Industrial Pharmacy-I
Unit IV

Parenteral Products

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Contents

- **Production procedure**
- **Production facilities and controls**
- **Aseptic processing**

- **Product characteristics determine the provisions or facilities required in production area.**

- **Liquids or solutions are typically made from concentrates which are sterile filtered and then transform to a fill hold tank.**

- **From this tank the solution is pumped directly to the filling equipment.**

- **For small volume products, the actual filling tank is often manually carried directly into the filling suite, with appropriate sanitization.**

- **Powder filling areas must be maintained at relatively low humidity levels in order to prevent moisture absorption and thereby enhance powder flow through the filling equipments and in some cases to prevent degradation of the product itself.**

- **Relative humidity (RH) levels in powder filling rooms at 20% are fairly typical.**

- **Alternatively, a RH that is too low may enhance electrostatic problems with the powder.**

- **Dust control systems are absolutely necessary and provision will be necessary for frequent cleaning of the systems.**

- **Emulsion may require compounding areas close to filling lines to ease transfer problems.**
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- **Pumping systems will be very critical.**

- **Overhead gravity feed to filling might be desirable.**

- **Suspensions will require a means of maintaining a homogeneous mixture prior to filling.**

- **To minimize the time the suspension resides in the piping reservoir and pump system, filling rates should be kept high and the distance from compounding to filling should be minimized.**

Area Planning

- **The design of the parenteral plant should be such that it will arrange and combine all the processes which are required for processing out the product in a logical manner, which is achieved by area planning.**

- **Area planning is done by designing various processing areas which are adjacent or around to critical area in such a way that cleanliness is maintained.**

- **The goal of designer to group manufacturing operations in such way that the flow of the people, product and components proceeds in the direction of successive steps of increasing cleanliness.**

- **The flow of waste materials and products must be thoroughly separated from the flow of clean personnel and product in order to prevent contamination.**

- **In addition no two products may cross paths during the manufacturing operations.**

- **This control is achieved by the physical layout of the facility to achieve the required separation, as well as by the design of the HVAC systems serving the plant.**

Environmental control zones:

