# PREMISES

# DESIGN, CONSTRUCTION AND PLANT LAYOUT

## - LOCATION, SURROUNDINGS AND GENERAL REQUIREMENTS

- Any building used in the manufacture, processing, packaging or holding of drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, manufacturing and proper operation.
- The factory building used for manufacturing of drug product shall be so situated and shall have such measures to avoid the risk of contamination from external environment including open sewage, drain, public lavatory or any other factory producing disagreeable or harmful fumes, odour, dust and smoke, chemical or biological emission.
- The Premises/ building used for factory shall be designed, constructed, adapted or maintained to suit the manufacturing and other operations so as to permit production of drugs under hygienic conditions.
- The premises/ building shall conform to all conditions laid down in Factories act 1948.
- The premises used for manufacturing, processing, warehousing, packaging, labelling and testing should be compatible with manufacturing operations carried out in same area.
- Adequate space should be provided for logical and orderly placement of equipments and free movement of staff to avoid the risk of cross contamination.
- The premises /building should be designed and constructed to prevent the entry of insects, birds, rodents etc.
- HVAC system should be there where it is required (For environmental monitoring).
- Proper drainage and waste disposal system should be there and the system should be designed to avoid the back- flow and entry of rodents and insects to the manufacturing areas.
- The walls and floors of the areas should be free from cracks to avoid dust accumulation.
- The walls and floors should be smooth and washable to facilitate ease of cleaning in the areas.
- Premises should be carefully maintained and it should be ensured that repair and maintenance operations do not prevent any hazard to the quality of the products.
- Premises should be cleaned and where applicable disinfected according to the written standard operating procedures.
- Electric supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect directly or indirectly either the

pharmaceutical product during their manufacturing and storage of the accurate functioning of the equipment.

**Some principle areas of premises**

**1. Ancillary areas:** Ancillary areas covers:

- Rest and Refreshment rooms.
- Toilets and Washrooms.
- Clothes storage areas.
- Changing rooms for employees.
- Rest and Refreshment Rooms should be separate from other areas.
- Facilities for Toilets should not communicate directly with production or storage areas.
- Areas for change rooms and storage of clothes and for washing, and toilet purpose should be easily accessible and appropriate for the number of users.

**2. Warehousing Areas**

- Storage areas should have sufficient capacity to allow orderly storage of the various categories of materials and products like:

i. Raw materials.
ii. Packaging Materials.
iii. Intermediates.
iv. Bulk and finished products.
v. Products in quarantine.
vi. Released, returned, rejected and recalled products.

- Storage areas should be designed to meet the required environmental conditions like: Temperature and Humidity and Records of such environmental conditions monitoring should be maintained.
- Separate sampling areas should be provided for active and raw materials, Such sampling cubicles may be designed with suitable size and also provided with cleaning, drying and storage for sampling tools.
- Sampling of liquid materials, solvents, flammable materials or toxic, poisons or potent materials should be done in separate areas with taking all the necessary precautions for Safety of people and materials both.
- All returned, rejected and recalled materials must be stored in lock and key and necessary precaution should
- Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling and special attention should be paid to the safe and secure storage these materials.
- Dispensing areas should be separate for active and raw materials.

**3. Production Areas**

- General category products (other than antibiotics, cytotoxic and hormones,) should be manufactured in separate manufacturing facilities.
- Highly potent, sensitive or live micro-organism etc. should be produced in separate areas to avoid cross contamination.
- Premises should be designed to have logical flow of materials, well organized layout of plant and machinery and ease of cleaning, both equipment and facility.
- Depending on the volumes of materials being handled, adequate space should be provided to avoid mix-ups.
- Production areas should be effectively ventilated with suitable designed HVAC system appropriate to products being handled; to the operations undertaken and to the external environment.
- Production areas should be regularly monitored during production and non-production periods to ensure compliance with their design specifications.
- Premises for packaging of pharmaceuticals should be specifically designed and out so as to avoid mix-up and cross contamination.

**4. Quality Control Areas**

- Q.C. laboratories should be separate from production areas.
- Areas where biological, microbiological, or radio isotope test methods are employed should be separate from each other.
- Q.C. laboratories should be designed to provide facilities for:

i. chemical analysis
ii. Instrumental analysis.
iii. Microbiological and biological analysis etc.
iv. Storage for control samples, glassware's, chemicals, microbiological media books, documents etc.
v. A separate room or area should be provided where highly sensitive instruments area handled to protect them from electrical interference, vibration, contact with excessive moisture, and other external factors.

