In-Plant Training at Healthcare Pharmaceuticals Limited

By:

Nowrin Rashid

17146014

Tania Ahmed Chowdhury

17146050

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Interns: **Alfa Ibne Rafi, Anamika Saha, Iftekhar Alam, Nowrin Rashid, Rajeswari Sharma, Tania Ahmed Chowdhury**

This document consists of the gist of the cognitions apprehended by the In-Plant interns who underwent their internship from 22nd June 2021 to 8th July 2021.

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List of acronyms

HR	Human Resource
HPL	Healthcare Pharmaceuticals Limited
ED	Executive Director
DMD	Deputy Managing Director
PPE	Personal Protective Equipment
SOP	Standard Operating Procedure
NFPA	National Fire Protection Agency
LPG	Liquefied Petroleum Gas
EHS	Environment, Health & Safety
SDS	Safety Data Sheet
QA	Quality Assurance
ETP	Effluent Treatment Plant
GMP	Good Manufacturing Practice
API	Active Pharmaceutical Ingredient
QC	Quality Control
SAP	Systems Applications and Products
GRN	Goods Receive Note
R&D	Research & Development
FDA	Food &Drug Administration
USA	United States of America
HVAC	High Ventilated Air Conditioning
RH	Relative Humidity
IPQC	In Process Quality Control
BOD	Biological Oxygen Demand
COD	Chemical Oxygen Demand
SBL	Sanofi Bangladesh Limited
IR	Infra-red
HPMC	Hydroxypropyl Methylcellulose
PEG	Polyethylene Glycol
FDS	Food and Drug Service
IU	International Unit
HPLC	High Performance Liquid Chromatography
µg	Microgram
mL	Milliliter
LOD	Loss on Drying
COE	Centre of Excellence
DGDA	Directory General of Drug Administration
BPL	Beximco Pharmaceuticals Limited

Acknowledgement

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Secondly, we would like to show my sincere gratitude to Ms. Suraya Bilkis, Chairperson of the Plant and Mr. Alauddin Ahmed, Managing Director of Healthcare Pharmaceutical Ltd. for giving us the opportunity to perform our in plant training in Healthcare Pharmaceutical Ltd. starting from 22nd June to 30th September, 2021 and 25th September to 30th September, 2021. Through this training, we were able to grasp how theoretical learning was implemented in practical settings, which further motivated us to work hard in the field of Pharmaceutical Science.

Thirdly, we would like to appreciate all the officers, senior officers and managers for assisting us throughout the training. In addition to that, we would also like to thank all the operators and workers at Healthcare Pharmaceuticals Ltd. for their unwavering support to teach us about working processes and machines during our training program.

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Preface:

Healthcare Pharmaceuticals Limited (HPL) is one of the best multinational pharmaceutical companies in Bangladesh that began its journey in Bangladesh in 1988 by the establishment of the associated company "Healthcare Distribution Limited" with the multinational pharmaceutical "Roche Limited" *(Healthcare Pharmaceuticals Limited, 2021).*

Though HPL set foot in Bangladesh as an importer and distributer of "Roche Pharmaceuticals" and served as so until 2001, now it is concerned with fabricating branded generic drugs for both the local and global markets *(Healthcare Pharmaceuticals Limited, 2021).*

HPL establishing its own pharmaceutical plant in 1996 is generating more than two hundred drugs now in the form of almost all the dosage forms- tablets, capsules, liquids, dry syrups, creams, ointments, gels, small volume parenteral and eye drops *(Healthcare Pharmaceuticals Limited, 2021).*

Like all the other pharmaceuticals, HPL organizes internships for the fresh graduates. We, coming from different parts of Bangladesh, consider ourselves to be legitimately fortunate to pursue our internships under such a reputed pharmaceutical like "Healthcare Pharmaceuticals Limited" as it facilitated us in mastering our theoretical knowledge practically.

1. Apprehension about the HR department:

HR stands for "Human Resource". The HR department works in accordance with the laws of labour approved by the government of Bangladesh. The core functions of the HR department are recruitment and selection. Their main functions include- planning management, training management, policy management and performance appraisal. Besides, this department also conducts the orientation programs and monitors the compliances of the employees.

1.1 <u>Recruitment and selection:</u> The recruitment process can be both internal and external. While the internal recruitment refers to the submission of the curricula vitae (CV) of the candidates by the current employees, the external recruitment refers to the paid job advertisements via internet.

Following this comes the selection process. In selection process, the collected CV are analyzed thoroughly by the HR department and are shortlisted. Then, the shortlisted primarily screened candidates are contacted for assessment that is conducted in two distinct steps- written assessment and oral assessment. When a candidate succeeds the written assessment, she or he is called for oral assessment. After this, the authority finally decides to recruit the suitable candidate to their vacant posts.

The recruitment and selection process can be represented as follows:

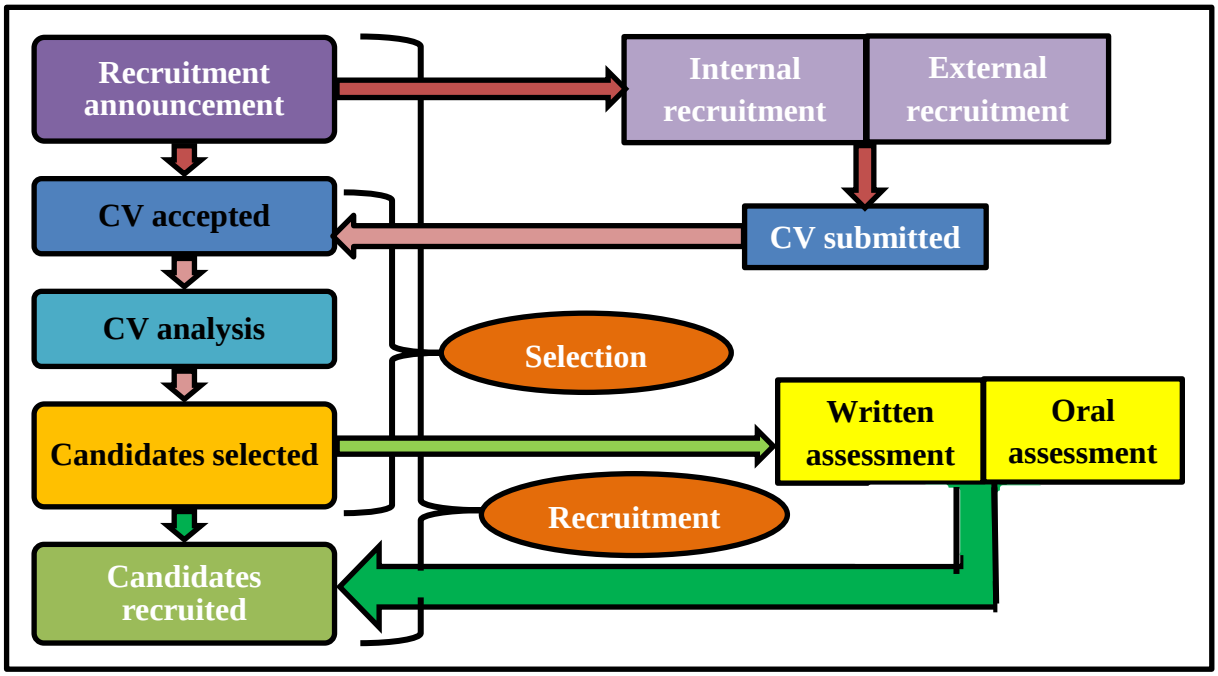


Figure 1: Recruitment and selection process

1.2 Planning management: This is one of the main functions of the HR department through which the department plans on the various aspects assigned to them to generate maximum outcome by the implementation of the efficient units in effective manner.

The department acts as a middleman between the employees and the approval authority consisting of the ED and the DMD. After the HR department plans something, they forward their plan to the approval authority. On approval of the approval authority, the plan is executed on the designated site.

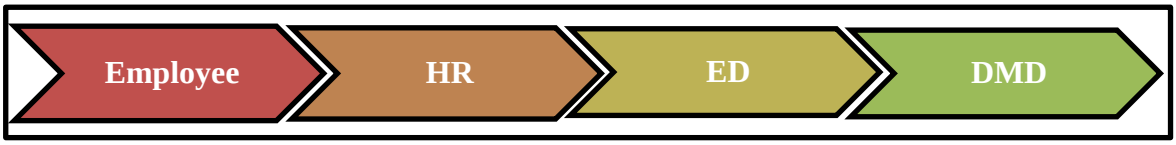


Figure 2: Plan approval process

1.3 Training management: The HR department organizes training programs for the employees that can be both internal and external. While the internal training also known as in-plant training refers to the training of the employees by the native trainer or by a paid external trainer within the territory of the organization, the external training also known as outside training refers to the training of the employees by sending them to the training sites beyond their organization.

Examples of internal training include- undergraduates pursuing internships under an organization, the newly recruited employees being trained by the native trainer. In case of external training, the organization bears the essential living expenses of the trainees during the training period. “Multiple intelligence” training pursued by the academicians is an example of external training.

1.4 Policy management: This function of the HR department is similar to their planning management. The department on the basis of the current situation of the organization and requirement formulates policies that are forwarded to the approval authority. On approval of the approval authority, the newly formulated policies are publicized to all the concerned employees so that, they can execute the new policies on necessities.

1.5 Performance appraisal: Performance appraisal basically refers to evaluation. The HR department monitors the performance of the employees of their organization. On the basis of their daily performance, the employees of the organization are graded annually and are subjected to increment, promotion and upgradation.

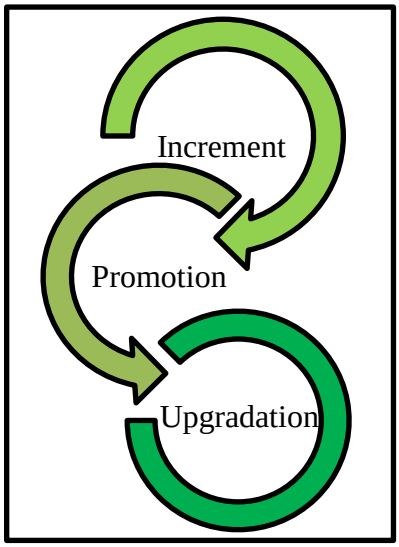


Figure 3: Performance appraisal

While the increment of the employees occurs every year, promotion occurs at an interval of 3 years according to the recorded performance of the employees. When both increment and promotion of an employee occurs that is when the upgradation occurs. Thus, the increment, promotion an upgradation of the employees depend on their performance appraisal.

For instance: a newly recruited employee is considered to be in probation period for 6 months. At the end of the probation period, the daily performance of that employee on evaluation determines if the person will be employed permanently. When the employee under the probation period is found to improve, then, she or he is employed permanently and is provided with a job description containing his or her responsibilities.

However, the employee on no improvement or average improvement is subjected to extended probation period for 3 months more. On re-evaluation when the employee is found to improve, then, she or he is employed permanently. However, when the employee on re-evaluation is not found to improve, then, she or he is permanently eliminated from the organization.

1.6 Orientation: The HR department arranges the orientation programs assigned to them by the higher authority in which they enlighten the freshly recruited ones with the terms and policies of the organization.

1.7 Compliance: All the activities of the employees of the organization are monitored within the territory of the organization by the HR department that is recorded in each of their employment history books. The HR department ensures the proper maintenance of attitude, outlook, attendance .etc. of their employees. Along with these, the HR department works on the leave management issues.

Anyone with a demoralizing attitude or with an inappropriate outlook or with delayed attendance is called by the higher authority and is asked for the justification of his or her committed overwhelming action. Depending on the intensity of his or her action he or she is either eliminated from the job or issued with an "Apology letter". The compliance affects the performance appraisal of the employees.

HPL facilitates 3 types of leaves to its employees on their requirement. The leaves are named as- earn leave, sick leave and casualty leave. While the earn leave is pre-planned, the sick leaves and the casual leaves are required on sudden mishaps. HPL annually facilitates earn leave for 15 days, sick leave for 16 days and casualty leave for 10 days. Though the surplus earn leave keeps on extending that is being added to the earn leave of the next year, the sick leave and the casual leave are not extended. In case of casual leave, the employees are permitted for consecutive 2 days only.

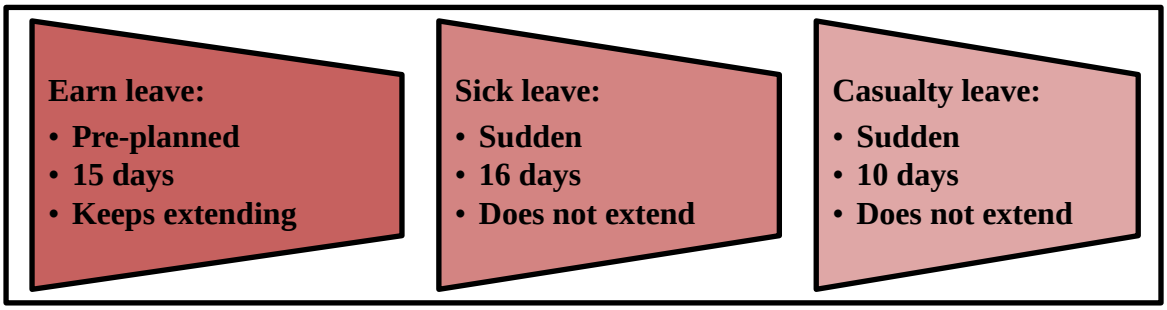


Figure 4: Types of leave facilitated by HPL

We apprehended the various roles performed by the HR department as mentioned above and aspire to develop professionalism as per the professional standards.

