all business units. For instance-planning, purchasing, supply chain, warehouse, engineering and site regulatory, QO, finance etc., various local regulatory bodies, customs etc.
- Supporting new source registration validation activities.

2. Export related activities

- Organizing export operations as per export policy order or other rules applicable for pharmaceutical products.

- Organizing products /company registration and renewal therein within the importing country and organize product Dossier with the support from site regulatory /QO as & when required.
- Follow up ad confirmation of export registration with importing company.
- Price analysis and fixation with the support from finance.
- Processing agreement as signing with the respective parties.
- Collecting export forecast or budget or tender etc. from importing country yearly basis and then compiling them in a file, sharing them with the planning a production for their action.
- Sharing planning and production plan information, product availability, details of importing country or affiliate if needed.
- Organizing form.
- Forwarding PO to warehouse.
- Issuing export Proforma Invoice (PFI) along with exporter, importer, pack size, value, quantity, terms of payment, shipping period, mode of shipment etc. in favor of importer/affiliates and sharing signed PFI with importing company/affiliates.
- Sharing signed PFI and others with planning/ production with a request to issue an internal order (IO) and circulate that IO to all concerned.
- Collecting and receiving LC from importing country/affiliates/local bank.
- Correspondence with planning/production through mail/phone/others and contact with responsible person of QO through mail/phone for issuance certificate of analysis and then contact to warehouse through mail.
- Preparing and processing shipping documents, processing insurance policy against the shipment, processing bank works.
- Sending relevant shipping document to the importing country, forwarding relevant shipping document to the warehouse, collecting documents and prescribed MUSAK forms duly signed from warehouse and forwarding those for authorization/permission of NRB-VAT Customs, Dhaka for exportation.
- Hand over the goods to the C&F agents for final exportation and contact local C&F.
- After completion of all shipments from BD ports, collecting all the shipping documents, insurance policies.
- Sending required documents to the warehouse, settling the C&F agent bills including freight charges through finance.

- Following up and collecting proceed realization certificate from local designated bank for export recordings, DGDA purposes.
- Monthly export reporting to local finance and affiliates through invoice documents.

Required Documents for Shipment and Custom Clearance purposes:

1 Commercial Invoice

2. Packing List

3. Bill of Lading/Airway Bill/Lorry Bill

4. Certificate of country of origin issued by chamber of commerce/ Government authorized agency of the exporting country.

5. Form-9

6. Certificate of analysis

7. Bill of exchange

8. Freight Certificate

6.2.1 Letter of Credit (LC)

Required document for opening LC-

- Bank account
- Import registration
- Trade license
- e-BIN (Electronic Business Identification No.)
- Income Tax Certificate

L/C Application Process:

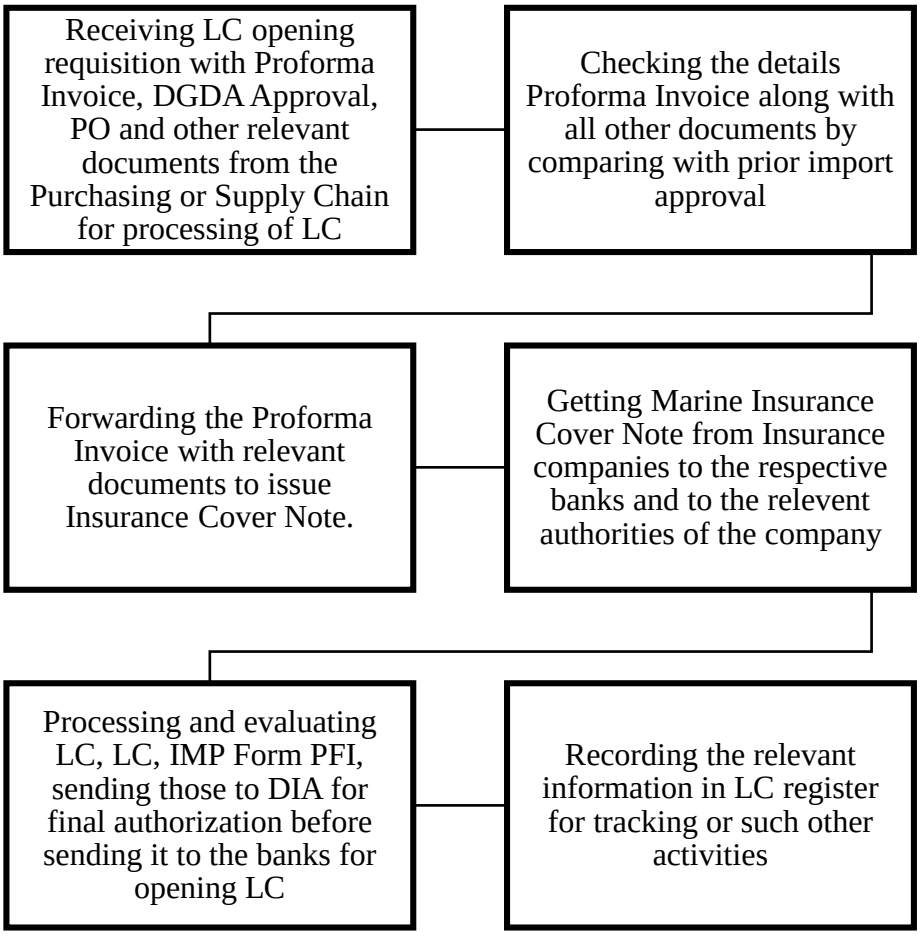


Figure 9: Letter of credit application process

6.3 Warehouse

The quality of a pharmaceutical product is defined as one that is pure, correctly identified, effective and safe to use. The warehouse plays a pivotal role in manufacturing products, as it is responsible for all incoming goods and for releasing finished products. Warehouse is the place where the bulk raw materials, packaging materials as well as finished products are kept at their optimum storage condition. It is a commercial building for storage of goods. Warehouses are used by manufacturers, importers, exporters, wholesalers, transport

businesses, customs, etc. They are usually large plain buildings in industrial areas of cities, towns and villages. They usually have loading docks to load and unload goods from trucks.

Warehouse Classifications:

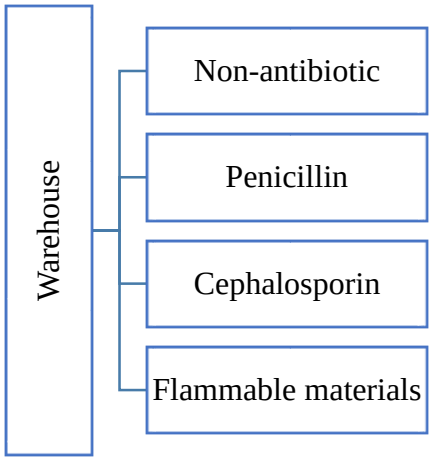


Figure 10: Warehouse classification (material wise)

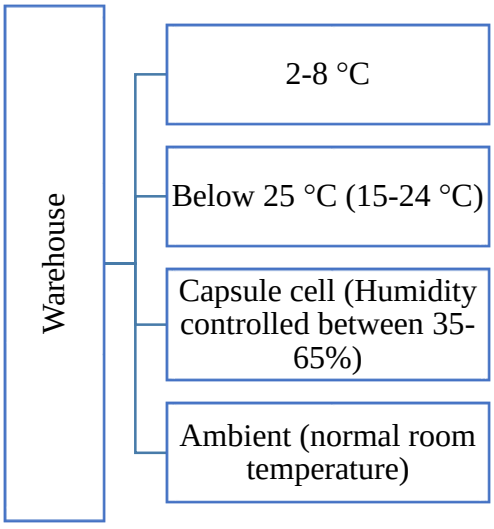


Figure 11: Warehouse classification (temperature wise)

Workflow:

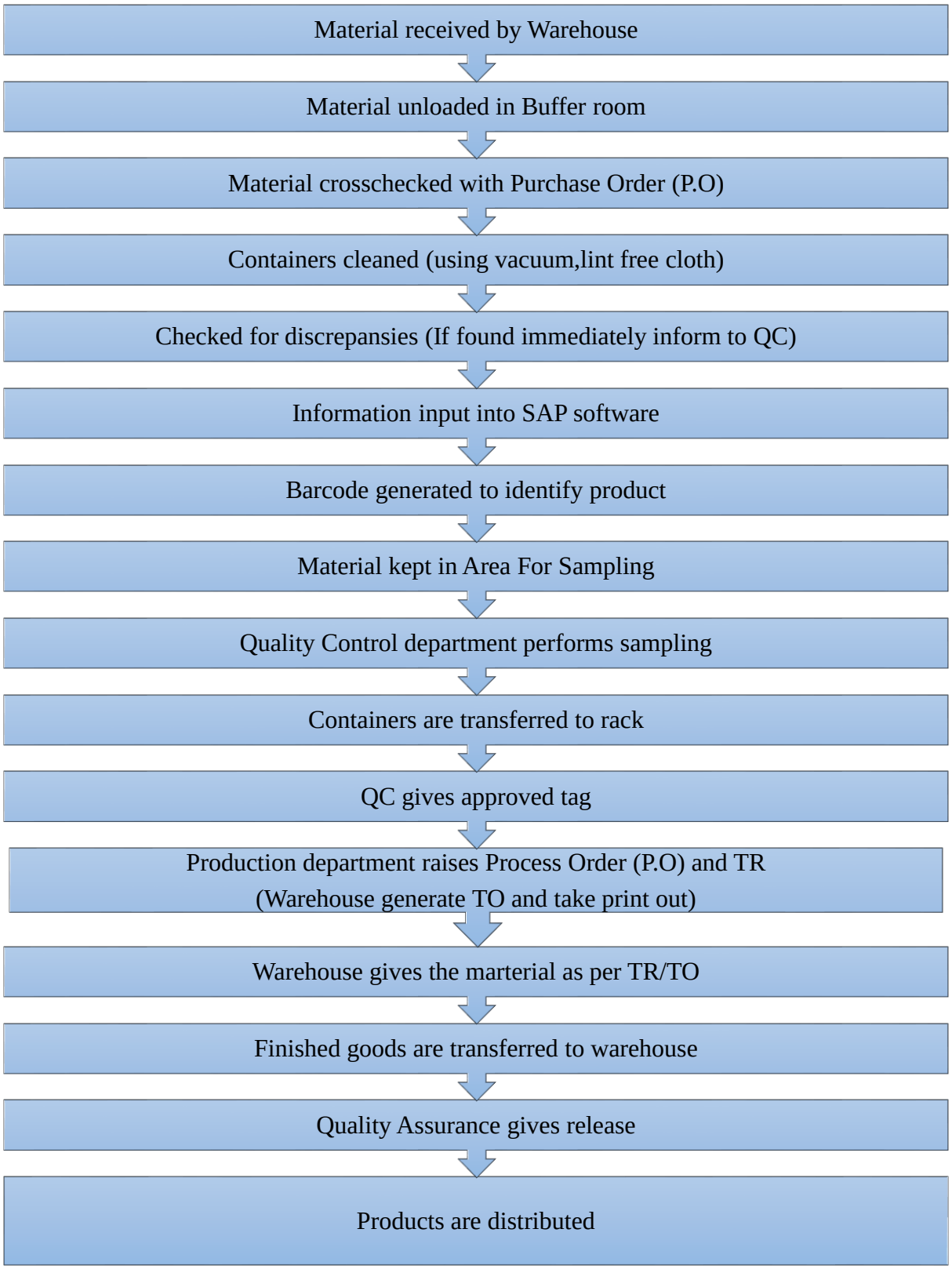


Figure 12: Workflow of warehouse department

How serial number for individual rack is assigned:

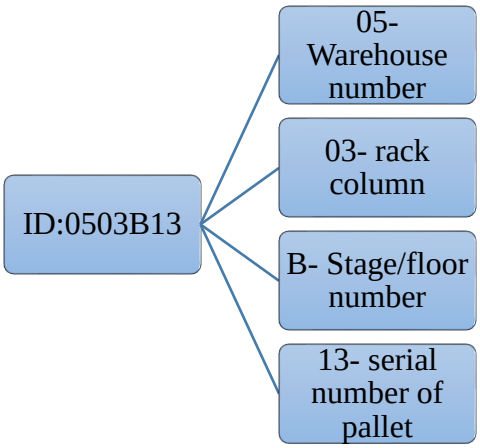


Figure 13: Serial numbers for individual racks

Sanofi has two different barcodes (Global Material Identification Number (GMID), Local Material Identification Number (LMID), providing a second unique identifier for the material and product. The barcode is used to electronically scan the identity of the item before use.

Additional responsibilities:

1. Pest control- Rodent beds are kept at different locations to ensure no rats or lizards enter the warehouse.
2. Controlling storage temperature- Hydrometer is used to record the temperature and humidity of the warehouse. This data is entered in the logbook two times a day.
3. Validation team designated 2 spots- hotspot and cold spot, where hydrometers are fixed. This is to monitor the temperature inside on regular basis.
4. All expired and damaged materials are given a rejected label (by QC) and destroyed via a third party.

Chapter 7

Central Dispensing Unit

The Central Dispensing Unit (CDU) in Sanofi Bangladesh Limited's is a separate unit. It belongs to the production department. In this area raw materials are weighed and dispensed in broken amount and the broken bulks are stored in clean containers. It is located near to the warehouse and is dedicated to ensure the quality and quantity of manufacturing products. The Central Dispensing area of Sanofi Bangladesh Limited is very sophisticated. The unit is run by authorized personnel who strictly abide Standard Operating Procedures (SOPs) and appropriate cGMP guidelines. The three basic principles which are followed in the pharmaceutical dispensing rooms are:

1. Unidirectional flow of materials and personnel.
2. Segregation between hazardous and non-hazardous materials.
3. Separation of storage and manufacturing items and spaces.

Generally, dispensing unit is located right next to the warehouses where materials were stored. The dispensing is considered as the entry point to manufacturing and the transition point for materials entering from the warehouse and going into process areas.

According to the PO (Process Order), raw materials are placed in the Central Dispensing Unit from warehouse. By following the BMR, the raw materials are accurately weighed and dispensed to the production floor based on OEB (Occupational Exposure Band). The raw materials that are needed in broken amount are only dispensed from the central dispensed unit. The bulk amount is sent directly from the CDU to the production. Once the raw materials are weighed, the remaining material, which is named as broken material is kept in central dispensing unit for further use with appropriate labelling.

Standard conditions for Central Dispensing Unit (CDU):

- Temperature: 22±3ºC (Range 19-25°C)
- Humidity: (40-65) %
- Differential pressure: (≥7.5 Pa)

Certain rules of dispensing and safety measurements:

- Trained personnel should be appointed in the Central dispensing unit and should be evaluated periodically according to SOP.
- All the materials including API and excipients should be measured in presence of dispensing officer.
- Each raw material is dispensed according to SOP.
- Laminar air flow, temperature, humidity, balance is checked and log books are written according to SOP/GMP.
- Work is done under total control HVAC system.
- Materials are accurately weighed and according to process order and dispensed to the production floor based on OEB.
- The dispensing activities are effectively maintained under proper supervision.
- Raw materials and store materials are dispensed under the appropriate conditions and in appropriate weights, coupled with their Code no, SAP no, expire date, retest date etc. which are properly monitored.
- API is dispensed after dispensing the excipients.

Factors to be maintained in laminar air flow:

1. The laminar air flow unit must turn on for at least half an hour before starting the operation.
2. LAF is free from air-borne contamination
3. Removes all particles of more than 5 microns in length.
4. The pre filter air is introduced to the LAF via HEPA filters, which remove all particles as small as 0.3 micron.
5. The average air flow velocity is maintained 0.36-0.54 m/s (0.45m/s + 20%)
6. The LAF machine is calibrated in 6 months to 1 year.

OEB (Occupational Exposure Band): OEB, which is known as occupational exposure band is carefully maintained in the Central Dispensing Unit. The OEB is labelled on a scale of 1-4, 1 being the least exposed and 4 being the most exposed material.

