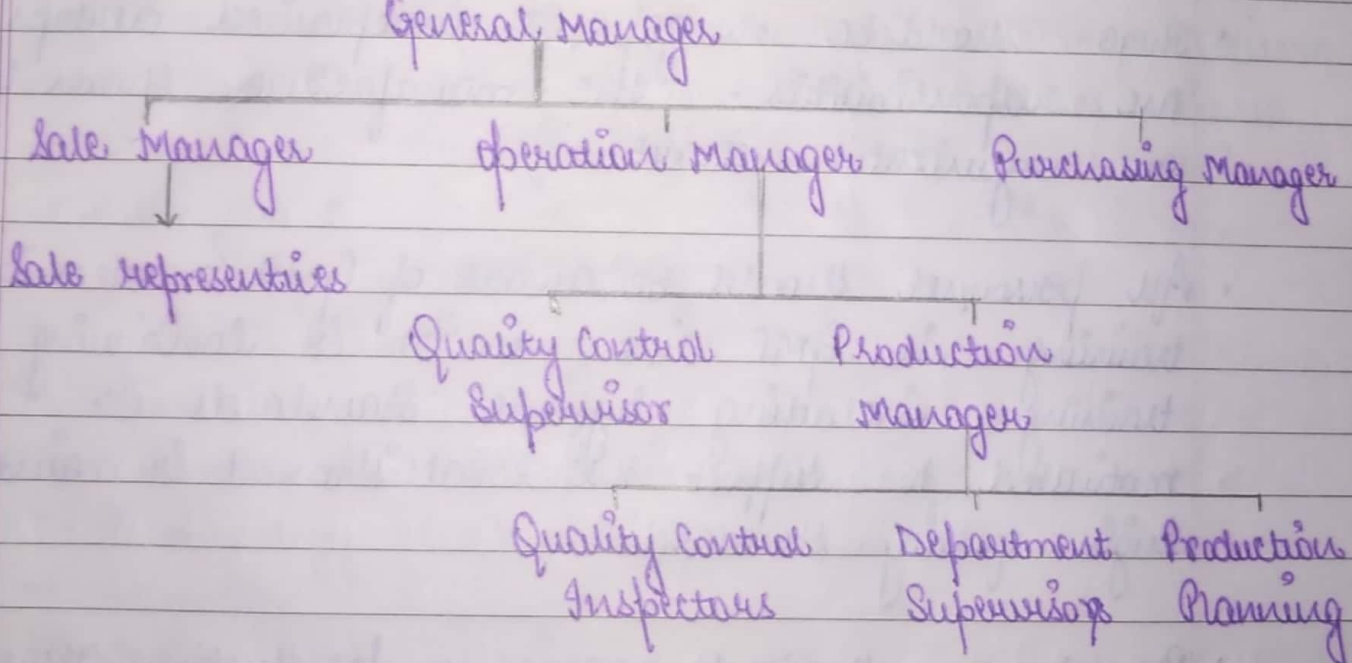
Unit-2

Organization & Personnel -

Organization:

Organization is a social unit of people which is structured & managed to meet a need or to pursue collective goals. All organization have a management structure that determines relationship between the different activities & the members.



Personnel:

The establishment & maintenance of a satisfactory system of quality assurance & the correct manufacture & control of pharmaceutical products & active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacture is responsible.

General :-

- The manufacturer should have an adequate no. of personnel with necessary qualification & practical experience. An individual's responsibilities should not be so extensive as to present a risk to quality.

- All responsible staff should have specific duties recorded in written description & adequate authority to carry out responsibilities. Their duties may delegated to designated deputies with qualification.

- There should be no gaps or unexplained overlaps in the responsibilities. The manufacturer should have an organization chart.

- All personnel should be aware of GMP & receive training in GMP like initial & continuing training including hygiene standards & motivated to support the establishment & maintain high-quality standards.

- Prevent unauthorized access to production areas, Storage area & Quality Control. Stop personnel who donot work in these areas using them as a passageway.