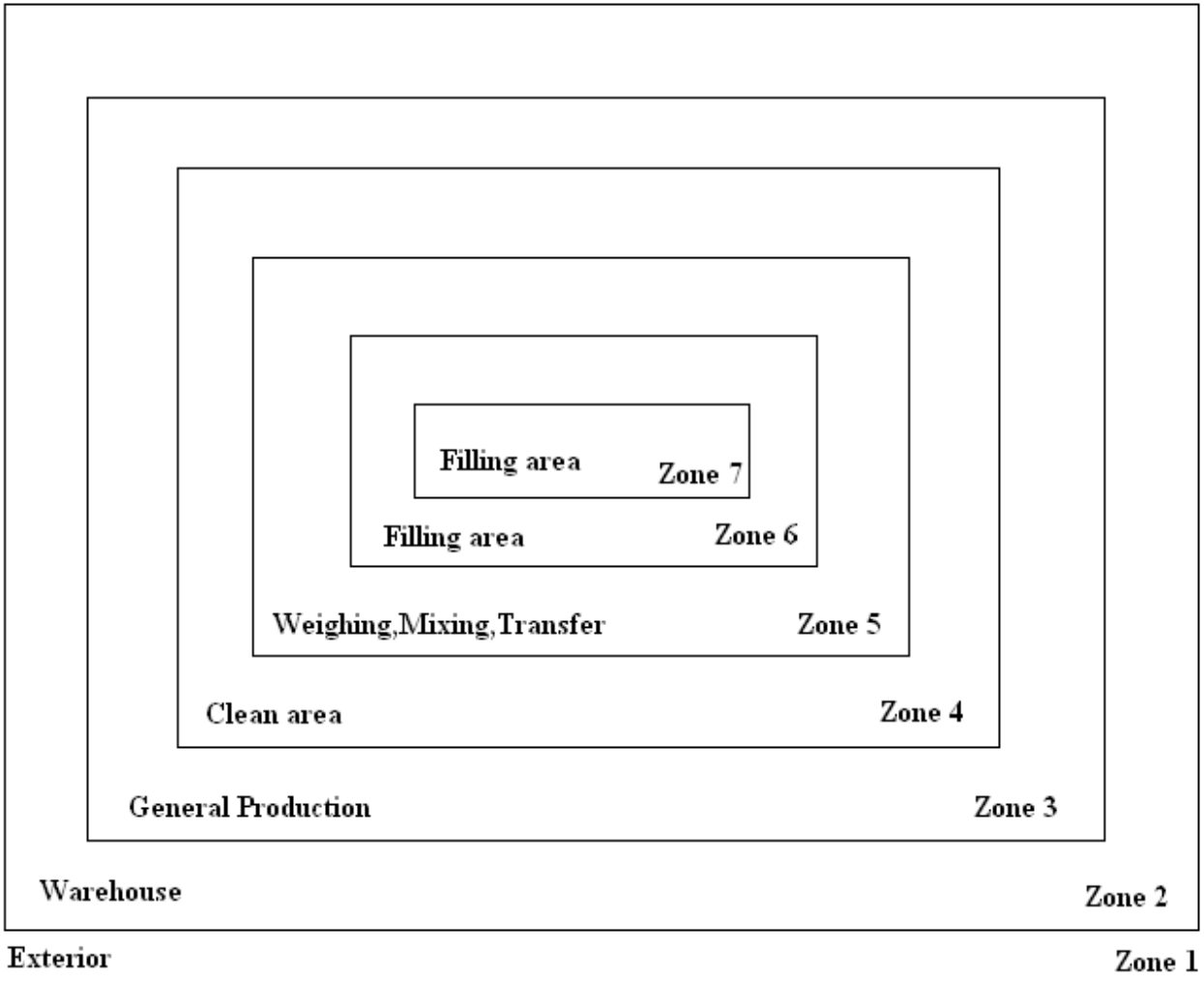


Fig: Enviromental control zones

- **Current Good Manufacturing Practices requires that the weighing, mixing or filling of large volume parenteral drug products and transfer operations shall be performed in specifically designed areas that shall meet the requirements for a controlled environment area.**

- **Air over filling areas and at microbiological testing sites shall have a per cubic foot particle count of NMT 100 in a size range of 0.5 micron and larger throughout the entire work area upstream of the work piece.**

- **From these environmental condition requirements emerge the first two of a series of cleanliness levels which provide together with the physical aspects of the facility, successive barriers to product contamination.**

- **These barriers from environmental control zones as illustrated in figure.**

Zone 1: Plant exterior

- **The environment within which the plant is located is the first environment control zone.**
- **Management actions to control zone 1 might include the maintainance of sterile areas around the facility where weeds, insects and rodents are controlled or eliminated.**

Zone 2: Warehousing

- **The second environmental control zone provides minimal protection for materials and products.**

Zone 3: general Production and administrative area

- **Openings into the area are usually well sealed and large enough only for essential material handling equipment and personnel.**
- **Windows are either absent or seal closed.**
- **Insects, crawling or flying and rodents must be absent, having been controlled in the general plant area.**
- **Air borne handling systems remove most airborne contamination in the visible range.**

Zone 4: Clean area

- **Production areas immediately preceding or following a controlled environment area in the production flow are often controlled as an area intermediate between a general production area and a controlled environment area.**

- **Air filters of slightly lower efficiency than HEPA filters per given room area, may be employed to control particulate contamination in the sub visible range. Some attempt is usually made to reduce or control the base microbiological load.**

Zone 5: Weighing, mixing and transfer area

- **Air handling systems are equipped with HEPA (high efficiency particulate air) filters capable of removing 99.97% of all particles over 0.3µm in size and have temperature and humidity control.**

- **Microbiological load is highly controlled or eliminated and special measures are taken to aid sanitation.**

Zone 6: Filling area

- **Zone 6 is a distinct zone of the controlled environmental area for an aseptic filling process.**
- **It is usually the most highly controlled environment created by a structural barrier in a parenteral facility.**
- **Air handling system requirements are the same as for zone 5, but for aseptic filling microbiological control is also specified.**

Zone 7: Filling line

- **The walls of the filling area are the last physical barrier to the ingress of contamination, but within the filling area a technique of contamination control known as laminar flow may be considered as the last barrier to contamination.**

Clean-in-place systems:

- **Clean-in-place systems are widely utilized in the pharmaceutical industry to ensure that equipment is free, both from contaminants and from the previously processed batch.**

- **These systems have traditionally been designed as recirculating systems i.e. the cleaning solution is reused for several applications.**

- **The main difference between the traditional systems and those used for biopharmaceutical manufacturing is the utilization of once through system i.e. cleaning solution is used only once and then discarded.**

- **This type of system ensures that any living organisms and other biological contaminants are not circulated through the operating facility.**

- **The solution is used to clean a piece of equipment and then is directed to the bio waste treatment system where any contaminates are destroyed prior to discharge.**

- **The type of cleaning solution for this system will depend on the products being manufactured and the materials remaining on the equipment and piping surfaces after the completion of manufacturing.**

- **CIP systems may consists of fixed or portable units.**

- **A problem with portable units is one of numbers and transport.**

- **If there are only one or two units in the facility, they may not be dedicated to a specific operating area and therefore must be transported between areas.**

- **This is not a recommended practice since the system will have to be decontaminated prior to entry into the various operating areas.**

- **Multiple systems can be provided to overcome this problem and the designer must weigh the cost and operating procedure of multiple portable systems as opposed to a fixed system, which conveys the cleaning solution to the needed area by way of a piping distribution system.**

- **Both systems are acceptable.**

- **The choice usually depends on initial and operating costs as well as the individual preference of the operating unit.**

While designing CIP system following factors must be considered

- **Time of cleaning solution exposure**
- **Temperature of cleaning solution**
- **Degree of turbulence of cleaning and rinse**
- **Solutions at the point of application**
- **Selection of cleaning agent**
- **Cleaning agent concentration &**
- **Characteristics of surface being cleaned.**

