# SHREE H. N. SHUKLA INSTITUTE OF PHARMACEUTICAL EDUCATION AND RESEARCH



## B.PHARM

**(SEMESTER –VII)**

**SUBJECT NAME: QUALITY ASSURANCE**

**SUBJECT CODE: BP706TT**

**UNIT 02 (b): PREMISES**

# Content

**Premises:** Design, construction and plant layout, maintenance, sanitation, environmental control, utilities and maintenance of sterile areas, control of contamination.

## Locations & Surroundings

Any building(s) used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations.

Regarding buildings and facilities, there are two major areas of concern: the external environment and the internal environment.

The external environment must be amenable to the location of well-designed and constructed buildings.

Several professional resources and functions will be involved in site selection. These are likely to include legal, real estate, and state and local government agencies, utility companies, engineers, and architects.

Before purchase, construct or alteration of existing facilities following should be taken into consideration:

1. adequate space for future expansion;
2. zoning laws to allow anticipated development while restricting undesirable developments in the vicinity;
3. availability of water (quality and quantity), power, fuel, sewage, and waste-stream removal;
4. accessibility for employees (availability of public transportation), materials, and visitors (customers and suppliers);
5. environmental issues such as site history; soil, water, and air quality; and geological and topological issues (potential for flooding, earthquakes, and foundation instability);
6. availability of a suitable labor force (people, skills, wage expectations, labor relations and attitudes, and access to further education sources);
7. ability to provide adequate security arrangements;
8. proximity or accessibility to interrelated operations of the company—research and development (R&D), marketing, and internally produced intermediates or components;

9. political situation—government stability, trade policies and taxation (for foreign-based operations), and financial incentives

## Building

### Layout of Building:

The first step in construction of building is to make layout. There are many points which should be kept in mind while designing a layout for factory premises. Salient points are given below.

- Total area of land available
- Percentage of area that can be covered under local laws
- Dosage forms to be manufactured (e.g. tablets, capsules, ointments, injection etc)
- Scale of operation i.e. small scale, medium scale, large scale
- Type of equipment, plant and machinery to be used i.e. manual, semi-automatic, automatic
- Different areas that are required, to be provided in a pharmaceutical factory (i.e. storage areas, weighing areas, production areas, quality control areas, ancillary areas)
- Requirements of separate buildings for hazardous materials/process or complete isolation of some buildings
- Specific requirements of a dosage forms (e.g. segregated area for granulation, compression and coating processes in manufacture of tablets)
- Specific requirements of utilities (e.g. boiler for generation of steam, gases, water)
- Logical flow of materials i.e. good in stores-production-quarantine and assembly-warehouse-goods out
- Provisions of national/ local factory laws (in India the factory buildings should comply with the provisions of the Factories Act and rules made thereunder)
- Future projects or expantion.

**Premises must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. For design and maintenance of plant following consideration should be taken.**

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

II. Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, or packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.

III. Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

IV. Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.

V. Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.

VI. Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.

VII. Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

VIII. Premises should be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals. There should be a procedure for rodent and pest control.

IX. Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

X. Premises should be designed to ensure the logical flow of materials and personnel.

Servicing of a practicing Architect may be availed in preparing layout of factory building and may be got approved from building construction regulatory authority like Municipal Corporation.

## Construction of Building

Construction of buildings should be such that it ensures protection of the product from contamination, permits efficient cleaning, avoids accumulation of dust and dirt and prevents entry of insects, birds, rodents etc.

- It is important, when choosing a material of construction, to keep in mind the characteristics of the manufacturing process.
- Parenteral manufacturing operations have different requirements than oral dosage manufacturing operations do. Similarly, biotech and vaccine manufacturing operation requirements can differ.

- It is imperative that these requirements be considered when specifying wall, floor and ceiling construction, and finishes.

## 1. Walls:

The position of walls should provide an orderly movement of materials and personnel and should also take into account noise levels to provide acceptable working conditions.

