Design Considerations for Parenteral Production Facility

GMP Requirements for Sterile Products:

- Specific points relating to minimizing risks of contamination.
  - Microbiological
  - Particulate matter
  - Pyrogen

General Requirements

- Production in clean areas
- Airlocks for entry
  - Personnel entry.
  - Material entry
- Separate areas for operations
  - Component preparation
  - Product preparation
  - Filling
  - Sealing etc…
- Level of cleanliness
- Filtered air
- Air classification: Grade A, B, C and D.

2

- Laminar air flow:
  - Air speed (horizontal versus vertical flow)
  - Number of air changes
  - Air samples
- Conformity to standards
- Work station and environment
- Barrier technology and automated systems.

3

- To achieve the goal of a manufactured sterile product of exceptionally high quality:
- Functional areas:
  - Warehousing or procurement;
  - Compounding (formulation);
  - Materials (containers, closures, equipment) preparation;
  - Filtration and sterile receiving;
  - Aseptic filling;
  - Stoppering;
  - Lyophilization (if warranted);
  - And packaging, labeling, and quarantine.

4

- The **design and control of an aseptic area** is directed toward **reducing the presence of contaminants**, so they are no longer a hazard to aseptic filling.
- Although the **aseptic area must be adjacent to support areas, so an efficient flow of components may be achieved**, barriers must be provided to minimize ingress of contaminants to the critical aseptic area.

5

Facility Design:

1. Manufacturing areas designed for aseptic processing smooth, easily cleaned surfaces.
2. Designed to control the manufacturing environment (personnel and process).
3. Adequate and separate areas, for various activities (testing, manufacturing).
4. HEPA-filtered air in manufacturing areas; higher control (classification) for critical manufacturing steps.
5. Product type and makeup. • Stage of manufacturing. • Scale of manufacturing.
6. Material and personnel flows designed to maximize efficiency and minimize product mix-ups and concurrent vs. campaigning – impact on HVAC, cleaning and personnel.

6

Basic Design:

- **Building Design, Construction And Layout:**
- The building layout and its construction are poor there is very little that an air conditioning system designer can do to satisfy the end-user of the sterile areas.
- Sterile zones are normally divided into three sub zones;
  1. Main sterile zone or white zone.
  2. Cooling zone which is also a white zone
  3. Set of three change rooms: black, grey and white in ascending order of cleanliness.
- In order to achieve a pressure gradient, it is imperative that zones are located such that the gradient is unidirectional, i.e. the room with the highest pressure should be located at one end and the room with the lowest pressure should be located near the opposite.

7

- Entry for people to the main sterile room should be from a set of three change rooms: black, gray and white.
- Entry for equipment and material must be through airlocks. In case any wall of the sterile area is exposed to the outdoor, care should be taken that no glass is provided.
- Any glass window provided in an internal partition should be sealed.

1. Sharp corners should be avoided between floors, walls and ceiling.
2. Tile joints in the floor should be carefully sealed and epoxy painting should be carried out in these areas and special attention should be given to the type of ceiling.

8

- In such cases the air conditioning system is required to be designed before slab construction is started in order to provide the following:

a. Location and size of the cutouts for terminal filters.

b. Location and size of the cutouts for return air risers and inserts in the slab.

c. Provide floor drain locations for air handling units and sleeves for drain line and cabling should be provided in inverted beams. In areas where air handling units are located water proofing must be carried out.

- Additional cut outs are required to be left for other services.

9

a. All cutouts should have curbing at the edge to prevent water seepage into the working area and mounting frames for terminal filters/terminal filter boxes should be grouted at the time of casting the slab.

b. Lighting layout and equipment should be matched with the cut-out location and size.

- The ceiling slab should have inverted beam construction in order to avoid projections into the clean rooms.
- In the case of a false ceiling in the sterile area, the following points should be considered:

a. Inserts should be provided for false ceiling supports and mounting of filters.

b. To prevent fungus growth and eliminate air leakage, the false ceiling should be of non shedding variety, such as aluminium or PVC coated CRCA sheet.