Excipients are dispensed beforehand Active Pharmaceutical Ingredient (API) as excipients are mostly inert so that they prohibit the possibility of contamination.

General cleaning in CDU:

General cleaning explains the procedure which includes the general cleaning, preparation and use of disinfectant at central dispensary. It ensures:

- Proper cleaning: using Savlon & Dettol solution alternatively (every alternate week).
- Prevention of microbial count
- Prevention of cross contamination

Flow chart of operation at central dispensing unit

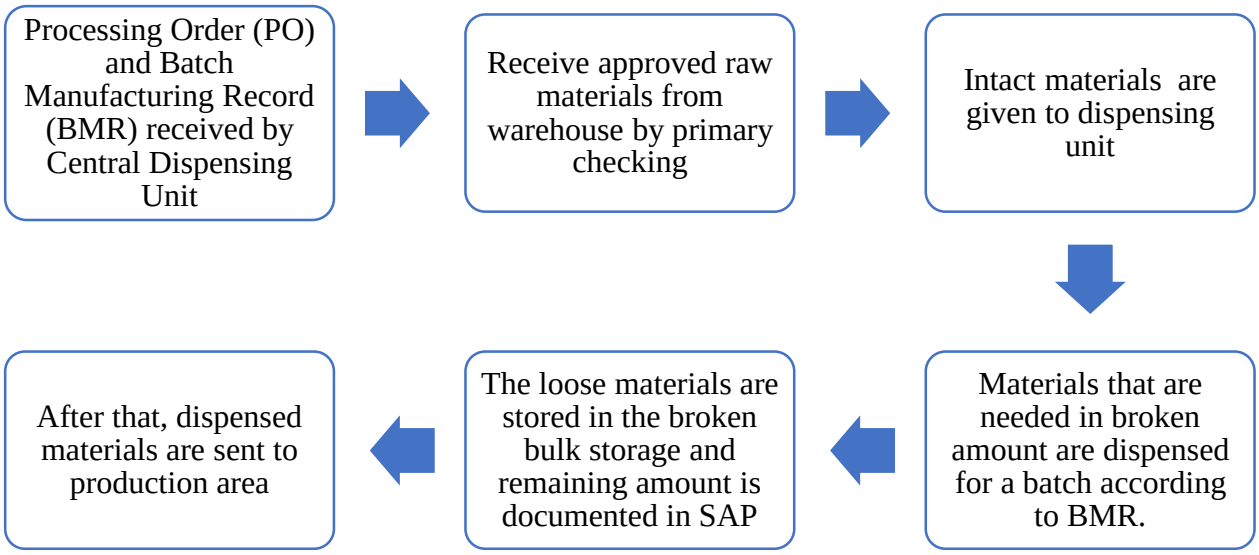


Figure 14: Flow chart of operation at central dispensing unit

Equipment used in Central Dispensing Unit (CDU):

Table 3: Equipment used in CDU

Brand name & Model	Capacity	Booth no.
Metler, Toledo	12100gm	01
Metler, Toledo	12100gm	02
Ohaus, Defender	40kg	01

Ohaus, Defender	40 kg	02
Telster, Spain (qty.2)	Unidirectional flow; vertical or horizontal	01 & 02

Areas of Central Dispensing Unit:

Table 4: Areas of Central Dispensing Unit

Room no.	**Name of the room**	**Characteristics and functions**
1	Material air lock for pallet change	• Receiving of raw materials from the warehouse • Dispensing of raw materials as required by different manufacturing unit and send to them.
2	Buffer staging room	Raw materials are kept here.
3	Weighing module 1(W-1) for OEB 3&4	Maintaining OEB 3&4
4	Weighing module 2 (w-2) for OEB 1&2 and all excipients	Maintaining OEB 1&2.
5	Waste airlock	Wastage is kept here
6	Corridor	Corridor
7	Buffer staging room for batch	Materials are weighed and stored here, after that materials are send to manufacturing department
8	Broken material storage	Broken APIs and excipients are kept here.
9	Cleaning room	Cleaning is done here to prevent microbial count, to prevent cross contamination and to keep the area clean
10	Storage (consumable)	Polythene bag, rubber band, security seal, personnel protective equipment, tread ball, adhesive tape, label
11	Storage clean bins, trolleys, scoops	Used to store bins, trolleys, scoops.

Chapter 8

Manufacturing Unit

8.1 Solid:

The manufacturing of all the products is done mainly on two areas, non-antibiotic area and antibiotic area.

- List of some non-antibiotic solid products manufactured by Sanofi Bangladesh Limited:

Table 5: Non-antibiotic products of Sanofi Bangladesh Limited

Products	API
Flagyl	Metronidazole
Amaryl	Glimepiride
Xerosec	Omeprazole
Lasix	Furosemide
Epilim	Sodium Valproate
Stemetil	Prochlorperazine Maleate
Betanol	Atenolol
Metsa	Metformin Hydrochloride
Qpine	Quetiapine Fumarate
Telfast	Fexofenadine Hydrochloride

Equipment used in manufacturing unit:

1. Granulation Equipment:

Table 6: Granulation equipment

Equipment Name	Capacity	Origin
Jaguar Mixer	600 L	India
Saizoner Mixer	300 L	India

2. Drying Equipment:

Table 7: Drying equipment

Equipment Name	Time	Origin
Alliance Fluid Bed Dryer	70-75 min	India
Ganson Fluid Bed Dryer	70-75 min	India

3. Sieving Equipment:

Table 8: Sieving equipment

Equipment Name	Origin
Alexander	China
Rotogram Oscillator	Canada

4. Blending Equipment:

Table 9: Blending equipment

Equipment Name	Capacity
Clinocone Blender 1	700L
Clinocone blender 2	250L

5. Compression Equipment:

Table 10: Compression equipment

Equipment Name	Station	RPM	Origin	Product in process
Sejong (bilayer)	21	20	Korea	Epilime

Korsch XL 200	30	80	Germany	Lasix
Cadmach CMB4	35	20	India	-
Cadmach Cadpress II	45	28	India	_

6. Encapsulation:

Table 11: Equipment for encapsulation

Equipment Name	Station	RPM	Capsule size	Origin
Sejong	12	7.5	0,1,2,3	Korea

7. Coating Equipment:

Table 12: Coating equipment

Equipment Name	Origin	Product in process
Sejong (SFC-170) Coating Machine	Korea	-
Accela Cota Coating Machine	England	Flagyl

Solid dosage form manufacturing area - Solid dosage form have definite shape and volume. Solid dosage production area is one of the vital areas in manufacturing unit. There are some requirements to be followed while manufacturing solid dosage forms. Those are

a. Temperature-22(±3) °C
b. Humidity- 40-65%RH
c. Pressure difference- ≥7.5 pascals

Mostly, Sanofi manufactures two types of solid dosage form. Those are-

- Tablet – Large scale production of various tablets are done in Sanofi manufacturing unit. The tablet manufacturing process is discussed below-

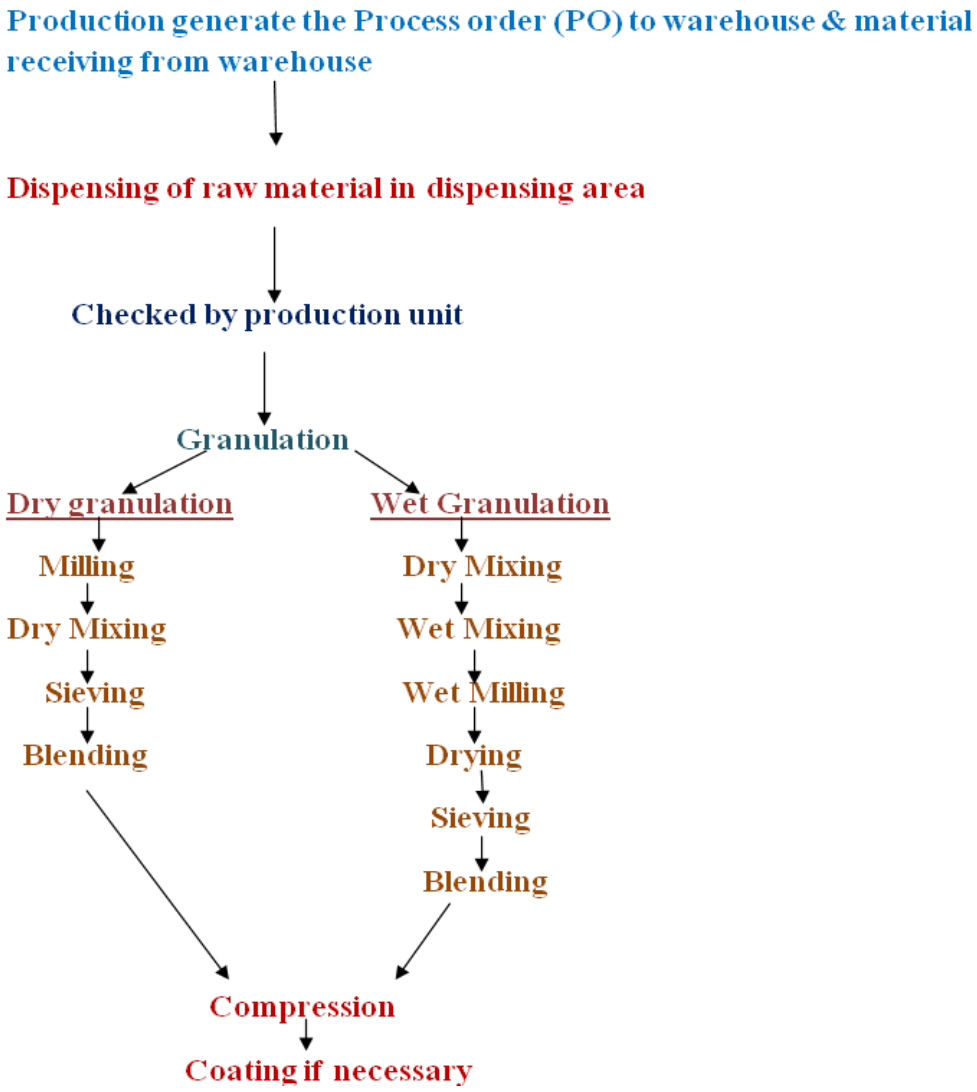


Figure 15: Tablet processing

Process:

- After Dispensing, API and Excipients are mixed together and granules are made by Dry granulation method.
- After Dry granulation, starch paste mixed with them and continuously mixing are done. This process is called wet granulation.
- Wet milling occurs by wet miller.
- Drying is necessary after wet milling which is done by using Fluid Bed Dryer.

- Sieving is necessary after drying and lubricant will be added. After this, Blending is done by Clinocone blender.
- After the granules are prepared, they are transferred to the bulk room and waiting for compression. Powders are placed into compression machine and compressed them and give perfect tablet size.
- Tablets are placed into coating machine (If needed). There are two types of coating- Sugar coating and Film coating.
- Tablets are prepared for packaging and release to the market.
- During preparation, IPC test done by quality operation department.

8.2 Semi-solid

Creams are semisolid emulsion products which are viscous with an opaque appearance. The consistency and rheological character of the formulation will depend on whether the cream is water in oil (W/O) or oil in water (O/W). Properly designed O/W creams are an elegant drug delivery system, pleasing in both appearance and feel post-application. Each type of cream is good for most topical purposes and is considered particularly well suited for application to open wounds.

Creams are semi-solid emulsions that are mixtures of oil and water. A cream is referred as a topical medication (used on skin), which contains water base. In Sanofi, the cream manufacturing and filling unit is in T4 building.

Sanofi mainly manufactures three types of semi-solid dosage form. Those are-

- Cream
- Gel
- Suppository

Environment of cream manufacturing and filling room-

- Temperature is 18 to 25°C
- Pressure difference is ≥7.5 Pa
- Humidity is 45% to 65%.

Machines used in Cream manufacturing and Filling process-

Table 13: Machines used in Cream manufacturing and Filling process

Sl.	Name	Origin	Capacity	Function
1.	AGI Homomixer	Korea	300kg	Manufacturing of cream.
2.	Yan Tai automatic cream filling & sealing machine	China	55 tubes/min	Filling of cream for both laminated and aluminum tube.

Product in process - Pevisone (Econazole Nitrate) 10gm

- Tube weight- 9.00-9.65cm
- Sealing teamperature-198-220°C
- Room temperature- 18-25°C
- Pressure ≥7.5

Process flow of cream manufacturing:

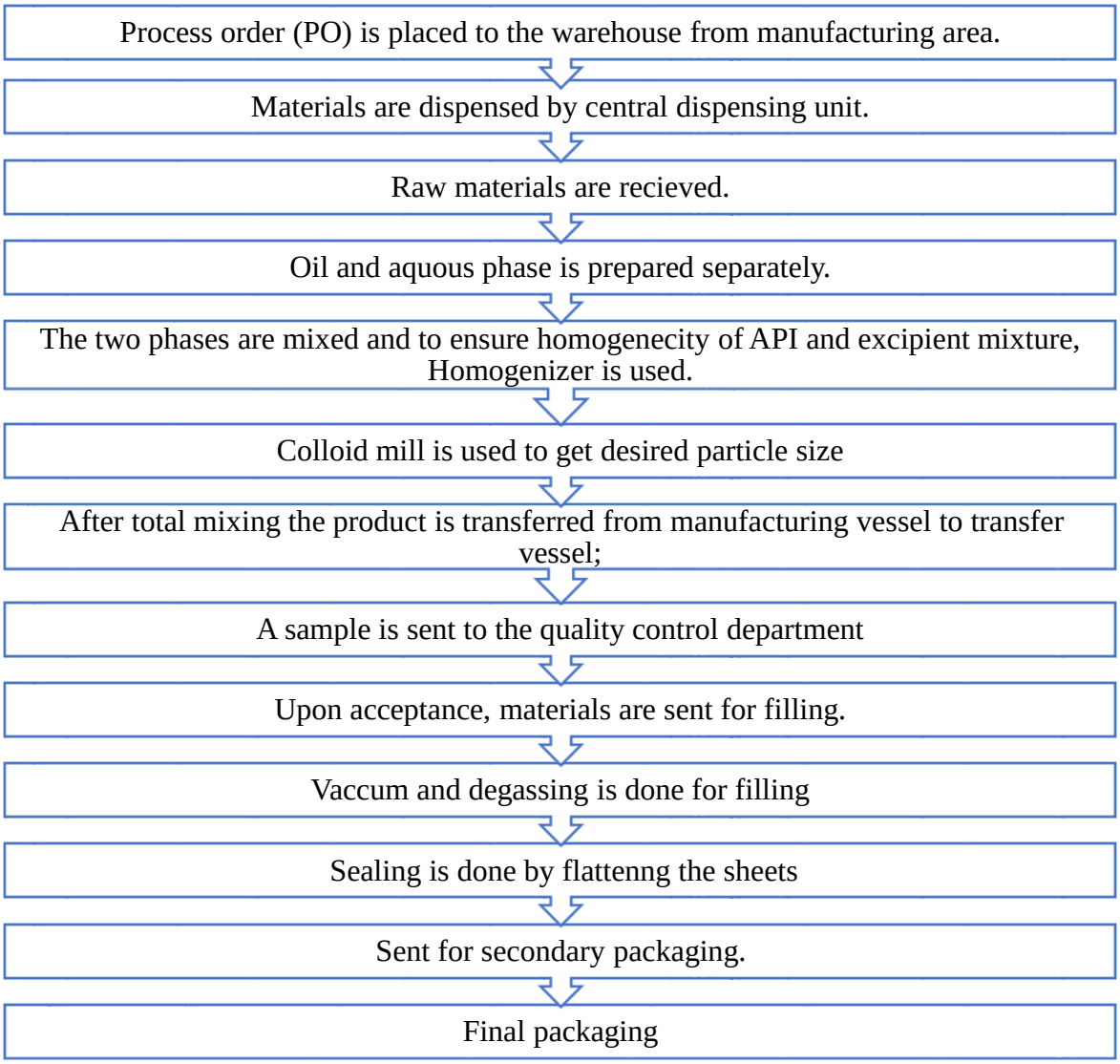


Figure 16: Process flow of cream manufacturing

8.3 Liquid Sterile Area:

- Liquid sterile products are liquid dosage forms of therapeutic agents that are free from viable microorganism. So, manufacturing of liquid sterile products requires special care.
- All sterile products must pass a sterility test. In addition, any solutions that are injected directly into the bloodstream poured into body cavities and surgical area must be

formulated into non pyrogenic preparation that are essentially free from particulate matter.