The interrelationship of different operations should minimize the potential for cross-contamination and component mix-up during storage and interdepartmental shipping.

Walls in manufacturing areas, corridors, and packaging areas should be of plaster finish on high-quality concrete blocks or gypsum board. The finish should be smooth, usually with enamel or epoxy paint.

Prefabricated partitions may be used in packaging areas as well as in sterile areas.

## 2. Floors:

Floor covering should be selected for durability as well as for cleanability and resistance to the chemicals with which it is likely to come into contact.

1. Terrazzo provides a hard-wearing finish; both tiles and poured-in-place finishes are available. The latter is preferable for manufacturing areas; if tiles are used, care must be taken to ensure effective sealing between the tiles, which, otherwise, could become a harboring area of dirt and microorganisms.

2. Usually, ceramic and vinyl tiles are not recommended for production areas. However, if used, the between-tile sealing should be flush and complete.

3. Welded vinyl sheeting provides an even, easy to clean surface. This is not practical for heavy traffic areas, but can be of value in production areas, especially for parenteral and biotech products. Here, the lack of joints improves the ease of cleaning and sanitation.

4. Epoxy flooring provides a durable and readily cleanable surface. However, the subsurface finish is extremely important.

## 3. Ceilings:

Suspended ceilings may be provided in office areas, laboratories, toilets, and cafeterias. They usually consist of lay-in acoustical panels of nonbrittle, nonfriable, nonasbestos, and noncombustible material.

Manufacturing areas require a smooth finish, often of seamless plaster or gypsum board. All ceiling fixtures such as light fittings, air outlets and returns, PA system, and sprinkler heads should be designed to assure ease of cleaning and to minimize the potential for accumulation of dust.

### 4. Services:

In the building design, provisions must be made for drains, water, steam, electricity, and other services to allow for ease of maintenance. Access should, ideally, be possible without disruption of activity within the actual rooms provided with the services.

**Some general guidelines and some specific guidelines for specific areas are given below which will be helpful in preparing layout, designing and construction of buildings.**

## Ancillary areas

There are certain ancillary areas in manufacturing unit. Salient of them are:

- Rest and refreshment rooms
- Change rooms
- Toilets
- Maintenance of work shop
- Animal homes

1. Rest and refreshment rooms should be separate from manufacturing and control areas. These could be located in the administrative wing or on the top floor.

2. Facilities for changing clothes and storing used clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users.

3. Toilets should not communicate directly with production or storage areas.

4. If there are maintenance workshops, these should be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

5. Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

## Storage areas

Various categories of materials are required to be stored in a pharmaceutical manufacturing unit. Categories of material which need special attention are:

- Starting materials
- Packaging materials
- Intermediates
- Bulk finished products
- Finished products

- Products in quarantine
- Released materials/products
- Rejected materials/products
- Returned products
- Recalled products

Sufficient space should be provided for different categories of materials. These areas should be maintained clean and dry. Where these should be provided, checked and monitored.

Materials like narcotics, highly active materials and materials presenting special risk to abuse, fire or explosion should be stored o safe and secure areas. These materials should be handled in accordance with the provisions of the legislation, if any.

1. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.

2. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, controlled, monitored and recorded where appropriate.

3. Receiving and dispatch bays should be separated and should covered to protect materials and products from the weather.

4. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned, if necessary, before storage.

5. Areas meant for materials of quarantine status should be segregated and clearly marked. Entry to these areas should be restricted only to authorized personnel.

6. Segregation should be provided for the storage of rejected, recalled, or returned materials or products.

7. Highly active and radioactive materials, narcotics, other dangerous medicines, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.

8. Printed packaging materials are considered critical to the conformity of the pharmaceutical product and there should be safe and secure areas for storage of printed packaging materials like labels, carton, package inserts.

9. There shall be a separate sampling area in the warehousing area for active raw materials and excipients. In case, separate area for sampling has not been provided and sampling is to be done in storage area, it should be conducted in such a way as to prevent contamination, cross-contamination and mix-up.