**- Drainage system**

- Potable water shall be supplied under continuous pressure in a plumbing system free of defects that could contribute contamination to any drug product.
- Water not meeting such standards of regulatory guidelines shall not be permitted in the potable water system.
- Drains shall be of adequate size.

- Drainage should be connected directly to the sewer and it should be provided with an air break or other mechanical devices to prevent back Spoilage.
- Drainage system maintenance in the manufacturing facilities is very critical from the Point of view of cleaning and sanitation of the facilities.
- A detailed SOP should be there for cleaning and sanitation of drains and their records should be maintained and reviewed periodically.

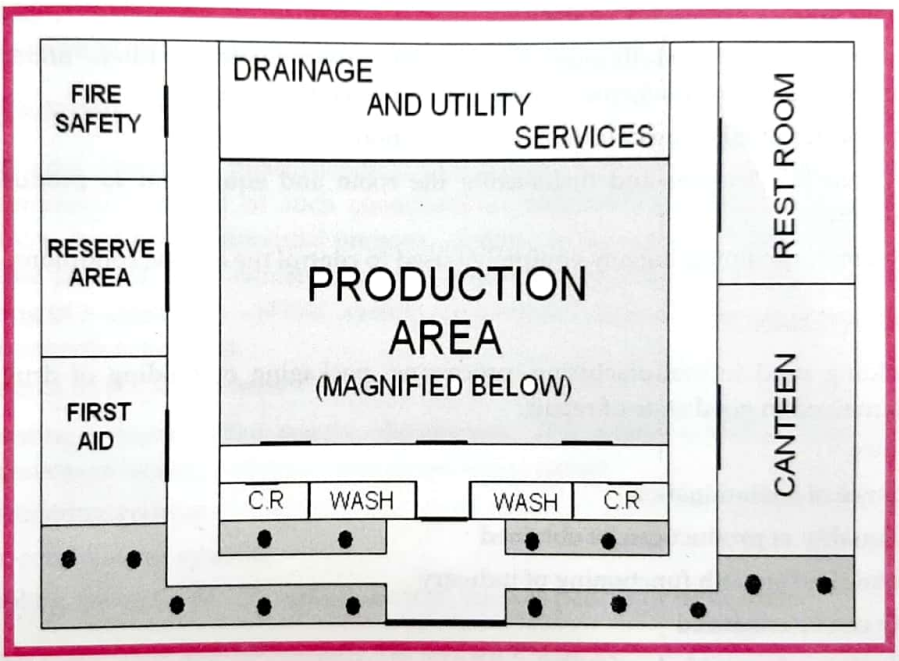


**Fig: Simple Layout of Pharmaceutical Industrty**

**- Disposal of Waste**

- Sewage, waste and biomedical waste in and from the building premises shall be disposed of in a safe and sanitary manner according to the laws.
- The disposal of sewage and effluents (solid, liquid, and gas) from the manufacturing premises should be done in conformity with the requirements of the Environment Pollution Control Board.
- All biomedical waste shall be destroyed as per the provision of Bio-Medical Waste and Handling) Rules, 1996.
- Additional precautions shall be taken for the storage and disposal of rejected drugs/ materials and all the Records shall be maintained for disposal of waste.
- Provisions shall be made for proper and safe storage of waste materials awaiting disposal.

- 'Hazardous, harmful, toxic substances and inflammable materials shall be stored in suitably designed and separate enclosed areas in conformity with Central and State Legislation.
- Records of all disposed material must be kept and should be available for inspection or audit when required.

## MAINTENANCE

- Any building, premises used in the manufacture, processing, packing or storage of a drug product shall be in a good state of repair.
- Facility maintenance includes maintenance of following things:

i. Leakage from ceiling or other surfaces.
ii Leakages from pipe lines of waters, steam, gases etc.
iii. Plumbing problems.
iv. Loose or broken tiles.
v. Improper closing of doors, windows.
vi. Improper electrical wiring
vii Improper electrical fittings/ fixtures.

- A detailed check list may be prepared for maintenance.
- During routine inspection of the facilities the deficiencies should be identified and corrected immediately and the facility must always be maintained in a state of good.
- Deterioration of building and facilities represents poor image of facilities and it can affect product quality.
- Cracks/ holes in walls, ceilings etc. can provide access to the rodents, insects, microorganisms and it can directly affect the quality of the product, sanitation and hygiene.
- Roof leakage can affect the quality of materials and may cause damage to the equipments.
- Hence all the facilities should be checked regularly and maintained and records related to it should be maintained.