- Liquid sterile manufacturing area is in T4 building.
- Purified water and water for injection (WFI) are treated within this area though it's separate water plant.
- Liquid sterile area also has its own dispensing as well as packaging area

Parameters to be considered:

- ✓ **Room temperature:** 17-25 C
- ✓ **Humidity:** 30-60% RH
- ✓ **Positive Pressure:** ≥ 15 Pascal

Environmental Zones of Sterile Area:

- **Zone A:** Filling area
- **Zone C:** Surrounding area of filling
- **Zone D:** Final compartment of gowning room, Dispensing, Manufacturing

Water plant: Two types of water plants are present in liquid sterile area:

- ✓ Purified water
- ✓ WFI (water for injection)

1. **Purified Water Plant:**

Table 14: Machine used in purified water plant

Name of the Machine	**Capacity**	**Utility**
SCION Hipol	2000L	✓ Compressed Air ✓ Portable water ✓ Electricity

2. WFI Plant

Table 15: Machine used in WFI plant

Name of the machine	Capacity	Utility
Higu fine	700L	✓ Compressed Air ✓ Steam ✓ Portable water ✓ Purified water ✓ Electricity

Steps involved in Purified water plant

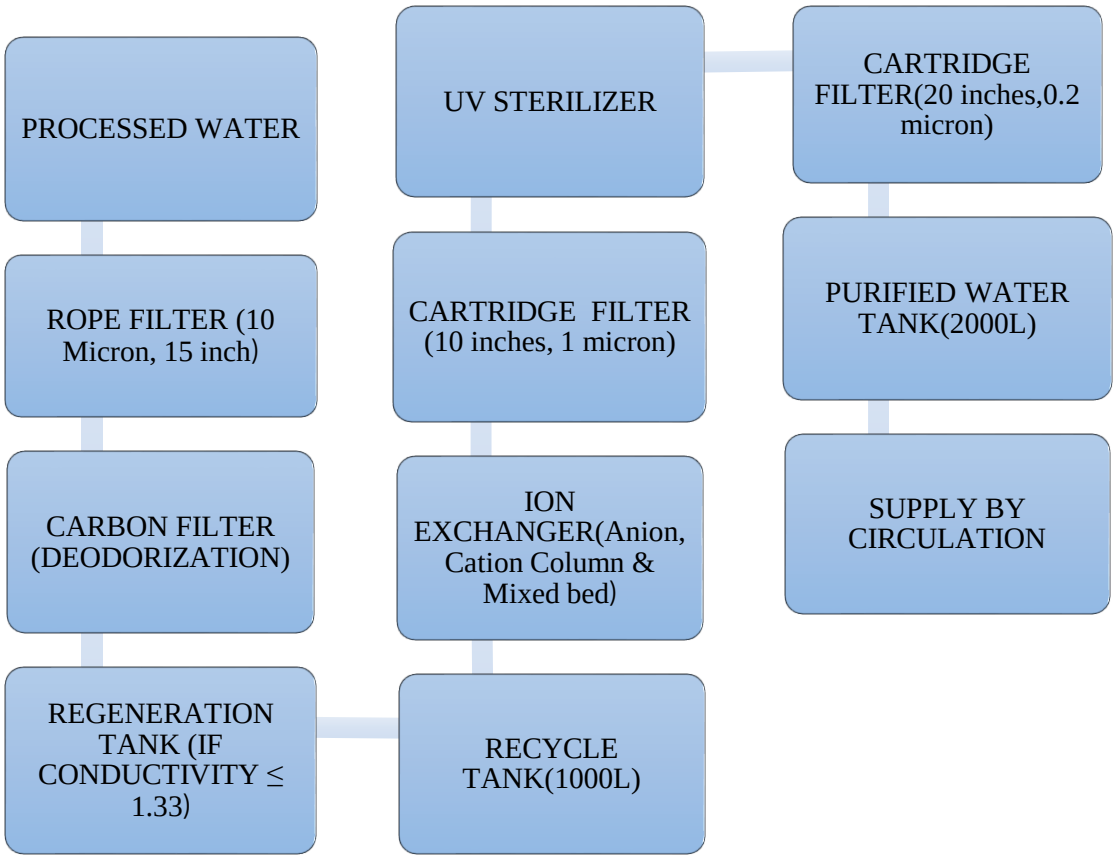


Figure 17: Process flow of purified water plant

Steps Involved in WFI plant

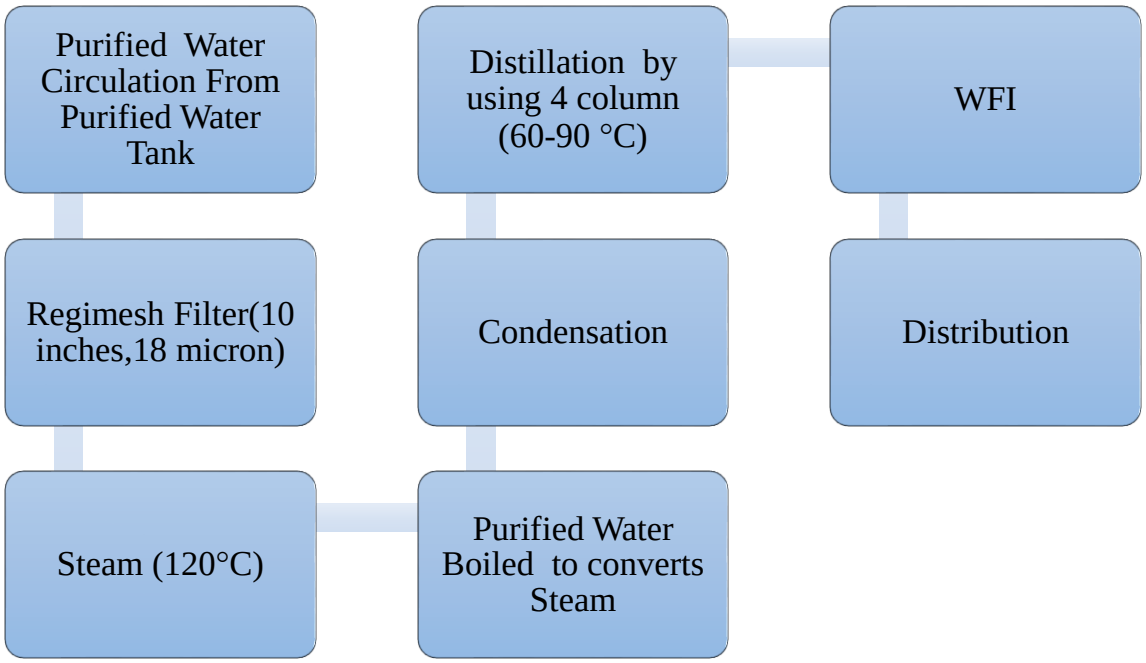


Figure 18: Process flow of WFI plant

Terminally Sterilized Product:

In Sanofi Bangladesh Terminal sterilized product is manufactured in liquid sterile area. Terminal sterilization is the process of sterilizing a product in its final container. It is an important process as it ensures the product remains sterile. All medical, ophthalmic and parenteral equipment are sterilized in batches, and usually sterilized using heat.

Following features are maintained in manufacturing and packing area of sterilized products:

- ✓ Airlock exist system both personnel and materials
- ✓ Complete separation of Material entry and personnel entry
- ✓ Special gowning procedure required
- ✓ The maximum allowable particle size entry through the HEPA filters is 0.2µm
- ✓ Laminar airflow present in both filling and sealing process

Steps involved in Manufacturing of Sterile product

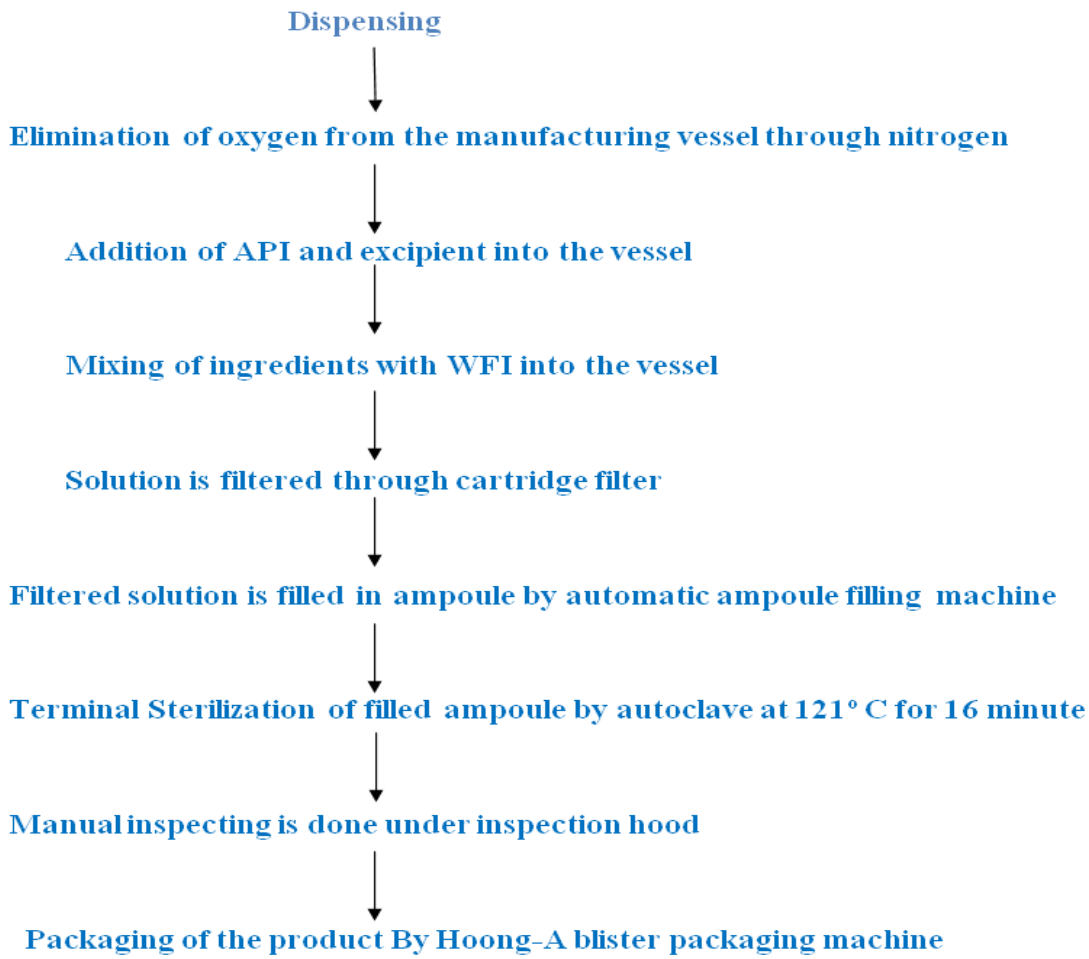


Figure 19: Flow chart of sterile product manufacturing

Products Manufactured in sterile area

Table 16: Products manufactured in sterile area

Brand Name	Generic Name	Dose
Avil	Pheniramine Maleate	45.5mg/2ml
Lasix	Furosemide	20mg/2ml

Machines used in liquid sterile area

- ✓ Manufacturing vessel
- ✓ Hot air sterilizer
- ✓ Filter integrity test machine
- ✓ Cap sealing machine
- ✓ Automatic Ampoule filling machine

Chapter 9

Antibiotic

9.1 CPS Area

CPS area is designated for Cephalosporin and Penicillin and Solid at Sanofi Bangladesh this area is known as antibiotic area. Cephalosporin and Penicillin are group of antibiotics (β-Lactum antibiotics) that kill or prevent the growth of bacteria. At Sanofi Bangladesh, CPS area is located in separate building as antibiotics should completely be contamination free**.**

9.2 Cephalosporin Unit

Cephalosporins are a type of beta-lactam antibiotic. They can be taken orally or injected into a vein (intravenous injection), depending on the infection. To prevent any kind of contamination, antibiotic unit is separated from the non-antibiotic manufacturing area. Sanofi Bangladesh houses two separate antibiotic units, namely Cephalosporin and Penicillin unit. Not only two separate buildings, but also separate staffs, HVAC system, equipment and different utilities are allocated especially for antibiotic unit to prevent contaminations. Cephalosporins are originally derived from the fungus named *Acremonium*, which was previously known as "*Cephalosporium.*" Cephalosporins are indicated for the prophylaxis and treatment of infections caused by bacteria susceptible to this particular form of antibiotic. They interfere with bacterial cell wall synthesis.

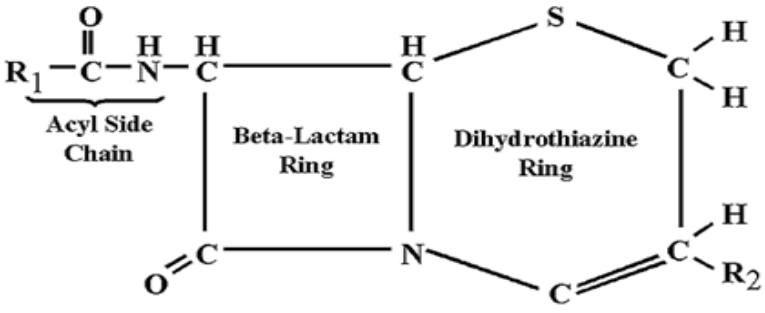


Figure 20: Structure of cephalosporin

The facility produces 4 dosage forms of Cephalosporin:

- Tablet (Sefurox 250 mg, 500mg)
- Capsule (Sefrad 250 mg, 500 mg)
- Powder for Suspension, PFS (Sefrad 100 mL, Sefrad DS)
- Powder for Injection (Penomer 1 gm IV injection)

Apart from making their own products, Sanofi manufactures different toll products. For example, Triocim PFS and capsules for Beximco Pharmaceuticals.