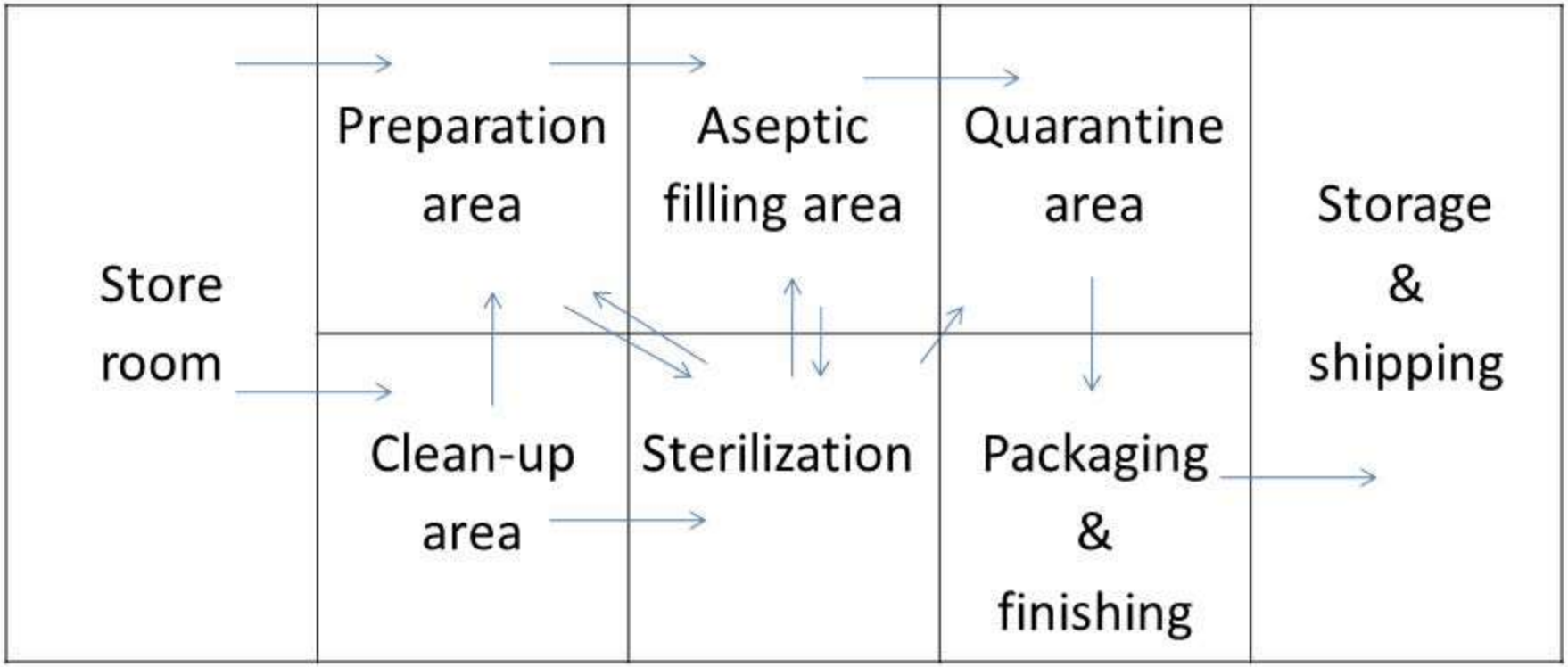
Steam-in-place sterilization (SIP)

- **SIP sterilization is a procedure whereby the entire processing system can be sterilized as a single entity thereby eliminating or reducing the need for aseptic conditions.**
- **Manufacturing tanks, filling lines, transfer lines, filtration systems, and WFI systems are currently being in this manner.**
- **All low points in the system are initially opened for complete elimination of air in the system.**
- **All condensate is removed as it forms to maintain sterilized condition.**

- **In SIP processes, it involves the introduction of a sterile gas (air or nitrogen) into the system, while the total system is still under positive steam pressure.**
- **The system must then be purged of steam and condensate and maintained under a slight positive pressure (2-3 psi) until ready for use.**
- **This may involve the addition of fittings or valves to the system to protect components and surfaces from microbial contamination until ready for use.**

- **The introduction of gas can also serve to dry the system prior to use, an issue of importance if the product to be introduced into the equipment is non-aqueous in nature.**
- **SIP is specialized form of CIP.**
- **With SIP, clean system is used to provide heat sterilization and/or decontamination to closed systems, such as process tanks and transfer piping.**
- **If the system to be steam cleaned is likely to contain significant contamination material a manual or CIP process must precede SIP sterilization.**

Process Flow Diagram



Production facilities and controls

The manufacture of parenteral preparation requires special precautions and facilities in order to maintain sterility and freedom from particulate matter. The production area where sterile parenteral preparations are manufactured can be divided into five sections:-

- Clean-up area
- Preparation area
- Aseptic area
- Quarantine area
- Finishing & packaging area

Clean-up area:

- It is not aseptic area.
- All the parenteral products must be free from foreign particles & microorganism.
- Clean-up area should be withstand moisture, dust & detergent.
- This area should be kept clean so that contaminants may not be carried out into aseptic area.

Preparation area:

- In this area the ingredients of the parenteral preparation are mixed & preparation is made for filling operation.
- It is not essentially aseptic area but strict precautions are required to prevent any contamination from outside.

Aseptic area:

- The parenteral preparations are filtered, filled into final container & sealed in aseptic area.
- The entry of personnel into aseptic area should be limited & through an air lock.
- Ceiling, wall & floor of that area should be sealed & painted.
- The air in the aseptic area should be free from fibers, dust and microorganism.
- The High efficiency particulate air filters (HEPA) is used for air.