Key Personnel:-

- Key personnel which normally should be full-time position include:
  - → Authorized person
  - → Head of Production
  - → Head of Quality Control
  - → May delegate function in large organization but not delegate in responsibility.
  - → Heads of production & Quality Control should be independent of each other.

- Key personnel responsible for Supervising the manufacture & quality Control of pharmaceutical products should possess the qualification of a scientific education such as:
  - → Chemistry or Biochemistry
  - → Chemical engineering
  - → Microbiology
  - → Pharmaceutical sciences & technology
  - → Pharmacology & toxicology
  - → Physiology
  - → other related sciences

- The should posses adequate practical experience in the manufacture & quality assurance & Preparatory period under professional guidance.

- Education & experience should enable personnel to take difficult decisions in an independent, professional & scientific way to resolve the problems encountered in manufacturing & Quality Control.

Personnel Responsibilities:

Shared Responsibilities -

Head of Production & Quality control may share exercise some responsibilities relating to quality:

- Authorization of written procedures (SOPs) & other documents, including amendments.
- Monitoring & control of manufacturing environment.
- Plant hygiene.
- Process validation & calibration
- Training including application & principles of QA.
- Appraisal & monitoring of suppliers & contract acceptors.
- Retention of records
- Designation & monitoring of storage conditions for materials & products.
- Performing & evaluating in-process controls.
- Monitoring compliance with GMP.
- Inspection, investigation & taking of samples to monitor factors which may affect quality.

Head of the Production -

- Product production & storage according to appropriate documentation.
- Approval & implementation of production instructions, in-process QC & ensure strict implementation.
- Ensures that production records are evaluated & signed by designated person.
- Checks maintenance of production department, premises & equipment.

- Ensures process validation & calibration performed, recorded & reports are made available.
- Ensures initial & continuous training of production personnel.

Head of Quality Control -

- Approval or rejection of materials - eg- Packing materials, intermediates, bulk and finished products, in accordance with specification.
- Evaluation of batch record.
- Ensures carrying out of necessary testing
- Approval of quality control procedures - eg- Sampling & testing specification.
- Approval & monitoring of all contract analysis.
- Checks maintenance of quality department, premises & equipment.
- Ensures validation & calibration of control equipment.
- Ensures initial & continuous training of QC personnel.

Head of Quality Assurance - (They are authorized person)

- Compliance with technical & regulatory requirements.
- Approval of the release of finished products for sale.
- Establishment & implementation of quality system
- Development of quality manual.
- Supervision of self-inspection & quality audits.
- Oversight of the QC department.
- Participation in external audits & vendor audits.
- Participation in validation programmes.

Training :

- The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories & for other personnel as required.

- Induction & continuing training based on the theory & practice of GMP & their duties. Training records should be kept. Practical effectiveness periodically assessed.

- Specific training for staff in all areas, eg -
  → where contamination is a hazard
  → clean areas
  → Areas where highly active, toxic, infectious sensitizing materials are handled.

- The concept of QA should be fully discussed during training to facilitate proper understanding to ensure its implementation.

- Visitors or untrained personnel should preferable not to enter production & control areas. If this is unavoidable, they must be given information in advance, particularly about personal hygiene & protective clothing requirements. They must be accompanied & closely supervised at all times.

Personnel Hygiene:

- The personnel should regularly undergo medical examination once a year & proper records thereof should be maintained.
- All the personnel engaged in the manufacturing processes should be provided training to foster healthy habits for maintaining personnel hygiene & sanitation.
- The personnel should inform about their illness to their intermediate supervisor so that appropriate actions can be taken.
- To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including hair covering.
- Direct contact between the unprotected hands of personnel & raw materials, intermediate or finished products should be avoided.
- Before entering the manufacturing areas, separate changing rooms for men & women with proper facilities for personnel cleanliness. The changing room should have cabinets for the personnel to store their belonging.
- If the used clothes are reusable, they should be stored in separate closed containers until they are properly dry cleaned & should be regularly disinfected or sterilised.
- Smoking, eating, drinking & chewing should be strictly prohibited in the production & testing areas.