## SANITATION

- "Any building/premises used in the manufacture, processing, packing or holding o a drug product shall be maintained in a clean and sanitary condition".
- All the premises shall be free of infestation by rodents, birds, insects, and other vermin' (other than laboratory animals).
- 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 the cleaning the buildings and facilities; such written procedures shall be followed

- There shall be written procedures for use of suitable Rodenticides, insecticides, fumigating agents and cleaning and sanitising agents.
- Such written procedures shall be designed to prevent the contamination of equipment, components, drug product container and closures, packaging, labelling material or drug products and shall be followed.
- Rodenticides, insecticides, and fungicides shall not be used unless registered and used in accordance with the Federal Insecticides, Fungicides and Rodenticide Act.
- Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full time employee during the ordinary.
- SOPs should be available even for cleaning and sanitation of external areas of the facilities like roads, lawns etc.
- In pharmaceutical industries, operations have to be carried out in clean areas to avoid contamination, cleaning of areas, equipments and microbial monitoring, disinfection of areas and equipments are very important and have to be carried out regularly.
- In order to maintain sanitation and cleaning we have to consider following points

i. Create and maintain safe working environment.
ii. Remove dust and dirt which can affect product quality.
iii. Minimize the risk of cross-contamination occurring between products.
iv. Lastly, reduce the levels of microbial contamination.

## ENVIRONMENTAL CONTROL IN STERILE AREAS

Sterile products are very critical and sensitive in nature hence it requires very high degree of
precaution and prevention is required in its preparation and there shall be strict compliance with standards prescribed by regulatory authorities.

1. Air handling units for sterile product manufacturing shall be different from those of other areas.
2. Critical areas such as aseptic filling areas, sterilised components unloading areas and changing room should conform to grades B, C and D respectively and shall have separate "Air
handling units". The filter configuration in the Air handling unit shall be suitably designed to
achieve the grade of air as given in Table below:

**Air Borne particulate classification for manufacture of sterile areas:**

| Grade | At rest (b) | | | In operation (a) |
|---|---|---|---|---|
| | Maximum number permitted particles per cubic meter | | | |
| | 0.5µm | 5µm | 0.5µm | 5µm |
| A | 3520 | 29 | 3500 | 29 |
| B (a) | 35200 | 293 | 352000 | 2930 |
| C (a) | 352000 | 2930 | 3520000 | 29300 |
| D (a) | 3520000 | 29300 | Not Defined | Not Defined |

(Grade A: The local zone for high-risk operations. e g. filling. Grade B: In aseptic preparation and filling, Grades C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products or carrying out activities during which the product is not directly exposed)

3. For products which are filled aseptically, the filling room shall meet Grade B condition at rest.
4. The Filling operation shall take place under Grade A condition which shall be demonstrated
under working of simulated conditions which shall be achieved by providing Laminar air flow
work station with suitable HEPA Filters.
5. For products which are terminally sterilized, the filling room shall meet Grade C conditions.
6. Manufacturing and component preparation areas shall meet Grade C conditions.
7, After Completion of preparation, Washed components and vessels shall be protected With
Grade C background.
8. 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.
9. For Grade A Laminar air Flow work stations, the air flow rates shall be 0.3 meter per second (For Vertical air flow) and 0.45 meter per second (For Horizontal ail flow).
10. Differential pressure between areas of different environmental shall be at 15 Pascal (0.06 inches or 1.5 mm water gauge), Suitable manometers or gauges shall be installed to measure and verify pressure differential.

11. Unless there are product specific requirements, temperature and humidity in the aseptic
areas shall not exceed 27°C and 55% Relative Humidity respectively.
12. All the parameters listed above shall be verified and monitored at regular periodic intervals.
13. Recommended frequencies for Periodic monitoring shall be as follows:

- Particulate monitoring in Air : 6 monthly
- HEPA Filter integrity testing : Yearly
- Air Change Rates : 6 Monthly
- Air Pressure differential : Daily
- Temperature and Humidity : Daily
- Microbial monitoring : Daily

14. There shall be written environmental monitoring programs and Microbiological shall be recorded.
15. Recommended limits for microbiological monitoring of in operation clean areas is give in below Table :