- UV lamps are fitted in order to maintain sterility.

Quarantine area:

- After filling, sealing & sterilization the parenteral product are held up in quarantine area.
- Randomly samples were kept for evaluation.
- The batch or product pass the evaluation tests are transfer in to finishing or packaging area.

Finishing & packaging area:

- Parenteral products are properly labelled and packed.
- Properly packing is essential to provide protection against physical damage.
- The labelled container should be packed in cardboard or plastic container.
- Ampoules should be packed in partitioned boxes

Requirement for Design of Aseptic Area

- Aseptic techniques are defined as a set of procedures carried out to obtain an environment with minimal contamination from pathogenic microorganisms.
- These procedures are carried out under controlled conditions.
- The main goal of aseptic technique is to provide protection against infections.
- It also helps in controlling the spread of pathogens while other processes like cleaning, sanitation or disinfection are not efficient enough to prevent infection.

1. Site of Premises

- Aseptic areas should be designed at a site away from stairs, lift shafts, corridors and general manufacturing areas as these areas are capable of providing routes by which microorganisms may travel.
- Each stage of the production should be carried out in separate rooms of the aseptic area.
- Store rooms should be adjacent to an aseptic area where all sterile equipment and products can be stored.
- Washing and changing rooms should be located before the entrance of the aseptic area. Even some space should be provided for keeping records, label-writing, inspection and finishing of products.

2.Size of Premises

- Aseptic area should be constructed in such a manner that maximum number of personnels can work at a time.
- The rooms should be large and spacious by which the overall effect of microorganisms can be reduced which ultimately results in minimal contamination.
- The ceiling of rooms should be at a low height which facilitates easy cleaning.
- In large rooms, heat-sterilized injections and particle free solutions are prepared.
- In small rooms the equipment which helps in controlling microbial content, temperature and humidity are placed.

3.Windows

- Large windows with transparent glass are suitable for aseptic areas. These windows should remain closed and ventilation should be produced artificially by air filtration systems.
- Window should be double-glazed wherein its inner sheet is fixed and the outer sheet can be opened for cleaning purposes. These types of windows are used to prevent heat loss from glass material.

4.Doors

- Entrance should have double doors with an air-lock system.
- In this way, air entering from outside into the aseptic area can be prevented.
- Even sliding and swing doors can be used.

5.Floor, Walls and Bench Tops

The floor, walls and bench tops should be,

1.Easy to clean

2.Smooth with no cracks and pores Impervious to cleaning agents like disinfectants etc

3.Chemically resistant to solvents, dyes, strong acids or alkalis.

Floor

It should be made up of the following materials,

1.Terrazzo-It is a mixture of cement and marble (crushed) which is mostly used as flooring material in aseptic area. It is available as tiles or can even be spread in plastic form.

2.Linoleum-Linoleum of heavy grade is best suited for flooring. It is available in the form of sheets and tiles. Sheets are more preferred than tiles as the tiles consist of joints and surface irregularities which can trap dust particles.

3.**Plastics-**Polyvinyl chloride (PVC) of non-slip and matt-finish grade is ideal for aseptic areas. They are available in the form of sheets and tiles. The joints of sheets and tiles can be welded.

Walls and Ceiling

They should have surfaces made up of,

(a) Tiles: They are smooth, non-absorbent in nature and tend to crack on prolonged usage. They can be easily cleaned. Modern tiles have replaced traditional tiles due to their good quality. However, dust might accumulate in cavities of tiles due to breakage of intermediate cement.

(b) **Glass Paint:** This type of paint is applied on smooth plaster. It provides good protection when new but upon cracking or peeling the paint has to be reapplied. These plaster walls get easily damaged.

(c) Plastic Laminate: This type of material is used to cover the walls and ceiling of an aseptic room. However, it is expensive.

Tops of Working Bench

The tops of the working benches should be made up either of the following materials.

(a) **Stainless Steel:** It is durable in nature. The screws used in benches should be located under the surface of the bench to avoid accumulation of the dust.

(b) Plastic Laminates: They are available in various bright colours. One complete sheet of plastic should be used to make the surface of a bench.

Advantages

1. Low cost and less noisy compared to stainless steel.
2. Resistant to heat.
3. Resistant to reagents(except strong solution of phenol).

Disadvantage: May get stained with dyes.

Design of Aseptic Area/Production Facilities and Control

- The design of aseptic area depends upon the requirements and economic condition of the pharmaceutical industry.
- High standards should be maintained while manufacturing of sterile products.
- Cleanliness should be of maximum degree in aseptic area whereas in other areas such as compounding area etc., cleanliness can be of low degree

1.Environmental Control

The environmental control maintained is different for different areas (clean-up area, compounding area, filling and packaging areas). Stringent environmental control is required before and during the processing of parenteral to assure an area free from contamination and where there is no accumulation of dust particles, lint, viable microorganisms etc.

i.Particle Count: The number of particles in a volume of air sample is measured by particle measuring systems which not only count the particles but also provide size distribution details based on the magnitude of light scattered by the particles. This instrument although detects all forms of particulate matter (dust or microorganisms) but fails to differentiate between viable and non-viable forms.