Personnel Records:

These are records pertaining to employees of an organization. These records are accumulated, factual & comprehensive information related to concern records & detained.

All information with effect to human resources in the organization are kept in a systematic order.

Premises :

→ Design & Constructions :

Location -

Regarding building & facilities, there are two major areas of concern, the external environment & the internal environment.

Consideration prior to purchase, construction, or alteration of existing facilities includes the following :

(a) Adequate space for further expansion.
(b) Availability of water power, fuel, sewage & waste-stream removal.
(c) Accessing for employees, material & visitors
(d) Environmental issues such as water & air quality.
(e) Availability of a suitable labour force.
(f) Availability of proper security arrangements.

Design & Construction -

The premises to be used for the manufacturing, processing, packing or holding of drug products should be of suitable size, design, construction & location. This reduces the risk of errors & allows effective cleaning & maintenance to prevent cross-contamination or any adverse effect on the product Quality.

The premises should also abide by the conditions laid down in Factories Act, 1948.

A Site development plan addressing the following should be prepared :

- Site resources & infrastructure like green spaces,

parking, road & rail access, etc.
- Storm water & waste management.
- Compliance with appropriate laws & regulations.
- Site security & access like installation of fences, guard posts, cameras, etc.
- Layout, usage & possible expansion of building.
- Utilities like design, layout, electricity backups.
- Equipment like design, layout, spares & capacity.
- Pedestrian & vehicular traffic flow.
- Safety for personnel & equipment.
- External architecture to consider the local environmental consideration.
- Ease of maintenance & cleaning
- Selection & use of experienced constractors.
- Identification of project management responsibility.
- Validation plans & an effective change control procedure
- Construction materials.

Construction Type

Department	Walls	Floors	Ceilings
warehouse	Painted	Harden & Concrete, Sealed	Suspended ceiling
Dispensary	Epoxy Covered	Epoxy or in situ terrazzo covered	Epoxy Covered
Solid Manufacturing	Epoxy covered	Epoxy or in Situ terrazzo Covered	Epoxy covered
Liquid Manufacturing	Epoxy Covered	Epoxy or in Situ terrazzo Covered	Epoxy covered.

Solid Packaging	Painted	Sealed Concrete, terrazzo tile or vinyl	Suspended ceiling
Liquid Packaging	Epoxy covered	Epoxy or in situ terrazzo covered	Epoxy covered
Laboratory	Epoxy	Terrazzo tile or epoxy sheet	Suspended ceiling

→ Plant layout :

Plant layout refers to the arrangement of physical facilities such as machinery, equipment, furniture etc. within the factory building in such a manner so as to have quickest flow of material at the lowest cost & with the least amount of handling in processing the product from the receipt of material to the shipment of the finished product.

Importance of Plant layout -

- It provides optimum relationship among output, floor area & manufacturing process
- It allows easy production flow
- It provides flexibility of operation
- It makes economic use of building
- It promotes effective utilisation of manpower
- It provides employee's convenience
- It provides safety & comfort at work
- It provides maximum exposure to natural light & ventilation.

Types of Plant layout -

Plant layout

- Manufacturing units
  - Product or one line layout
  - Process or functional layout
  - Fixed position or location layout
  - Combined or group layout.
- Traders
- Service Establishment

→ **Product or one line layout :**
The arrangement of machines doing various operation in a line as one department.

Advantages :-
- low cost of material handling
- Continuous work flow.
- Optimum use of floor space
- Shorter processing time or quicker output.

Disadvantages :-
- High initial capital investment
- Suitability
- Heavy overheaded charges
- Mass production of standardised products.

→ **Combined layout :**
This layout is a combination of product & process layouts to take the advantages of both.