10

1. Environmental Zone Groups:

Environmental control zone grouping:-

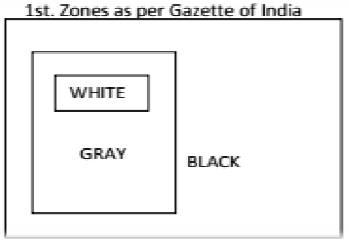
1st. Zones as per the c GMP:-

- Zone 7:- Filling line
- Zone 6:- Filling area
- Zone 5:- Weighing, mixing & transfer area.
- Zone 4:- Clean area
- Zone3:-General production
- Zone 2:- Warehouse
- Zone 1:- Exterior

11

❖ ZONES AS PER GAZZETE OF INDIA:

- **White zone**:- Final step (filling of parenteral).
- **Grey zone**:- Weighing, Dissolution & filtration.
- **Black zone**:- Storage, Worst area from contamination view point.



12

- The layout of the plant must be carefully developed in coordination with the needs of the HVAC system.

- **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 barrier to contamination.

13

- **Zone-6:- Filling area:-**

  Zone 6 is a distinct zone of the controlled environment area for an aseptic filling process. But may not be distinct zone for non-aseptic filling processes.

- **Zone-5:- Weighing, mixing, and transfer area:-**

  Zone 5 encompasses those activities of "weighing, mixing, filling or transfer operations" addressed by cGMP section 212.81 which are not handled as zone 6 but which require a controlled environment.

- **Zone-6:- Clean area:-**

  Activities in these may include washing and preparations of equipment or accumulation and sampling of filled product.

14

- **Zone-3:- General production and administration area:-**

  The third zone of environmental control is formed by the periphery of the general production area. Openings into the area are usually well sealed and large enough for only essential material-handling equipment and personnel.

- **Zone-2:- Plant exterior:-**

  The environmental with in which a plant located is first environmental control zone. It is a base point from which to work in determining the requirements for the various control barriers.

- Management actions to control zone 1 might include the maintenance of sterile areas around the facility where weeds, insects and rodents are controlled or eliminated.

15

2. Wall and Floor Treatment:

- All inside walls must be finished.
- Common methods of finish are block, plaster, or gypsum board.
- Concrete block walls are sturdy and easily constructed.
- The porosity of concrete block walls can be reduced by coating with block filler prior to painting.
- But even filled concrete block walls have a surface texture that is not conductive to cleaning.
- Painted concrete block walls are particularly susceptible to peeling if they are subjected to moisture as from leakage or rain on the backside.

16

- Use of ceramic-faced block can overcome the surface finish problems of concrete block.
- Epoxy paint is normally used to increase the durability and impermeability of the surface.
- Gypsum board is not an acceptable surface for use in powder-filling operations without incorporating an additional surface coating or vapor barrier. By itself, gypsum is susceptible to vapor barrier.
- To prevent fungus growth and eliminate air leakage, the false ceiling should be of non shedding variety, such as aluminium or PVC coated CRCA sheet.

17

- Floor can be composed of large sheets vinyl or polyvinylchloride laid on a concrete base floor and "welded" together with heat or sealed at the seams with cement.

3. Lighting Fixtures:

- Most lighting fixtures are not tightly sealed, the diffuser should be sealed integrally with the ceiling.

18

4. Change Rooms:

- Personnel access to all controlled areas should be through change rooms.
- Change rooms concepts and layouts vary from single closet size rooms to expensive multi-room complexes.
- Upon entry into the change room wash sinks are provided for scrubbing hands and forearms.
- After hands are dry, garments are taken from dispensers and donned while moving across a dressing bench.
- As a final gowning step, aseptic gloves are put on and sanitized.
- Exit from the change room to the controlled area is, like entrance, through an interlocked vestibule.