2. Apprehension about the Administration department:

The current head of administration department of HPL is Major Tarun Talukder, a retired army officer. HPL usually selects an army officer as administrator since the army officers are strict in their codes of conduct. The administration department performs the administrative roles like- security management, canteen management, site beautification and transport management.

2.1 Security management: The administration department manages all sorts of security system of the organization. They instruct the securities to check the possessions of the gate passers thoroughly during their entrance and their exit. This is done to ensure that the gate passers are not carrying any harmful objects with them during their entrance and also to ensure that they are not carrying anything from the organization intentionally or accidentally while leaving the premises of the organization. Apart from this, the securities are instructed to maintain a register containing the detailed data- time of entrance, purpose of entrance, intended site of visit and time of exit of the gate passers. Besides, closed circuit cameras are installed all over the premises of HPL to monitor all the activities.

Figure 5: Security check post

For well maintenance of the security system, HPL placed electronic card punching machines before the entrance of every important arena. Only the authorized personnel of that particular arena can pass through those entrances via their identity cards provided by the company. HPL also has interlock door systems as a preventive measure against contamination, consisting of two doors that are connected electronically and only one of them can be opened at a time while the other remains closed. Any of the two doors kept open for 60 seconds at a stretch buzzes the security alarm.

2.2 Canteen management: The supply of food, dining time and cleanliness of the dining premises are maintained by the administration department of HPL. The department decides the regular food menu and the daily amount of food to be served. Separate dining premises are there for the officers and the staffs.

The canteen runs on self-service. Every time the employees dine, the dining premises are cleaned. During their entrance each of the diners collect the required cutleries from the allotted cutlery arena and after dining the diners discard their individual cutleries to the allotted cutlery discarding racks.

2.3 Site beautification: The administration department works on beautifying site by keeping the premises of the organization clean. They appoint various categories of staffs for site beautification. Some work as cleaners while some as gardeners. This department of HPL out of respect towards the nature maintains an environment friendly atmosphere through the sustenance of proportionate combination of green and grey.

2.4 Transport management: HPL has separate transportation facilities for their officers and staffs. The transports travel to various locations exactly on their pre-planned timing keeping the regular traffic and any unwanted casualties in mind. The drivers of the transports regularly pick up and relinquish the employees on the estimated schedules.

Figure 6: Transport of HPL (LEASEHOUZ1., 2013)

We apprehended the various roles performed by the Administration department as mentioned above.

3. Apprehension about the EHS department:

EHS standing for "Environment, Health & Safety", is a compliance department complying with the government, international and local standards. In HPL, the efficiency of this department is monitored before any facilities are built. The department trains the newly recruited staffs under them with the precautionary measures- usage of PPE, firefighting, chemical safety, electric safety, first aid, emergency evacuation, waste management, personal hygiene, combating diseases, occupational health management and pest control following their SOP, on combating any unexpected casualties.

SOP standing for "Standard Operating Procedures" are the guidelines set up by an organization that are followed in every step of the organization in carrying out their routine activities. HPL has its own SOP containing all the codes of conduct for its smooth maintenance. The codes of conduct are set in such a way that complies with the government, international or local standards.

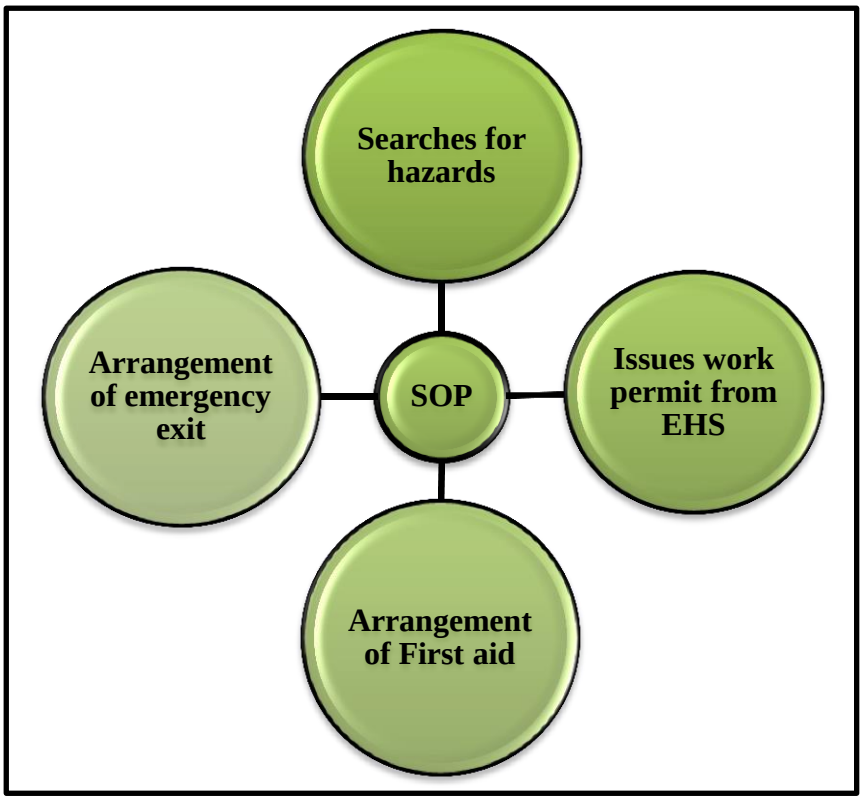


Figure 7: Core functions of SOP

3.1 PPE: PPE are the precautionary attires that differ on the basis of the working sites. PPE includes- safety gloves, safety masks, safety gowns, safety goggles, safety helmets, safety boots and safety shoe covers. While the outdoor sites mostly require safety helmets, and safety gloves the indoors mainly laboratories require safety gloves, safety gowns and safety goggles. However, the required PPE solely depends on the type of work to be performed irrespective of it being done in indoors or outdoors.

The safety helmets are used in the places where the probabilities of head injuries exist in both indoors and outdoors. While safety gloves and safety boots are used outdoors to prevent direct contact of electric sparks with the skin; safety gloves and safety are used in laboratories to prevent contamination and direct contact of chemicals with the skin. Along with these, safety goggles are used to prevent the entrance of any chemicals into the eyes and safety shoe covers are used to prevent contamination in the laboratories.

The safety masks are used to prevent the inhalation of toxic gases. These can be gas protective. The gas protective masks also known as gas masks must not be used by the people suffering from respiratory troubles as these masks inhibit the entry of oxygen inside the mask.

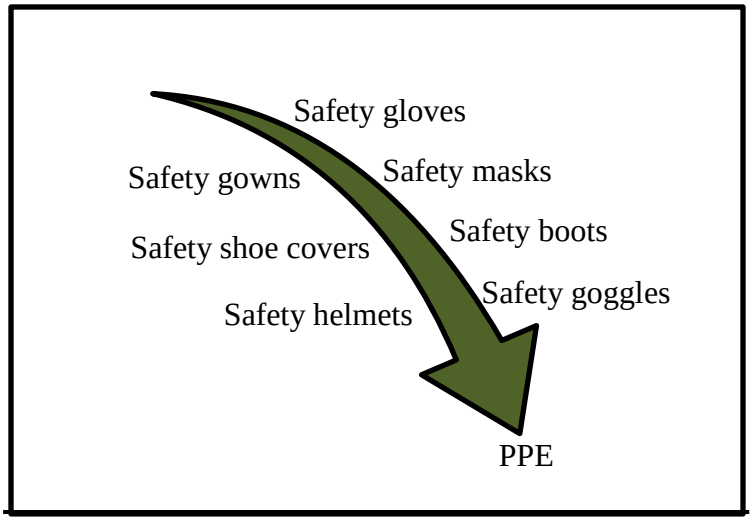


Figure 8: Various components of PPE

3.2 Firefighting: For ignition less than 19.5 % oxygen is required. Whenever fire breaks out any of the elements of the fire triangle must be inhibited to stop blazing. The fire triangle includes- oxygen, fuel and heat. This can be represented as:

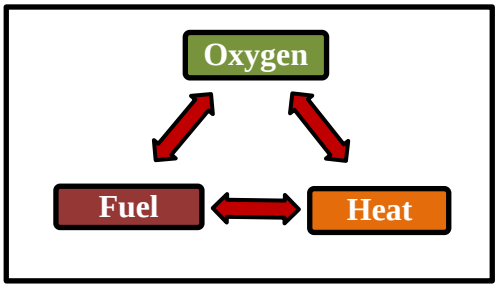


Figure 9: Fire triangle

Apart from the usage of fire extinguishers, any of the three techniques of fire extinguishing- fuel segregation, oxygen removal, heat reduction can be implemented to extinguish fire in an inflamed area or to prevent its further spreading. Fire can be extinguished by stopping the oxygen supply to the inflamed area for 2-4 seconds since, oxygen burns itself. Again, the elimination of all the fuels like- flammable liquids (kerosene, diesel, gasoline, acetone, alcohol .etc.), gases (LPG, natural gas .etc.) from the inflamed area or removal of the heat sources can extinguish fire. The gas supply can be stopped by bending the main pipe of gas supply in such a way that nothing can pass through the pipe.

3.2.1 **Classification of fire:** The NFPA has classified fire into five broad classes on the basis of the source of ignition as follows:

- **Class A fire:** The fires caused due to the ignition of carbon containing elements are included in this class. The carbon containing elements include- wood, hay, coal, cloth .etc. To combat these types of ignition the temperature or heat from the surrounding environment must be reduced. Extinguishers containing carbon-di-oxide must not be used in enclosed spaces ignited with Class A fire. Usage of extinguishers consisting of sand is highly effective in dousing these fires.
- **Class B fire:** The fire caused due to the ignition of flammable liquids or flammable gases are included in this class. While the flammable liquids include- diesel, kerosene .etc., the flammable gases include- LPG, methane .etc. Usage of water extinguishers should be avoided in dousing such fires since water spillage is ineffective in extinguishing such fires. However, extinguishers having ABC powder are highly effective in dousing these fires. Again, fuel removal from the ignited area can greatly help in extinguishing such fires.
- **Class C fire:** This class includes the fire caused due to electrical ignition because

of short-circuit connection or overheated electric wires. Water extinguishers must not be used to extinguish Class C fires as water being a good conductor of electricity can spread the fire instead of extinguishing it. However, usage of extinguishers consisting of carbon-di-oxide or sand is highly effective in dousing these fires.

- **Class D fire:** This class includes the fire caused due to metallic ignition. To combat Class D fires, extinguishers containing any sorts of stone powder should be used.
- **Class K fire:** The fires that breakout in the kitchen while cooking is Class K fires. Such fires can be extinguished by fire extinguishers consisting of soda ash.

3.2.2 Classification of fire extinguisher: The NFPA has classified fire extinguishers on the basis of the incorporated extinguishing agent that can be as follows:

- **Water:** The fire extinguisher consisting of water is considered to be natural fire extinguishers. Though this is considered as an effective fire extinguisher, it should not be used in extinguishing certain fires like Class C fires. Class C fires are caused by electrical ignition and water being a good conductor of electricity can spread Class C fire instead of extinguishing. Thus, despite of being a life saver water extinguisher cannot be used in extinguishing all sorts of fires.
- **Carbon-di-oxide:** The fire extinguishers consisting of carbon-di-oxide are convenient in extinguishing Class C fires. However, these must not be used to extinguish fire breakouts in an enclosed area.
- **Dry powder:** Fire extinguishers may consist of several types of dry powders like- ABC powder, sand and stone powder. ABC powder consisting of ammonium phosphate is named so as it can extinguish all the three classes- Class A, Class B and Class C fires. Sand having silica is considered as a natural extinguisher that can extinguish any class of fire. The SOP of HPL recommends the storage of large amount of dry sand or earth all over the premises to extinguish small oil fires. However, it does not recommend to use sand extinguishers in the premises having machines.

- **Foam type:** This type of fire extinguishers comprise of a mixture of water and ammonium sulfate. Foam type extinguishers exert cooling effect and thus, these can instantly reduce the temperature eventually dousing fire.
- **K-type:** K-type fire extinguisher consisting of soda ash that is, sodium carbonate is the most suitable fire extinguisher for extinguishing kitchen fires.

Table 1: Various types of fires with their respective extinguishers

Fire Classification	Reasons	Examples of igniting elements	Fire Extinguishers
Class A fire	Ignition of carbon containing elements	wood, hay, coal, cloth .etc.	Sand. (CAUTION: Carbon-di-oxide containing extinguishers must not be used)
Class B fire	Ignition of flammable liquids or flammable gases	diesel, kerosene, LPG, methane .etc.	ABC powder. Water extinguishers are least effective in extinguishing this fire
Class C fire	Electrical ignition because of short-circuit connection or overheated electric wires	Electric wires	Carbon-di-oxide or sand (CAUTION: Water must not be used)
Class D fire	Metallic ignition	Machineries	Stone powder
Class K fire	Carelessness while cooking	Cooking oil, leaked gas pipe	Soda ash

3.2.3 **<u>Precautions:</u>** The SOP of HPL suggests to undertake the following precautions to combat fire:

- Storage of large amount of dry sand to combat fires.
- Avoiding the usage of fire extinguishers containing water in dousing Class C fires.
- Avoiding the usage of fire extinguishers containing carbon-di-oxide in dousing fire in an enclosed area.
- Installation of automatic sprinkler system in the zones which are prone to catch fire.