→ Process layout :
The arrangement of machines of a particular class doing a particular type of work or process as a separate department.

Advantages :-
- Lower initial capital investment
- Effective supervision
- Flexibility of expansion

Disadvantages :-
- Higher cost.
- Greater storage space.
- Frequent inspection.

→ Fixed Position or location layout :
A complete product is produced at a fixed location. The facilities required are arranged around the particular work location.

Advantages :-
- Time & cost saving.
- Adjustments can be made.
- Flexible layout.

Disadvantages :-
- Heavy capital investment
- very long production period.

Factors influencing Plant layout -

- Factory building
- nature of product
- Production process
- Type of machinery
- Repairs & maintenance
- Human needs
- Plant environment.

→ Maintenance :

- Building used in the manufacturing, packaging or warehousing of a drug products should be properly maintained.
- A deteriorated building presents a poor image of the facility & affected the product quality.
- Written procedures must be established for the cleaning & sanitising agent.
- Equipments & utensils must be cleaned, Stored & wherever appropriate sanitized or sterilized to prevent contamination.
- Non dedicated equipment must be cleaned between production of different materials to prevent cross contamination

→ Sanitation :

- The manufacturing premises shall be cleaned & maintained in an orderly manner, so that it is free from accumulated waste, dust, debris & other similar material.

- A validated cleaning procedure shall be maintained.
- The manufacturing areas shall not be used for storage of materials, except for the material being processed.
- A routine sanitation programme should be conducted, properly recorded & should indicate the following:
  (a) Specific areas to be cleaned & cleaning material.
  (b) cleaning procedure to be followed, including equipment & materials to be used for cleaning.
  (c) Personnel assigned for the cleaning operation.

→ Environmental Control:
Pharmaceutical manufacturing plants produce large amount of waste materials that pollute the environment.
There are some pollution which control by the industries:

- Thermal pollution & control
- Water pollution & control
- Air pollution control

Thermal pollution & control:-

- Various off stream cooling system are required to handle thermal discharge from process.
- There different way for controlling thermal pollution:
  (a) wet cooling towers.
  (b) Dry cooling towers.

Water pollution & Control :-

- There is a great problem to handling a liquid waste effluent is more complex than gas effluent.
- The treatment could be done by :
  (a) Physical treatment.
  (b) Chemical treatment.
  (c) Biological treatment.

Air pollution Control :-

- There are two major categories :
  (a) Those suitable for removing particulate matter.
  (b) Those associated with removing gaseous pollutant.
- Removed chemical & physical way.

→ Utilities & Services :

(i) HVAC (Heating, Ventilation & Air Conditioning) - Ventilation is the process of exchanging or replacing air in any space to provide high indoor air quality which involves temperature control, removal of moisture, odors, smokes, dust, heat, carbon dioxide, and other gases. Ventilation remove unpleasant smells & excessive moistures, introduce outside air, keeps interior building air circulating, stagnation of the interior air.

(ii) Compressed air -

In general, compressed air should be supplied by an "oil-free" type compressor & must be free of oil & oil vapour unless vented directly to a non-controlled environment area. It should be dehumidified to prevent condensation of water vapour. Centrally distributed compressed air is generally provided at 100 to 125 psig & reduced as required.

(iii) Water -

Water for pharmaceutical purposes, it may be considered that there are 3 basic grades of water:

→ Potable water : They may be used in chemical synthesis & in the early stages of cleaning pharmaceutical manufacturing equipment unless there are specific technical or quality requirements for higher grades of water.
It is the prescribed source feed water for the production of pharmacopoeial grade waters.

→ Purified water : This is water for the preparation of medicinal products other than those that require the use of water which is sterile. Purified water which satisfies the test for endotoxins may be used in the manufacture of dialysis solution.

→ Water for Injection:
WFI meet the International pharmacopoeia requirements as it is purified water plus it must be free from pyrogen. Usually prepared by distillation Storage time should be less than 24 hours microbial limits must be specified.