Manufacturing requirements:

1. Temperature 19 to 25°C
2. 30 to 50% RH
3. Differential pressure 7.5 pascal or higher
4. All cleaned equipment
5. Proper HVAC system
6. Proper cleanliness of room
7. Proper dust collection system

9.2.1 Workflow of Cephalosporin Unit

For Tablet:

Figure 21: Workflow for Cephalosporin tablet

For Capsule:

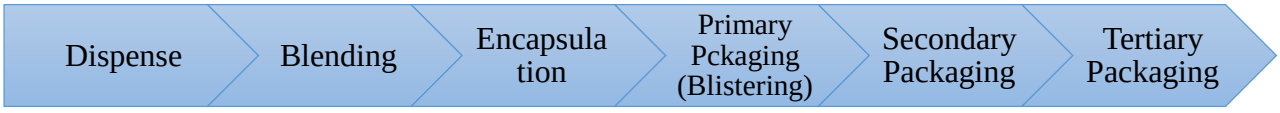
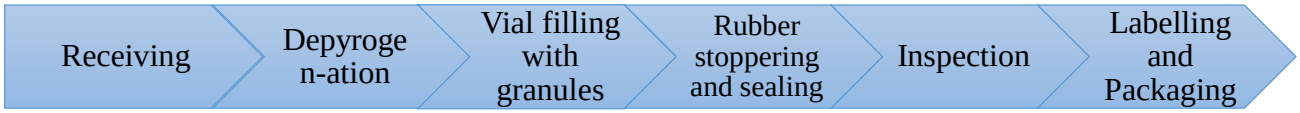


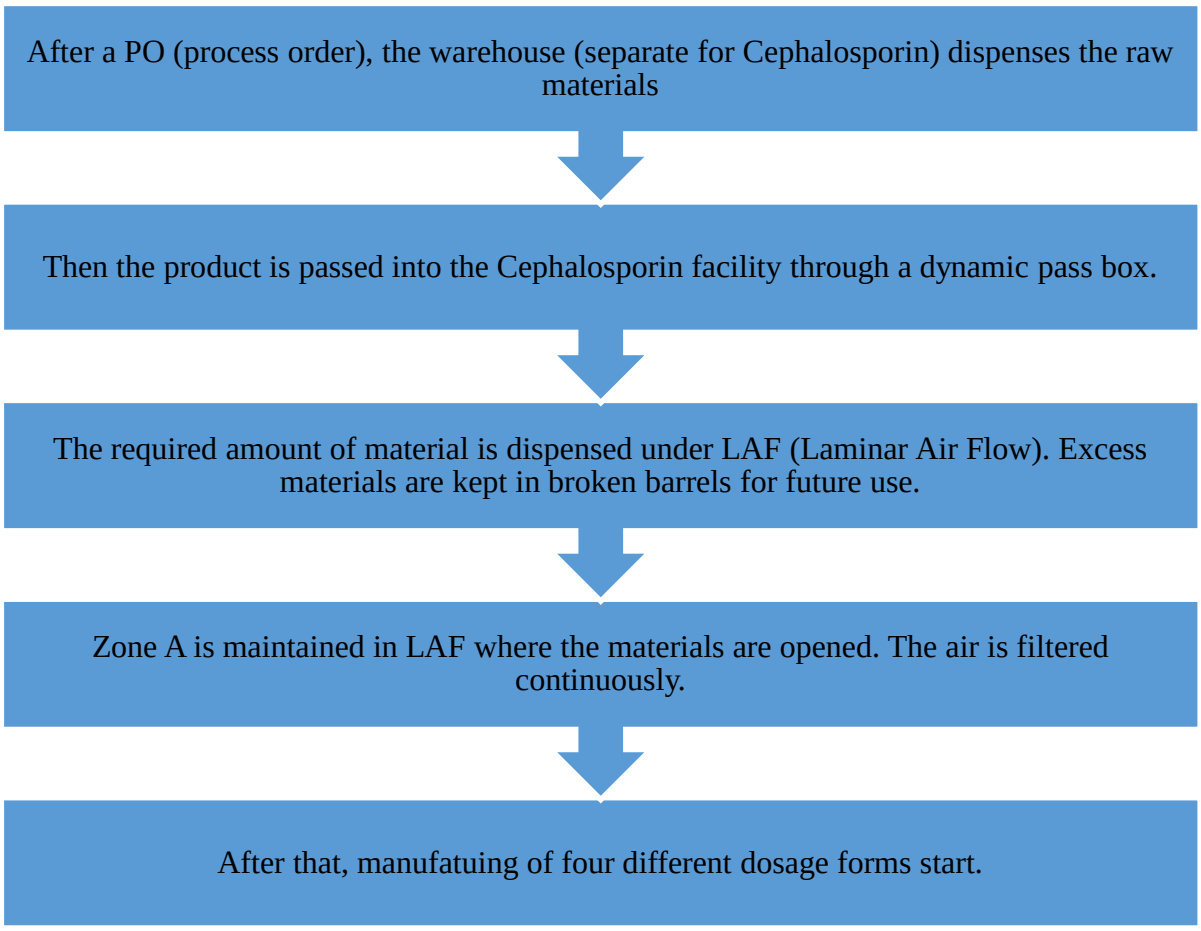
Figure 22: Workflow for Cephalosporin capsule

For Powder for Suspension:

For Powder for Injection:



General Process:



9.2.2 Procedure

Blending:

Blending refers to the process of mixing of API and excipients to ensure there is a homogenous mixture of all ingredients for each manufacturing process. Double cone blenders are used to mix the materials used to prepare desired product to get the desired uniformity.

Encapsulation:

It is a process where techniques are used to enclose medicines in a relatively stable shell known as capsule. They are one of the most efficient methods of taking medication. A capsule shell is made of gelatin. Capsules can be of two types, hard shell and soft shell capsules. Two capsule sizes are used in this facility: size 0 and size 2.

Basic process of encapsulation:

Granules and shells come from hopper

↓

Granules are filled

↓

Locking of the shells is done

↓

Delivery of the capsules

↓

Dedusting

↓

Polishing

↓

Sorting

↓

Perfect ones checked by metal detector

↓

Sent for packaging

Figure 23: Encapsulation process

Compression:

After the preparation of granules or mixing of ingredients they are compressed to get final product. The compression is done either by single punch machine or by multi station machine. Its 'squeezes' the ingredients into the required tablet shape with extreme precision. It can make the tablet in many shapes, although they are usually round or oval. Also, it can press the name of the manufacturer or the product into the top of the tablet. Problems encountered in tablet compression stage:

- Weight variation
- Friability
- Hardness
- Sticking
- Picking
- Capping
- Laminating
- Chipping
- Mottling
- Double press or impression.

Coating:

Coating maybe applied to a wide range of oral solid dosage form, such as particles, powders, granules, pellets and tablets.

Coating of dosage form is done for:

- Better appearance of the dosage form;
- To protect the dosage form;
- Mask bitter taste;
- Protect drugs in the stomach;
- Control release

Coating parameters:

- Spray rate
- Air flow
- Pan speed
- Inlet and outlet temperature

Basic coating process:

Dosage forms are placed into tablet bed

↓

Spray gun sprays the coating solution

↓

Dosage forms are collected after coating

Figure 24: Coating process flowchart

Machines used for manufacturing:

Table 17: Machines used in Cephalosporin manufacturing

Machine Name	**Capacity**	**Origin**	**Function**
Zanasi 40F	8 station, 48 dies, 400 capsules per minute	Italy	Encapsulation for making capsules.
Double cone blender	300L & 1000L capacity, 18rpm and 9rpm respectively	GMP China Ltd	Blending of API, excipients and lubricant.
Manesty Oscillator		England	Granulation
CMB4 Compression Machine	Per minute 1120 tablets	India	Tablet compression

Manesty D3 A machine	16 punch, 256 tablets per minute (1 hopper, 1 channel)	England	Tablet compression
Manesty Accela Cota	2 nozzles/ spray gun, per minute 3-10 rotations, speed 1-12, 52 kg load capacity, spray guns to bed distance: 11-inch, angle of the guns: 45^{o} Pressure: 3bar	England	Coating Machine. Coating Materials Used: • Dichloromethane • Ethanol • Opadry Yellow/White
Buchon Blister	35 SPM, 4 cutter and 3 cutters	South Korea	Primary Packaging
Brothers filling machine	Speed: 50; 40-60 bottles per minute	India	Bottle filling, capping and sealing
OTTO-HANSEL	18 SPM	Germany	Secondary packaging of vials
IMA Vial Filling Machine	Speed: 30-60, 12 pistons,	Italy	Vial filling

Products that was under production at the moment of visit:

- Furotil Plus 250mg and 500mg tablet (Toll-manufacture of Healthcare Pharmaceuticals Ltd.)
- Penomer 1gm IV-injection. (Toll-manufacture of Beximco Pharmaceuticals Ltd.)

9.2.3 Packaging

Primary, secondary and tertiary packaging is done in the packaging area. There are 3 packaging line. One is for tablet packaging, one is for blister packaging (PFI), and another one is for PFS packaging.

Table 18: Machine used in Cephalosporin packaging

Name of the machine	Origin	Temperature	function
Buchon blister	Korea	±146°C	Blistering
Condot Printing machine			Batch printing
OTTOHANSEL Blister packaging, Machine			Vial packaging.

9.2.4 Quality Control (Cephalosporin)

Cephalosporin QC lab conducts different tests that ensure the quality, safety and efficacy of Cephalosporin products. Once the tests are successfully passed, a batch is ready to release. The laboratory contains different equipment and instruments that are used to analyze different physicochemical properties of a product. All the tests are done by following SOP.

Laboratory equipment:

Table 19: Machine used in QC laboratory of Cephalosporin

Name of the machine	Origin	Function	Product in progress
Pharma Test Hardness tester	Germany	Testing tablet hardness	-
Pharmatest Tap density tester	Germany	To measure the tapped density of powders and granules	-
Jenway conductivity meter	USA	Checks the ability of a solution to conduct current	_

Metrohm Moisture analyzer and Karl Fischer titrator	Switzerland	To determine of trace amount of water in a sample	-
Electrolab electromagnetic sieve shaker	India	Particle size analysis, used to separate particles	-
Electrolab Disintegration tester	India	To measure the amount of time needed to disintegrate a tablet in a liquid medium	-
OHAUS electronic digital balance	USA	Material weight analysis	-
Kotterman Fume Hood	Germany	Contains hazardous, toxic, flammable materials	-
Erweka dissolution tester (DT)	Germany	Analyzing drug release	-
Shimadzu spectrophotometer	Japan	Drug concentration analysis	-
Erweka leak test apparatus, Model-LT-101p	Germany	Test for quality of primary packaging	Turboclav 500mg
Perkin Elmer IR spectrophotometer	USA	Identification of functional groups or chemical substances in product	-
3 Shimadzu HPLC machines with UV-vis detector	Japan	Analysis of different chemical components in a product	1. Furotil+ Turboclav 2. Furotil Plus
DAIHAN scientific Ultrasonic cleaner	South Korea	Cleaning different lab equipment	-

Clifton water bath with antibacterial protection	USA	Incubate samples in water at a constant temperature over a long period of time	-
Thermonik friability tester	India	Check physical strength of tablets	-
Hermle centrifuge machine	Germany	Centrifugation, separation of fluid , gas or liquid based on density	-
MEMMERT vaccum oven with pump	Germany	Used for drying of substances which are hygroscopic and heat sensitive	-

Assay-

An assay of Turboclav 250mg and 500 mg was being done to determine efficacy of the tablets after their shelf-life.

9.3 Penicillin unit

Penicillin is a broad range antibiotic that works by interfering with bacterial cell walls. The fungi *Penicillium* are the source of penicillin. This can be taken orally or intravenously. Penicillin antibiotics were among the first medications to be effective against many bacterial infections caused by *staphylococci* and *streptococci*. Like cephalosporin, this is a separate and isolated facility.

9.3.1 Workflow (General)

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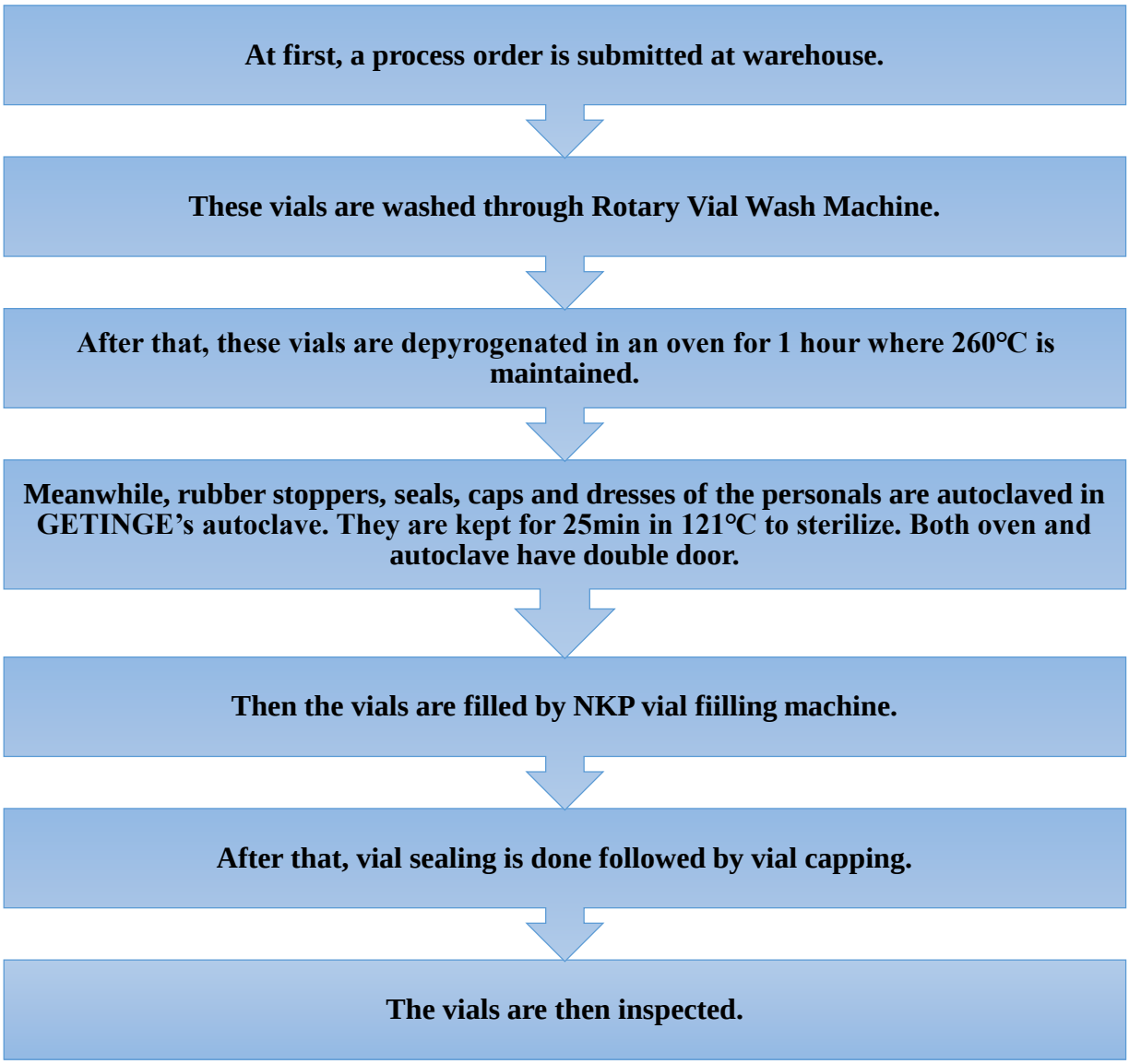
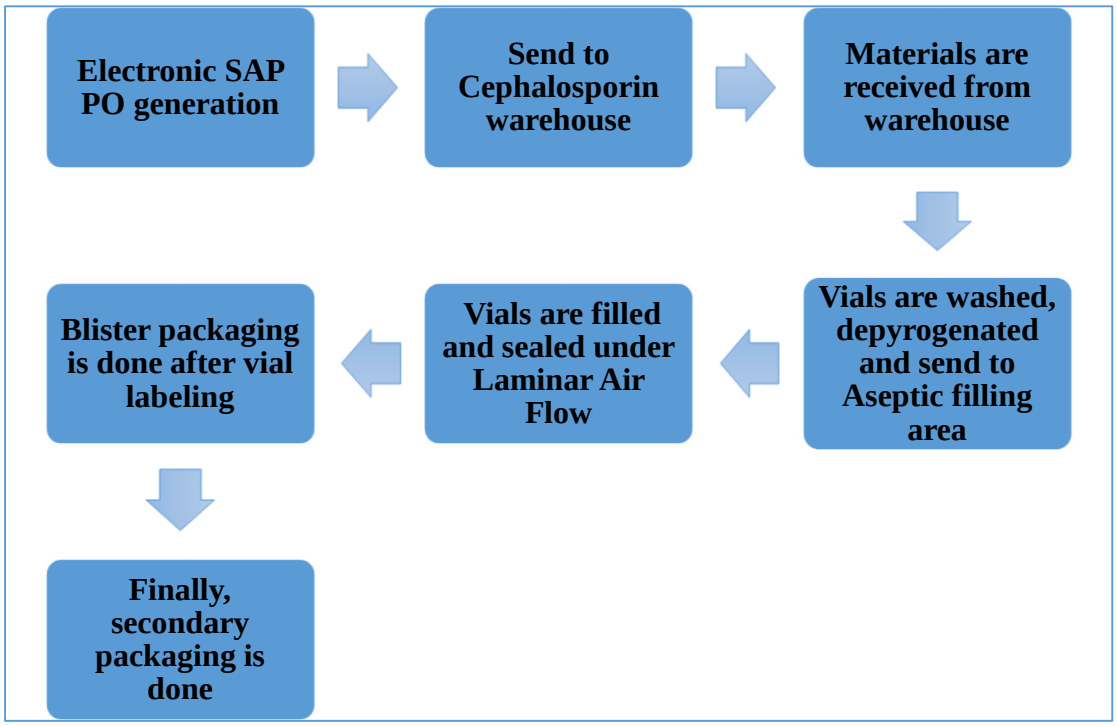


Figure 25: Penicillin unit workflow

For powder for suspension:



Aseptic Room Preparation:

To design of an aseptic room the following factors must be borne in mind:

1. Site

2. Size

3. Windows

4. Doors

5. Surfacing materials

6. Services

7. Corridors

The aseptic procedure comprises the following steps:

1) Sterilization of equipment

2) Sterilization of containers

3) Sterilization of gown.