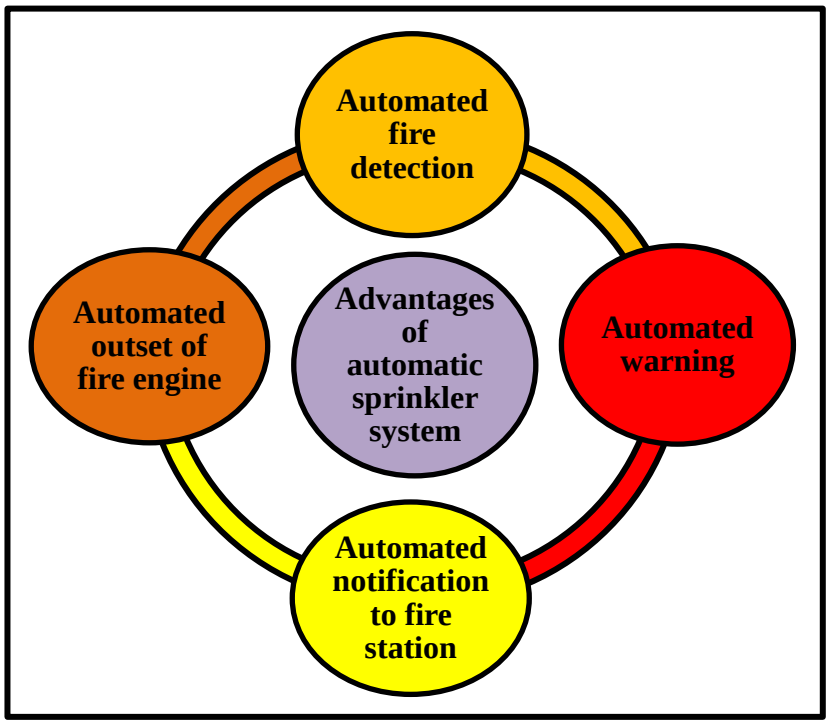


Figure 10: Advantages of automated sprinkler system

3.3 Chemical safety: HPL maintains SDS for proper management of every sector. Labeling is considered to be the most important chemical safety measure as the label contains all the important data of a chemical- usage procedure, requisite precautions, expiry date .etc. The SOP of HPL suggests the allocation of chemical extinguishers, safety showers and emergency eyewashes in all the laboratories to prevent and remedy accidents. It also claims the presence of at least 2 persons in the laboratory.

3.4 Electric safety: The EHS department of HPL maintains electric safety according to their SOP by training the authorized personnel and as a general training step it asks the employees to not shade themselves under electric poles during earthquakes or any natural disasters.

3.5 First aid: The treatment given to the injured before the doctor's arrival is first aid. Under the EHS department some personnel are trained to assist primary nursing to the injured ones after any injuries. They are trained to combat injuries by following gradual steps.

When someone is injured the authorized personnel examine the injured and decide the type of treatment she or he requires. If the injury is minor, the personnel treat by themselves. However, if the injury is a major injury, the personnel provide primary aid until a licensed doctor reaches the premises for further assistance. A medical officer perseveres thrice a week

at the medical center of the canteen building of HPL.

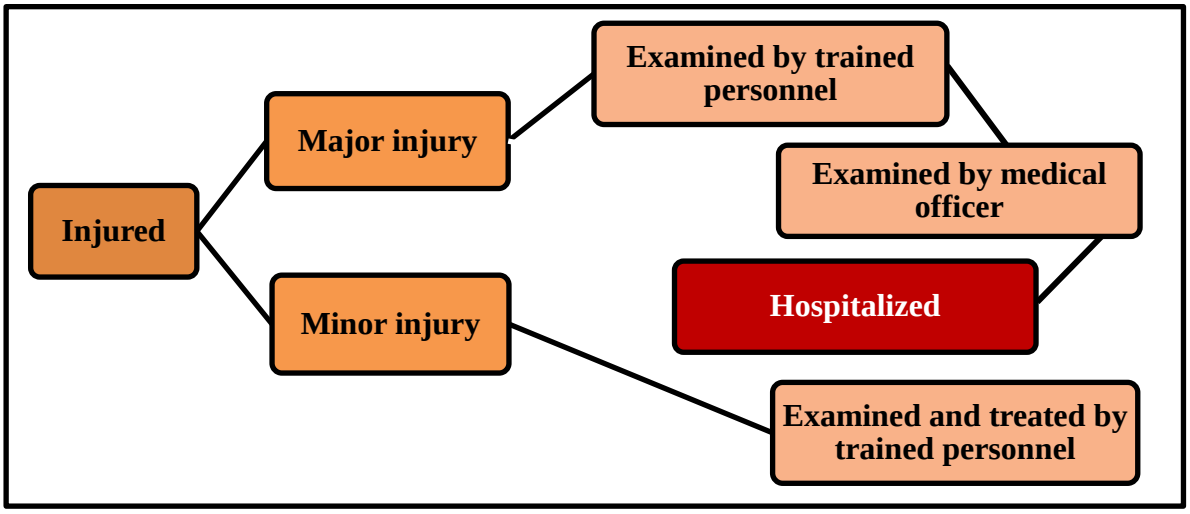


Figure 11: First aid service at HPL

3.6 Emergency evacuation: The EHS department of HPL trains its employees with the procedures of emergency evacuation required during earthquake or fire. During any emergency situation the employees are trained to ring emergency alarms. After the emergency alarms ring, the EHS analyzes the buzzed arena to ensure the urgency of evacuation. Then, the employees leave their respective sites through a door impregnated with "EMERGENCY EXIT" in red color. Following evacuation, the employees gather in the assembly room. The employees are asked to run cautiously since people tend to slip and die out of panicking rather due to the cause of emergency evacuation.

In case of earthquake, people undergo initial shock and aftershock. During the initial shock of an earthquake, the scarcity of oxygen arises as people keeps running within the surroundings. Lifts must not be used during the initial shock. Aftershock of earthquake refers to the destruction of infrastructures. At that time people should shade themselves beside something strong, however, electric poles should be avoided.

3.7 <u>Waste management:</u> The EHS, QA, HR and Administration departments are collectively responsible in proper and safe management of waste material disposal. The Head of the QA team will provides necessary approval and assures proper destruction of waste in waste material management system.

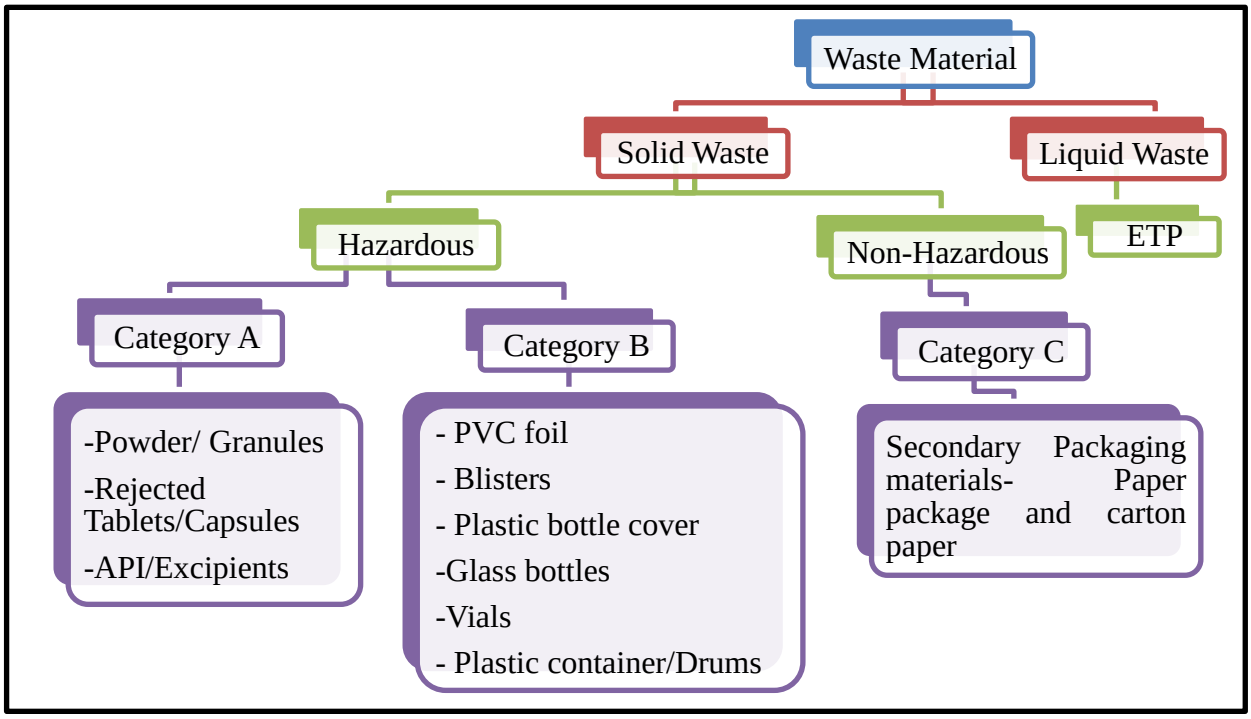


Figure 12: Schematic representation of waste management system of HPL

3.7.1 Solid Waste: The EHS department ensures proper disposal and treatment for waste materials generated in the industry. Waste material is divided into solid waste and liquid waste. Solid waste is further divided into hazardous and non-hazardous waste.

Hazardous waste materials are again classified into two categories- Category A and Category B. While the Category A consists of powders and granules, rejected tablets/capsules and active pharmaceutical ingredients and excipients, the Category B consists of primary packaging materials such as PVC foil, blisters, plastic bottle cover, glass bottles, vials and plastic container drums.

Non-hazardous waste materials consist of Category C which includes secondary packaging materials such as paper packaging material and carton paper. The solid waste materials are dumped in landfill sites and are sent to PRISM Bangladesh for being incinerated at 1200 °C.

A different handling procedure is implemented in case of solid waste generated in Cephalosporin manufacturing unit. For solid waste disposal, the solid and semi-solid waste collected from cleaning are collected in polythene bags with proper labeling and are handed to the EHS officers. Name, weight and quantity are recorded.

3.7.2 Liquid Waste: Proper waste management system is also employed in case of liquid waste materials generated in the industry. The EHS department employs ETP in treating liquids. It is a process where the industrial waste water is treated for reuse or safe disposal purpose. The polluted or contaminated water undergoes the mechanism to make the water reusable for gardening, cleaning and other domestic purposes.

The washing purpose water is collected in septic tank and Cephalosporin waste water is collected in the pre-treatment pit.

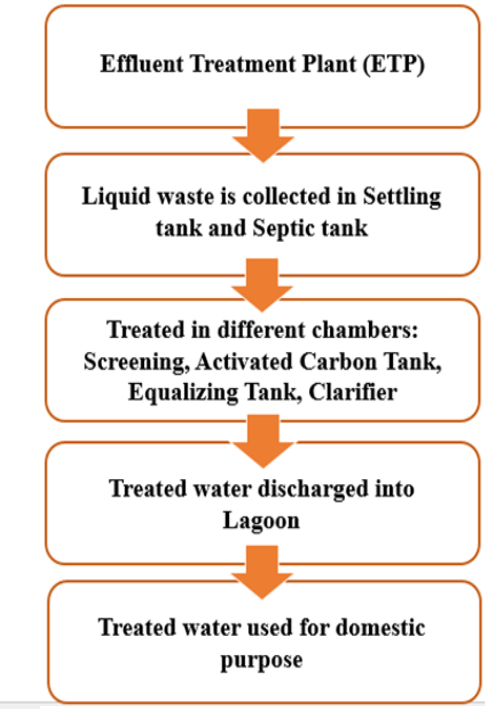


Figure 13: ETP flowchart

In the pre-treatment pit, Sodium Hydroxide Solution having pH 12 is added and left for 24 hours. Cephalosporin contains β-lactam ring and in presence of NaOH the ring breaks. Then, the pH is checked and if the desired pH of 6.5-8 is not reached, the waste water is further treated with Hydrochloric acid, HCl. When it reaches pH 6.5-8, it is transferred to ETP.

In case of treating waste water or cytotoxic waste products generated from oncology, biotechnology, hormone and sterile units, Sodium Hypochlorite is used and left for an hour that deactivates the cytotoxic chemicals. Later, the pH is checked to see if it reached the pH of 6.5 to 8.5 they will be transferred to ETP. There is also an activated carbon tank where the suspended solid, color and other particles are filtered by the process of adsorption.