10. Appropriate racks (e.g. slotted angle iron racks), wooden platform etc. should be provided in sttorage areas, so that materials are stored off the floor and away from walls. Plastic pallets are avilable in the market to keep goods off the floor.

11. Appropriate monitoring devices (e.g. thermometers for temperature, hygrometer for humidity) should be provided in storage areas where materials requiring special storage conditions are to be stored.

12. Adequate material handling equipments should be provided in storage areas.

## Weighing areas

1. The weighing of starting materials and the estimation of yield by weighing should be carried out in separate weighing areas designed for that use, because weighing operations can produce dust and floating dust can contaminate other materials.

2. Weighing operations are usually carried out in storage areas and production areas. Sensitizing materials can be weighed in dedicated facilities meant for such materials.

## Production areas

Multiple operations are carried out in production areas. This provides scope for cross contamination. Following are the guidelines to be followed when designing a manufacturing area.

1. In order to minimize the risk of a serious medical hazard due to cross contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. live microorganisms).

   The production of certain other highly active products, such as some antibiotics, hormones, cytotoxic substances and certain non-pharmaceutical products, should not be conducted in the same facilities. In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made.

   The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.

2. Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3. The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between

different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

4. Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth and free from cracks and open joints, should not shed particulate matter, and should permit easy and effective cleaning and, if necessary, disinfection.

5. Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

6. Drains should be of adequate size and designed and equipped to prevent back-flow. Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and disinfection.

7. Production areas should be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination, and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas should be regularly monitored during both production and non-production periods to ensure compliance with their design specifications.

8. Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix ups, contamination or cross-contamination.

9. Production areas should be well lit, particularly where visual online controls are carried out.

## Quality control areas

Like production areas, quality control areas also have some features that should be taken into consideration while designing and constructing. These include:

1. QC laboratories should be separated from production areas.

2. Different types of testing i.e. chemical, instrumental, microbiological and biological should be physically separated from each other.

3. QC laboratories should be designed to suit the operations to be carried out in them.

4. Sufficient space should be given to avoid mix ups and cross contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records.

5. Certain materials may require controlled conditions for storage, for example, reference standards, microbial cultures. For storage of such materials appropriate storage facilities should be provided. (e.g. refrigerated).

6. Certain work benches where corrosive materials like acids are used have acid-proof topds.

7. If the quality control laboratory is engaged in the testing of specialized products like radioisotopes, preparations either containing live pathogenic microorganisms or requiring use of live pathogenic microorganism in testing, dedicated facilities should be provided and appropriate precautions should be taken.

8. Sufficient space should be provided in the quality control laboratories for installation of equipment, instruments and movement of mean and materials. Crowding should be avoided as it has potential for mix-ups and contamination.

9. Adequate attention should be paid to light and ventilation in different laboratories. There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological and radioisotope laboratories.

10. Appropriate exhaust systems are required for removing laboratory fumes. Operation with excess fumes, fuming cupboards should be constructed with powerful exhausts.

11. A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors, or where it is necessary to isolate the instruments.

12. All laboratory room should be supplied with running water, drainage, electricity and gas. Water supply should be of adequate pressure (not less than 10 kpa or 20 $N/cm^2$) so that vacuum aspirators can be used. If water supply is scarce, suitable vacuum pumps should be installed.

## Sanitation

a) Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition. Any such building shall be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.

b) There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.

c) There shall be written procedures for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers,

closures, packaging, labeling materials, or drug products and shall be followed. Rodenticides, insecticides, and fungicides shall not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act.

d) Sanitation procedures shall apply to work performed by contractors or temporary employees as well as to work performed by full-time employees during the ordinary course of operations.