ii.Slit-to-Agar (STA) Sampler: This device consists of a rotating agar plate consisting of a slit through which a measured amount of air is accumulated by applying vacuum. This air comes in contact with the surface of the agar plate. Viable microorganisms (such as bacteria, fungi etc) stick to the surface of the agar plate and start growing in the form of colonies that are counted as colony forming units (CFUS).

iii.Rodac Plates: These plates consist of nutrient agar with a convex surface which is rolled on the surface to be tested. Microorganisms stick to the surface of agar following which the plates are incubated

Small volume parenterals (SVPS) prepared under stringent sterile conditions do not require terminal sterilizati the manufacturing area is maintained under most rigid control. However, the manufacturing area of large volume parent (LVPS) follow less rigid control therefore these products are terminally sterilized after primary packing. (Unit-IV)

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2. Traffic Control

- Traffic refers to supply of materials, entry and exit of workers etc., in the production area of an aseptic room.
- There should be strictly controlled in an aseptic area. A prescribed procedure should be followed which should be applicable to every person who enters the aseptic area.
- The personnel can enter an aseptic area only after passing through an air lock.
- When entering, they should change their clothes, wear fresh sterile gowns, cover their faces with masks, wear hand gloves, he covers or caps and shoes.
- Once a personnel enters the aseptic area, then he/she cannot leave until the manufacturing cycle gets completed.
- Entry of unauthorized personnel's in this area should be restricted

3. General Cleaning

- Microbial and particulate contamination can be sourced not only from the clothes of operators but also from other sources.
- In order to minimize this microbial contamination, measures adopted for cleaning should be strictly imposed, cleaning schedules should be developed and followed on a daily or monthly basis, based on sterility requirements.
- Separate workers should be appointed for maintenance and cleaning of all the equipment, walls, ceiling and floors before and after the completion of production cycle. Walls, floors and roofs of aseptic areas should be constructed in such a way that should facilitate ease of cleaning.
- Apart from this, even operators should wash their hands with cetrimide or chlorhexidine detergent before entering the aseptic area.

Sanitization is carried out using disinfectants or UV radiation before starting the production in two ways,

(a)By spraying a suitable liquid disinfectant over all the surfaces in aseptic areas. However, surface disinfection to wiping the surfaces with liquid disinfectant is more preferred.

(b) The aseptic area is irradiated to decrease the population of bacteria. It is carried out by a cold cathode mercury vapour lamp which gives maximum UV radiation. As these rays are harmful, the personnel are not allowed to come in contact with them. Hence, direct irradiation is carried out only when the aseptic room is vacant.

4. Clean Rooms

- Since it is prerequisite for parenteral products to meet extremely high standards of cleanliness and purity, the environment in which these preparations are manufactured have been classified and assigned with standard designations bythe
- United States and European countries and the International Society of Pharmaceutical Engineers.
- These specifications are based on the maximum allowed number of air-borne particles/ft' of 0.5 µm or larger and 5 um or larger.

Table: Clean Room Classification

Maximum number of particles/ft³, ≥ 0.5 µm	Maximum number of particles/ft³, ≥ 5 µm	International Society of Pharmaceutical Engineers	United States classification	European grade
350	0	Critical	100	A
3,500	0	Clean	1000	B
350,000	2000	Controlled	10,000	C
3,500,000	20,000	Pharmaceutical	100,000	D

Normally, the classification used in pharmaceutical practice range from class 100,000 (Grade D) to class