All kinds of waste water are collected in a big tank called equalizing tank. It consists

of bacteria that can break down the molecules present in the water. Inside the equalizing tank there are about 80 diffusers which supply oxygen for aerobic respiration of bacteria and the bacteria can obtain nutrients from the food products in the waste water. Then, the waste water is transferred to a clarifier where the sludge is collected below. After that, the processed water is collected in settling tank. The sludge that is collected is transferred to sludge dry bed and after a certain period of time, it will be sent for incineration. Finally, the clean water or the reusable water is collected in a place called lagoon.

Certain tests called BOD and COD are carried out to test the degree of pollutants present in water. BOD is the amount of dissolved oxygen needed by micro-organisms in water body to break down organic matter present in the water sample under aerobic condition. COD is the amount of oxygen consumed to oxidize organic contaminants present in water.

3.8 Personal hygiene: According to the SOP of HPL, one must not groom awkwardly within the premises of the pharmaceutical. Formal grooming must be maintained by all the employees irrespective of their posts.

3.9 Combating diseases: The working personnel and the products being manufactured affect each other. Therefore, it is essential for the working personnel to be in good health. According to the SOP of HPL when any working personnel falls ill, she or he must inform the EHS department about her or his illness. The department on being informed verifies the disease of the sick one and offers sick leave. On recovery the recovered must meet the EHS department with her or his legal medical fitness documents. Then, EHS will examine and ask the recovered to resume her or his operation at the plant.

3.10 Pest control: The EHS department along with the administration department of HPL controls all sorts of pests through the appropriate administration of pest controlling agents during site beautification.

We apprehended the various roles performed by the EHS department as mentioned above and aspire to develop professionalism as per the professional standards.

4. Apprehension about the Material Management department:

Material management department deals with storing of the raw material, primary packaging materials, secondary packaging materials and other accessory materials that are needed for drug administration in proper storage conditions- temperature and humidity. Usually, a pharmaceutical plant has 5 warehouses- General warehouse, Cephalosporin warehouse, Hormone warehouse, oncology warehouse and penicillin warehouse. HPL has 4 warehouses excluding the penicillin warehouse. It has a warehouse extension to accommodate the large amount of raw materials and also a separate storage area for the flammable solvents.

In the warehouses of HPL, the storage condition is maintained strictly where different room temperature controls are available such as: (15-25) ºC, (8-15) ºC, (2-8) ºC and (-20 to -25) ºC. Different types of materials are stored at different room temperatures. Most raw materials are kept under the temperature ranging between (15-25) ºC and, the biotechnological products and injections are stored under the temperature ranging between (-20 to -25) ºC.

A software called MADGE tech data logger software is installed in all the warehouses that provide the readings of the parameters of the room at an interval of 15 minutes. All the data loggers are connected via wifi and are placed by following GMP guidelines. The data loggers are installed through the measurement of the height, length and width of each room along with the consideration of the hot point and cold point.

4.1 General warehouse: At first, we visited the General warehouse where the raw materials and packaging materials needed for drug manufacturing were stored. While entering the General warehouse, we had to put on plastic shoe cover and helmets to move from one unit to another unit with the help of step over bench. Interlock door systems were prevalent at the junctions. At the beginning, there was the quarantine area that had drums of raw materials to be checked by the Material Management team by following the standard specifications relate to the materials. They carry out physical inspection of the raw materials.

Material management starts with unloading the materials needed for drug manufacture through a specific door and another specific door is used in case of distributing the finished product. The materials are obtained from approved vendors and source verification has been

conducted. Different kinds of tests are carried out for source verification. Initially, physical tests are carried out where they check for color, odor and crystals (if applicable) of the material with the specification available to the team.

The QC team carries out the required testing processes in the sampling room where only authorized person can enter the premises. For APIs, every single package or drum needs to be tested and, for excipient and packaging materials √(n+1) the amount of material is tested. the initial test, the raw materials can then, move on for chemical or microbiological tests. At times, when chemical and microbiological tests require a lot of time to obtain results, the accelerated stability testing are carried out.

When receiving any material, a material receive check list from the appendix is checked which is available in SOP of material management department. Then, a checklist is made and after that a discrepancy form is sent to QC and they come for physical inspection. If the materials pass the physical test, those are included in the received material list in the SAP software employed in the company. The QC team then, receives a GRN as they will be carrying out the necessary tests. After that, chemical test can be carried out. If the material pass the chemical test, it will be labeled with a green sticker label and if it is rejected it will be labeled with a red sticker label. We further got to know that a location log book is maintained which can be used to locate a particular material. A unique code for each product is generated and then maintained in the location log book.

After the quarantine area, materials were seen to be stacked and proper sticker labels were placed. A refrigerator was present that provided cool room condition and it was maintained within (8-15) ° C. It contained Apocarotenal 1% CWS and α-Tocopheryl-Acetate (Vitamin E USP).

Beside the refrigerator, there was another control room which contained capsule shells. It was a hygroscopic material and so, the maintenance of proper humidity condition of 35 % to 65 % relative humidity was crucial.

In the third room, the temperature was a little warmer where packaging materials were present. There were lid foil and bottom foil which are part of primary packaging material. The printed packaging material is important to be stored in lock and key premises. A separate room is designed for printing purpose, a machine called CVC label counter

machine is used for printing the label. A separate place was present for sending test sample to QC team for testing. After moving a little further, a freezer was present which maintained a room temperature of (-20 to -25) ºC that contained biotechnological products. In front of that room, a narcotic storage room was present where only authorized people were allowed to enter. Another storage room with a room temperature of (2-8) ºC was present that contained the following tabulated materials:

Table 2: Materials stored at (2-8) ºC in HPL

i.	Benzyl alcohol	ii.	Buffer for Darbepoetin FDS
iii.	Dabigatron Etexilate Mesylate IR pallets	iv.	Darbepoetin alpha sterile solution 60 µg/mL
v.	Darbepoetin alpha sterile solution 100 µg/mL	vi.	Darbepoetin alpha sterile solution 200 µg/mL
vii.	Misoprostol (1% mixture in HPMC)	viii.	Mupirocin
ix.	Orlistate pallets 50 %	x.	Omeprazole
xi.	Resovastin calcium	xii.	PEG Interferon α-2a (360 µg/mL)
xiii.	Erythropoietin (4000 IU/mL)	xiv.	Erythropoietin (1000 IU/mL)
xv.	Filgrastim (0.6 mg/mL)	xvi.	PEG Filgrastim 10 mg/mL
xvii.	Sodium Hyaluronate	xviii.	Teicoplamin
xix.	Resovastin Calcium (CED)	xx.	Buffer for Bevacizumab
xxi.	Buffer for Adalizumab	xxii.	Astaxanthin (natural) powder
xxiii.	Carbetocin	xxiv.	Remdisiver
xxv.	Fosfomycin trometamal	xxvi.	Tenofovir

4.2 <u>Warehouse Extension:</u> After Warehouse general, we visited Warehouse Extension. It stored materials which are not affected by any temperature or humid conditions, such as packaging materials like non sterile syringes, spoons, inner carton, shipping carton, leaflet paper and actuator inhaler. All the materials were arranged in stacks. Two machines were used for carrying and stacking the materials.

Figure 14: Roll pallet truck (Taizou Huize Machine Co., Ltd., 2006)

Figure 15: Pallet racking machine (Toyota Forklift)

4.3 <u>Oncology warehouse:</u> In the oncology warehouse, De-dusting tunnel from Fabtech, Germany, was prevalent that was under installation. The de-dusting tunnel basically de-dusts the packages or boxes before those are taken into the premises of HPL. Apart from these warehouses there were also dedicated warehouses for Cephalosporin and Hormone related materials.

Figure 16: Fabtech De-dusting tunnel from Germany (Fabtech, 2018)

4.4 <u>Toll manufacturing:</u> From the warehouse of HPL we also learnt about toll manufacturing. Toll manufacturing is the generation of products of a company in another company due to the unavailability of facilities that can be of 2 types: toll-in manufacturing and toll-out manufacturing. The unavailable facilities include- required machines, required environment, skills, man-power .etc.

Before initiating toll manufacturing, the concerned personnel of both the companies visit the company premises of each other to ensure the presence of their unavailable facilities in the other company. Drug being manufactured in HPL for BPL is an example of toll-in manufacturing and drug being manufactured in SBL for HPL is an example of toll-out manufacturing.

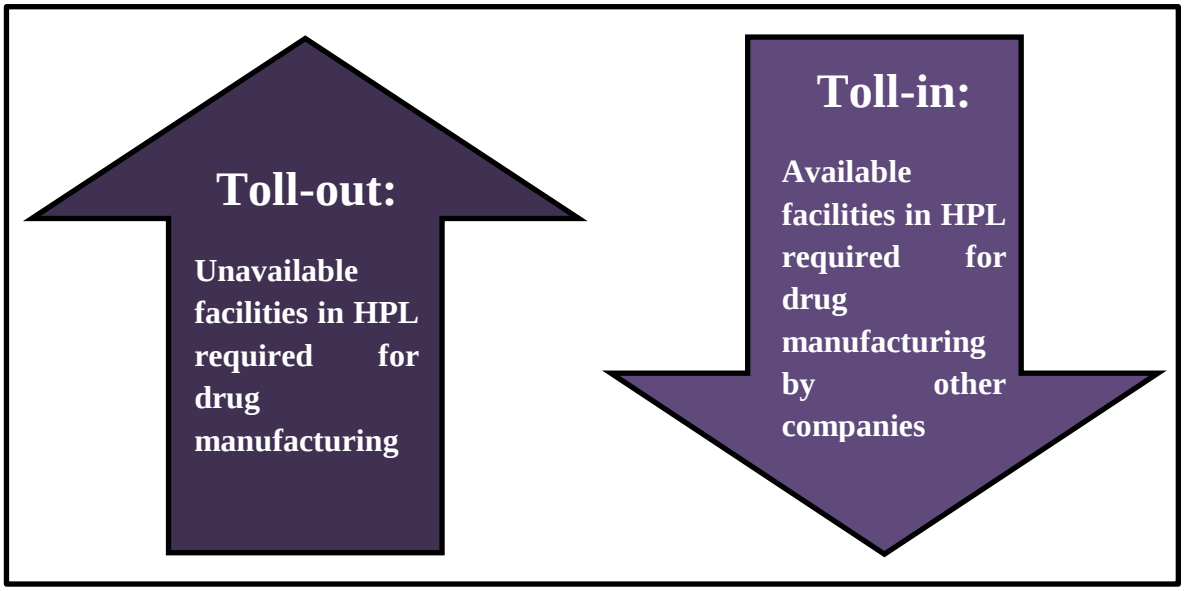


Figure 17: Toll manufacturing

4.5 <u>Monitoring forms:</u> In all the warehouses of HPL, three types of forms are maintained. There are change control forms for monitoring any sort of physical changes of the materials like- color change. For monitoring any sort of defects deviation forms are maintained. Apart from these, discrepancy forms concerned with the QC department are maintained to remark the minor deviations occurring from the standard range.

We apprehended the various roles performed by the Material Management department as mentioned above and aspire to develop professionalism as per the professional standards.

5. Apprehension about the Research & Development department:

The "Research & Development" (R&D) department is one of the most crucial departments in a pharmaceutical company as it is concerned with the formulation of new drugs. The R&D department performs two major operations- formulation and analytics. While the formulation is concerned with new drug generation at smaller scale, the analytics is concerned with the testing of the newly generated formulation. The R&D of HPL formulates such drugs that comply with the FDA of USA.

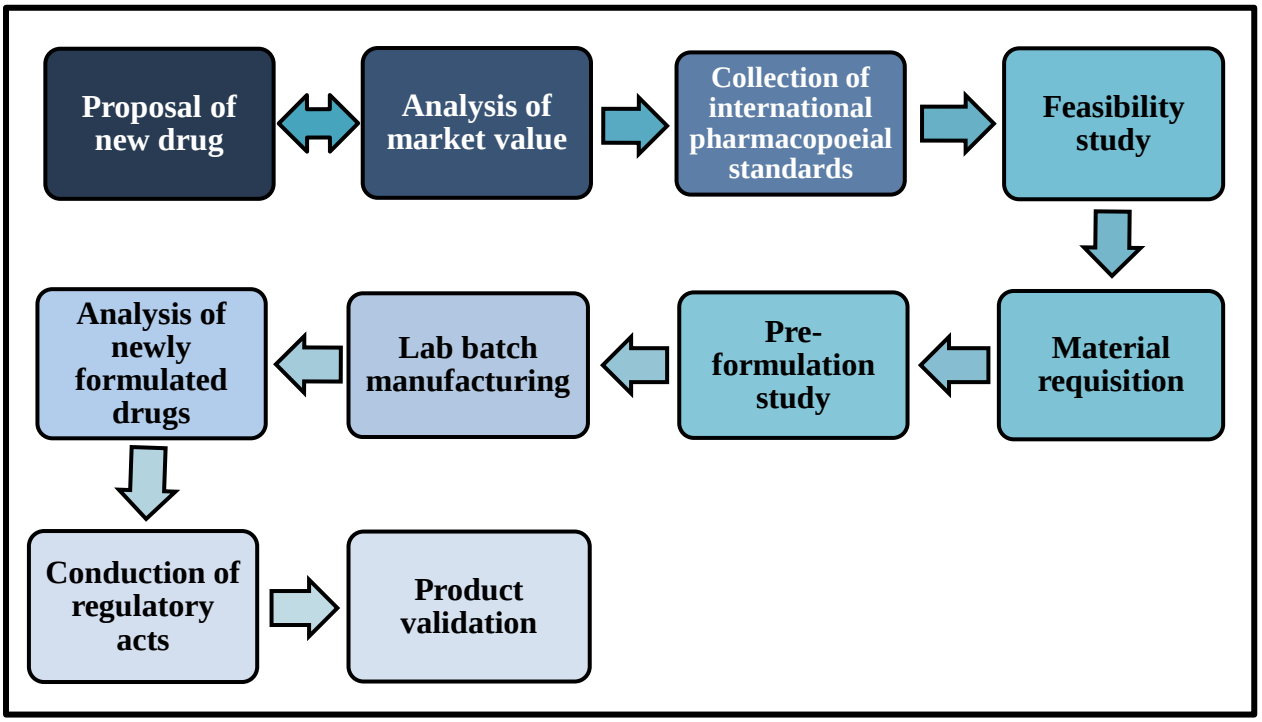


Figure 18: Schematic representation of the task of R&D

5.1 <u>Formulation:</u> Any drug under formulation is also considered to be prevalent under product development stage. Formulation proceeds through the conduction of feasibility study, material requisition, pre-formulation study and lab batch production.