**Recommended limits for microbiological monitoring of in operation clean areas**

| Grade | Air sample cfu / $m^3$ | Settle Plates (dia.90mm) cfu / 2 hrs | Contact Plates (dia.55mm) cfu per plate | Glove points (five fingers) cfu per layer |
|---|---|---|---|---|
| A | <1 | <1 | <1 | <1 |
| B | 10 | 5 | 5 | 5 |
| C | 100 | 50 | 25 | - |
| D | 500 | 100 | 50 | - |

(Cfu: Colony forming units)

16. Appropriate action shall be taken immediately if the result of the results of particulate and microbial count exceeds limit and all the necessary action should be done before production
commences.

## UTILITIES AND MAINTENANCE IN STERILE AREAS

- Sterile areas/ aseptic processing areas should have:

1. Smooth and easily cleanable Floors, 'Walls and Ceilings.
2. Temperature and humidity controls.
3. Air supply with HEPA filters under positive pressure.
4. Environmental conditions monitoring system.
5. A system for Cleaning and disinfecting to produce aseptic/ sterile conditions.

- Floors, walls and ceilings of sterile areas should be subjected to intensive and frequent cleaning and sanitation.
- Floors, walls and ceilings of sterile areas should be composed of smooth and hard surfaces with minimum joints and should be resistant to abrasion.
- Temperature and humidity in the sterile areas should be controlled and maintained according to operations performed (68°F temperature and 45% Relative Humidity is suitable).
- The air in sterile areas should be provided by air supply fitted with HEPA filters (less than 100 particles of 0.5 Micron with Not more than I Cfu/$cm^3$); air flow rate 90 feet/ minute is recommended.
- Sterile areas should have positive differential pressure related to adjoining areas and "Air pressure differentials should be monitored automatically.
- HEPA filters should be tested at regular intervals.
- Cleaning and disinfection of sterile areas, Facilities and equipments should be done regularly and procedure used for cleaning and disinfection must be validated with respect to both removal of previous product contamination and effective disinfection, disinfectant should be changed periodically to minimise the possibility of microbial resistance and residual amounts of disinfectant should be at low level.

## CONTROL OF CONTAMINATION IN STERILE AREAS

- There are two main Sources of Contamination i.e. Area/Facilities and People.

**1. Control of Contamination — Areas/Facilities**

i. In the areas/ Facilities where sterile products are manufactured air should be supplied under positive differential pressure with HEPA filters designed to keep Microorganisms and other particles at low level.

ii. In sterile areas all the surfaces of floors, walls, ceilings etc should be hard and free from cracks to avoid dust and microorganism accumulation and should permit easy cleaning.

iii. Access to sterile areas must be Controlled/ Restricted to people and entry and exit to sterile areas should be only permitted through change areas.

**2. Control of Contamination — People**

All the personnel working in aseptic/sterile areas should emphasize on following points to control the contamination:

i. Keep Body, hair, face, hands and nails clean.

ii. Report illness, injury, respiratory and skin problems. iii. Follow the written changing and wash-up procedures.

iii. Do not use cosmetic and wear jewellery and wrist watches.

iv. Do not take papers and documents in sterile area.

v. Avoid eating, chewing, drinking and smoking in sterile areas.

vi. Avoid coughing and sneezing (If it is unavoidable, please leave the sterile area).

vii. Use gloves and disinfect them regularly.

viii. Follow the written changing and wash-up procedures.

ix. Always check on worn and damaged garments.

x. Unless there is a special hazard, do not pick anything from floor.

xi. Keep talking to the minimum while working in sterile areas.

xii. Do not move vigorously, always move gently and steadily.

**3. Control of contamination by cleaning and disinfection**

i. The written procedures regarding Cleaning and disinfection should be followed exactly and
strictly.

ii. Before disinfection, it is necessary to clean the area completely.

iii. All the cleaning and disinfecting agents and materials themselves should be clean.

iv. Avoid cleaning by mops use equipments.

v. Use vacuum cleaners for sucking dust.

vi. Always start cleaning walls and ceiling from top to avoid recontamination.

vii. Special care should be taken for selecting right Cleaning and disinfecting agents in right dilution.

viii. All the equipments and accessories must be cleaned after used and stored in clean dry place.

ix. Split materials such as liquids, Powders should be cleaned in such a way to minimize the risk of further contamination and if there is a chance of contamination, clean and disinfect that place.