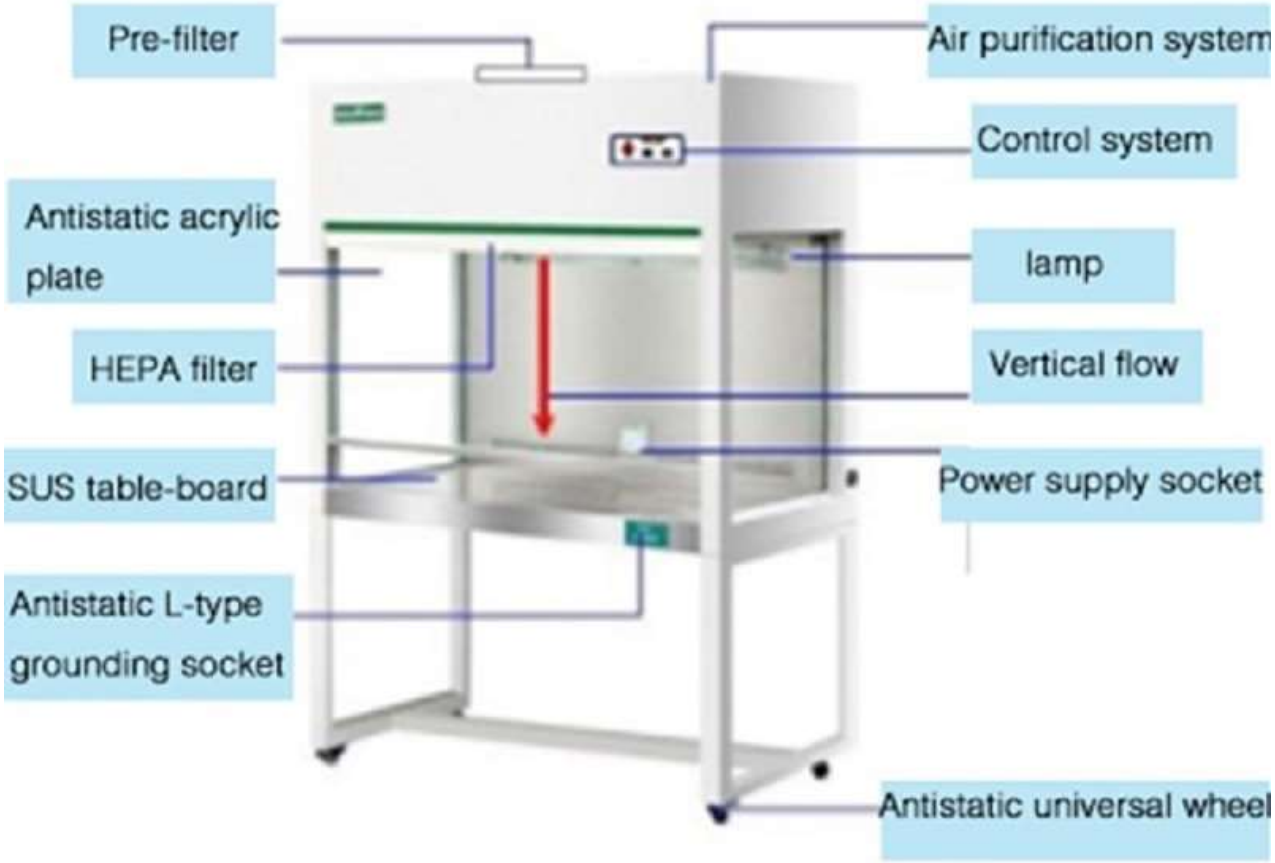
(a) Class 100- Class 100 cleanroom is defined as an area in which the particle count in the air is not more than 100/ft3 of 0.5um and larger in size. This level of cleanliness is achieved by HEPA filters which blow the effluent a lines (laminar air flow) at a uniform velocity of 90-100 ft/min ±20%. Class 100 work environments are specified for the most critical aseptic filling, sealing and cleaning because it is expensive and requires effective maintenance and monitoring.

(b) Class 1000- This cleanroom is defined as an area consisting of not more than 1000 particles of 0.5 um and larges This is a buffer area between the critical (class 100) and controlled (class 10,000) area wherein main aseptic conditions are not required but control of microorganisms and particulate matter should be stringent T.his level of cleanliness is essentially maintained in compounding area to control the dust generated and compounding operations.

(c) Class 10,000 This room is the one in which the particle count is not more than 10,000 per cubic foot of 0.5 um an This kind of clean room is also a buffer area in which operations such as handling of pre-cleaned aseptic gowning of the personnel is performed.

(d) Class 100,000- The particle count of this room should not be more than 100,000 particles/ft of 0.5 um and larger in size. Material support area, stock staging area and finishing and packaging area which do not require of cleanliness like aseptic area fall under class 100,000. This area is constructed to withstand moisture, steam and detergents as preparations for the filling operations such as cleaning and assembling of equipment is undertaken here.

- **5. Cleaning of air**
- **Laminar Flow Systems-Class 100 cleanrooms (aseptic rooms) can be achieved by laminar flow systems in which clean air is obtained by passing it through HEPA (High Efficiency Particulate Air) filters which are the most efficient cleaning device.**
- **The clean air flows at a uniform velocity of 100 ± 20 ft/min and simultaneously sweeps the dust particles and makes the entire area of the aseptic room free from dust particles.**
- **Examples of commercially available laminar flow systems are Clean air, Clestro, Liberty, Air control, Laminaire etc.**


Pre-filter
Air purification system
Control system
Antistatic acrylic plate
lamp
HEPA filter
Vertical flow
SUS table-board
Power supply socket
Antistatic L-type grounding socket
Antistatic universal wheel

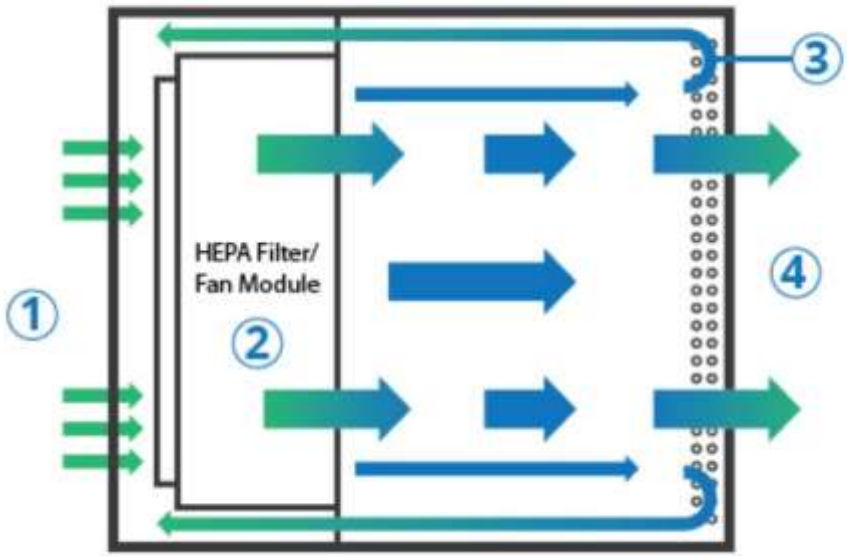
a)Vertical flow system

- This system consist of false floor and false ceiling. The air is filtered through pre-filters, electrostatic filters and HEPA filters in sequence situated in the false ceiling.
- The filtered air is devoid of particles ranging from 0.1-0.3um or even larger.
- This phenomenon of obtaining filtered air is known as false ceiling washing.
- The filtered air enters into the false floor through second set of HEPA filters. From the false floor, small proportion of filtered air is recirculated into the false ceiling through a re-circulation duct.