The formulation unit of HPL of R&D is located at the "Oncology unit" building. Before we entered the formulation unit, we had to pass through an interlock door system. Then, we had to put on plastic shoe covers wearing which we crossed a step-over bench. Following the entrance we were taken to the change rooms. Separate change rooms were there for male and female. There we put on safety gowns provided by HPL. After grooming up we were taken to

different rooms concerned with formulation.

In the corridor of the formulation unit of R&D a HAWKEYE controlling machine was prevalent that kept the track of temperature, pressure and RH of that area. The corridor had 10 inlet HVACs and 2 outlet HVACs totaling to 12 HVACs, for proper ventilation and changing air.

5.1.1 Feasibility study: After the submission of new drug proposal to R&D, feasibility study on the proposed drug is conducted. In feasibility study the availability of machine and man-power are checked. During our internship in HPL we came across various machines each located in different rooms having the required facilities. A summary of the equipment and their locations is tabulated below:

Table 3: Equipment in formulation unit of HPL

Sl. no.	Rooms	Equipment		Number of HVACs	Temp. (°C)	Pressure (Pa)	RH (%)
		Names	Functions				
i.	328: IPQC room	ERWEKA hardness tester (from Germany)	Determination of the length, width, diameter and hardness of the tablets	2	N/A	N/A	N/A
		hp laser jet printer	Printing the machine reading				
		METTLER TOLEDO moisture analyzer (from Switzerland)	Determination of the moisture content of the tablets				
		SOTAX DT3 disintegration tester	Determination of the nature and time of breaking tablets inside the body				
		METTLER TOLEDO pH tester (from Switzerland)	Determination of pH				
		Grace Digital friabilator (from India)	Determination of durability of tablets				
ii.	329: Blending room	ZHEJIANG HSD15 blending machine (from China)	Mixing the materials uniformly	3	20 °C	0 Pa	40 %
		HAWKEYE digital display unit	Tracking and maintaining the environmental parameters				
		memmert universal oven	Drying the mixture				
		Dust collector	Dust removal				
iii.	330: Wet Granulation room	ptk PFB-L fluid bed granulator (from Korea)	Mixing, and granulating the materials and drying the mixture	4	22.7 °C	29-32 Pa	55 %

		ptk PM-C granulator (from Korea)	Mixing the materials				
		HAWKEYE digital display unit	Tracking and maintaining the environmental parameters				
		Dust collector	Dust removal				
iv.	331: Washroom	HAWKEYE digital display unit	Tracking and maintaining the environmental parameters	2	N/A	26–28 Pa	N/A
		Sink	Cleansing the equipment				
		Shelf	Storage of the required elements				
v.	332, 338: Tablet compression room	ptk compressing machine (from Korea)	Compression the tableting materials and shaping the tablets	4	20.8 °C	33-34 Pa	38 %
		Dust collector	Dust removal				
		Vacuum cleaner	Litter removal				
		HAWKEYE digital display unit	Tracking and maintaining the environmental parameters				
		Shelf	Storage of the required elements				
vi.	334: Tablet coating room	Coating machine	Coating the tablet surface with a thin coat to mask the taste and smell, prevent color change and to protect the drug from physical or chemical harm	4	23.3 °C	12 Pa	41 %
		Oscillating granulator	Homogenization, sieving, size reduction and grading of dry sensitive powders and granules				
		HAWKEYE digital display unit	Tracking and maintaining the environmental parameters				
vii.	336: Lyophilization room	ZIRBUS aeration chamber	Maintenance of proper ventilation	4	19.3 °C	31 Pa	53 %
		Desktops	Recording data				
viii.	337: Liquid, cream, ointment room	BOECO electronic balance (from Germany)	Weighing materials	4	21.5 °C	20 Pa	44 %
		evoQUA water filter (from India)	Impurity removal from laboratory water				
		PHARMACON water purifier	Assurance of chemical purity and contamination prevention of laboratory water				

			SILVERSON L5 M high shear mixer	Emulsification, homogenization, particle size reduction, dispersion, suspension, disintegration and mixing				
			Water bath	Heating solutions				
			HAWKEYE digital display unit	Tracking and maintaining the environmental parameters				
ix.	339: room	Blister	AUTOPACK blister packaging machine	Packaging of the tablets in blisters	4	N/A	N/A	N/A
			Dust collector	Dust removal				

Apart from the aforementioned rooms we also came across “Approved Excipient room” and “Dispensing room” having room numbers of 333 and 335 respectively.

5.1.2 Material requisition: After the conduction of feasibility study the materials required for the intended drug production are listed and sent to the material management department. On receiving the requisite raw materials from approved vendors the material management department scans those following several steps and putting different labels on those, as discussed previously in the material management section.

5.1.3 Pre-formulation study: The formulation unit on receiving the qualified raw materials passed through several stages conduct pre-formulation studies. Through pre-formulation studies the suitable dosage form of the intended drug, the strength of the formulation, the required excipients for the intended drug .etc. are determined.

5.1.4 Lab batch production: Following the pre-formulation studies the formulation unit of the R&D department goes for “lab batch” production. It is named so as it is produced at a smaller scale for the analysis of the produced drug. The products of the “lab batch” are then, subjected to analysis by the conduction of several analytical tests. The machines required in “lab batch” drug production in accordance to the drug dosage form along with their mechanisms are tabulated below:

Table 4: Mechanism of the machines employed in "lab batch" drug production

Sl.no.	Machine	Mechanism
i.	Blending machine	The blades of the blending machine on insertion of the materials blend those thoroughly into a homogenous mixture.
ii.	Granulating machine	Consisting of impeller and chopper granulators work by rising, whirling and tumbling the inserted materials. Granulation converting the powder materials into attachable form for the formation of larger particles called granules is always performed without the inclusion of lubricant and glidant.
iii.	Compressing machine	Having hopper, turret, feeder, 8 dies (4 upper punches and 4 lower punches) and outlet compressing machines work by collecting materials from the feeder, shaping those in the form of tablets inside the dies through compression.
iv.	Coating machine	Comprising of coating pan, spray gun and heating unit the coating machine work by drying and spraying. The tablets when inserted in the coating machine on a coating pan are dried through the passage of hot air. Then, the dried tablets are sprayed with the coating material through the spray gun. On drying in the heating unit the color resides on the tablets as the water evaporates.
v.	High shear mixer	Being used in preparation of semi-solid dosage forms these work by following 4 consecutive stages- suction, milling, shear forcing and material projection.
vi.	Fluidized bed dryer/ Fluidized bed processor	Consisting of a compressed air system, heating device, a perforated platform and a harmonizer fluidized bed dryer dries the inserted materials. The wet granules on the perforated platform when surmounted on with compressed hot air stream of the harmonizer create fluidized state. During the fluidized state hot gas surrounds the suspended wet granules to dry those completely and the granules remain there until those dry uniformly. While fluidized bed dryer only dries the inserted materials, fluidized bed processor granulates, coats and dries the suspended materials.

A separate floor is dedicated to R&D department for studying oncology related materials. Some part of the floor is still under construction. There were isolators in few rooms that provided a closed environment in protecting both the operator and the materials under study. Since, oncology products possess mutagenic properties, it is essential to undertake strict protective measure. Glove boxes are also installed with the isolators providing safe working

environment. Besides these there were instruments for granulation, drying, sieving, encapsulation and coating anti-cancerous agents.

In a cleanroom setting, two types of airflow are maintained, namely- laminar and turbulent airflow. The type of airflow maintained in a pharmaceutical grade cleanroom is crucial to ensure minimum contamination inside the room. Inside the oncology floor rooms, laminar airflow was maintained. Laminar airflow is defined as the airflow where the direction of air is in the same direction; it ensures a particle free environment and also protects the product from particulate contamination. Moreover, pressure differences were maintained in between the rooms and the corridor, where the rooms had positive pressure and corridors maintained a negative pressure. This secures the movement of air in one direction, from the rooms to the corridor.

5.2 Analysis: The analytical operation of R&D department deals with testing raw materials, final products and determining their potency. The analytical sector of R&D is located at the oncology unit of HPL. When entering the laboratory area, we had to put on plastic shoe covers, safety gowns and keep our belongings in the cabinets and move from one unit to another with the help of step over bench. Before it we crossed an interlock door system that was installed at the entry of the COE of HPL. We were introduced to wet laboratory and IR room where there were different instruments. LOD test and Karl Fischer titration tests are conducted on the raw materials. The instruments used in analytical sector of R&D department are as follows:

5.2.1 HPLC: HPLC is an analytical technique for separating, identifying, and quantifying each component in a mixture. The mobile phase (eluent) flows through the stationary phase and carries the components of the sample mixture (analyte) with it. Sample components that display stronger interactions with the stationary phase move more slowly through the column than the components with weaker interactions. This method separates analytes on the basis of polarity where HPLC employs polar

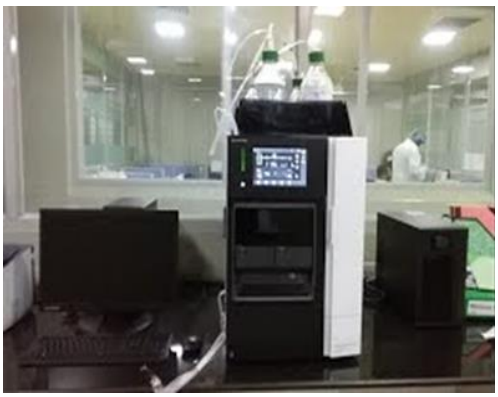


Figure 19: HPLC machine (LabX, 2017)

stationary phase and non-polar mobile phase. Therefore, the stationary phase is usually silica and typical mobile phases are hexane, methylene chloride, chloroform, diethyl ether, and mixtures of these. Polar samples are thus retained on the polar surface of the column packing longer than less polar molecules. Pharmaceutical application includes tablet dissolution study of pharmaceutical dosages form and pharmaceutical quality control testing.

5.2.2 UV spectrophotometer: UV-Vis Spectroscopy also known as Spectrophotometry is a quantitative technique for determining how much light is absorbed by a chemical substance. This is accomplished by comparing the intensity of light passing through a sample to that passing through a reference sample or blank. UV-Visible Spectroscopy is based on the absorption of ultraviolet or visible light by chemical substances, which produces unique spectra. When matter absorbs ultraviolet radiation, the electrons present in it undergo excitation. This causes them to jump from a ground state- an energy state with a relatively small amount of energy associated with it, to an excited state- an energy state with a relatively large amount of energy associated with it. When using UV-VIS Spectrophotometry a blank is used at the very beginning of any analysis. A reference blank is a sample (distilled water or solvent without the component we want to analyze) for nullifying an instrument. It can calibrate the instrument, therefore it subtracts the absorbance of the compounds other than the analyte being determined. This step is very crucial if we want to obtain an accurate absorbance or concentration reading of the analyte.

Figure 20: UV spectrophotometer (SHIMADZU, 2019)

5.2.3 Karl Fischer titrator: Karl Fischer titrator is used to determine the amount of moisture present in a sample, it also employs Tiamo 2.5 software in HPL. The instrument uses Karl Fisher reagent to determine the amount of moisture in the sample. There were also

Figure 21: Karl Fischer Titrator (Metrohm, n.d.)

molecular sieves with absorption capabilities filled in the drying tubes so that moisture cannot escape into the surrounding and also protecting the sample from atmospheric moisture. It was seen that the Karl Fisher reagent and the solvents were connected to the instrument by tubes. There was an inlet and outlet button to add and discard solution when needed.

5.2.4 Hardness tester: An instrument was also present for determining the hardness of the tablets. Hardness tester from ERWEKA, Germany, was used where they determined the length, thickness and hardness of the tablets (oblong and circular). Before placing the tablets, information about the shape, size and number of tablets are fed into the instrument's display screen. Ensuring proper hardness of tablets is an important parameter as it will determine the therapeutic effectiveness of the tablets. If the tablets are too hard they will not disintegrate in the biological system and if the tablets are too soft the patients will have a difficult time taking the drug. In addition to that, soft tablets might lose their shape during transportation.