19

5. Personnel Flow:

- The flow of material and personnel through corridors are inefficient and unsafe paths for moving materials, particularly if heavy forklifts are required.
- Parenteral plants, like any other plant have visitors and the degree of access to be granted must be determined.
- A glassed mezzanine or balcony provides absolute solution yet may give an excellent view of the processes, but may not be adaptable for single-floor layouts.
- Personnel flow path from zone to zone must be such that access to higher level of cleanliness is only through change rooms, gowning rooms, locker rooms, or other areas as may be required to prepare the personnel for the cleaner area.

20

6. Utility and Utility Equipments Location:

- Exposed overhead piping is not acceptable from a cleanliness or contamination standpoint since it collects dirt, is difficult to clean and may leak.
- Buried or concealed pipe may require unacceptable demolition for cleaning or repair.
- Whenever possible, major utility distribution services should located outside of clean areas.

21

Utilities equipments location:

- Plant generated utilities typically require steam boilers, air compressors, and distillation, the typical "boiler room" approach.
- Although a central location minimizes distribution problems and minimizes service distribution distances.
- Proper equipment maintenance is difficult in foul weather, especially winter.
- Heavy equipment may damage the roof structure, particularly if the equipment location requires numerous penetrations through the roof which, coupled with equipment vibration, will invariable lead to leakage.

22

Environmental Control:

❖**Definition of clean room:**

- **PART 1:** Specification for control environmental clean rooms, work stations and clean air devices.
- **PART 2:** Guide to construction and installation of clean rooms, work stations and clean air devices.
- **PART 3:** Guide to the operational procedure and disciplines applicable to clean rooms, work stations and clean air.

23

❖ Classification of Clean Rooms:

The class is directly related to the number of particles per cubic foot of air equal to or greater than 0.5 micron.

(1) Class 100,000:

Particle count not to exceed a total of 100,000 particles per cubic foot of a size 0.5µ and larger or 700 particles per foot of size 5.0µ and larger.

(2) Class 10,000:

Particle count not to exceed a total or 10,000 particles per cubic foot of a size 0.5µ and larger or 65-70 particles per cubic foot of a size 5.0µ and larger.

24

(3) Class 1,000:

Particles count not to exceed a total of 1000 particles per cubic foot of a size 0.5µ and larger or 10 particles per cubic foot of a size 5.0µ and larger.

(4) Class 100:

Particles count not to exceed a total of 100 particles per cubic foot of a size 0.5µ and larger.

25

- **Class 1:**
  The particle count shall not exceed a total of 3000 particles/m3of a size 0.5µ.
- **Class 2:**
  The particle count shall not exceed a total of 3000 particles/m3of a size of 0.5 µ or greater; 2000 particles/m3 of size 0.5 µ or greater; 30 particles of a size 10 µ.
- **Class 3:**
  The particle count shall not exceed a total of 1,000,000 particles of a size of 1 µ or greater; 20,000 particles/m3 of size 5 µ or greater; 4000 particles/m3 of a size 10 µ or greater; 300 particles of a size of 25 µ or greater.
- **Class 4:**
  The particle count shall not exceed a total of 200,000 particles of a size of 5 µ or greater.

26

❖ For the manufacture of sterile medicinal products normally 4 grades can be distinguished.

- **GRADE "A":**

  The local zone for high risk operations. eg. Filling zone, stopper bowls, open ampoules and vials.

- **GRADE "B":**

  In case of aseptic preparation and filling, the background environment for grade "A" zone.

- **GRADE "C" &"D":**

  Clean areas for carrying out less critical stages in the manufacture of sterile produce.

27

FS209 Cleanroom Classification	ISO 14644-1 Cleanroom Classification	NMT 0.5um Particles/m3	Viable Microbes (cfu/m3)	Average Airflow Velocity (fpm)	Air Change/hr
100,000	8	3,520,000	100	5-10	5-48
10,000	7	35,200	10	10-15	60-90
1000	6	35,200	7	25-40	150-240
100	5	3,520	1	40-80	240-480

28

Table 26-4A. Clean Room Classifications

European Grade	United States Classification	International Society of Pharm. Eng. Description	Max No. of Particles per m ^{3} >/= 0.5 µm	Max No. of Particles per m ^{3} >/= 5 µm
A	100	Critical	3,500	0
B	100	Clean	3,500	0
C	10,000	Controlled	350,000	2,000
D	100,000	Pharmaceutical	3,500,000	20,000