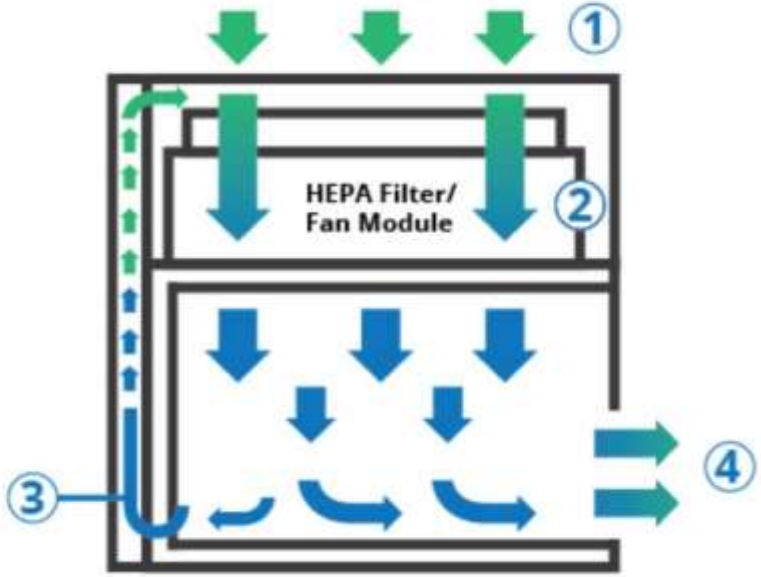
b)Horizontal flow system-

- In this system, the flow of air is horizontal.
- The air is filtered through pre-filters and HEPA filters which are placed in the lateral walls.
- Some portion of the filtered air is recirculated through a recirculation duct

Horizontal Laminar Flow Hood Diagram (*Cutaway Side View*)

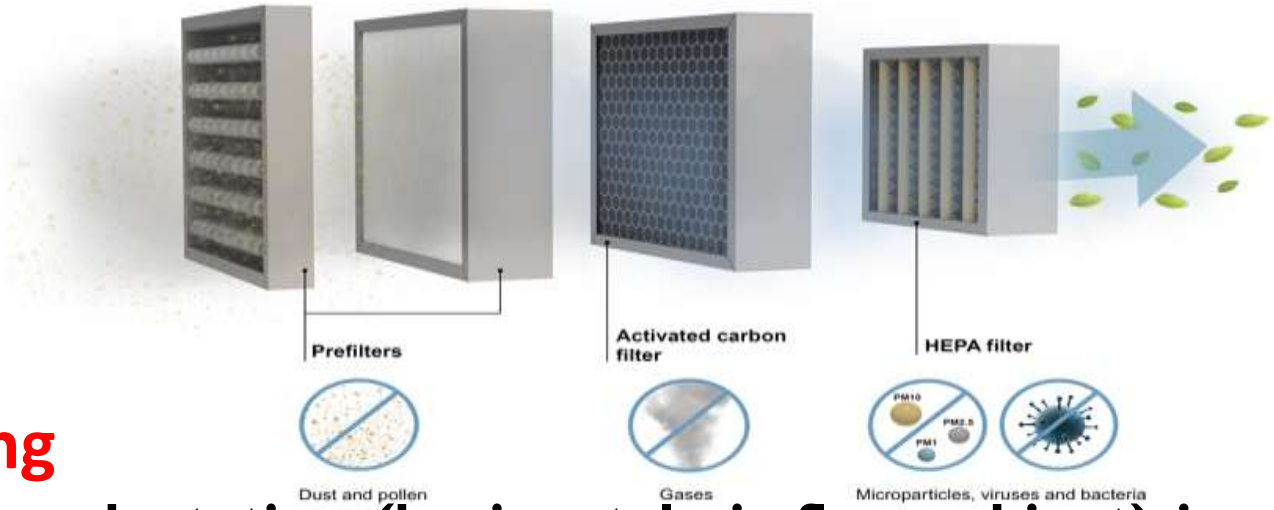


Vertical Laminar Flow Hood Diagram (*Cutaway Side View*)