Figure 22: Hardness tester (ERWEKA, 2020)

5.2.5 Sonic hot water bath: A water bath is laboratory equipment made from a stainless steel container which is filled with water that is heated. It is used to incubate glass apparatus containing samples in water at a constant temperature over a long period of time. Accelerated stability study can be conducted where they apply higher temperatures and monitor the changes in the sample over sample over a specific period of time.

5.2.6 Centrifuge machine: A centrifuge machine separates fluids of various densities or separates liquids from solids by applying centrifugal force to the components of the sample solution in a rapidly rotating container. They are widely used in separation of liquid and solid in a sample.

Figure 23: Centrifuge machine (DR MEDITECH, 2018)

5.2.7 Orbital shaker machine: An orbital shaker is an used to blend, mix, or agitate samples in a vessel by shaking them. There are parallel tubes over a board where the glass apparatus will be placed and it will be set for agitation for a certain period of time. This will ensure uniform mixing for soluble samples and solutions.

5.2.8 IR spectrometer: In a separate room IR spectrometry machine called IRTracer 100 Infrared spectroscopy from SHIMADZU, Japan, was installed. This instrument is used to determine the presence of functional groups in a sample. The wavelength range of IR is between 780 nm and 1 mm.

Figure 24: IR spectrophotometer

5.2.9 Melting point tester: Melting point is the temperat (which a given solid material changes from a solid state to a liquid, or melts. The melting point is a physical property of a solid and can be used to help identify a substance, as each element has a particular melting temperature. In addition to identifying a particular solid sample, melting point results can be used to understand the purity of a sample. In general the smaller the range of melting temperatures, the higher the purity of the sample and if the impurity is high, they will show a wide range of melting temperatures. The sample is inserted into the machine with the help of capillary tubes, where the sample is tapped into the tube.

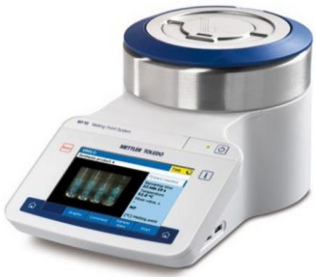


Figure 25: Melting point tester (MedicalExpo, n.d.)

5.2.10 Dissolution Tester: Dissolution is the process by which an oral dosage form when administered forms a solution so that it can be absorbed in our systemic circulation. Dissolution testing measures the extent and rate of solution formation from a dosage form, such as tablets. The dissolution of a drug is important for the bioavailability and therapeutic effectiveness of the tablet. Samples are drawn after a certain period of time with the help of syringes connected to individual cylinders. The buffer solution used in dissolution tester is made mimicking gastrointestinal environment of the

stomach. With the help of mathematical formulas, we can calculate the concentration of the drug and the amount of drug released (dissolute) in a given period of time.

Figure 26: Dissolution Tester (ERWEKA, 2021)

5.2.11 Disintegration Tester: The disintegration test is used to determine how rapidly a tablet can break down into smaller particles, resulting in a larger surface area and increased bioavailability when consumed by a patient. The temperature of the buffer solution is maintained at 37 ± 0.2ºC. The water level is maintained following USP guidelines, where the upward stroke will be 15 mm and downward stroke will be 25 mm. The rate or cycle per minute will be set to 29 to 30 according to the SOP. There were two baskets with 6 glass tubes each. As a general rule, for uncoated tablets the disintegration time is about 15 minutes and for coated tablets it is 30 minutes.

Figure 27: Disintegration Tester (ERWEKA, 2020)

5.2.12 Analytical balance: Analytical balances are sensitive laboratory equipment used to quantify mass of sample materials precisely. Their operating range is from 10 mg to 110 mg. To keep samples from being influenced by air currents, analytical scales feature a draft shield, which can be opened and closed as per the need. The bubble point is balanced can be checked if the machine is working properly or not.

Figure 28: Analytical balance (METTLER TOLEDO, 2013)

5.3 Following analysis come the regulatory activities and product validation. After the conduction of analysis for 6 months on three consecutive batches and on providence of the recipe of the new drug it is issued with drug administration number by Annexure and with license by the DGDA. The drug recipe submission process is of two types. While the submission of type-1 recipe does not require the inclusion of toxicological data of the new drug, the submission of type-2 recipe requires the inclusion of toxicological data of the new drug. Annexure also sets the marketing parameters- who to market, how to market, where to market .etc. of the newly formulated drug. A drug when issued with its drug administration number accomplishes product validation after 3 months of its stability testing. Achievement of product validation by any drug signifies that it is officially approved for its effectiveness.

We apprehended the various roles performed by the R&D department as mentioned above and aspire to develop professionalism as per the professional standards.

Quality Control Department

Quality control is an essential operation in the pharmaceutical industry. Quality control department is the area of good manufacturing practices (GMP) which deals with processes involving sampling, specifications and testing, and with the organization, documentation and release procedures. These help ensure that the necessary and relevant tests are executed and that materials are not released for use, nor products released for sale or supply, until their quality has been confirmed to comply with international standards.

2 types of testing:

1. **Physical testing:** it is within the production area e.g. hardness, friability
2. **Chemical testing:** it is within the QC department e.g. dissolution, assay

Machines in QC Department:

1. **Atomic Absorption Spectrophotometer (Shimadzu – Japan):** It is used for the detection, identification, and quantification of metals in a product. The process is performed in two ways; Flame (large quantity samples), and Furnace (small quantity samples). The sample is burned and then the light is absorbed by lamps. Different lamps are available for the detection of different metals which shows the concentration of metals present. The process is performed by comparing the working standard with the reference standard. The critical parameters of the machine are machine performance, method selection, and sample preparation validation.
2. **Semi-Micro Balance (Mettler Toledo – Germany):** Used for weighing samples of 10 mg to 110 grams.
3. **Karl Fischer Titration Machine:** Used for quantification of water amount (both bound and unbound water) in a sample. Here titrator is Karl Fischer reagent and solvent is methanol.
4. **HPLC Machine (Shimadzu – Japan, Waters – USA):** Used for detection and quantification of the desired material in a sample solution. The sample solution is kept in a vial and placed into a tray of the machine. The mobile phases are kept into different chambers according to their chemical properties for example buffer and

water in A &D chamber and the organic mobile phase is kept into B & D chamber. There is an oven in the machine that keeps the temperature under controlled temperature if needed. The column is used as the stationary phase. The injector takes 20 microliter sample each time. The mobile phase carries the sample to the column and separates it. A peak is found at a specific time for defined materials which is called retention time. At first standard solutions are run and the retention time is recorded. The sample is run and the time for obtaining peak and peak area is compared with the standard. If the variance in peak retention time and area between the standard and the sample is within 2 percent then the result is accepted. There are different detectors in an HPLC machine; Photo Diode array, Florescence, Refractive Index ad UV-Visible.

5. **UPLC Machine (Waters – USA):** Operation and mechanism same as HPLC machine. But the column length is less than the HPLC column, the applied pressure is higher than the HPLC machine and the run time is less than the HPLC machine.
6. **Particle Size Analyzer (Malvern Mattersizer 3000 – the UK):** Analyzes the number of particles of a defined size from both dry and wet samples. Light is passed through the sample and particles are separated based on light obstruction by the particles. The higher the light obstruction the higher the particle size. It also gives the percentage and amount of defined size particles from the sample.
7. **Vacuum Oven:** Used for drying to check LOD (Loss on drying) of a sample. 20 mbar pressure and the specific temperature are applied for this purpose.
8. **UV-Visible Spectrophotometer (Shimadzu – Japan):** Used for identification and quantification of a material desired from the sample solution. Works based on the principle of Beer-Lambert law.
9. **Sieve Shaker:** Separate different size particles
10. **UV chamber:** Used to check TLC plates
11. **Pump:** Used to facilitate filtration of the sample solution.
12. **Disintegration Tester (Erweka - Germany):** Used to check time for tablets and capsules to disintegrate completely. The media is kept at 37±2 degree Celsius.
13. **Dissolution Time Tester (Erweka – Germany):** Used to check the time for the

tablet or capsule to completely dissolve into the dissolution media. The media is kept at 37±0.5 degree Celsius.

14. **Potentiometer:** To check potency and quantification of the material tested and facilitate titration procedure.
15. **Refract meter:** Checking the Refractive index of liquids.
16. **Osmometer:** Checks the osmolality of the liquids especially parenteral products.
17. **Conductivity Meter:** Checks the conductivity of water and other solutions.
18. **Muffle Furnace:** It has maximum temperature of 1000 degree Celsius. It determines the residue in solid dosage forms after burning them at 1000 degree Celsius. Sulfuric acid is used to mask the bad odor produced during burning the samples.
19. **Gas Chromatography Machine:** The purpose of using this machine is same as he HPLC machine. Here mobile phase is gas mainly air, hydrogen and nitrogen among them air and nitrogen are commonly used. The column is thin in width and long in size compare to the HPLC column. The sample is evaporated at 200 degree Celsius which is carried by gaseous mobile phase in order to separate the desired material from sample. Here Flame Ionization Detector is used.
20. **Total Organic Carbon Analyzer:** Detection of amount of total organic carbon in water. At first 816 microliter water is taken from sample by an injector. Then it reacts with HCl present in the HCl chamber to remove the inorganic carbon. After that in presence of 99.997% pure nitrogen gas, platinum catalyst and 679-680 degree Celsius temperature oxidation reaction occurs that causes organic carbons to form carbon dioxide. NDIR detector is used to detect the carbon dioxide produced from organic carbons. The USP guideline for TOC in WFI is 500 ppb. Potassium hydrogen phthalate is used for calibration of the machine.

Calibration is done daily. For example, calibration of pH meter is measured by 3 pH values. pH 4, pH 7, pH 10 are measured. If the slope is over 95%, the calibration is accepted and the slope is linear.

Microbiology lab is part of QC department. There are four microbiology labs in HPL industry.

They are: General Microbiology Lab, Oncology Microbiology Lab, Cephalosporin Microbiology

Lab, Hormone Microbiology Lab.

2 types of drug products:

1. Sterile Product: IV, Ophthalmic
2. Non-sterile: oral, subcutaneous

Sterilization: Sterilization refers to any process that removes, kills, or deactivates all forms of life (in particular referring to microorganisms such as fungi, bacteria, virus etc.

Bacteria Endotoxin test, Sterility test, Water Endotoxin test, TAMC (Total aerobic microbial count), TYMC (Total yeast microbial count) are done to measure the microbial growth.

E.coli count is measured from finished product. *E.coli*, pseudomonas, *Staphylococcus aureus*, Salmonella counts are measured from raw materials.

Environment Monitoring:

Passive monitoring uses "settle plates", which are standard Petri dishes containing culture media, which are exposed to the air for a given time in order to collect biological particles which "sediment" out and are then incubated. Results are expressed in CFU/plate/time or in CFU/m^2/hour. Air sampling is done using settle plate technique.

Contact plates efficiently monitor environmental surfaces for microbial contamination. Used to determine the sanitation techniques and schedules required, the plates enumerate the colonies collected before and after cleaning is completed. Ex: floor, wall

Viable count is a method used in cell culture to determine the number of living cells in a culture. A non-viable particle is a particle that does not contain living microorganism but acts as transportation for viable particles. Non-viable particles are monitored using particle counter.

Tests:

1. Media Simulation Test
2. Growth Promotion Test
3. Water test

4. Biological Assay test (antibiotic sensitivity test)

Sterility Testing Area:

1. D grade room
2. C grade room
3. B grade room
4. Sterility Testing Room (B) which contains autoclave

Machines:

1. Autoclave- Zirbus technology
2. Incubator- Thermolab (Germany)

An incubator is a device used to grow and maintain microbiological cultures or cell cultures. The incubator maintains optimal temperature, humidity and other conditions such as the CO_2 and oxygen content of the atmosphere inside. There are 9 incubators in microbiology lab.

Many autoclaves are used to sterilize equipment and supplies by subjecting them to pressurized saturated steam at 121 °C (250 °F) for around 15–20 minutes depending on the size of the load and the contents.

Liquid particle test, block heater, kinetic analyzer are used.

Clean room classification:

	maximum particles/m^3			
Class	At Rest	At Rest	In Operation	In Operation
Particle size NMT	**0.5 µm**	**5 µm**	**0.5 µm**	**5 µm**
Grade A	3,520	20	3,520	20
Grade B	3,520	29	352,000	2,900
Grade C	352,000	2,900	3,520,000	29,000
Grade D	3,520,000	29,000	n/a	n/a

There are Grade A biosafety cabinets in Grade B rooms of HPL industry. There are HEPA

filters.

Media used:

1. FTM- anaerobic bacteria
2. TSB- bacteria, fungi

There is competency of operators. Theoretical assessment and practical assessment are required for qualification of operators in microbiology lab. There are change rooms and visitors' lab coats to maintain cleanliness.

Quality Assurance Department

Quality assurance (QA) is a way of preventing mistakes and defects in manufactured products and avoiding problems when delivering products or services to customers; which ISO 9000 defines as "part of quality management focused on providing confidence that quality requirements will be fulfilled".