## Utilities and maintenance of sterile areas

- Plant services, systems and utilities requirements include the following:
  - Lighting
  - Pluming
  - Sewage and refuse
  - Washing and toilet facilities
  - Eating facilities
  - Water (of various grades)
  - Steam
  - Heating, ventilation, and air conditioning (HVAC).
  - Compressed air
  - Vacuum
  - Electricity
  - Bulk solvent and other bulk liquid supply systems
  - Lubrication services

### 1. Light

Adequate lighting in pharmaceutical unit is necessary. Without adequate light workers can not carry out their work satisfactorily. If the work area has too little light, it will cause eye strain and fatigue particularly when detailed work is to be performed. Too much light is also not desirable as it can cause glare and dazzle.

Where possible daylight is preferable to artificial light because eye is more accustomed to natural light but more often than not, artificial light is used.

For adequate lighting, points that should be kept in mind are

(i) position of source of light

(ii) Selection of tubes or bulbs

(iii) Intensity of light – The minimum recommended intensity of light is 500 lux. For detailed work an intensity of 1000 lux is recommended. Intensity of the light can be measured with the help of Lux meter.

Special lighting for some operations, such as inspection of filled vials. Once the light levels have been defined, it is necessary that they be measured periodically and the results recorded.

## 2. Pluming

- Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the Environmental Protection Agency's (EPA's) Primary Drinking Water Regulations set forth in 40 CFR Part 141. Water not meeting such standards shall not be permitted in the potable water system.

- Drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent back-flow.

## 3. Sewage and Refuse

Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.

A pharmaceutical plant may consider disposal in several different ways.

**a. Product Disposal:** Any product requiring disposal should initially be separated from its packaging if appropriate. For example, any product to be disposed of in an approved landfill site should not be left in impermeable glass, plastic, or other containers, which would significantly delay destruction.
There are risks associated with the destruction of products—potential for the product to get diverted, legitimately or otherwise, during the disposal sequence and contamination of groundwater.

**b. Printed Packaging Disposal:** The disposal of printed packaging components including labels, inserts, and cartons poses no health risk. However, ineffective disposal, such as into public landfill, can give rise to public concern that product may be associated with the packaging.

**c. General Trash and Sewage:** Normal local services will usually be adequate for trash and sewage. However, internal procedures should be sufficiently rigorous and monitored, to ensure that product and packaging waste do not get intermixed. Containers used within the plant to accumulate waste materials should be clearly marked to denote their designated use.

## 4. Washing and toilet facilities

Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas.

These require toilet rooms to be separate for each gender except where individual locked toilet rooms are available and also define the minimum number of water closets based on the number of users.

## 5. Eating facilities

- Eating and drinking are permitted only in separate eating facilities, well segregated from all production areas. Smoking is now usually prohibited in manufacturing building.
- Prominent signs indicating these rules are posted at entrances to production areas.
- Enforcement procedures against violators are taken by management.
- Permanent facilities for breaks and people bringing lunches are required. Cafeterias serving hot meals are ideal to reduce the amount of food, a potential contamination source, being brought into the plant.

## 6. Water Systems

Water is used for different purposes in a pharmaceutical unit e.g. drinking, cleaning, processing of pharmaceutical etc. Water because of its polarity and hydrogen bonds can dissolve, absorb or suspend different compounds including contaminants. Therefore, quality of water is a matter of concern.

Apart from this, water promotes bacterial growth. Because of this, microbiological quality of water is also a concern.

**a. Drinking Water:** Drinking water is supplied by local bodies like municipal corporation or own tube well of industry. Water may have different contaminants, like ions organics, silica, gases, non-living suspended particles and living suspended particles. Hardness of that water should be maintained to make it drinking or potable water.

**b. Purified water:** Water is an important vehicle and is used extensively in liquid preparations. Almost all the pharmacopoeias prescribe standards for purified water (PW) and water for injection (WFI).

Water purification can be done by treating drinking water. Different processes that are used include:

- De-ionization
- Reverse osmosis
- distillation

## 7. Steam

Possible uses of steam include:

- General factory heating.
- Production process heating (steam-jacketed vessels, heating coils)
- Steam cleaning.
- Sterilization (autoclaving, “live-steaming” of vessels and pipes, sterilization in place [SIP].

