PREMISES

All the buildings where the manufacturing & analysis of the product will take place are called premises.

Premises should be located, designed and constructed in such a way that:

- It contributes toward product quality.
- Minimize the risk of contamination.
- Permits the effective cleaning and maintenance.
- Minimize the builds up of dirt & dust.
- Ensure the logical flow of materials and personnel.
- Ensure maximum protection against the entry of insects, birds or animal.

In an industry, manufacturing operations must be carried out under clean and hygienic conditions because of the nature of the products being manufactured. Special care must also be taken to prevent contamination of the products. Therefore, the location, design, construction and layout of premises is a vital part of Good Manufacturing Practices Premises refers to the buildings and facilities where pharmaceutical processing is done. These places must comply with cGMP requirements.

OBJECTIVES

- To review general requirements.
- To list key requirements for site choice.
- To consider specific requirements for main areas.
- To list major facilities required in a site.
- The objectives to be achieved according to Schedule M:
- Suitability of premises to carry out intended operation.
- Minimizing risk of errors.
- Permitting effective cleaning and maintenance.
- Minimizing contamination.

PRINCIPLE

To achieve these objectives, consideration has to be given to

- Location
- Layout
- Design
- Construction
- Maintenance
- Control of contamination

LOCATION

- Ideally the location of the premises should be in a hygienic surrounding.
- The pollution sources must be minimum.
- The site for selecting the pharmaceutical industry must be away from open drainage, public lavatory and sewage.
- It must be separated from obnoxious odour fumes or large quantity of soot dust or smoke

Factors which must be mainly taken into consideration while selecting the site for pharmaceutical industry are

- Transportation facility
- Availability of water, electricity
- Maintenance facility for repair
- Fuel availability, sewage and waste stream removal from plant
- Proximity for civil facilities for factory personals
- Adequate space for future expansion
- Adequate security arrangements

LAYOUT, DESIGN & CONSTRUCTION

- The building(s), used for the factory shall be designed, constructed, adapted and maintained to suit the manufacturing operations so as to permit production of drugs under hygienic conditions. They shall conform to the conditions laid down in the **Factories Act, 1948**

LAYOUT

First step in construction of building is to make layout.

There are many points we should be kept in mind while designing a layout for factory premises.

- Total area of land available
- Percentage of area that can be covered under local laws.
- Dosage form to be manufactured (ex: tablets, capsules, ointments, injections etc.)
- Scale of operation i.e., small scale, medium scale, large scale.
- Type of equipment, plant and machinery to be used i.e., manual, semiautomatic, automatic.
- Different area that are required to be provided in a pharmaceutical factory (i.e., storage area, weighing area, production area, quality control area, ancillary area).
- Requirements of separate buildings for hazardous materials/process or complete isolation of some buildings.
- Specific requirement of a dosage form (ex: segregated area for granulation, compression and coating processes in manufacture of tablets) Specific requirements of utilities (ex: boiler for generation of steam, gases, water).
- Logical flow of materials i.e., goods in store-production-quarantine and assembly-ware house-goods out.

- Provision of national / local factory laws (in India the factory buildings should comply with the provisions of the factories act and the rules made there under). Future projects.

Some guidelines in preparing layout, designing & construction of buildings:

- Rest and refreshment rooms should be separate from manufacturing and control areas.
- Facilities for changing and storing clothes should be easily accessible and appropriate for the number of users.
- Toilets should be separate from production or storage area.
- Maintenance workshops if possible be separate from production area.
- Animal houses should be well isolated from other areas, with separate entrance and air-handling facilities.
- Floors should be smooth & impervious. Internal walls, ceiling should be plastered with cement to smooth finish.
- Pipe work, light fittings, ventilation and other services should be designed to avoid the difficulty to clean.
- Drains should be of adequate size and designed to prevent back-flow. Open channels should be avoided.
- Production area should be effectively ventilated, with air-control facilities.

CONSTRUCTION

Construction of the building should be such that it ensures protection of the product from contamination.