4) Filling of the solution in the containers under aseptic conditions

5) Double door air lock system.

6) Pass box for materials.

9.3.2 Process

Granulation:

Dry mixing of API and excipients

↓

Wet mix done by adding starch paste

↓

Drying

↓

Sieving of granules along with the added lubricant

Figure 26: Flow-chart of Penicillin granulation process

Blending

Proper mixing can be obtained with the help of blending procedure

Compression

Compression is the process of applying pressure to a material. In pharmaceutical sector, an appropriate volume of granules in a die cavity is compressed between an upper & lower punch to consolidate the material into a single solid matrix, which is subsequently ejected from the die cavity as an intact tablet.

Encapsulation:

Empty capsules shells are loaded;

↓

A vacuum pipe separates the cap and body of capsule;

↓

There are 6 stations which fills the dose;

↓

There are 10 stations for locking pin which locks the cap and body. Capsules move down the slider

Figure 27: Penicillin unit encapsulation process flowchart

Coating:

Not every dosage form needs to be coated, it is basically done for

- Better appearance of the dosage form;
- To protect from moisture content;
- To mask the bitter taste of the dosage form

Tablets are placed into tablet bed

↓

Spray gun sprays the coating solution

↓

Tablets are collected after coating

Figure 28: Coating process flowchart

Machines used in manufacturing:

Table 20: Machine used in Penicillin manufacturing

Machine Name	**Origin**	**Capacity**	**Function**
Brothers filling machine	India	16 vials per minute	Vial and bottle filling
P+AMAF90T Encapsulation Machine	India	Rpm 8.0, 14 Channels, 1 station	Encapsulation for making capsules
Shezong Rotary Compress Machine	South Korea	Rpm 25, 63 tablets per hour	Tablet compressing
Ganson FBD (Fluid Bed Dryer)	India	1.5 L capacity	Drying
Oscillating granulator: Manesty	England	12 mm mesh	Granulation
Double cone blender	Bangladesh	400L &1000L, RPM: 15,18	Blending to create a homogenous mixture
N R cota machine	Australia	65 kg, 2 spray guns	Tablet coating, coating materials: Ethanol 96%, Dichlomethane
Clinocone Blender	India	RPM: 9, 1000L capacity	Blending
Compression Machine: Manesty D3A16	England	RPM-15, 250 tablets per minute.	Tablet compression

9.3.3 Packaging

Labeling: Then the drugs are sent to CVC Labeling machine. It is originated from Taiwan. Its maximum speed is 100 rpm but it is validated to 45/min for better performance. However, ampoules, vials, bottles all are labeled here. There is a typing machine and its temperature is set to 185c.Here due to high heat important information such as manufacturing date, expiry dates are printed here.

Mix up prevention system: Then the drugs are checked by mix up prevention system. The main function of this system is at first the important information is set here first for a specific product. If this machine found any problem in that information in a bottle then it quickly gives signal and the machine is stopped automatically.

Condot Printer: the function of this printer is it prints certain information in the main pack of the drug. Such as manufacturing date, expiry date etc.

In the blistering area we found two types of blistering machine:

1. Buchon Blister Machine: this blister machine is originated from Korea. It is the latest machine. It is applicable for both the tablet and capsule. ALU FOIL AND ALU PVC is used here.

2. Hong A Blister Machine: this blistering machine is originated in Korea. Vials, capsules, tablets all can be blistered here.

9.3.4 Quality Control (Penicillin)

This lab is dedicated to check the physicochemical properties of Penicillin products only.

Lab Equipment:

Table 21: Equipment used in Penicillin QC Laboratory

Machine Name	Origin	Function
METTLER DL18 Karl Fisher	USA	Moisture content of raw materials and finished products

OHAUS electronic digital balance	USA	Material weight analysis
Shimadzu UV machine	Japan	Product concentration analysis
Kotterman Fume Hood	Germany	Contains carcinogen, hazardous, toxic, flammable materials
Ultrasonic bath	India	To dissolve solvents
Pharma test dissolution tester (DT)	Germany	Analyzing drug release
Hardness tester	UK	Testing tablet hardness
Water conductivity meter	-	Checks the ability of a solution to conduct current
Thermonik friability tester, RPM-25, 4 min, 100 times	India	Check the physical strength of tablets
WXG-4 Polarimeter	China	Optical rotation analysis of raw materials
Dessicator	-	To keep sample till test
Water HPLC (Software: Empower 2)	USA	Analysis of different chemical component in a product.
Shimadzu HPLC (software: Lab Solution BB)	JAPAN	
Gellen Kemp water bath	Germany	Incubate sample
Logan Disintegration tester	China	Drug release analysis

Products that were under production at the moment of visit:

- Brodactam IV infusion 4.5gm vial
- Fimoxyclav 1.2g IV injection
- Oracyn- K 250mg and 500 mg tablet
- Fimoxyl capsule 500mg

Chapter 10

Quality Operations

Quality operations is a combination of three departments which are controlled by the head of quality operation. Each department has its own individual personnel responsible for ensuring the responsibilities of the respective department. Departments of Quality Operation are given below:

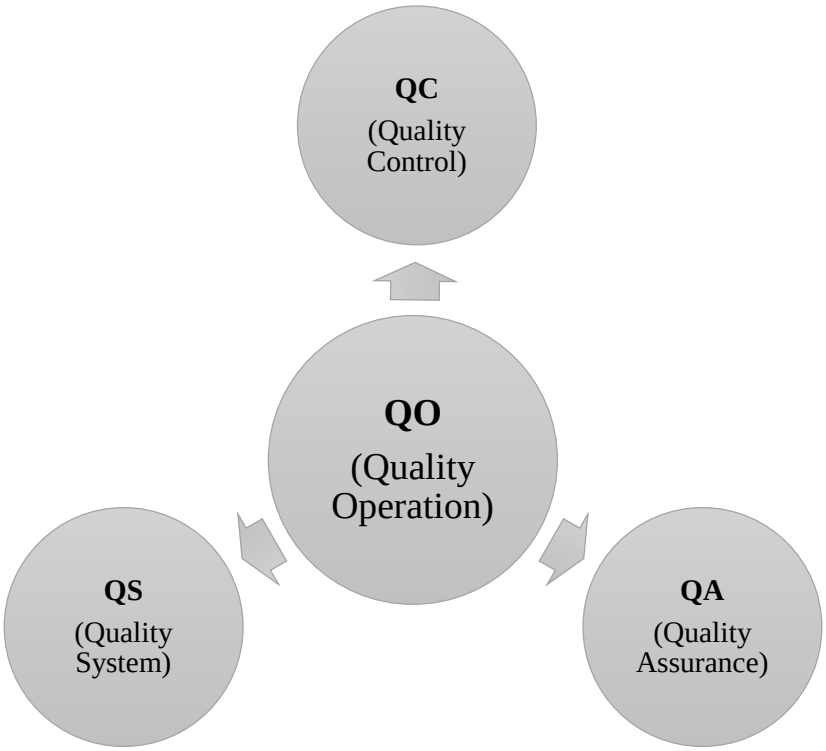


Figure 29: Quality operations of Sanofi Bangladesh Limited

10.1 Quality Control

The QC (Quality Control) department is divided into four labs:

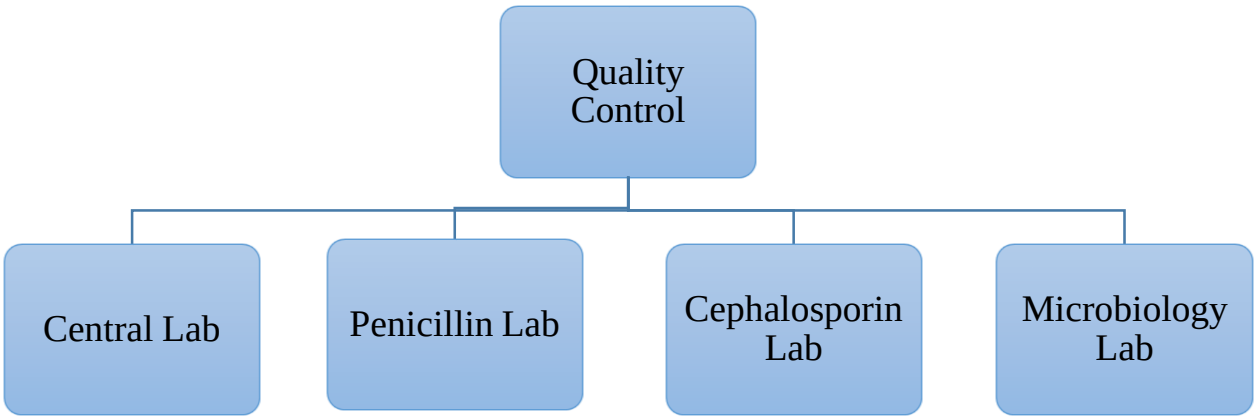


Figure 30: Laboratories of Quality Control department

Equipment used in central QC:

Table 22: Equipment used in central QC laboratory

Name of the Equipment	Use	Brand & Origin
Karl-fischer titrator	Water content test	Labindia, India
TOC meter	Total Organic carbon of WFI & purified water	Japan
Gas chromatography	Volatile assay and Impurity Test	Thermo scientific, USA
Ion chromatography	Separation	Dionex, Germany
UV - Spectrophotometer	Identity and assay	Shimadzu, Japan
Disintegration tester	Disintegration time	Electrolab, India
Distillation unit (K-350)	Determination of nitrogen Content	Buchi, Switzerland
Dissolution tester	Dissolution testing	Pharmatest, Germany
Stability chamber	Stability sample storage	Thermolab, India
Humidity cum Photo stability machine	Photo stability study	Thermolab, India
Electromagnetic sieve shaker	Particle size analysis	India
Centrifuger	Sedimentation	England
Potentiometric titrator	Non-aqueous titration	Labindia, India
Drying oven	LOD test	Griffin, USA

COD reactor	Determination of chemical oxygen demand	USA
Halogen moisture analyzer	Moisture content Determination	Switzerland
Friabilator	Friability testing	Electrolab, India
Conductivity meter	Conductivity testing	Jenway, UK
P^H meter	P^H measurement	senSION+, Spain
Vortex mixer	Sample dissolving purpose	Korea
Ultrasonic bath	Sample dissolving purpose	England

10.1.1 Analytical Support (AS) and Analytical Development (AD)

This section of QC has three major functions which are as follows:

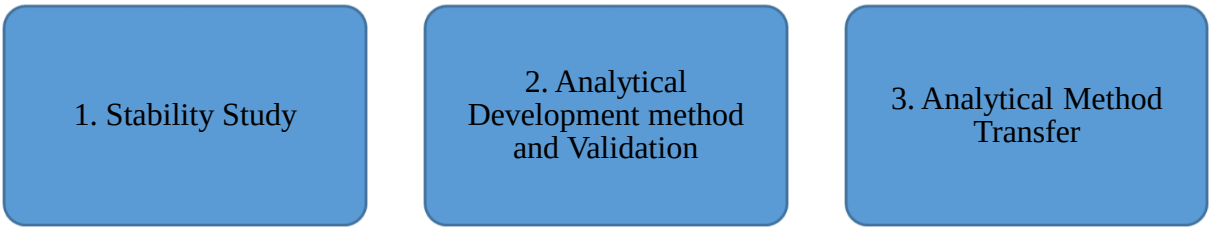


Figure 31: Functions of Analytical Support and Analytical Development

1. Stability study

In order to execute stability testing for various products, stability chambers are required. There are six stability chambers situated at central laboratory and capacity of three is 8000 L and the other three being 400 L. The entire necessary equipment mandatory for stability test are located at stability chamber area.

These chambers are maintained in three different types of conditions-

Table 23: Conditions maintained in stability chamber area

Condition Type	**Temperature**	**Relative Humidity (RH)**	**No. of Chambers with capacity**
Accelerated Condition	$40^0C \pm 2^0C$	75% ± 5%	2 chambers of 400 L capacity
Ideal Ambient Condition	$30^0C \pm 2^0C$	75% ± 5%	2 chambers of 8000 L capacity
Controlled Room Temperature	$25^0C \pm 2^0C$	60% ± 5%	1 chamber of 400 L capacity
			1 chamber of 8000 L capacity

Stability study is implemented for three types of products:

1) Marketed Products

2) New/Development Products

3) Product Variation Changes (Product under change control)

1) Marketed products:

Samples form one batch of a product is stored in following two different chambers-

$30^0C \pm 2.C$ with 75% ± 5% RH

$25^0C \pm 2.C$ with 60 % ± 5% RH

Shelf life of marketed products are tested for 4 times-

Table 24: Stability testing of marketed products

If shelf life product is of-	Testing time for these products are-
18 months	0 month (Initial)
	6 months
	12 months
	18 months
24 months	0 month (Initial)
	12 months
	18 months
	24 months
36 months	0 month (Initial)
	12 months
	24 months
	36 months

2) New Products: For new product three batches are manufactured and kept in three different environmental conditions in the stability chambers.

Table 25: Stability testing of new products

Conditions	**Test timing**
$40^0C \pm 2^0C$ with 75% ± 5% RH	0 month (Initial)
	3 months
	6 months
$30^0C \pm 2^0C$ with 75% ± 5% RH	0 month (Initial)
	3 months
	6 months
	9 months
	12 months
	18 months
	24 months
	0 month (Initial)

$25^0C \pm 2^0C$ with 60 % ± 5% RH	3 months
	6 months
	9 months
	12 months
	18 months
	24 months

If the stability test in 1st condition ($40^0C \pm 2^0C$ with 75% ± 5% RH) is not successful, 2nd condition ($30^0C \pm 2^0C$ with 75% ± 5% RH) is applied for 1-year stability testing and after that; stability test is completed in 3rd condition ($25^0C \pm 2^0C$ with 60 % ± 5% RH).

2. Analytical Method Development and Validation

Most of the Products are enlisted in the Pharmacopoeia (BP & USP) and their analytical methods for drug analysis are obtained from these sources. If the analytical method is non-pharmacopoeial method (INN), then it has to be validated by which Sanofi SOP is followed. In this process, approximately 1 month may be required for the method validation. Before starting any commercial production, AS and AD personnel train the QC personnel thoroughly.

3. Analytical Method Transfer

AS and AD section is accountable for undertaking Analytical Method Transfer Function where analytical method, protocol, samples will be available from sites such as HR, production, training department etc. This method/protocol/sample is tested by two analysts and then the results of these tests are sent back to the donor sites from the QC. After finding same result by comparing between the results of QC and donor site, it is approved.