Where steam is not associated with product manufacture, and does not come into contact with product or manufacturing materials (or with surfaces that will contact product or materials), then

the steam should be of such a quality that, when condensed, the water thus produced would comply with the requirements for purified water.

When used as the sterilizing medium (e.g., in autoclaves, SIP systems) the steam should be clean steam. That is, steam that, when condensed, will form water for injections quality water.

## 8. Heating, Ventilation and Air conditioning (HVAC) system

## Guidelines:

**a)** Adequate ventilation shall be provided.

**b)** Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.

**c)** Air filtration systems, including pre-filters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.

**d)** Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use.

Ambient air may have different contaminants, the most common being the dust. Dust can be roughly classified by size.

- Coarse dust (particle size 50 to 500 µ) – settles rapidly
- Fine dust (particle size 1.0 to 50 µ) – settles slowly
- Ultrafine dust (particle size 0.5 to 1 µ) – remains constantly suspended

Normally bacteria settles themselves on dust particles. Environment is one of the sources which can cause bacterial contamination.

Extremes of weather may have a very high or low temperature. For proper working, a comfortable temperature is required. For this reason, air may either be required to be heated or cooled. Therefore air handling systems are often called HVAC systems.

Ingress or ambient air can be prevented by creating barriers by providing air-locks. But sometimes air-locks may not be sufficient. Air will be required to be filtered to bring down particulate matter. Depending upon pore size of filter, particulate, matter can be contained & this has emerged as clean room concept.

**Four grades of clean areas are distinguished as given below for the manufacture of sterile pharmaceutical products.**

| GRADE | Operations to be carried out |
|---|---|
| A | Local zone for high risk operation (e.g. filling and making aseptic condition) |
| B | In aseptic preparation and filling (this is background environment for Grade A zone) |
| C & D | Clean areas for carrying out less critical steps in the manufacture of sterile products or carrying out such activities in which the product is not directly exposed. |

**Air-handling systems should consider the following factors.**

- Placement of air inlet and outlet ports. These should be sited to minimize the entry of airborne particulates or odors from the surrounding areas. Outlets should not be sited near inlets.
- Where recirculation of air is acceptable, adequate precautions must be taken to ensure that particulates from a processing area are removed. This will usually require an alarm system or an automatic cutoff in the event that a filter develops a hole. Dust extraction systems should be provided, where appropriate, to further minimize this potential problem.
- The degree of filtration and the air volumes should be matched to the operations involved.
- Temperature and humidity conditions should provide personnel comfort, which will enhance employee performance.
- Where differential pressures are required between adjacent areas, suitable monitoring equipment must be provided. For example, solids manufacturing areas are usually maintained at a negative pressure in relation to adjacent rooms and corridors in order to minimize the possibility of dust migration to these other areas.
- The siting of final air filters close to each room being serviced eliminates concerns regarding the possibility of small leaks in the air duct system. Air usually enters rooms near the ceiling and leaves from the opposite side near the floor.

## Maintenance in Sterile area

Sterile products, being very critical and sensitive in nature, a very high degree of precautions, prevention and preparations are needed.

Dampness, dirt and darkness are to be avoided to ensure aseptic conditions in all areas. There shall be strict compliance in the prescribed standards especially in the matter of supply of water, air, active materials and in the maintenance of hygienic environment.

## Buildings and Civil Works

1. The building shall be built on proper foundation with standardized materials to avoid cracks in critical areas like aseptic solution preparation, filling and sealing rooms.

2. Location of services like water, steam, gases etc. shall be such that their servicing or repair shall not pose any threat to the integrity of the facility. Water lines shall not pose any threat of leakage to aseptic area.

3. The manufacturing areas shall be clearly separated into support areas (e.g. washing and component preparation areas, storage areas etc.), preparation areas (e.g. bulk manufacturing area, non-aseptic blending areas etc.) change areas and aseptic areas.