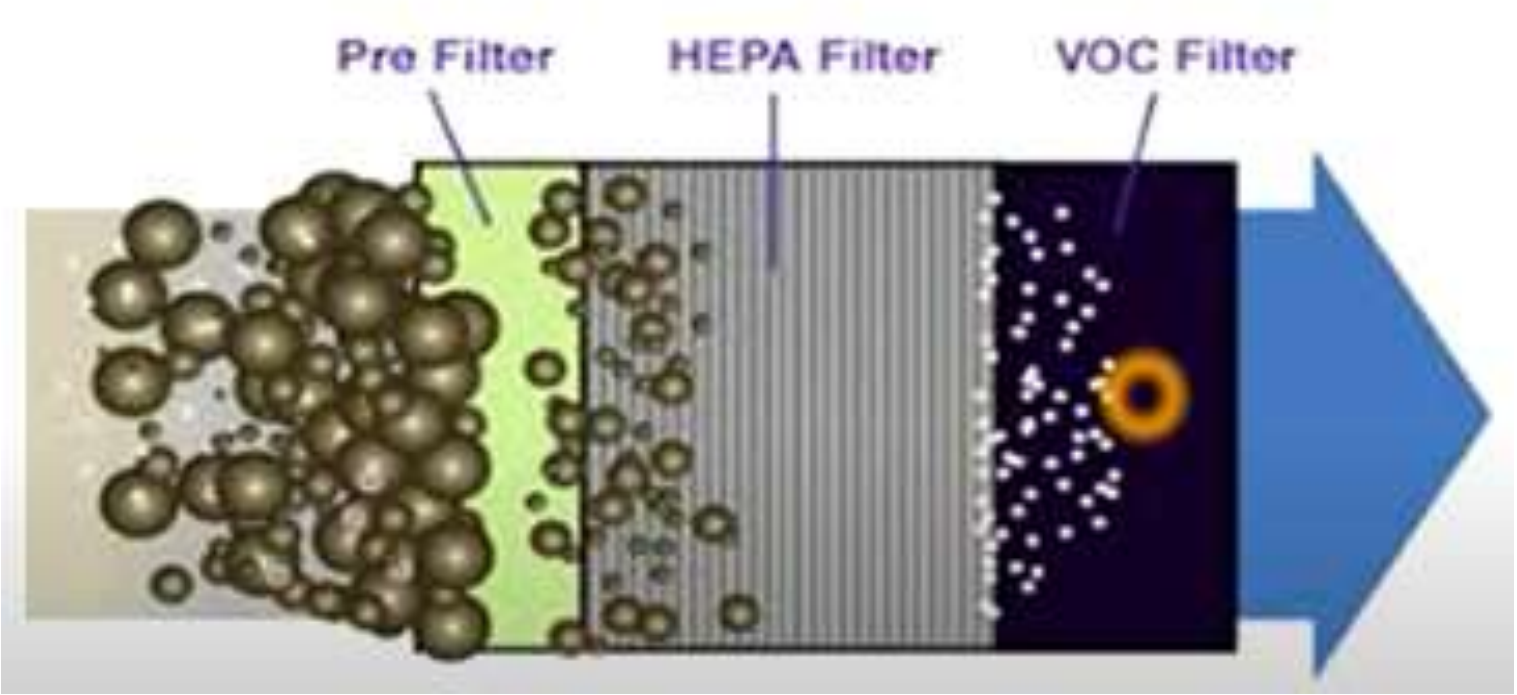
HEPA filters

- HEPA filters are primarily used for the sterilization of air. These can remove 99.99% of particles of size greater than 0.3 μm.
- Hence, they can produce air free from dust particles and bacteria. These are employed in laminar air flow cabinets, overhead canopies, ducts, walls and ceiling panels.
- HEPA filters consist of banks of filter medium and spacers. The filter medium is made up of pleated sheets of glass microfibres separated and supported by spacers made up of aluminium.
- The filter material is sealed with aluminium frame and one side of the filter is protected with a mesh of coated mild steel. The pleated sheets of glass microfibres are placed parallel to each other.
- This helps in increasing the surface area of the filter, thereby increasing the airflow through the filter. These HEPA filters help in maintaining the velocity of air at 230 +90 cm/min.



Working

- The work station (horizontal air flow cabinet) is placed in an aseptic area where the flow of air is minimum.
- The work station is started 15 minutes prior to the actual operation. This is done to make the work station area free of particulate 3. matter.
- The fan forces the air through the HEPA filters which releases pure air into the area used for working purpose.
- The air during its course of flow through the working area, sweeps away the contaminants from the walls, equipment, personnel etc.
- In this way, the contamination arising from the operator and the process itself is avoided during critical procedures.


Pre Filter
HEPA Filter
VOC Filter

6.Personnel Requirements

- Highly, skilled professionals and well trained workers should be engaged in the manufacturing of sterile preparations.
- If workers from non-professional background are employed, then training should be given according to GMP (Good Manufacturing Practice) requirements.
- After training, the personnel should be evaluated for the knowledge and skills to ensure that adequate training has been provided.
- The personnels should also be retrained on periodic basis to increase their level of expertise.
- The personnel employed should not be suffering from any infectious diseases and even dermatological conditions which might increase the microbial contamination.
- Periodic medical examination of all the employees or workers should be carried out.
- The uniform of workers should be sterile and so designed that it should confine the discharges released from the body.
- The personnel are required to wear fresh and sterile uniforms, head-covers, shoe covers, face masks, goggles and gloves while working in the aseptic area.
- The gloves should be worn after the hands have been thoroughly crubbed with a disinfectant.

THANK YOU