It consists of two parts:

1. In-Process Quality Assurance (IPQA)
2. Documentations

Change Control Procedure:

1. Control the change.
2. Risk analysis is done.
3. Audits/Documentations are made.
4. Self-inspection/department inspection is done.
5. Vendor approval Batch is either released or rejected.
6. Any market complain is notified to QA in the plant. Retention sample is kept to the plant after the release of the product to market.
7. QA identifies the root cause of the problem and compare the faulty drug with retention sample.
8. Corrective Action & Preventive Action (CAPA) is done to reduce recurrence. Awareness of training is needed. Training department is part of QA. Feedback is given to customer.

Cleaning Validation:

B-type cleaning: Same product, different batch

A-type cleaning: Different product, different batch

SOP distribution, STP, BMR logbooks are approved by QA.

Production department has IPQA labs. These labs solve problems instantly during processes of production.

IPC (IN-PROCESS CONTROL/CHECK) room has machines. They are:

1. Disintegration machine
2. Leak test apparatus
3. Hardness tester (measures hardness, thickness, length)
4. Friabilator
5. Weight balance

Friability Test: This test is additional to check crushing strength of tablet. By this test one can check Capping &/or Lamination. USP limit is 0.5 to 1%. Rotation: - 25 rpm or 100 rotations in 4 min. For tablets weight equal to or less than 650 mg, take tablets corresponding to 6.5g.

USP Standards for Disintegration Time Test

S/N	Type of Tablet	Medium	Temperature	Limit
1.	Normal Release Tablets (Uncoated Tablets)	Water/ as specified in the individual monograph	37° ± 2°C	As specified in the individual monograph
2.	Coated Tablets	Water/ as specified in the individual monograph	37° ± 2°C	As specified in the individual monograph
3.	Delayed-Release/ Enteric-Coated Tablets	i. Simulated Gastric Fluid TS	37° ± 2°C	No evidence of disintegration after 1 hour
		ii. Simulated Intestinal Fluid TS	37° ± 2°C	As specified in the individual monograph
4.	Buccal Tablets	Water/ as specified in the individual monograph	37° ± 2°C	After 4 hours
5.	Sublingual Tablets	Water/ as specified in the individual monograph	37° ± 2°C	As specified in the individual monograph

Note: If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Weight Variation Limits

IP/BP	Limit	USP
80 mg or less	10%	130mg or less
More than 80mg or Less than 250mg	7.5%	130mg to 324mg
250mg or more	5%	More than 324mg

Weigh individually 20 units selected at random or, for singledose preparations in individual containers, the contents of 20 units, and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table and none deviates by more than twice that percentage.

QA Procedure:

1. Room cleaning checklist procedure
2. Machine setting
3. In work (okay for operation)
4. Logbook for cleaning room is approved by production & QA officer.
5. Hydrometer is checked. Temperature: 18 degree Celsius, Relative humidity: 30-65%, Pressure: 5-25 Pa
6. Batch manufacturing record is then checked for dispensing, granulation, compression, encapsulation and coating of bulk product before packaging.
7. Tablet/capsule parameters (ex: weight, appearance, hardness etc.) are checked.
8. Primary packaging & secondary packaging are checked through batch packaging record (BPR).
9. Before production, the raw materials, machines, rooms are cross-checked by production & QA officers.

Engineering Department

The main job of the Engineering department is divided into two types-

Project: Expansion of existing facilities. Includes- addition of new machine or replacement of less efficient machine. Developing new facilities.

Maintenance:

Utility: Utility includes- HVAC, sub-station, generator, boiler, water, compressed air generation facility.

Machineries: Their operation and maintenance is maintained here.

Facilities:

Common Facility System: Electricity, Chilled water, steam generation

Independent Facility System: HVAC, compressed air system, nitrogen generation system

Central Utility System:

Power Supply: Power is usually supplied by Rural Electrical Board (REB). In case of power outage or low supply generator is used to compensate.

Generator: Three generators available (CAT- USA). The generators run on diesel. Each of them has a capacity of 2 KV.

Breaker: Circuit breakers are used. They work by shutting the system down when the load of electricity goes out of limit. This is how breakers avoid hazard.

Distribution part: Distributes electricity to all the needed areas.

PFIs (Power Factor Improvement supplies) are used so that the output of electricity distribution remains highest.

Chiller: TRANE. Healthcare Pharmaceuticals ltd has three chillers with the capacity of 600ton (each). The main job of chiller is to bring the temperature of water down to 5-8 degree Celsius

and deliver to areas where chilled water is needed.

Compressed Air: COMPair. Air is compressed to achieve kinetic energy. Two air compression machines are available with the capacity of 17.55-meter cube per minute and 18.00-meter cube per minute. This kinetic energy is then used for lifting and also for valves.

Nitrogen System: Used for vacuum and cleaning. The air is mainly extracted from the environment. Used for the maintenance of places requiring high purity. Uses nitrogen reserve tank (capacity- 2000L).

Boiler: COCHRAN (capacity- 2ton). 4 boilers are available for steam generation. Steam is generated and provided to areas according to their requirement. The system is isolated so that heat is not lost. As it is a very important part of any plant, thus requires specialists to operate.

Water Treatment Plant: The main job of this plant is to purify the raw water and remove all sorts of microorganism and ion present in it. This water is mainly used for production. The most amazing thing of this plant is that Healthcare Pharmaceuticals has this plant inside their industry and this water is purified and generated by the industry itself.

Water generation System:

Softener: Total 4000 liters of water enter softener whose main job is to remove ions like calcium, magnesium through ion exchange system. A Brine tank is attached to the softener to provide strength to this system. The system consists of- conductive sensor and pressure gauge.

Ultrafiltration: 0.002-micron filters are used to remove any present microorganism. Some amount of water is lost in this process and around 3000 liters of water remain after this step.

Reverse Osmosis: This consists of two stages-

1st RO: removes as much microorganism as possible. Here 0.001-micron filter is used.

2nd RO: Removes almost all microorganisms.

Conducting sensor: is used to monitor the number of ions and organisms present in the water. The main target is to keep the conductivity under 1.3micro siemens per centimeter.

Electrode-ionization (EDI): This acts like a battery with positive and negative charges. And using the charges it removes ions present to purify water and lower the conductivity.

Water Distribution Loop: Water is supplied to the production system from here. There is a chance of microbial growth in stored water. So the water is checked via UV lamp and Ozone continuously and then sent to the required areas.

Total Automation system: The water supply system is monitored here.

Heating, Ventilation, and Air Conditioning (HVAC): Total manufacturing area of Healthcare Industrial is under HVAC system. It is used- To prevent cross-contamination, Temperature control, Particle count control, Pressure control.

Particle count in different zone

Class	Running condition		Rest condition	
	0.5 micron	5 micron	0.5 micron	5 micron
B	≤352000	≤2900	≤3520	≤29
C	≤3520000	≤29000	≤352000	≤2900
D	No limit	No limit	≤3520000	≤29000

The HVAC system is maintained through by AHU. The process is described below:

Fresh air from environment + Returned air from the rooms

↓

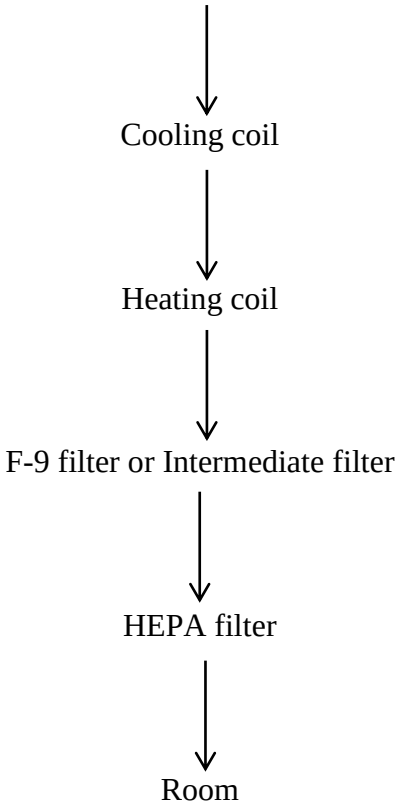
Pass through Preliminary Filter (G-4 filter)

↓

Blower (circulates the air)

↓

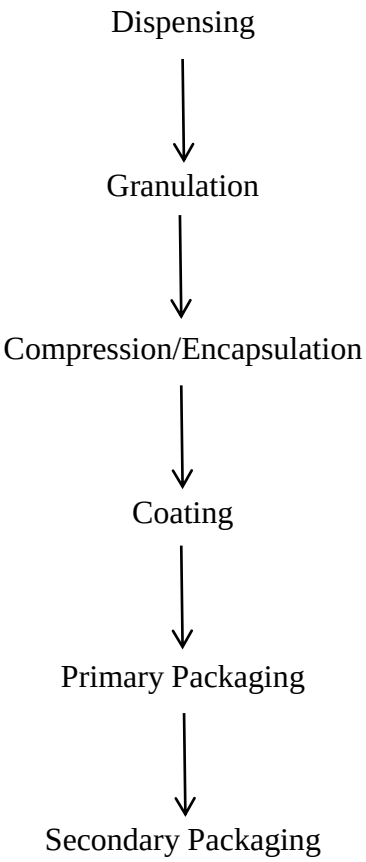
Dehumidifier (If needed)


Cooling coil
Heating coil
F-9 filter or Intermediate filter
HEPA filter
Room

Production Department

Oral Solid Dosage Form Production: In Healthcare Pharmaceuticals, the production of oral dosage form includes, Tablets, capsules and PFS.

The production of oral solid dosage form consists the following steps:



Tablet: Tablets are strong measurements shape with or without covering which are set up by pressure. Excipient may incorporate diluents, covers, breaking down specialist, ointment, sweetening operator, enhancing operator and shading specialist. Tablets contain a solitary measurement of at least one dynamic fixings and acquired by pressure of uniform volume of molecule. They are planned for oral organization.

Dispensing: From the warehouse at first all the raw materials are received through primary hatching and then bought into the dispensing room where the required amount of material is weighted. Dispensing is the first step of manufacturing. Dispensing of raw material is done in the

dispensing booth under laminar airflow. At first all excipients are dispensed and then the active ingredients are dispensed. For every individual dispensing full line clearance must require and for same ingredient some partial line clearance has done.

Process of dispensing:

1. Requisition is given to warehouse for raw materials prior to granulation
2. Raw materials are collected from warehouse and transferred to a clean dispensing room.
3. Dispensing condition should be maintained
4. Weighing of raw materials should be according to PO (process order)
5. Checking of quantity dispensed
6. Excess material returned to warehouse.

Dispensing booth: Dispensing booth can be defined as a chamber where weighing of raw materials and excipients occur. Raw materials and excipients are collected through primary hatch and then brought into dispensing room. In dispensing room, they are weighed and dispensed as necessary. Laminar air flow is maintained within the booth to prevent cross contamination and to protect operator from toxic materials. In healthcare Pharmaceuticals, two types of dispensing booth are used. They are Safe Klenz and Fabtech. Dispensing room condition such as temperature and relative humidity are maintained to ensure proper room condition. Air flow within the booth is unidirectional, which helps to avoid contamination and cross contamination. The booth condition is monitored on hourly basis.

Dispensing booth type	Filter parameters
Safe Klenz	Pre filter- (5-55) Pa Intermediate filter- (10-70) Pa HEPA filter- (80-170) Pa
Fabtech	Pre filter- (2-8) mm WC Intermediate- (2-8) mm WC HEPA- (8-15) mm WC

Dispensing Booth Balance Machine:

Fabtech Booth: Both floor balance and table balance is used for dispensing product within the dispensing booth. Balance function is checked before dispensing of any materials and when balance are displaced from their position.

Balance Type	Name	Maximum capacity	Function test weight
Floor balance	Sartorious	< 50kg	100g, 20kg, 50kg
	Mettler Toledo	< 50kg	100g, 20kg, 50kg
Table balance	Sartorious	< 2 kg	1g, 1kg, 2kg

Balance Calibration and Function Test:

Calibration: Calibration is a comparison between a known measurement (the standard) and the measurement using your instrument. In the pharmaceutical industry particularly, where instrument accuracy is critical to product quality and safety, strict calibration practices are essential to ensure compliance and minimize costs associated with lost batches and potential fines. Typically, the accuracy of the standard should be ten times the accuracy of the measuring device being tested. Balance calibration is performed once in every year against the standard document provided by the supplier. Calibration is a vital step in Pharmaceutical Industry to ensure the maximum performance of the instruments and machineries.

Function Test: The qualification or function test of balance is performed once in every six months where, four parameters are tested to ensure the maximum performance. The parameters are mentioned below:

1. Linearity: The test is performed to ensure that the balance is accurate at the desired level in the operating range. This tests the ability of balance to follow the linear relationship between a load and the indicated weighing value.
2. Repeatability: In this test, same weight is placed for 3 to 4 times in general, to check whether the balance gives consecutive similar results or not.
3. Eccentricity: Here, weight is placed at the center and around the corners of the

balance and is used to measure any deviation in reading between the center and off-center load.