10.1.2 Microbiology Laboratory

Following tests are performed in case of the following materials:

Table 26: Tests performed in microbiology laboratory

Non-sterile products	**Environmental monitoring**	**Sterile Products**
Microbial limit count (MC)	Active air sampling Passive air sampling Surface monitoring Personnel monitoring Non-viable particle count	Pre-sterilization test Endotoxin test Sterility test

Endotoxin test/ Pyrogen test:

Limulus Amebocyte Lysate (**LAL**) reagent is made from the blood of the horseshoe crab. In the presence of bacterial endotoxins, the lysate reacts to form a clot or cause a color.

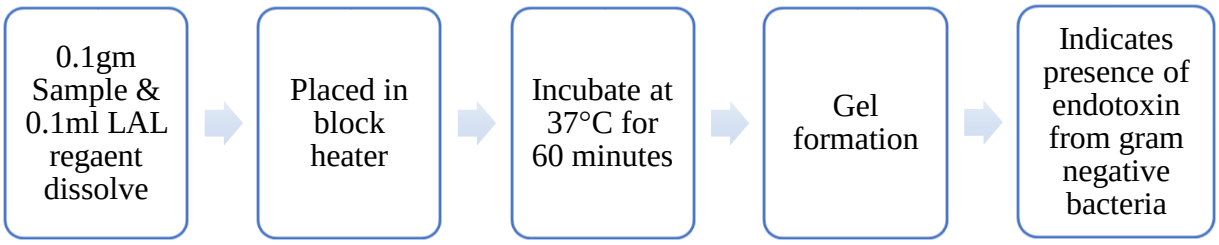


Figure 32: LAL Test process

Water test for-

(i) Water for Injection (WFI):

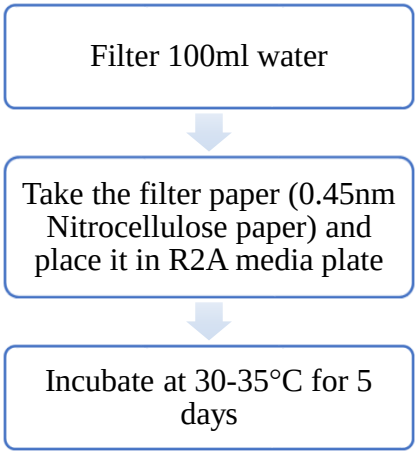


Figure 33: Water testing process for WFI

(ii) Purified water (PW)

(iii) Raw and process water

MC test for products and raw materials:

1. Total aerobic microbial count (TAMC)→ TSA (Tryptic Soy Agar) is used
2. Total yeast and mold count (TYMC)→ SDA (Saboraud Dextrose Agar) is used

TAMC (pour plate or filtration method):

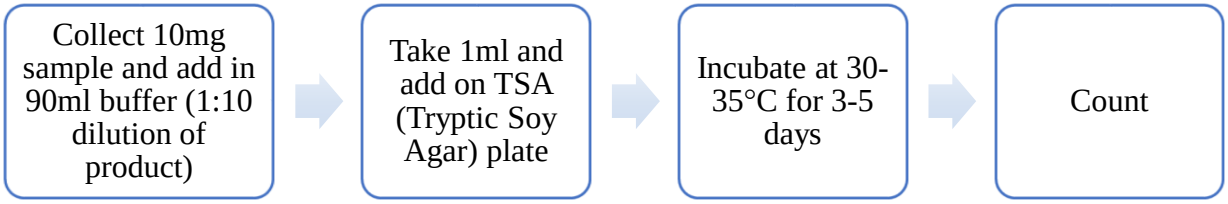


Figure 34: TAMC process

TYMC:

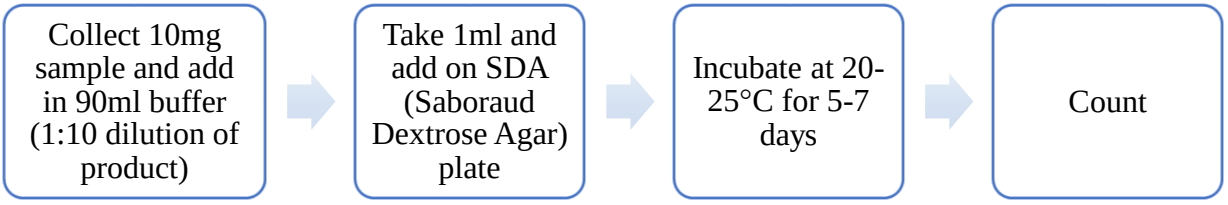


Figure 35: TYMC process

Media used in Microbiology lab:

1. MCA (MacConkey-Sorbitol Agar) media
2. XLD (Xylose Lsine Deoxycholate agar) media
3. CETA (Cetrimide Agar) media
4. MSA (Mannitol Salt Agar) media
5. TSA (Tryticase Soy Agar) media
6. MHA (Muller Hinton Agar) media
7. SDA (Sabouraud Dextrose Agar) media
8. TA (Tinsdale Agar)

Sterility test (for parenteral and antibiotics):

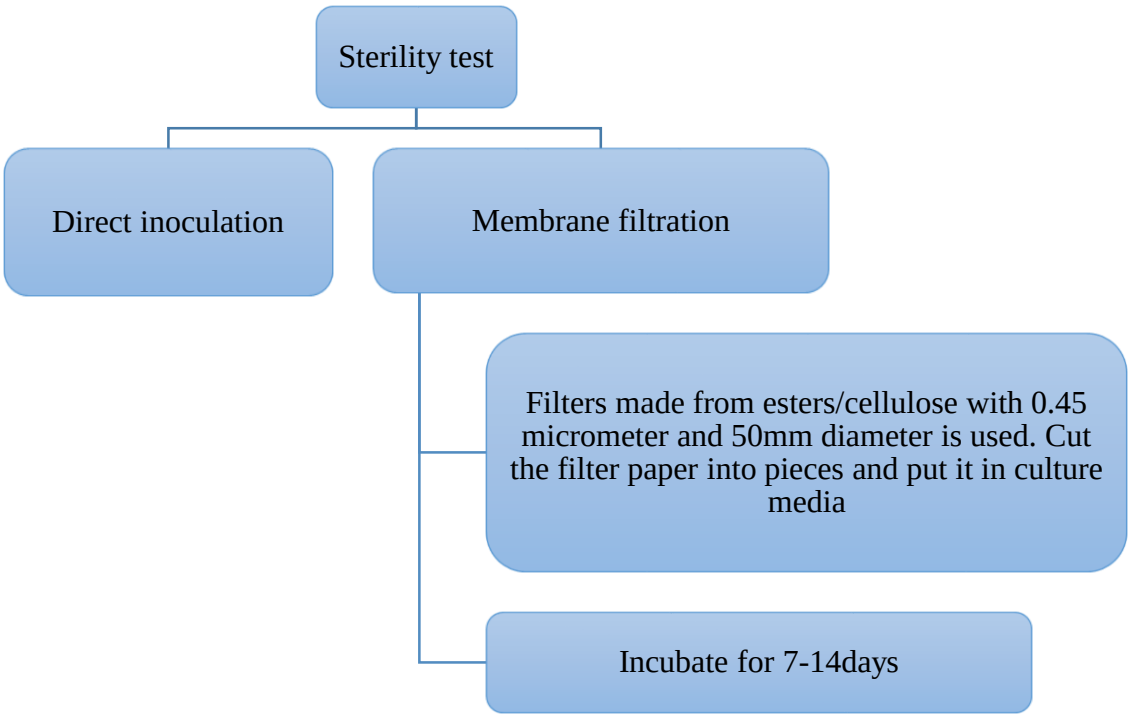


Figure 36: Sterility testing process for parenteral and antibiotic products

Types of incubators:

Table 27: Incubators used in Microbiology laboratory

Model Name	Temperature range
Incucell, MMM Group (Capacity- 222 liter)	42-44°C
Conductivity meter, Memmert	30-35°C
Sheetal	20-25°C

Other equipment:

Table 28: Equipments used in Microbiology laboratory

Instruments	Name	Info
Depyrogen oven with HEPA	MMM	226°C
Autoclave	1. Priorclave 2. RVSEB	- 121°C (30 mins) - 115°C (30 mins)

Biochemical Assay:

Only for Clexane (enoxaparin sodium) using Hamilton robotic liquid handler.

10.2 Quality assurance

Quality assurance is the totality of the courses of action made with the object of ensuring that pharmaceutical items are of the quality required for their expected utilize. It is a way of preventing mistakes or defects in manufactured products and avoiding problems when delivering product to customers. A quality assurance system is said to increase customer confidence and a company's credibility, to improve work processes and efficiency, and to enable a company to better compete with others. The Quality Assurance Department is vital for a pharmaceutical industry since it controls and assures the quality of the products starting from the raw material.

Quality assurance in this way incorporates GMP and different factors.

QA= Product design + GMP + QC + Quality goal

Quality Assurance have two wings:

- In Process Quality Assurance (IPQA)
- Quality Management System (QMS)

In-process quality Assurance: In-process quality control tests are simply routine checks that are performed during production. They are those tests carried out before manufacturing process is complete to ensure that quality is met before they are approved for consumption and marketing. IPQA for different dosage forms are performed in Sanofi Bangladesh LTD.

Table 29: In-process quality assurance for different products

Dosage form in Sanofi	**In-process quality Assurance**
Solid dosage forms	- Appearance - Disintegration time - Hardness - Friability - Average weight - Thickness
Ampoule (Liquid Sterile)	- Average volume - Height - Print- product name, exp, mfg. date

	- Room condition
Semi-solid	- Height and weight of fill tube - Sealing temperature - RH - Pressure differential
Powder for suspension	- Volume - appearance - Identification of active ingredient - Microbial contamination (satisfactory/unsatisfactory)

IPC test for packaging:

Solid-

Table 30: IPC testing for solid dosage form packaging

Blister	- Empty pocket - Ruptured pocket - Broken tablet - No of tablet - Embossed digit - No of blister for leak test - Result of leak test (%)
Leaflet	- Material code - Print - Pharma code
Printed carton	- Material code - Print - Pharma code
Outer	- Print - No of packs

Semi-solid-

Table 31: IPC testing for semi-solid packaging

Blister	- Tube - Sealing - Print of price
Semi-solid tube	- Average weight - Tube height - Batch information (batch no, mfg., exp date) - Room condition
Outer	- Print - No of packs

QA works through **Quality Management System (QMS)** which are recorded. This incorporates:

- ✓ Deviation
- ✓ Change control
- ✓ Quality Risk Assessment (QRA)
- ✓ CAPA (Corrective Actions and Preventive Actions)
- ✓ SOP management
- ✓ Document Archival
- ✓ Retention sample management
- ✓ Product Release
- ✓ Product technical complain (PTC)
- ✓ In process quality control (IPC) or In process quality assurance (IPQA)
- ✓ Audit management

1. Deviation

For any type of deviation first QA finds out the root cause and takes CAPA. Every detail is documented in PHENIX software within 24 hours when deviation occurs. Based on this an investigation is formed and that team prepares report by using various methods. After that necessary actions are taken depending on reports.

The methods are –

a) 6 M analysis

In order to determine root cause, this method follows analysis of these things mentioned below-

i) Manpower

ii) Measure

iii) Machines

iv) Medium

v) Methods

vi) Materials

b) The 5 why? Analysis

It is one of the simplest tools and easy to complete without statistical analysis. It can be used individually or as a part of the fishbone analysis.

Actions included in investigation team are

- Immediate action
- Correction
- Corrective action
- Preventive action

2. **Corrective and Preventive Action (CAPA)**

- **Corrective action**: Action to eliminate the cause of a detected non conformity or other undesirable situation in order to prevent its recurrence.
- **Preventive action:** Action to eliminate the cause of a potential non conformity or other undesirable potential situation in order to prevent its occurrence.

3. Product Technical Complaint (PTC) Any product complaint in market first comes to supply chain quality management who hand over this issue to QO investigation team identifies the root cause and after that QA takes corrective action. COMET used for relevant information of complaint registered. Assessment class for complaint are of 4 types –

- Class I – Leading to death
- Class II – Permanent problem (Kidney damage, ADR)
- Class III – Side effects
- Class IV – Affects market image

4. Product Quality Review (PQR)

Product Quality Review is done to assess the trend, to determine the need of revalidation of process the product undergoes. Every year QA plans all products to review and analyze all the information including critical process parameters of those products to make a report. The review helps the manufacturer to understand processes better and to gather additional information for further improvements.

Requirements:

- one year rolling period
- Trend analysis of critical parameters, in process and release parameters.

5. Re-call - Any product that call back from the market. There are 2 types of Re-call:

a) Voluntary recall – initiated by Sanofi.
b) Mandatory recall – initiated by regulatory authorities

6. **Audit Management**

- Global Quality Audit: Performed by the representatives of other branches of Sanofi
- External Quality Audit: Performed by third parties (customer) or government (regulatory inspections)
- Internal Audit: 6-8 Internal audit every year within the company

- Supplier audit: Sanofi authority regularly inspects the certified suppliers to ensure the quality. Audit done by regular interval-
  - For Sterile product 2 years
  - For API and excipients 3 years.
  - For primary packaging materials 3 years
  - For Secondary & tertiary packaging materials 4 years

10.3 Quality System

Quality system is a specific implementation of quality concepts, standards, methodologies and tools for the purpose of achieving quality-related goals. Quality System (QS) consists of -

- Qualification
- Validation
- Training
- Regulatory

10.3.1 Qualification

It is the documented testing that demonstrates with a high degree of assurance that a specific process will meet its pre-determined acceptance criteria.

Qualification of facility, utility and equipment:

i. Facility: Important factors include adequate space and light.

- Area qualification
- Room qualification

ii. Utility: HVAC qualification: (Qualification of HVAC system is one component in the overall approach that covers premises, systems/utilities, equipment, processes etc. which includes temperature and relative humidity.

iii. Equipment: User requirement specification should be prepared first.

- A model is prepared
- Ensure design
- Ensure safety by Health, Safety and Environment (HSE)
- Ensure specification required by user
- Electricity, voltage is included in this section.

Stages of Qualification:

There are four stages of qualification:

1. Design qualification (DQ) - Premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP.
2. Installation qualification (IQ) - Premises, supporting utilities and equipment have been built and installed in compliance with their design specifications.
3. Operational qualification (OQ) - The premises, supporting utilities and equipment operate in accordance with their design specifications.
4. Performance qualification (PQ) - Specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

10.3.2 Validation

According to the Food and Drug Administration (FDA), the goal of validation is to:

"Establish documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes." It is a requirement for Good Manufacturing Practices and other regulatory requirements.

Objectives of validation

- ✓ It reduces risk of manufacturing.
- ✓ Assures the repeatability of the process.
- ✓ Assures that the product is continuously produced according to market specification.
- ✓ Reduction of time to the market for the new products.
- ✓ The final release of the product batch would be expedited.

- ✓ It requires less in-process control & end process testing.
- ✓ Eliminates the scrap & reduces the defect cost.
- ✓ Reduces the chances of product re-call from market.

- **Process validation**: In this part need to check both protocols and report and also need documented. At least three consecutive batch data should be checked. This is of 3 types-
  - **Prospective validation (or premarket validation):** It is done for market release products and for stability studies. Prospective validation is the most appropriate validation process used. Extensive sampling of three consecutive batch run is performed.
  - **Concurrent validation:** It is done for slow moving products. Products those are already present in the market but not much present in quantity. The market is created on emergency situations through the DGDA. This validation is done in three months.
  - **Retrospective validation:** It is done for products those are already in the market. The analyses of such products are named as train analysis. Usually such validations are not performed anywhere in Sanofi Bangladesh Ltd.

When Process validation is done-

→ New formulations
→ New machines
→ Formulations changes
→ API and raw material source change
→ Procedure change

- **Analytical method validation**: Method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Results from method validation can be used to judge the quality, reliability and consistency of analytical results; it is an integral part of any good analytical practice.