   Operations like removal of outer cardboard wrappings of primary packaging materials shall be done in the de-cartoning areas which are segregated from the washing areas. Wooden pallets, fiber board drums, cardboard and other particle shedding materials shall not be taken inside the preparation areas.

4. In aseptic areas –

   a) Walls, floors and ceiling should be impervious, non-shedding, nonflaking and non-cracking. Flooring should be unbroken and provided with a cove both at the junction between the wall and the floor as well as the wall and the celling;

   b) Walls shall be flat, and ledges and recesses shall be avoided. Wherever other surfaces join the wall (e.g. sterilisers, electric sockets, gas points etc.) these shall be flush with the walls. Walls shall be provided with a cove at the joint between the ceiling and floor;

   c) Celling shall be solid and joints shall be sealed. Light-fittings and air-grills shall be flush with the walls and not hanging from the ceiling, so as to prevent contamination;

   d) there shall be no sinks and drains in Grade A and Grade B areas;

   e) Doors shall be made of non-shedding material. These may be made preferably of Aluminium or Steel material. Wooden doors shall not be used. Doors shall open towards the higher-pressure area so that they close automatically due to air pressure. ;

   f) Windows shall be made of similar material as the doors, preferably with double panel and shall be flush with the walls. If fire escapes are to be provided, these shall be suitably fastened to the walls without any gaps;

   g) the furniture used shall be smooth, washable and made of stainless steel or any other appropriate material other than wood.

5. The manufacturing and the support areas shall have the same quality of civil structure described above for aseptic areas, except the environmental standards which may vary in the critical areas.

6. There should be three air-locks before entering production area. The final or third air-lock should have the same class of clean air as the room to which it gives entry. Separate exit space from the aseptic areas is advisable.

   Change rooms to the aseptic areas shall be clearly demarcated into 'black', 'gray' and 'white rooms' with different levels of activity and air cleanliness. The 'black' change room shall be provided with a hand-washing sink.

   The sink and its drain in the unclassified (first) change rooms may be kept clean all the time. The specially designed drain shall be periodically monitored to avoid presence of pathogenic micro-organisms.

   Sliding doors are undesirable for this reason in clean areas. Change room doors shall not be opened simultaneously. An appropriate inter-locking system and a visual and/ or audible warning system may be installed to prevent the opening of more than one door at a time.

7. For communication between aseptic areas and non-aseptic areas, intercom telephones or speak-phones shall be used. These shall be minimum in number.

8. Material transfer between aseptic areas and outside shall be through suitable air-locks or pass-boxes. Doors of such air-locks and pass-boxes shall have suitable interlocking arrangements.

9. There should be a minimum number of projecting ledges, shelves and cup boards.

10. Personal welfare areas like rest rooms, tea room, canteen and toilets shall be outside and separated from the sterile product manufacturing area.

11. Animal houses shall be away from the sterile product manufacturing area and shall not share a common entrance or air handling system with the manufacturing area.

## Air Handling System (Central Air-Conditioning)

- Air Handling Units for sterile product manufacturing areas shall be different from those for other areas. Critical areas, such as the aseptic filling area, sterilized components unloading area and change rooms conforming to Grades B, C and D respectively shall have separate Air Handling Units. The filter configuration in the air handling system shall be suitably designed to achieve the Grade of air as given in Table I. Typical operational activities for clean areas are highlighted in Table II and Table III.

- For products which are filled aseptically, the filling room shall meet Grade B conditions at rest unmanned. This condition shall also be obtained within a period of about 30 minutes of the personnel leaving the room after completion of operations.

- The filling operations shall take place under Grade A conditions which shall be demonstrated under working of simulated conditions which shall be achieved by providing Laminar Air flow work stations with suitable HEPA filters or isolator technology.

- For products, which are terminally sterilized, the filling room shall meet Grade C conditions at rest. This condition shall be obtainable within a period of about 30 minutes of the personnel leaving the room after completion of operations.

- Manufacturing and component preparation areas shall meet Grade C conditions.