(iv) Lighting -
Adequate lighting should be provided in all areas. Adequate lighting may be done by defining the amount of light reaching the working surface for each area involved in the production of pharmaceuticals. A range 30-50 foot candles ensures worker comfort & ability to perform efficiently, however, 100 foot candles may be needed in some areas as well as special lighting for some operation, such as inspection of filled vials.

→ Maintenance of Sterile Areas:
- For sterile drugs are separately enclosed area specially designed for the purpose shall be provided.
- Area shall be provided with air lock for entry & shall be essentially dust free & ventilate with air supply.
- For all area where aseptic manufacture has to be carried out air supply shall be at a pressure higher than in the adjacent area.

- Routine microbial count of all sterile area shall be carried out during manufacturing operation.
- Area where manufacturing progresses going on that area must not be occupied by access people.
- Special procedure should be followed for entering & leaving the manufacturing area.

→ Control of Contamination: Contamination:-
Contamination is the undesired introduction of impurities or foreign matter, into a starting material or intermediate or API during Production, Sampling, Packaging, Storage, Transport

Common Sources -
- Equipments
- Airflow extraction
- Personnel
- Manufacturing
- Cleaning
- Facility / Design.

Types -
(a) Physical Contamination: eg- fiber material, particles
(b) Chemical Contamination: eg- vapour, gasses, moisture, molecules.
(c) Biological Contamination: eg- fungus, Bacteria, virus

Prevention of Contamination -
- Test one material at a time to prevent cross Contamination
- Use proper tools designed for the Something
- Ensure proper cleaning of equipment to prevent any biological Contamination.

- Properly design airflow system to prevent airflow contamination.
- Dispensing stations should have proper dust extraction system.
- Donot return used samples to their original containers.
- Regularly monitor water to check for presence of microbial system.
- Avoid unloading different material for different batches.
- Line clearance must be observed during product changeover.
- Total impurity must not exceed 0.5% & single individual impurity not more than 0.1%.

Cross Contamination :-

Cross contamination is defined as the contamination of a starting material, intermediate product or finished product with another starting material or product during production.

Cross-contamination of any product is caused by :

- Contamination of a batch with a previous batch of the same product.
- Contamination with a different product through carryover or proximity of production lines
- Contamination by a foreign starting material of the dispensary or in the store.

Prevention of Cross Contamination -

- Personnel Procedures.
- Adequate premises
- use of closed production systems.
- Adequate, validated cleaning procedures.
- Appropriate levels of protection of product.
- Correct air pressure cascade.

Equipments & Raw Materials :

Equipment :-

- Equipment may be defined as a physical entity which is used to carry out a general or specific activity in the pharmaceutical plant.

eg - tablet compression, weighing Machine.

Selection of Equipment -

- Availability of spares & servicing
- The frequency & ease of maintenance will significantly impact on productivity & even quality.
- Construction materials & design
- Equipment breakdown during processing could adversely effect quality. Included in the maintenance evaluation should be the cleanability of the equipment.
- This will invoke accessibility to the parts to be cleaned & the relative ease of disassembly & reassembly process.
- The type of process controls such as automatic weighing adjustment on tablet.
- Environmental issues are important constrains. Is the design of the equipment conductive to the application ? Such attributes as the ability to contain toxic products, the ability to maintain aseptic condition, etc need to be reviewed.

Purchase Specification -

Before we take decision to purchase an equipment we need to look many aspects.

- This primarily helps the user requirement specification for the equipment.

Following question may arise in relation to design, size, location, adaptation & construction of the equipment :

Why the need arises for the purchase of equipment ?
eg- Creation of new facility, increasing capacity, Adapting to new & imposed technology.

Which operation we want perform with proposed equipment?
eg- equipments capability analysis, granulation, sterilization.

What capacity the equipment should have in terms output & holding ?
eg- 10 lakhs tablets per shift or 10 thousand litres of liquid

How the equipment will be cleaned ? And also need to consider that do we face any problem in validating the cleaning process of the equipment ?