Analytical methods need to be validated or revalidated

- before their introduction into routine use;

- whenever the conditions change for which the method has been validated (e.g., an instrument with different characteristics or samples with a different matrix); and
- Whenever the method is changed and the change is outside the original scope of the method.
- Analytical method validation is done by QC.

- **Transport validation**: Transportation system need to be validated and also study, documentation is mandatory. Cost effective way and qualified way are the main focus.

Computerized system validation: CSV (Computer System Validation) is the process of ensuring that any technology component (software or hardware) is fulfilling its purpose in line with the regulatory guidelines for a certain industry. It is especially crucial in FDA-regulated industries like biotech and pharma, since products from these sectors impact public health and safety.

A validation assessment program is a necessity in the pharma industry to ensure adherence to pharmaceutical cGMP guidelines, and to help companies maintain consistent quality. The same principles are applied in computer system validation to a computer system or an information technology system.

It's essential to maintain quality standards in pharma since non-conformance can have far-reaching consequences. Computer system validation checks the effectiveness and the efficiency with which the system is meeting the purpose for which it was designed.CSV is dependent on the complexity of the project and can be largely broken down into the following processes:

- ✓ **Master Plan**: This check whether the specifications are in line with user requirements. During this stage, teams are also established which will run the entire process. The set of activities to be carried out during validation are established too. This is basically the process of preparing the blueprint for the entire CSV.This process is the pivot of a validation program since it covers the complete setup such as the physical hardware, software, sites and also validates processes such as risk mitigation and redundancy strategies.

- ✓ **Project Plan**: This process defines the standard operating procedures for each process in a validation assessment program and is a subset of the master validation plan. More importantly it defines a deadline within which the CSV must be completed.A detailed documentation and training on the standard operating procedures (SOPs) is carried out during this process. Additionally, activities such as risk assessment, backup planning and change management are also undertaken during this phase. If a master plan is defining the outline, then a project plan is the execution stage.

- **Cleaning validation:**

  (1) Cleaning procedure should be validated. It is done for contamination, quality control and microbiology. Cleaning validation is done yearly.
  (2) Area should be separated and three consecutive batches should check and the matrix parameters are: toxicity test, clean-ability, solubility, minimum dosage are checked. Also risk values are calculated.

10.3.3 Regulatory

Site regulatory compliance and regulatory affairs work hand in hand. It stands under QS. In order to manufacture a pharmaceutical product two main documents needed are-

- License and certificate approved by Director General of Drug administration, DGDA.
- Dossier preparation
- GMP certificate (issued by DGDA).

In every 5 years, product registration renewal is done for each product.

Export: International regulatory boards are connected with the exporting of drugs. Some documents are needed for exporting of a drug-

- Manufacturing License
- GMP Certificate
- Global Quality Documents (as per the country in which exporting takes place) – Consists of GQA, OQG, STP, GOP, OQS etc.

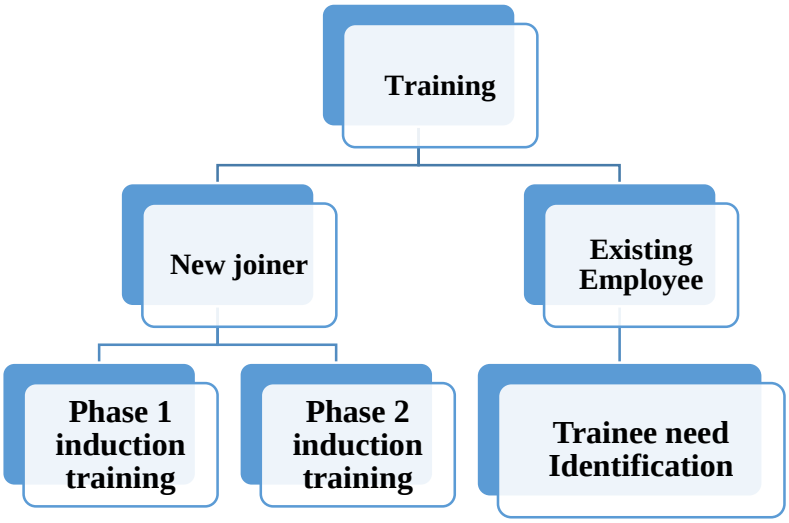
- Gap Assessment - Assessment of the SOP referring to the GQD for the purpose of updating the SOP accordingly.

10.3.4 Training

Training is conducted on Sanofi according to "Personnel Qualification and Training SOP" (TONGI-SOP-000904).

Sections:

- HR related training
- GMP related training
- HSE related training
- SOP training
- External Training
- Re-training



New joiners- There are two phases for new joiners

- Phase 1 - It will be ensured by HR department and it has to be completed within 10 working days from the date of joining. After Phase 1 training, HR will hand over the new joiners to the respective department. After phase 1 induction training, head of the department will ensure the job description (JD) and also prepare 'Training Need Identification (TNI)' and submit it to the QS.

- Phase 2 – Two parts:
  1. SOP training and
  2. On the job training.

Duration of this phase is 1 month. For every kind of SOP training, evaluation needs to be done.

For the employees who have been on a prolong leave (over 3 months) need to do Phase 2 training again as their TNI and JD get obsolete. New training must be completed according to new TNI and JD. There are 12 mandatory trainings that have to be completed every year for every employee in Sanofi Bangladesh Ltd. Department of Quality Systems is responsible for the archival of the training documents except HSE department. Last but not the least, annual training plan need to be prepared by each department. Quality systems is responsible for preparing monthly status vs plan. Annual training plan need to be submitted to QS department by the end of January; also TNI for each employee need to be prepared for each employee within this time frame and submitted to QS department. Moreover, QS department also prepares Qualified Trainer list. There are many more responsibilities regarding training. However, new joiners training, Annual training plan, TNI preparation, Qualified trainer list are most important part of training.

Chapter 11

Packaging

Packaging is the technology of enclosing or protecting products for distribution, storage, sale and use. Packaging also refers to the process of design, evaluation and production of packages. The package must ensure adequate stability of the product throughout the shelf life. Pharmaceutical packaging has to be carried out for the purpose of the safety of the pharmaceutical preparations. Packaging is a critical tool in the pharmaceutical industry for product delivery and regulatory compliance such that at any time point before expiration of the drug product, a safe & efficacious dosage form or products is available.

Importance of Pharmaceutical Packaging:

- Ensure product safety through the intended shelf life.
- Protects from physical & chemical damage.
- Keep the product from contamination.
- Protects from microbial growth.

Packaging Area of Sanofi Bangladesh LTD:

There are two types of packaging area in SANOFI Bangladesh Industry area under which there are some sub-division.

Non-Antibiotic Packaging Area:

It includes:

- Solid manufacturing and packaging section
- Liquid/Suppository/ Ointment packaging section
- Liquid (sterile) packaging section.

Antibiotic Packaging Area:

It includes:

- Penicillin packaging section
- Cephalosporin packaging section.

11.1 Types of Packaging

1) Primary Packaging:

Primary packaging is the term used to designate the layer of packaging in direct contact with the product. In other word, it is first packaging layer in which the product is contained. Primary packaging also serves to keep a product in storage, often for long periods of time.

Types of primary packaging consist of:

- Blistering
- Striping
- Bottle filling
- Vial filling
- Ampoule filling
- Tube filling

Materials used for primary packaging:

- Aluminium foil
- PVC film/ PVDC film
- Bottle
- Vial
- Ampoule
- Tube

Primary packaging machines for solid Product: There are 6 Blister Packaging machine and a strip packaging machine in solid packaging area.

1. Buchon 1, 3 packing machines is used for Alu-PVC blistering
2. Buchon 2 packing machine is used for Alu-Alu Blistering
3. Hoong-A packing machine is used for Alu-Alu blistering

Leak Test:

Leak Test is done for ensuring leak proof of the primary packaging material. 40 Tablet/ 4 blister is tested for leak test.

Solution: Methylene Blue

Apparatus: LT 101 P

Pressure: 405-410 Vacuum Pressure

Time: 3-4 min

Applying Pressure: for 2 min

Releasing Pressure: for 1-2 min

Packaging Machines:

Table 32: Packaging machines

Machine Name	Origin	Parameter	Product in process
Buchon-1 Blister Packaging Machine (Model: Wider-IA)	Korea	RPM 30-40 Stroke/min	Avil 22.7
Buchon-2 Blister Packaging Machine (Model: Wider-IA)	Korea	RPM 15-20 Stroke/min	Orva 10

Buchon-3 Blister Packaging Machine (Model: Wider-IA)	Korea	RPM 25-50 Stroke/min	-
HOONG-A Blister Packaging Machine (Model-MINISTER-AV)	Korea	RPM 25-50 Stroke/min	-

Steps of Automatic blister packaging machine:

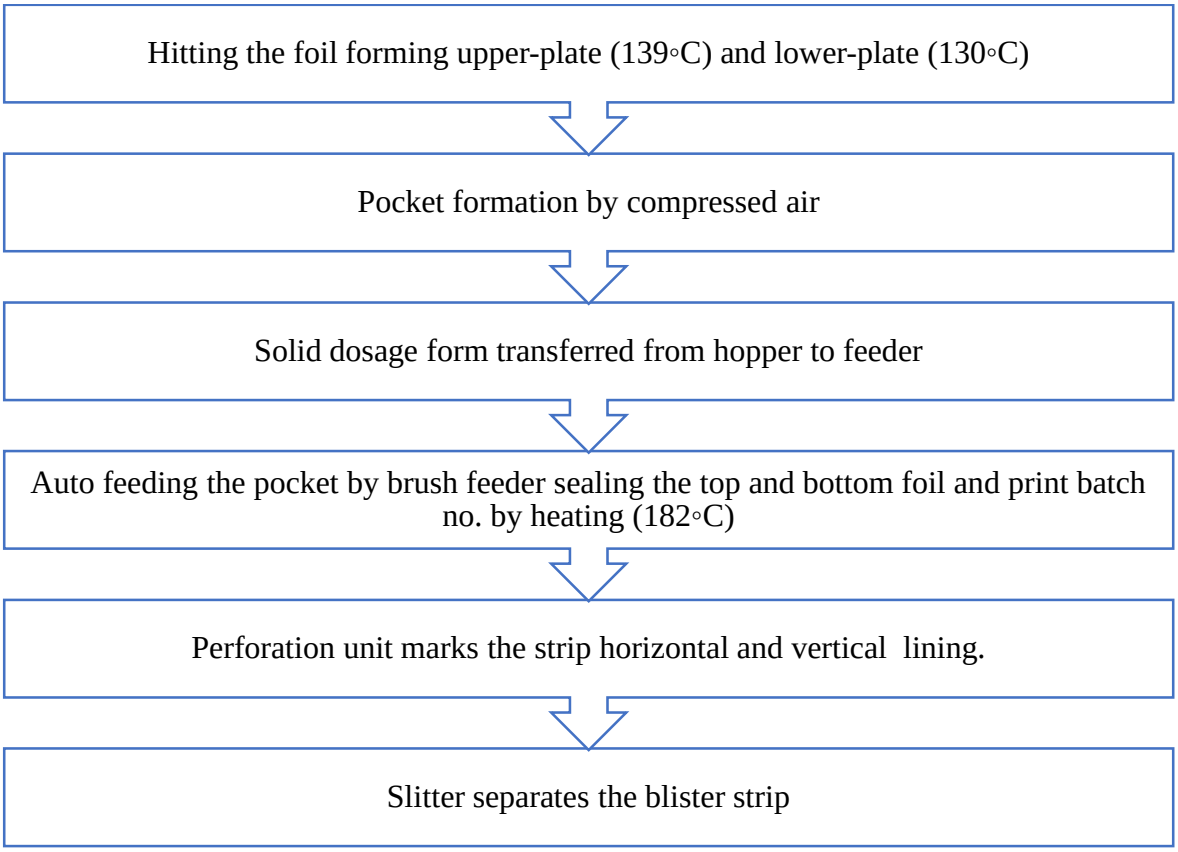


Figure 37: Flowchart for steps of automatic blister packaging machine

2) Secondary packaging:

Secondary packaging is outside the primary packaging area used to group primary packages together. Secondary packaging is intended to protect not only the product, but

also the primary packaging. This often is the packaging most visible to the consumer in retail displays.

It keeps the primary packaging in its original condition during storage.

Material used in secondary packaging:

Packaging carton:

- Printed carton
- Over-printed carton
- Shipping carton

The followings are printed on label, carton or outer label of each product -

- Batch number
- Manufacturing date
- Expiry date
- MRP or IP of Products.

3) Tertiary Packaging:

Tertiary packaging is used for bulk handling, warehouse storage and transport shipping. Examples of tertiary packaging might include brown cardboard.

Room Condition for Packaging Area:

- Temperature: (22±3)˚C
- Relative Humidity (RH): ≤65%
- Pressure: ≥ 2.5pa.
- There should be negative pressure or low pressure in solid packaging room and positive pressure or high pressure in corridor so that particle could not backflow to the corridor and thus prevent cross contamination.

In other hand positive pressure or high pressure should be maintained in sterile filling room and negative or low pressure in corridor so that sterile room is under septic condition.

Chapter 12

Engineering Department

Sanofi Bangladesh Ltd. consists of man, machines and materials among which machines are under total supervision of the engineering department. The engineering office at Sanofi Bangladesh Limited is located on the T-7 building. Engineering department is the supporting department of the industry which is responsible for design, setup, qualification, validation of required machines and equipment aimed for facilitating the manufacturing of quality product, identification of critical steps and relevant monitoring of machines and equipment. The department consists management officers and non-management staffs in total who are responsible for some significant operations of the engineering department which are planned for utility operations and preventive operations, breakdown maintenance, calibration with collaboration of the production team. Among these the first two operations are planned annually, the calibration and maintenance on the breakdown is an on-demand operation. The project-based operations are performed during the renovations or when any new machines are adopted in the industry. The utility operation is based on electricity, gas, steam and compressed air system. Steam is produced through the boilers which are another important part necessary for autoclave, spraying, coating etc. The other small facilities like fire alarm, security, lighting, buildings are also maintained by them.