- After completion of preparation, washed components and vessels shall be protected with "Grade D background and should be handled in such a way that they are not re-contaminated".

- The minimum air changes for Grade B and Grade C areas shall not be less than 20 air changes per hour in a room with good air flow pattern and appropriate HEPA filters. For Grade A Laminar Air Flow work stations, the air flow rates shall be 0.3 meter per second ± 20 % (for vertical flows) and 0.45 meter per second ± 20 % (for horizontal flows).

- Differential pressures between areas of different environmental standards shall be at least 15 Pascal (0.06 inches or 1.5 mm water gauge). Suitable manometers or gauges shall be installed to measure and verify pressure differential.

- The final change rooms shall have the same class of air as specified for the aseptic area. The pressure differentials in the change rooms shall be in the descending order from 'white' to 'black'.

- Unless there are product specific requirements, temperature and humidity in the aseptic areas "shall be 27 ± 2 °C and relative humidity 55 % ± 2, respectively".

**TABLE I: The Air Borne Particulate Classification for Manufacture of Sterile Products**

| Grade | **At rest (b)** | | **In operation (a)** | |
|---|---|---|---|---|
| | **Maximum number of permitted particles per cubic meter equal to or above** | | | |
| | **0. 5 µm** | **5 µm** | **0. 5 µm** | **5 µm** |
| A | 3500 | 0 | 3500 | 0 |
| B (a) | 3500 | 0 | 3,50,000 | 2,000 |
| C (a) | 3,50,000 | 2,000 | 3,50,000 | 2,000 |
| D (a) | 3,50,000 | 2,000 | Not Defined (c) | Not Defined (c) |

**TABLE II: Types of Operations to be Carried out in The Various Grades for Aseptic Preparations**

| **Grade** | **Types of operations for aseptic preparations.** |
|---|---|

| | |
|---|---|
| **A** | Aseptic preparation and filling. |
| **B** | Background room conditions for activities requiring Grade A. |
| **C** | Preparation of solution to be filtered. |
| **D** | Handling of components after washing. |

**TABLE III: Types of Operations to be Carried Out in the Various Grades for Terminally Sterilized Products**

| Grade | Types of operations for terminally sterilized products. |
|---|---|
| **A** | Filling of products, which are usually at risk. |
| **C** | Placement of filling and sealing machines, preparation of solutions, when unusually at risk. Filling of product when unusually at risk. |
| **D** | Moulding, blowing (pre-forming) operations of plastic containers, Preparations of solutions and components for subsequent filling. |

**Environmental Monitoring**

The recommended frequencies of periodic monitoring shall be as follows:

- ✓ Particulate monitoring in air – 6 monthly.
- ✓ HEPA filter integrity testing (smoke testing) – Yearly
- ✓ Air change rates – 6 monthly
- ✓ Air pressure differential – Daily
- ✓ Temperature and humidity – Daily
- ✓ Microbiological monitoring by settle plate and/or swabs in aseptic areas – Daily, and at decreased frequency in other areas

It has been further recommended that there shall be written environmental monitoring program and microbiological results shall be recorded. Recommended limits of microbiological monitoring of clean areas: "in operation" have been given in the table.

| Grade | Air Sample ($cfu/m^3$) | Settle Plates (dia 90 mm) Cfu/2 hrs | Contact plates (dia 55 mm) cfu per plate | Glove points (five fiinger) Cfu per glove |
|---|---|---|---|---|
| **A** | <1 | <1 | <1 | <1 |
| **B** | 10 | 5 | 5 | 5 |
| **C** | 100 | 50 | 25 | - |
| **D** | 500 | 100 | 50 | - |

**Guidelines for manufacturing sterile products:**

- In isolators & glove boxes, unidirectional air flow and lower velocities may be used.
- Leakage test in installed HEPA filters should be carried out in accordance with ISO 14644-3.
- Clean rooms & Clean-air devices should be routinely monitored which in operation.
- At critical location, airborne particles should be monitored periodically "in operation" in addition to "at rest" status.
- Preparations of solutions to be filtered through bacteria retaining filters should be done in Grade C environment.
- Water sources, water treatment equipment and treated water should be monitored regularly for chemical, biological contamination with endotoxins to ensure compliance of water for specifications.
- Presence of containers and other materials liable to generate fibers should be minimized in clean areas and should be avoided completely in case of aseptic processing.