What will be the starting & stoping time of the equipment ?

Do we have trained operators to operate this equipment or whether the manufacturer helps in training our existing operator.

WHO Guideline :

(12.1) Equipment must be located, designed, constructed, adapted & maintained to suit the operation to be carried out.

- The layout & design of the equipment must aim to minimize the risk errors & permit effective cleaning & maintenance in order to avoid cross contamination, build up dust or dirt & in general any adverse effect on the quality of the product.

(12.2) Equipment should be installed in a such a way as to minimize any risk of error or of contamination.

(12.6) Production equipment should be designed, located & maintained to serve its intended purpose.

(12.7) Production equipment should be designed, so that it can be easily & thoroughly cleaned on scheduled basis.

(12.10) Production equipment should not present any hazard to the products.

- The parts of the production equipment that come into contact with the product must not be reactive, additive or absorption to an extent that would affect the

quality of the product.

- The equipment must design to be compatible with most materials & process being used.

Maintenance -

use of cleaned equipment is one of the basic step in avoiding Contamination & meeting the purity of the product.

WHO Guideline :

(12.1) The layout & design of the equipment must aim to minimize the risk of errors & permit effective cleaning & maintenance in order to avoid cross-contamination build-up of dust or dirt.

(12.9) washing & cleaning equipment should be chosen & used so as to prevent source of Contamination.

- Defective equipment should, if possible be removed from production & quality control or atleast clearly labeled as defective.

Raw Materials :-

All materials that used into manufacturing of a finished bulk & which are consumed by a person using it are called raw material.
Raw material can be either active drug or inactive substances.
Eg - Hard gelatin capsules, even though its is used to fill the blend of medicine, it is not consid.

Purchase specification -

written guidelines that precisely define the physical, operational & chemical properties as well as the quality & quantity of a particular item to be acquired.

Mode of Purchasing :

(1) By inspection
(2) By sample
(3) By description of brand
(4) By Grading

Steps of Purchasing :

(1) Purchase requisition or application.
(2) Selection of supplies
(3) Inviting quotation.
(4) Placing the order.
(5) Receiving the material.
(6) Checking the invoice or bill.
(7) Recording of bills in books.
(8) Releasing the payment to the supplier.

Purchasing staff should have a specific & intense knowledge of products & suppliers. Purchasing of raw material should be done from supplier named in relevant specification or directly from producer. Pharmacist or chemist having knowledge & experience of quality requirement of various material purchase department can be the head of purchase department.

Maintenance of Stores for Raw Materials -

(1) Storage Area Specification :
(a) Sufficient capacity
(b) Clean, dry & maintained within acceptable temperature limit
(c) Designed & equipped reception area.
(d) Ensuring of quarantine status
(e) Separate sampling area.
(f) Segregation for storage of rejected, recalled or returned materials.
(g) Safe & secure area for narcotics & highly active, dangerous & risky materials.
(h) First in first out Rule (FIFO)
(i) First expiring first out (FEFO)

(2) Storage conditions :
(a) Room temperature should be 30°C & R.H. should be 60%.
(b) A.C. Storage (25 ± 2°C & R.H. 45-55%)
(c) low temperature storage at 2-8°C
(d) Separate area for sterile product storage in A.C.
(e) Sensitive material in amber color container.
(f) Hermetically sealed containers.

(3) Labelling of Materials in Storage Area :
(a) Designated name of product & internal code reference.
(b) Batch no. given by supplier
(c) Status of content
(d) Expiry date or date beyond which retesting is necessary.
Note - During fully computerized system used, labelling with all above information need not be necessary.

(4) Check list before Storage :
(a) Integrity of package & seal.
(b) Correspondence note for the order, delivery & Suppliers labels.

(5) Check list during Storage :
(a) Separation of rejected, Recalled, quarantine, on test & packaging materials.
(b) Quality of materials.

(6) Released by QC unit only.