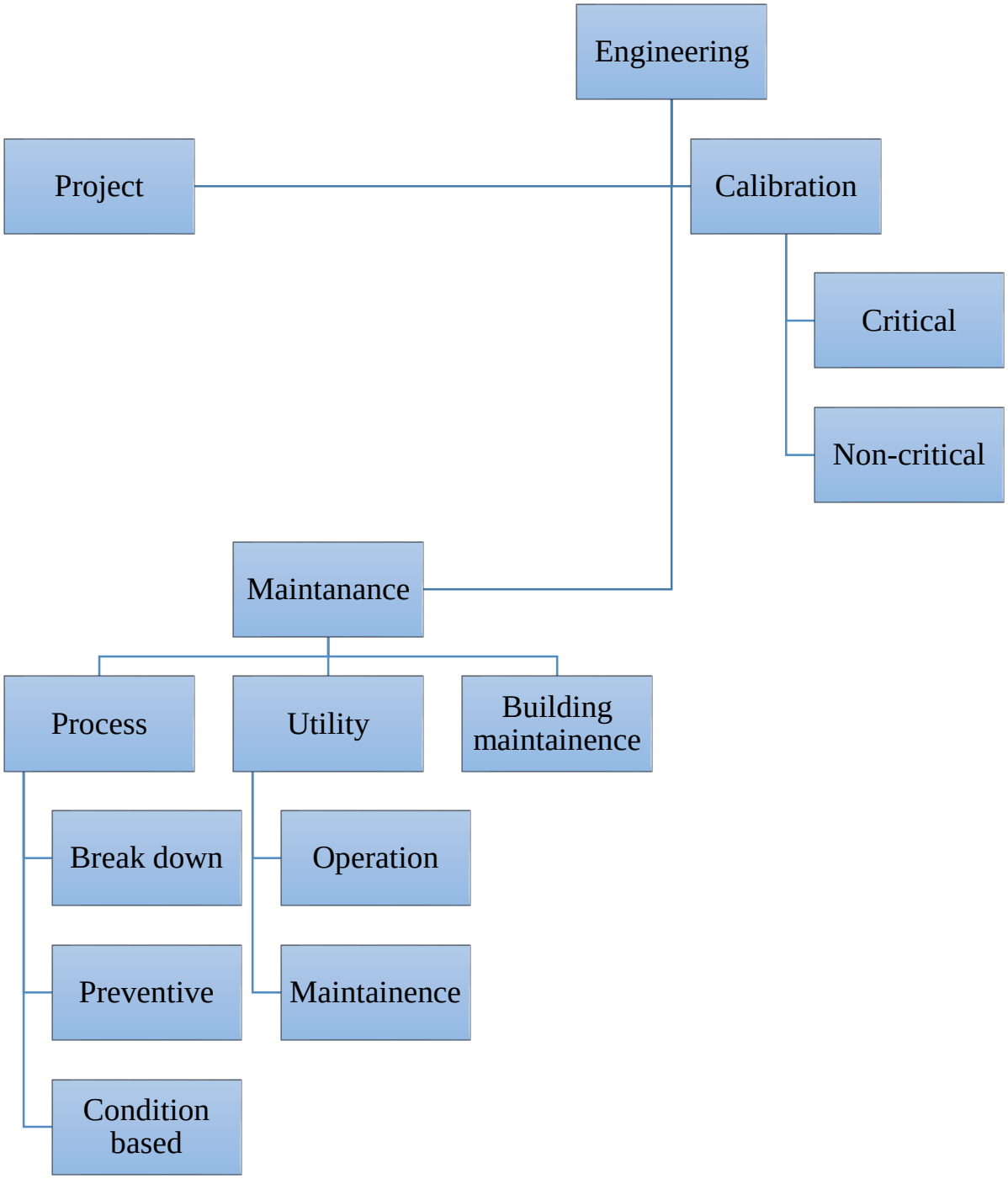


Figure 38: Engineering department work process

Utility Services:

- HVAC
- Electricity
- Compressed Air
- Process/ Potable water
- Natural Gas
- Effluent Treatment Plant
- Steam

12.1 HVAC System

Heating, Ventilation Air Conditioning (HVAC) system is designed to maintain the room temperature, pressure and humidity at the required set point. Air change rates, temperature and humidity are closely monitored and controlled on a continuous basis. The system provides adequate ventilation to remove fumes, odors, airborne contaminants. They are designed to maintain relative pressure differentials between rooms to prevent contamination and cross contamination. HVAC system operates without interruption while being efficient to operate both in terms of energy consumption and from a maintenance perspective.

The process by which effective control of parameters in an air-conditioned space is maintained are as follows:

-Heating: To increase the temperature by adding thermal energy to a space

-Cooling: To decrease the temperature by removing thermal energy from a space.

-Dehumidifying: The process of removing the water vapor or humidity of a space

-Particle Count: The process of removing dust, pollens, smoke and contaminants from air inside the space.

-Ventilating: The process of adding external air to freshen up the air and maintaining gas ratio and pressure.

-Air velocity: To control the movement of the supplied air so that the inhabitants of the space do not feel discomfort.

Flow chart of HVAC

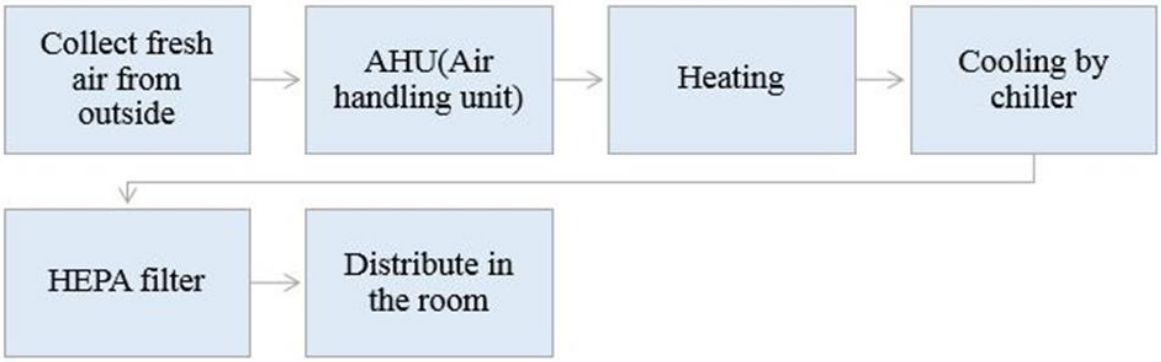


Figure 39: Flowchart of HVAC system

Filters are used to keep the air free of unwanted particles. Three kinds of filters are used in HVAC system which are prefilter, secondary filter and HEPA filter with the capacity to retain particle sizes of 10 microns, 0.5 micron and 0.3 micron respectively. H13 efficiency is 99.99% and H14 efficiency is 99.7%. F-9 filter also used which efficiency is 95.95%.

Chillers:

Chillers are used in HVAC through Air Handling Unit (AHU).

Components of chiller

Evaporator: Heat exchanger. Water transfer heat to refrigerant and becomes cool.

Condenser: Here refrigerant emits heat to atmosphere.

Compressor: Compressed refrigerant to send it to condenser.

Table 33: Chillers of HVAC system

Brand Name	Country of Origin	Capacity	Used for
Trane- 3	France	275	CPS area
Trane- 4	France	375	CPS area
Trane	France	375	other
Trane	France	175	other

Chiller temperature is maintained between 6-7^{o}C. R_{11} (Trichlorofluoromethane) refrigerant as a chilling agent.

Air Handling Unit:

Air handling unit act as a heat exchanger where fresh air transfers to the cool water coming from the chiller. Passing through filter using ducts enters into the AHU. Then cooled air is transferred to the room. It is used to supply and circulate clean air around a building or to extract stale air as part of a building's heating, ventilating and air conditioning (HVAC) system. There is five AHU for cephalosporin production area and six AHU in penicillin production area. Fan coil unit (FCU) only handle air flow.

Boilers:

Boilers are used to generate steam for HVAC. Produced steam travel through a heat exchanger and then through heating coils. There are 2 boilers which are combined and distribute steam through the industry. Steam is required to produce heat and pressure. Sanofi uses fire-tube boiler to produce steam which has capacity of 3ton/hour. Both the boiler blown out 3 times in a day. Full overhaul is done once in every year.

Table 34: Boilers used for HVAC system

Machine name	**Brand name**	**Country of Origin**	**Capacity**	**Location**
Fire tube boiler	Cocharan	UK	3 ton/ hour	T-7 building
Fire tube boiler	Cocharan	UK	2 ton/ hour	T-12 building

Air Compressor:

An Air compressor is device that converts power into potential energy by forcing air into a smaller volume and thus increasing its pressure. The energy can be used for variety of Application.

Uses-

- To create hydraulic pressure
- To open the valve
- To create pocket in blister machine
- Cleaning

12.2 Electricity

Two substations are distributing the electrical power all over the area. The whole industry is run by electricity provided from two different electricity source. The non-antibiotic site electricity is distributed by the DESCO electricity system and diesel generator is utilized when normal government distributed electricity is not available. Electricity comes from the DESCO and there are transmitter and PFI system which is responsible to keep the electricity consumption up to the mark and efficient, also reduces the load on distribution. It maintains the ratio of voltage and electric current consumption. On the other hand, in case of antibiotic site electricity is distributed through gas generator normally. There are two water cooling system to minimize those extra produced heat.

Table 35: Generators used in Sanofi Bangladesh Limited

Generator	Fuel	Capacity	Brand Name	Country of origin
Gas generator	Natural gas (supplier Titas gas)	1030 KW	Caterpillar	USA
		1030 KW	Caterpillar	USA
Diesel generator	Diesel	800 KW	Perkins	England
		500 KW	Perkins	England
		500 KW	Perkins	England
		125 KW	Rolls-Royce	UK
		200 KW	Perkins	England

10.3 Effluent Treatment Plant (ETP)

Waste water from the plant is treated to adjust oxygen level and pH and to remove impurities before draining. Waste water from the CPS section also goes through a chemical neutralizer before going into the ETP. Rotating biological contactor is used to purify the waste water from different departments where caustic soda is used as chemical.

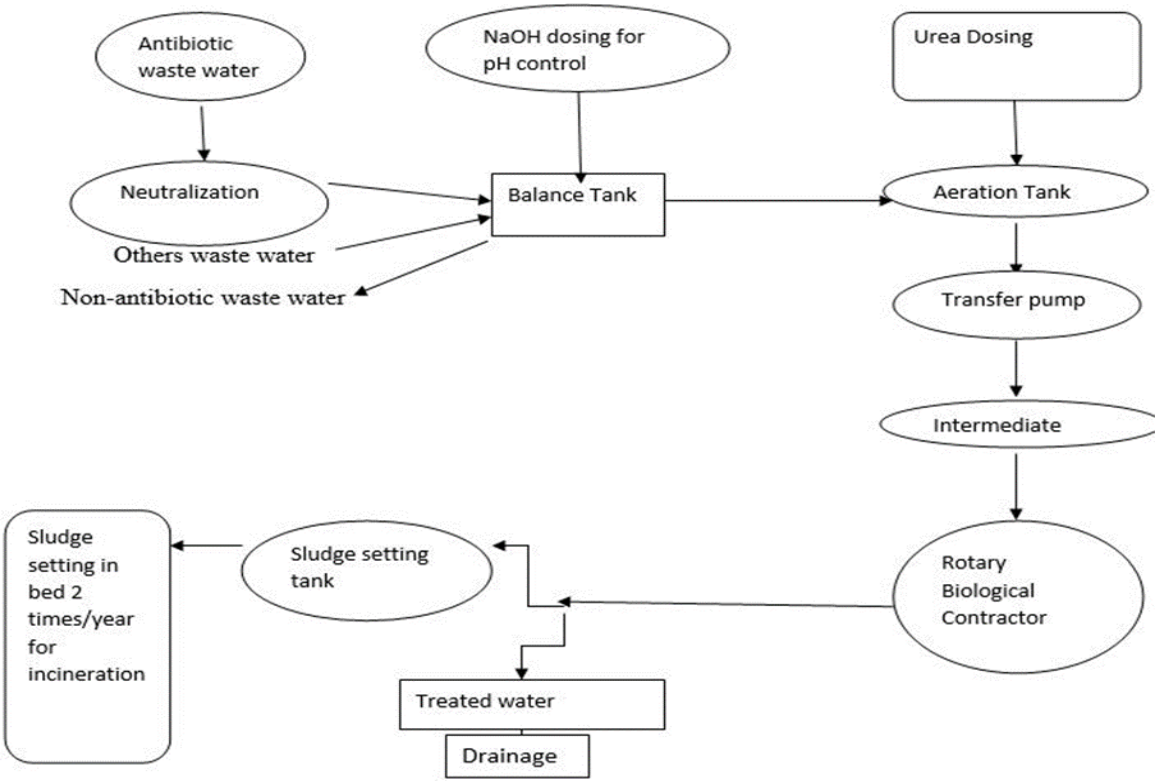


Figure 40: Flowchart of ETP process

Water Purification Plant:

There are three types of water used in the industry Potable water, purified water and water for injection. There is one type of water plant used to convert potable water to purified water and another type to convert purified water to water for injection.

There are quite a few water plants in the pharmaceutical plant premises. These plants generate:

-Purified Water and

-Water for Injection

Water plants are one of the vital areas of the pharmaceutical manufacturing plant. Quite a few techniques can be employed for water purification, e.g. reverse osmosis, demineralization etc.

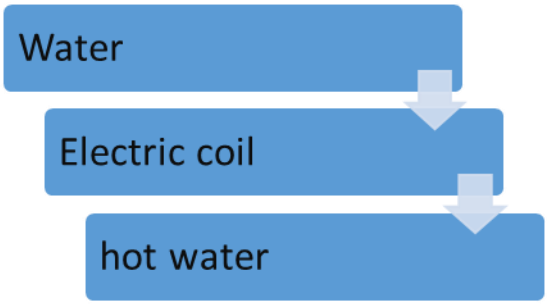


Figure 41: Process of water purification

Water Softening Plant:

Water softening is the removal of calcium, magnesium, and certain other metal cations in hard water. The resulting soft water is more compatible with soap and extends the lifetime of plumbing. Water softening is usually achieved using lime softening or ion-exchange resins. In Sanofi Bangladesh plant resins are used in water softening plant. When water is hard, it can clog pipes, can damage the quality of the products.

10.4 Engineering Maintenance:

Maintenance Engineering is applying engineering concepts to the optimization of equipment, procedures and departmental budgets to achieve better maintainability, reliability and availability of equipment.

Engineering maintenance include-

1. Breakdown maintenance
2. Preventive maintenance

Breakdown maintenance is probably the most commonly used approach, but it is easy to see its limitation. When equipment fails it often leads to downtime in production. In most cases this leads to inefficiency. Also, if the equipment needs to be replaced, the cost of replacing it alone can be substantial. It is also important to consider health, safety and environment (HSE) issues related to malfunctioning equipment.

Preventive maintenance is maintenance performed in an attempt to avoid failures, unnecessary production loss and HSE violation. It is an extra layer of precautions. It is a routine maintenance

work of machines to avoid machine breakdown. In this section all the machines and their ancillary parts are subject to routine maintenance.

Project work of engineering department:

Project Engineers are responsible for any new renovation or new project or to change the facility of an area. For example, the engineering project works to change the environment, such as changing temperature, pressure, humidity, particle count for a clean room by designing HVAC systems etc.

Table 36: Engineering department project work

Machine purchasing:	Engineering department select the best machineries for purchasing according to the requirements and specification of production department.
Renovation work/Civil Work:	Engineering department also involved in renovation work of any unit. Renovation work means changing of machineries, setting of new machines in new building.
New facility built:	Engineering department also involved in new facility built which is related to the setting of new building.

10.5 Calibration

Calibration is regarded as the process of adjusting the output or indication on a measurement or monitoring to agree with value of an applied standard within a specified accuracy. It is routine checkup of measuring and monitoring instruments. This is done once a year.

Instruments are divided into following four classes for this purpose:

Table 37: Classes of frequency of calibration on instruments

CLASS	FREQUENCY of CALIBRATION	SCHEDULE to TOLERANCE
CLASS 1	182 days	±7 days
CLASS 2	365 days	Within validity period
CLASS 3	365 days	±14 days
CLASS 4	Indefinite (when stops working properly)	As per requirement

To maintain up to date calibration a monthly plan is prepared. Upon calibration completion the instrument is tagged, signed and dated by the calibrating officer and records of the work is documented in files and retained for the length of 10 years.

Purpose - To define the procedure for management of instrument calibration program in compliance with all applicable international and local regulatory requirements, and with Sanofi global quality documents.

Identify instruments/equipment with a unique number as follows:

WW-XXX-YYY-ZZZ; for example: 06-001-DAL-001

Where:

WW= 2-digit numeric code for product family/plant in which the instruments/equipment is normally located. Here, 06 is used for cephalosporin (antibiotic).

XXX= 3-digit numeric code (here 001) for process area in which the instruments/equipment is normally functioning.

YYY= 3/2 characters used to define the type of instruments/equipment.

ZZZ= 3-digit sequential number for a particular piece of instruments/equipment.

Chapter 12

Conclusion

Pharmaceutical Internship is a good way to link up the distance between academic pharmacy learning and pharmaceutical jobs. Internships guide in developing pharmaceutical industry experience through learning from experienced and professional individuals. As a result, at the end of internships, interns gather immense experience in relevant areas which helps in deciding whether a pharmaceutical career is the right choice or not. Sanofi presented us an opportunity to become a part of a unique, fast paced, innovative and accountable pharmaceutical company. We are thankful to the authority for giving us this chance to flourish our knowledge. The last two weeks were a great experience being a member of Sanofi Bangladesh Limited.