4. Precision: It measures how precisely the balance gives reading against the standard weight.

Granulation: Most powders cannot be compressed directly into tablets because-

- The lack the proper characteristics of binding or bonding together into a compact entity and
- They do not ordinarily possess the lubricating and disintegrating properties required for tableting.

Reasons of granulation:

1. To prevent segregation of the constituents in the powder mix
2. To improve flow properties of the mix
3. To improve compression characteristic of the mix
4. The granulation of toxic materials will reduce dust generation
5. Granules are denser and thus occupy less volume per unit weight.

Granulation is of two types:

1. Wet granulation
2. Dry granulation

Wet granulation: Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvent-based systems but may not be suitable for drugs which are degraded by hydrolysis.

Following are the steps of wet granulations:

Step 1: The active ingredient and excipients are weighed and mixed.

Step 2: The wet granulate is prepared by adding the liquid binder–adhesive to the powder Blend

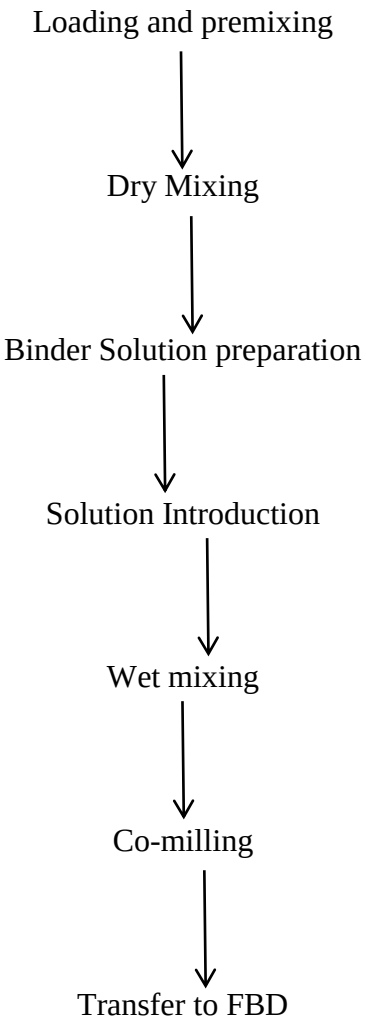
and mixing thoroughly. Examples of binders/adhesives include aqueous preparations of cornstarch, natural gums such as acacia, cellulose derivatives such as methyl cellulose, gelatin, and povidone.

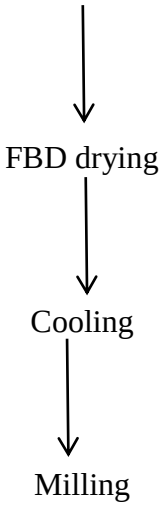
Step 3: Screening the damp mass through a mesh to form pellets or granules.

Step 4: Drying the granulation. A conventional tray-dryer or fluid-bed dryer are most commonly used.

Step 5: After the granules are dried, they are passed through a screen of smaller size than the one used for the wet mass to create granules of uniform size.

Wet Granulation at a glance:





Advantages of wet granulation:

- Improve flow properties
- Densification
- Improved compression characteristics
- Reduction in dust
- Prevention of segregation of powder mix

Disadvantages of wet granulation:

- Stability may be a concern for moisture sensitive drug
- Time, space and equipment required are costly

Dry granulation: Dry granulation processes create granules by light compaction of the powder blend under low pressures. The compacts so-formed are broken up gently to produce granules (agglomerates). This process is often used when the product to be granulated is sensitive to moisture and heat. Dry granulation can be conducted on a tablet press using slugging tooling or on a roll press called a roller compactor. Dry granulation equipment offers a wide range of pressures to attain proper densification and granule formation. Dry granulation is simpler than wet granulation, therefore the cost is reduced.

Steps of dry granulation:

- Raw material weighing

- Sieving through vibratory shifter
- Dry mixing in double cone blender
- Slugging
- Milling
- Sieving
- Final mixing (Lubrication)
- Compression

Advantages of dry granulation:

- One step process
- Time saving
- Moisture sensitive drugs can be granulated

Disadvantages of dry granulation:

- Decreased compression characteristics
- Excess dusting

Equipment used in granulation:

Name of the equipment	Country of origin	Function
Collete Gral 300	Belgium	Rapid Granulation Mixer
GEA High Sheer Mixer	India	Granulation Mixer
Aeromatic Fielder AG	Switzerland	Fluid Bed Dryer
Servolift Drum Blender	Germany	Blender
GEA PLV 700	India	Blender
Delta Mini Drum Blender	India	Blender

Blending purpose: To lubricate the granules and powder mix for easy ejection during compression and to render the tablet surface polish and smooth.

Compression: It is the final step of tableting. After compression, tablets are ejected from punch.

Tableting cycle is as follows-

1. Hopper: contains the granulated material
2. Feed frame: Fed by the hopper to hold the granules as it is fed into the die
3. Feed paddles: ensures that the granule is keep agitated to correct filling of the die bore
4. Compression station: where full compression of the tablet is achieved
5. Ejection station: this is the station where the tablet leaves the die for take-off.

Compression Equipment: Fette 2200i (Germany), Single rotary, 30 punch, Fette 3200i (Germany), Double rotary, 49 punch, Sejong MRC 30 N (Korea).

Problem during tablet compression:

Capping & Lamination:

Cause:

- Use of too dry granules in compression
- If compression pressure is too high

Remedy:

- By altering the pressure adjustment
- By using proper granules and required amount of fine particles

Picking and sticking

Causes:

- For using wet granule during compression
- Excessive moisture content of the granules.
- Improper drying

Remedy: By using dry granules and by adding a lubricant to the granules by replacing the worn dies and punches.

Hardness variation

Causes:

- Space between upper & lower punches at the time of compression.
- Inappropriate pressure applied in the upper punches

Remedy: The defect can be overcome by solving the causative effects.

Coating: Coating can be defined as deposition of a layer on the outer surface of a tablet to increase the stability of the tablet and protect it from environment. Temperature and humidity must be controlled during coating process.

Coating types depend upon: Tablet surface, Tablet shape, Nature of active ingredient.

Types of Coating:

1. Sugar coating: Protection from sun, moisture and environment; To mask bitter taste & odor to increase the aesthetic value; Prevent dusting.
2. Film coating: Masking of taste, odor and appearance; Can act as a barrier over the surface of the tablet.
3. Enteric coating: Modification of drug release, Repeat action and sustain release of product, Stops gastric irritation.

Equipment: Glatt GCsi (Indian), Driacoater (Germany), Pam Glatt (Indian), Lab coater (Canada)

Problems during Tablet coating:

Wrinkling or blistering: occurs due to the Gases forming on tablet surface during coating.

Remedy: Reduce drying air temperature.

Mottling: occurs due to inadequate pigment dispersion and Problem with dyes.

Remedy: Alter suspension preparation. Replace dyes with pigments.

Orange peel: occurs when the Film coat droplets are too dry or too viscous to spread.

Remedy: Reduce solid content, Reduce drying temperature, Reduce viscosity of polymer.

Blooming: occurs due to Migration of low molecular weight components on tablet surface.

Remedy: Decrease temperature and length of drying process, Increase molecular weight of plasticizer.

Capsule: Capsule is a solid dosage form; in which medicine are enclosed in hard or soft capsule shell, made from gelatin. Generally, in Healthcare Pharmaceuticals empty hard gelatin shells are used.

Steps of encapsulation;

1. Sieving of raw material (active & excipients)
2. Mixing (Double cone blender)
3. Compaction (If required) if bulk material is micronized or normal grain
4. Encapsulation
5. Polishing
6. Blister/ foil pack

Encapsulation process:

Empty shell are taken in empty shell hopper

↓

Empty shells are transferred from hopper to die holder

↓

Body and cap are separated by vacuum pump

↓

Pellets/ ingredients are incorporated into the body

↓

Sealer seal the body and cap

Ejection

Equipment: Bosch GFK 2500 (Germany) -18 capsules/station. -maximum 1,40,000 capsule/hr; Pam 90T (India); MG2 encapsulation (Italy)

Packaging:

Packaging is the process by which the pharmaceutical products are suitable packed in such way that they should retain their therapeutic effectiveness from the time of their packaging to consume by the consumers. Effective packaging is very important for the product to retain its stability and therapeutic efficacy.

There are three types of packaging

1. Primary packaging. (Direct contact with the product. Example: PVC)
2. Secondary packaging. (No contact with the product. Example: Inner Carton)
3. Tertiary packaging. (No contact with the product. Example: Shipper carton)

Three types of packaging material are used in the Oral solid dosage form.

1. Alu foil
2. PVC (poly vinyl chloride)
3. PVDC (poly vinylidene chloride)

Two different types of packaging are used:

1. Alu-Alu foil (moisture sensitive product).
2. Alu-PVC/Alu-PVDC (opaque foil is used for light and moisture sensitive product).

Environment Condition: Temperature: (18-27°C), Pressure: (5-25) Pa ,RH: (30±2%-50±2%)

Inner label Information: Manufacturing date, Expiry date, Batch no, Price

Shipper label information: Product name, Generic name, Batch no, Manufacturing date, Expiry

date, Storage condition

Equipment: Following equipment is used for packaging Purpose.

Blister machine: Noack N 623 (Germany) -64 spm -sealing temperature (150-230°C) -108/64 mm blister size; Uhlmann (Germany) -480 blister/min, Horn Noack (Germany)**,** Hoonga (Korea)**,** Mediseal (Germany)

Auto Cartooning Machine: Romaco Promatic auto cartooning and video jet printer (Italy)

Foil Printing machine: HAPA (Switzerland)

PFS filling machine: Semi-automatic auger filling machine HPR 019 (Taiwan), Semi-automatic cap sealing machine HPR 014 (Bangladesh)

Production of sterile unit:

Environmental Control of Sterile Area: In HPL, total environmental control is done properly according to the GMP guideline.

Area control:

a. Corridor: negative pressure
b. Room: positive pressure

Air flow control: Air flow is in between 70-80 feet/mm attained by HEPA filter.

Air filtration: By HEPA filters with an efficiency of 99. 97% for removing of particles of 0.20 micron or greater than it.

Temperature control: 22° C

Humidity control: 40%-60% By using protective clothing

Fumigation at every weekend by using 40% water solution of formaldehyde (formalin) by using UV light (Wave length 254 to 265 nm) or by using cleaning and disinfecting agents.

- Sterilization by heat: Moist heat sterilization or Autoclave [under 181 lb pressure for 25

minutes at 121°C] Dry heat sterilization

- Sterilization by chemicals: Alcohol (70%), Lysol (cresol with soap)
- Sterilization by gas: Fumigation by liquid formaldehyde
- Sterilization by radiation: UV radiation 225-265 nm

Sterility Test of Finished Product

- Visual inspection for visual glass particles and fibers that is called Clarity Test
- The Secondary Packaging area is class E specified. Inside the manufacturing area is Class A Specified. This area is used for production of sterile. Besides all the area is under HVAC system and strictly controlled. Different class room is used for different purpose-

Packaging & inspection – E class or controlled not classified

Terminal product filling - C class

Compounding manufacturing – C class(amino acids)

Sterile filling – room B class but filling under A class area.

This facility is Class C specified area. The products manufactured in this area include—

- Eye Drops
- Powder in Vial
- Liquid in Vial

Instruments Used in Sterile Unit

Equipment Name	**Manufacturer name**	**Country of origin**
Prefilled syringe filling machine	Colanar	India
Large vessel	Adam Febriwerk	India
Eye drop filling machine	Yoosung	Korea
Inspection machine	CMP	Italy
Embossing machine	Morico	Japan

Freeze dryer	Zirbus Tech	Germany
Lyophilization machine	Tofflon	China
Blister machine	JMP	Germany

Mechanism of vial / ampoule washing:

Ampoules are placed manually on tray

↓

Passed to ampoule washing room

↓

Ampoule's trays are placed in washing machine where a flash of DM + WFI flows from upper and lower part of the machine.

↓

After certain period of time, it is removed and the ampoules are replaced from that tray to another tray

↓

The ampoules are sterilized by dry heat sterilization for depyrogenation at 230 degree Celsius for 2.5 hours

↓

Then, it is allowed cool and removed for filling and sealing in aseptic area

Vial Filling and Sealing Process:

Receive ingredients

↓

Deboxing

↓

Passed through change box under laminar air flow

↓

Filling and sealing in aseptic condition

Primary packaging materials (in contact with products) which are- For Blister packing Aluminum foil and PVC film. For Strip packing Aluminum foil only.

Ampoule, Bottle, Vial, Label o Inserts, Inner carton

MDI Production:

Materials are received from warehouse according to PO and dedusted

↓

Passed to the unboxing room

↓

required materials are dispensed with balance

↓

balanced materials are manufactured

↓

filled, labeling and spray testing

Instruments:

Equipment name	Manufacturer	Country of Origin
Dispensing Booth	AirTech	Singapore
Filling machine	PAMASOL	Switzerland
Vacuum cleaner	PAMASOL	Switzerland
Encapsulation machines	PAMASOL	Switzerland
Blister machine	Zicon	India
Labeling and spray checking machine	MAHARSHI	India
Vial washing machine	ROMACO	Italy
Labeling Printer	Video Jet Printer	U.S.A

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