- It must permit efficient cleaning facilities
- It must be in such a way that it must avoid accumulation of dust and dirt
- It must be prevented from entry of insects, birds, rodents etc

- Provisions were been satisfactory to the factory act 1948.

It must be mainly related to

- Cleaning
- Disposal of waste
- Temperature
- Artificial humidification
- Ventilation
- Lighting
- Drinking water supply
- Toilet facilities
- Safety aspects

CONSTRUCTION MATERIALS:

The materials used for the construction must be of good quality.

WALLS:

- The position of the walls should provide an orderly movement of materials and personals.
- Walls in the industry must be made up of plaster finish on high quality concrete blocks or gypsum board
- The finishing must be smooth and must be usually done by enamel or epoxy paints
- In packing areas prefabricated portions may be used Flush and projections of the walls must be avoided

FLOORS:

- Floor covering selection must be for durability and resistance to the chemical with which it is likely to come into contact
- Most preferable things for flooring are terrazzo, ceramic and vinyl tiles, welding vinyl sheeting, epoxy flooring etc

CEILINGS:

- Suspend ceilings may be provided in office area, laboratories, cafeteria, toilets.
- Manufacturing area requires a smooth finish often of seamless plasters or gypsum boards
- All ceiling fixtures such as light fitting air outlet and returns, sprinkler heads should be design to assure case of cleaning and to minimize the potential for accumulation of dust.

DOORS AND WINDOWS:

- Doors and windows must be smooth and impervious, should close tightly
- Windows of the manufacturing area should be tightly closed and not permitted to open
- Outside doors must be tightly closed and sealed except for entry or exit

LIGHTING:

- Adequate lighting in pharmaceutical units is necessary

The important points in providing adequate lighting are

- ❖ Position of source of light
- ❖ Selection of tubes or bulbs
- ❖ Intensity of light
- ❖ Different type of works may require different intensity of light supply and it must be provide as required
- ❖ Once the light levels are fixed its necessary to measure it periodically and the results should be recorded

HVAC:

- Heating Ventilation Air-conditioning System
- It can provide comfortable conditions for operators

- Factory premises of pharmaceutical units should be provided with adequate ventilation
- When the natural ventilation is not sufficient then exhaust fans must be provided
- Some area may require conditioned air and this may be achieved by window type air conditioners or central air conditioners
- Objectives of air conditioning system,
- It should prevent the air bone contaminants into working areas
- Enclosed or semi enclosed systems should recirculation particulate free air
- In coming volume of the air should be adequate so that particulate contaminations were swept into exhaust
- Dust or floating particulate matter generated in manufacturing areas should be removed before setting
- Temperature and humidity should be so controlled that these do not affect the product to be processed and comfort to workers
- No turbulence in incoming air

PLUMBING:

- Adequate supply of water is essential for a pharmaceutical unit
- In pharmaceutical industry mainly used types of water are
- Potable water
- Purified water
- Water for injection
- The frequency of examination of the water is necessary and it may depend upon the size of the population served

SEWAGE AND REFUSE:

- Any products requiring disposal should initially be separated from it packing appropriate.
- This is because packing materials may delay the destruction
- Then they are safely disposed in the procedure preferred
- The disposal of printed packing components like labels inserts and cartons poses no health risk
- In effective disposal in public land fill preferably be incinerated
- It may destroy under the supervision of an authorized person
- Waste containing dangerous or highly toxic materials may be disposed after suitable treatment

WASHING AND TOILET FACILITES:

- Adequate washing facilities may be provided including hot or cold water, soap or detergent water, air drier or single service towels
- Must provide with neat and cleaned toilets

MAINTENANCE

- All building used in the manufacture processing, packing or holding of a drug product shall be maintained in a good state of repair
- Deterioration of buildings not only make a poor image of the facility but also it may make an impact on the product quality
- Cracks and holes in walls floors or ceiling provide access for insect's rodents, birds and also hinder the cleaning and sanitation
- Low maintenance may increase the potent of cross contamination or microbial multiplication
- Ingress of water from roof tops may cause a significant damage to materials, equipments and may give rise to electrical failure

- Light fitting may need regular cleaning to remove any accumulation of dust acts as potent source of contamination and reduced light intensity
- Temporary repair should undergo for the correction of the building deficiencies
- Routine maintenance is required for the essential services which includes water supply HVAC, steam, vacuum, compressed air, other gases, electricity, dust extraction, pipe lines, drainages and sprinkler system .