Table 26-4B. ISO 14644 Classification of Cleanroom Particle Limits

ISO Classification	Maximum Concentration Limits (Particles per Cubic Meter of Air) for Particles ≥ the Sizes per Each Column				
	0.1 µm	0.3 µm	0.5 µm	1 µm	5 µm
1	10	-	-	-	-
2	100	10	4	-	-
3	1,000	102	35	8	-
4	10,000	1,020	352	83	-
5	100,000	10,200	3,520	832	29
6	1,000,000	102,000	35,200	8320	290
7	-	-	352,000	83,200	2,930
8	-	-	3,520,000	832,000	29,300
9	-	-	-	8,320,000	293,000

29

HVAC System:

- Since air is one of the greatest potential sources of contaminants in clean rooms, special attention must be given to air drawn into clean rooms by the **heating, ventilating, and air conditioning (HVAC) systems.**
- In one such series, air from the outside, first, is passed through a prefilter, usually of glass wool, cloth, or shredded plastic, to remove large particles.
- Then, it may be treated by passage through an electrostatic precipitator. Such a unit induces an electrical charge on particles in the air and removes them by attraction to oppositely charged plates.
- The air then passes through the most efficient cleaning device, a HEPA filter.

30

- The clean, aseptic air is introduced into the Class 100 area and maintained under positive pressure, which prevents outside air from rushing into the aseptic area through cracks, temporarily open doors, or other openings.
- Temperature in the 68-74°F (19-23°C) range and humidity in the 45-55% RH range are considered acceptable.
- Humidity range 15-30% this is the case with many freeze dried substances.

31

- **Air in controlled environment shall have:**

1. A per-cubic-foot particle count of not more than 100,000 in a size range of 0.5 micron and larger when measured with automatic counters or 700 particles in a size range of 5.0 microns or larger when measured by a manual microscopic method.
2. A temperature of 720°F±50 or 22°C±30°C and maximum relative humidity of 50 percent and a minimum of 30 percent.
3. A positive pressure differential of at least 0.05 inch of water with all.

32

- **Ventilation:**

  Ventilation requirements for a controlled environment are determined by the number of people working in the environment, the number of air changes per hour required to achieve the desired level of cleanliness, the amount of air added for pressurization, and the nature of the manufacturing process.

33

- **Entry and Exiting:**

  Entry and exit passage ways are also required for the transfer of personnel, equipment, and materials, locations of these rooms, sometimes referred to as "airlocks," must satisfy the internal and external requirements for the flow of materials and personnel.

34

HEPA Filter:

- HEPA (High Efficiency Particulate Air)
- A screen that filters out particles in the air by forcing them through microscopic pores.
- HEPA filters have different ratings for efficiency, which are generally posted on the filter itself.
- HEPA filter is so efficient that for every 10,000 particles that enter the filter within its filtering range, only 3 particles will get through .
- The required environmental control of aseptic areas has been made possible by the use of laminar airflow, originating through a HEPA filter.

35

- It bathes the total space with very clean air, sweeping away contaminants.
- The orientation for the direction of airflow can be horizontal (Figure A) or vertical (Figure B) and may involve a limited area, such as a workbench, or an entire room.
- Figure C shows a syringe-filling line in a Grade A/Class 100 area using vertical laminar airflow.
- The machine guarding is a stainless steel frame that can hold the LF hood. The panes are safety glass.