**Guidelines related to personnel working in sterile area:**

Personnel required to work in sterile areas should be selected with care and should be such who can be relied upon to observe appropriate disciplines. The other points related to personnel required to work in sterile areas are:

- As personnel clothing may shed particulate matter, only the minimum number of persons should be present in sterile areas.
- Training of personnel required to work in sterile areas including those concerned with cleaning and maintenance is necessary. There should be a regular training programme.
- Nowadays many drugs are manufactured using animal tissue cultures or microbial cultures. The person who have been processing cultures other than those being processed in sterile area should not enter the area without having undergone laid down decontamination procedure.
- Persons required to work in sterile area should be instructed to observe high degree of personal hygiene.
- Outdoor clothing should not be brought into clean areas. Person required to work in sterile area should change their outdoor clothing in general change room and put on standard factory protective garments and then should go to the change rooms preceding sterile areas and follow written procedure for washing and changing clothes.

- The persons required to work in sterile areas should be instructed not to use cosmetics that can shed particles. They should be instructed not to wear wrist watches and jewellery.

**Sanitation**

Clean areas should be cleaned frequently and thoroughly as per cleaning schedule and SOPs.

Fumigation of clean areas is useful in reducing microbiological contamination. Formaldehyde is the most commonly used stirilient for fumigation of clean areas, it may be used as spray or vaporous may be liberated by heating formaldehyde solution in order to prevent polymerization of formaldehyde in droplets in air and after deposition on surfaces.

Other than formaldehyde other disinfectants are also used which are given below:

i. Chlorine containing compounds (e.g sod. Hypochlorite)
ii. Alcohols (iso propyl alcohols)
iii. Iodine containing compounds (iodophores)
iv. Quaternary ammonium compounds (Cetrimide)
v. Aldehydes (Alkaline glutaraldehyde)
vi. Peroxides (hydrogen peroxide)
vii. Phenols (LPH)

## Control of Cross-contamination

**Precautions against mix-up and cross-contamination**

- The licensee shall prevent mix-up and cross-contamination of drug material and drug product (from environmental dust) by proper air-handling system, pressure differential, segregation, status labeling and cleaning. Proper records and Standard Operating Procedures thereof shall be maintained.

- The licensee shall ensure processing of sensitive drugs like Beta-Lactum antibiotics, sex hormones and cytotoxic substances in segregated areas or isolated production areas within the building with independent air-handling unit and proper pressure differential. The effective segregation of these areas shall be demonstrated with adequate records of maintenance and services.

- To prevent mix-ups during production stages, materials under process shall be conspicuously labeled to demonstrate their status. All equipment used for production shall be labeled with their current status.

- Packaging lines shall be independent and adequately segregated. It shall be ensured that all left-overs of the previous packaging operations, including labels, cartons and caps are cleared before the closing hour.

- Before packaging operations are begun, steps shall be taken to ensure that the work area, packaging lines, printing machines, and other equipment are clean and free from any products, materials and spillages. The line clearance shall be performed according to an approximate check-list and recorded.

- The correct details of any printing (for example of batch numbers or expiry dates) done separately or in the course of the packaging shall be rechecked at regular intervals. All printing and overprinting shall be authorized in writing.

- The manufacturing environment shall be maintained at the required levels of temperature, humidity and cleanliness.

- Authorised persons shall ensure change-over into specific uniforms before undertaking any manufacturing operations including packaging.

- There shall be segregated enclosed areas, secured for recalled or rejected material and for such materials which are to e reprocessed or recovered.