SANITATION

Objectives of sanitation are

- Removal of dust and dirt and other waste materials
- Minimize the risk of cross contamination between different products in the same area
- Reduce the number of microorganisms in work areas
- Controls pest so that these do not affect the quality of materials to be used in the manufacturing of drugs.
- Sanitation of the manufacturing area is more important than other area because risk of contamination is more in these areas
- Protection from outside environment too is necessary
- Sanitation Manufacturing area should not be used for any other purpose.
- It should be maintained clean, orderly manner and free from accumulated waste, dust, debris etc.
- Eating, chewing smoking or any unhygienic particle should not permit in manufacturing area.
- Production areas shall be well lit, particularly where visual on-line controls are carried out.

- A routine sanitation program shall be drawn up and observed, which shall be properly recorded and which shall indicate

(a) specific areas to be cleaned and cleaning intervals

(b) cleaning procedure to be followed, including equipment and materials to be used for cleaning; and

(c) personnel assigned to and responsible for the cleaning operation.

STERILE AREA

- Sterile products are manufactured in the area specially designed and maintained
- Since most of the sterile products are injected directly into human body, it must be very careful in designing and maintaining sterile area

Sterile area provided for manufacturing of sterile products are given below:

- Equipment and component washing area
- Water for injection preparation and compounding area
- Filling and sealing area
- Multiple air lock entrance
- Sterilization area containers visual examination area
- Quarantine area
- Filling and sealing area must be separated from other areas in such a way that aseptic condition is maintained by sealing the partitions
- Floors of the areas must be hard, smooth, impervious It should not affect by detergents and disinfectants
- Floor coverings are used in these areas
- Walls and ceiling materials should be smooth and low particle shedding and easy to clean

- Air locks should provide air seals to provides pressurization of aseptic room
- The air lock may be designed in such a way that only one door opens at one time

ENVIRONMENTAL CONTROL

- 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 ways for controlling thermal pollution
    - ❖ Wet cooling towers
    - ❖ Dry cooling towers

WATER POLLUTION

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

AIR CONTROL

- There are two major categories
- Those suitable for removing particulate matter

- Those associated with removing gaseous pollutant
- Removed by chemical And Physical way

TEMPERATURE AND RELATIVE HUMIDITY:

This is main factor which is to controlled

- In working areas, the temperature preferred are 25℃
- Regulation of humidity may depend upon the materials to be processed
- If the material to be processed is not highly sensitive to moisture the humidity must be maintained below 50 % RH.
- If it is not possible to construct and maintain entire room as laminar air flow rooms then laminar air flow benches can be used.

CONTROL OF CONTAMINATION

- Contaminates in the pharmaceutical industry includes dust, microorganisms, etc.
- Such contaminants normally float in air but settle down on counter floor and other exposed surfaces
- Exhaled breath of personals also contains microorganisms
- Air is main source of contamination and so the prevention of dust particle in air can also cause the control of number of microorganisms
- Clean air is required to be feed into the sterile product. This can be achieved by series of treatments or by air cleaning It must be done as follows:-
- Air first must be passed through primary filter mad of glass or wool. This primary filter must remove the larger particles
- Next pass through a passage narrowing electrostatic precipitator

- Finally, the air is passed through HEPA filter and thus it may filter up to the particle size of 0.3 microns and may remove with better efficiency
- Direction of air flow is horizontal or vertical
- The laminar flow may be carried out and it may sweep the enterer confined area with uniform velocity with maximum eddies
- Air cleanliness classes defined under fed standards no 209B (cleanroom standards)
- Classification is based on the particle count with maximum allowable number of particles per unit volume

DOCUMENTATION

- Facility Design
- Personnel training
- Processing
- Maintenance
- Service Audit

All data should be documented.