36

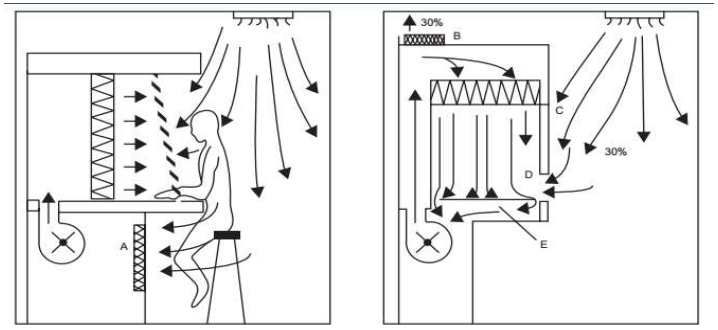


Fig. A & B Horizontal and vertical laminar air flow. (Courtesy of Cosslett AG, The design of controlled environments. In: Denyer SP, Baird RM, eds. *Guide to Microbiological Control in Pharmaceuticals and Medical Devices*, 2nd ed. London: CRC Press, Taylor & Francis, 2007: 69–88.)

37

Figure C High speed syringe filling machine for pre-sterilized syringes. (Courtesy of Robert Bosch GmbH.)

38

❖ Optimum Parameters:

- Air changes per hour (fresh + re-circulating)
- Total 20-25 ACH = Fresh air 10 + 15 total 15-25 Velocity 0.2 m/sec.
- Air filtration HEPA 99.97% efficiency and pressure relationship to adjacent areas positive.
- Optimal temperature 18 -25°C and optimal humidity 15-20%.

39

❖ HEPA Filters Specifications:

- HEPA filters remove at least 99.97% of airborne particles 0.3 micrometers (µm) in diameter.
- The filters maximum resistance to airflow or pressure drop is usually specified around 300 Particles and its nominal flow rate used to prevent the spread of airborne radioactive contaminants.

40

❖ Function:

- The common assumption that a HEPA filter acts like a sieve, HEPA filters are designed to target much smaller pollutants and particles.
- Diffusion predominates below the 0.1 µm diameter particle size near to the Most Penetrating Particle Size (MPPS) 0.3 µm, both diffusion and interception are comparatively inefficient .

41

❖ Five classifications of HEPA filters exist:

- **Type A HEPA filters:** Also referred to as industrial filters. An efficiency performance of 99.97 % retention of particulate matter 0.3 micrometers in size at an airflow of 85 L/minute.
- **Type B HEPA filters:** Known as nuclear type are designed to handle nuclear containment. Filters are tested for pinhole leaks, as significant numbers of these leaks lead to an efficiency drop at slower air flows. The test checks for 99.97 % retention of particulate matter 0.3 micrometers in size, but at 20 % the normal airflow.

42

- **Type C HEPA filters:** Called laminar flow filters due to their mostly exclusive use in biological laminar flow systems, filters are tested for particulate matter of larger sizes. Filter has an efficiency of 99.99 % .
- **Type D HEPA filters:** Known as ultra-low penetration air. an efficiency rating of 99.999 % retention of particulate matter 0.3micrometers in size at airflow of 85 L/minute.
- **Type E HEPA filters:** Referred to as biological filters. These filters are created with a focus on stopping toxic, nuclear, chemical and biological threats.

43

❖ Type of HEPA Filter:

- **Horizontal Flow (Laminar Flow Hood)**

1. Air blows towards worker.
2. Used for non-chemotherapy preparations.

- **Vertical Flow (Biological Safety Cabinet or Chemotherapy Hood)**

1. Air blows from top to bottom maintain sterility and protect the worker.
2. Used to make chemotherapy.
3. The HEPA filter is located in the fragile mesh between thin metal strips at the back of the hood behind the HEPA filter screen.
4. Nothing should be permitted to come in contact with the HEPA filter.

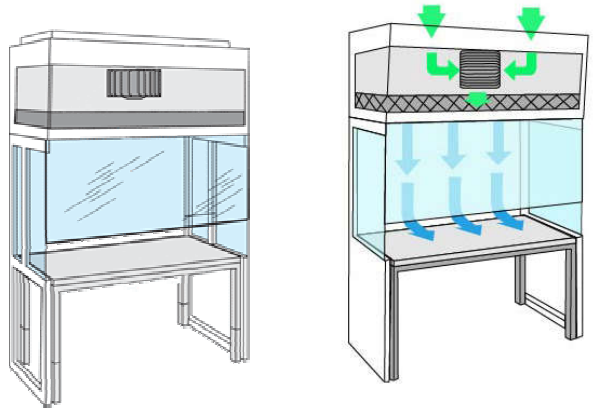
44

❖Laminar Air Flow (LAF) System:

- High efficiency particle air filtration. “HEPA” filters + Lamination of Air flow.
- Laminar flow ensures a directional air flow for a distance of 140-200cm Combined by HEPA filters remove particles > 0.3 micron in an efficiency of 99.97% over the aseptic operating field in a uni-direction flow offering.
- Laminar airflow system should provide a homogenous air speed of 0.45 m/s ±2.0% at the working position. “AN ULTRA CLEAN AIR”.

45

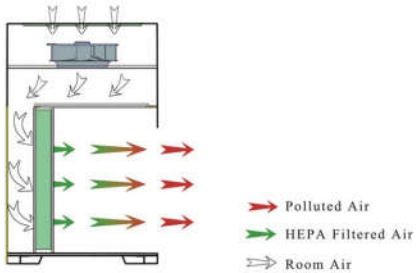
❖Vertical Laminar Flow Diagram:



Room air (in red) enters the system from above the HEPA filter; 99.99% particle-free air is forced downward toward the work surface.

46

❖Horizontal Laminar Flow Diagram:



Horizontal Type

Room air enters the system from behind the HEPA filter; 99.99% particle-free air is forced in a back-to-front direction across the work surface.

47

❖Validation of HEPA Filter:

▪ Hot DOP Testing:

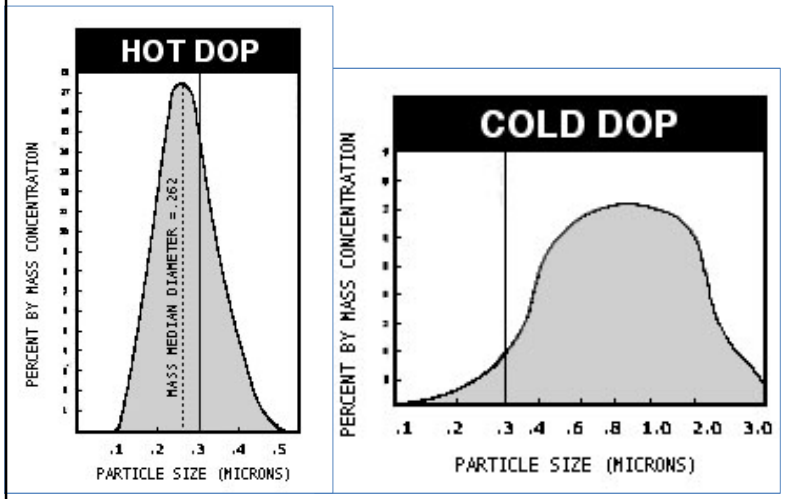
1. The DOP aerosol used to challenge HEPA filters to test for efficiency by this standard is known as "hot" or "thermally generated" DOP because it is derived from heated dioctylpthalate oil.
2. Sophisticated equipment is used for carefully controlling oil and air temperatures, air flow rates and mixing conditions.
3. This "hot" DOP aerosol has a very narrow particle size distribution (monodisperse). Because the only way to determine the efficiency of a filter on a specific particle size (fractional efficiency) is to test with particles of that size,
4. DOP is used to produce a high concentration of 0.3 micron particles - that which theory indicates and has historically been considered to be the most penetrating of filter media.

48

▪ Cold DOP Testing:

1. DOP aerosol can be generated in the field but the equipment used, while relatively simple and portable, cannot produce truly "hot" DOP that is monodisperse.
2. The DOP generated by such equipment is "cold" DOP which having a broad particle size distribution is polydisperse.
3. Such an aerosol is useful for field testing for leaks and ensuring the integrity of an installation, however, without the ability to particle count the 0.3 micron size particles, "cold" DOP does not provide the ultimate test of filter efficiency.
4. "Cold" DOP has a broad particle size with larger average size than "Hot" DOP. Efficiencies are, therefore, higher with "Cold" DOP than with "Hot" DOP.

49



50

DOP (Dioctyl phthalate) Test

HOT DOP	COLD DOP
• Efficiency test	• Integrity test
• Vaporization	• Pressurization
• Mono-disperse aerosol	• Poly-disperse aerosol
• 0.3 µm	• > 0.3 µm < 0.3 µm 0.3 µm (20-30 %)

51

❖CIP (Clean in Place)/SIP (Steam in Place):

- **Clean-in-place (CIP)** is a method of cleaning the interior surfaces of pipes, vessels, process equipment, filters and associated fittings, without disassembly.
- The process can be one shot, where everything goes to drain, or recovery, which recycles most of the liquid. Overall, CIP can be a very efficient way of cleaning.
- CIP has evolved to include fully automated systems with programmable logic controllers, multiple balance tanks, sensors, valves, heat exchangers, data acquisition and specially designed spray nozzle systems.
- Simple, manually operated CIP systems can still be found in use today.

52

- **The Steam-In-Place (SIP) System** is responsible for repeatedly steaming areas of product contact, including vessels, flow paths, and sample ports.
- This may be done to reduce the bio-burden on the system, or to kill harmful materials at the end of a batch.
- A typical SIP system will ensure that all areas being steamed have been exposed to live steam for an adequate time to ensure the desired "kill" effect.
- The steam system must be able to measure and control steam temperature, pressure, and/or flow to ensure adequate steaming.
- Calculation of Fahrenheit or other measures is often required to meet process needs.

53

❖Personnel Factors:

1. Personnel selected to work on the preparation of a parenteral product must be neat, orderly, and reliable.
2. They should be in good health and free from dermatological conditions that might increase the microbial load.
3. If personnel show symptoms of a head cold, allergies, or similar illness, they should not be permitted in the aseptic area, until recovery is complete.
4. However, a healthy person with the best personal hygiene will still shed large numbers of viable and nonviable particles from body surfaces.
5. This natural phenomenon creates continuing problems, when personnel are present in clean rooms; effective training and proper gowning can reduce, but not eliminate, the problem of particle shedding from personnel.

54

6. Aseptic-area operators should be given thorough, formal training in the principles of aseptic processing and the techniques to be employed.
7. Subsequently, the acquired knowledge and skills should be evaluated, to assure that training has been effective, before personnel are allowed to participate in the preparation of sterile products. Retraining should be performed on a regular schedule to enhance the maintenance of the required level of expertise.
8. An effort should be made to imbue operators with an awareness of the vital role they play in determining the reliability and safety of the final product.
9. The uniform worn is designed to confine the contaminants discharged from the body of the operator, thereby preventing their entry into the production environment.

55

❖Processing of Parenteral products:

- **Types of sterile products processing:**

1. **Terminally sterilized** → prepared, lled and sterilized
2. **Sterilized by filtration**
3. **Aseptic preparations**

56

1. Terminally sterilized: -

1. This involves filling and sealing product containers under high-quality environmental conditions.
2. Products are filled and sealed in this type of environment to minimize the microbial and particulate content of the in-process product and to help ensure that the subsequent sterilization process is successful.
3. In most cases, the product, container, and closure have low bio-burden, but they are not sterile.
4. The product in its final container is then subjected to a sterilization process such as heat or irradiation.

57

2. Sterilization by Filtration:-

1. Previously sterilized container are taken.
2. Filters having nominal pore size 0.22 µm or less are used for filtration
3. Remove bacteria and moulds but not viruses & mycoplasmas
4. Double filter layer or second filtration
5. No fiber shedding or asbestos filters
6. Filter integrity testing

58

3. Aseptic Preparation:-

1. In an aseptic process, the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together.
2. Because there is no process to sterilize the product in its final container, it is critical that containers be filled and sealed in an extremely high-quality environment.
3. Before aseptic assembly into a final product, the individual parts of the final product are generally subjected to various sterilization processes.
4. Any manual or mechanical manipulation of the sterilized drug, components, containers, or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control.

59

❖Biological Indicators:

- Biological indicators are the standardized preparations of specific micro-organisms that have known stable and high resistance towards one or more sterilization methods.
- Micro-organisms widely recognized as suitable biological indicators are spore forming bacteria. This is because these micro-organisms are more resistant than micro flora except towards ionizing radiation process.

60

WHY ARE BIOLOGICAL INDICATORS USED?

1. To assist the physical operation of a sterilizer.
2. In order to establish a validated sterilization process for an article.
3. Sterilization of equipments, materials and packaging components used in aseptic processes.
4. To keep a check on the sterilization cycle.
5. Recheck the established sterilization cycles and revalidate if necessary.

61

THE BIOLOGICAL INDICATORS USED ARE THREE TYPES

1. The organisms or its spores are added to a carrier such as filter paper or glass and packed in order to maintain their integrity.
2. In the other the spores are added to the representative lots that are to be sterilized.
3. It is a self contained indicator which is designed such that the primary package used for incubation contains growth medium for recovery. In this the entire system is resistant to the sterilization process

62

FACTORS GOVERNING THE CHOICE OF BIOLOGICAL INDICATORS:

1. The strain should be stable
2. It should be non pathogenic
3. The resistance of the test strain should be the maximum towards the sterilization process when compared to other species of microbes
4. The test strain should be easily recovered and reproducible

63

THE CHARECTERISTICS OF A BIOLOGICAL INDICATOR:

1. The strain of test organism
2. The total viable spore count
3. D-value (Decimal reduction value): This value is a measure of resistance of particular type of sterilization process
4. Z- Value: In case of heat sterilization Z-value denotes the resistance of micro-organisms with changes in temperature
5. Expiry date

64

RECOMMENDED BIOLOGICAL INDICATORS FOR VARIOUS STERILIZATION PROCESSES:

❖ **MOIST HEAT STERILIZATION**:

- Spores of ***Bacillus stearothermophilus*** **or** ***Clostridium sporogenes***
- The number of viable spores should be more than 10 to the power 5 per carrier
- The D-value at 121 degrees is 0.8 minutes for Clostridium sporogenes

65

❖ **DRY HEAT STERILIZATION**:

- Spores of ***Bacillus subtilis*** **var.** ***niger***
- The number of viable spores should not be less than 10 to power 5 per carrier.
- The D-value at 160 degrees should be about 5 to 10 minutes.

❖ **RADIATION STERILIZATION**:

- Spores of ***Bacillus pumilus***
- Viable spores per carrier should be about 10^7-10^8.
- D-value should be about 3kGy.

66

❖ **CHEMICAL STERILIZATION (ETHYLENE OXIDE)**:

- Spores of ***Bacillus subtilis*** **var.*niger***
- The stock suspension should contain non-germinating spores held in non-nutritive liquid

67

Sterilization Method	Biological Indicator	Standard
MOIST HEAT STERILIZATION	*Bacillus stearothermophilus* or *Clostridium sporogenes*	The number of viable spores should be more than 10 to the power 5 per carrier The D-value at 121 degrees is 0.8 minutes for Clostridium sporogenes
DRY HEAT STERILIZATION	*Bacillus subtilis* var. *niger*	The number of viable spores should not be less than 10 to power 5 per carrier. The D-value at 160 degrees should be about 5 to 10 minutes.
RADIATION STERILIZATION	*Bacillus pumilus*	Viable spores per carrier should be about 10^7-10^8. D-value should be about 3kGy.
CHEMICAL STERILIZATION (ETHYLENE OXIDE)	*Bacillus subtilis* var.*niger*	The stock suspension should contain non-germinating spores held in non-nutritive liquid

68

Question Bank

2 Marks

1. What do you mean by Hypodermoclysis?
2. Define the terms-pyrogens and terminal sterilization.
3. Differentiate between sterilization and depyrogenation.
4. Give biological indicators for filtration, moist heat, dry heat and radiation sterilization methods.
5. How will you perform leaker test on ampoules?
6. Why water attack test performed on type II glass and powdered glass test on type I glass?
7. What are ideal requirements of parenterals?*
8. What do you mean by class 100?
9. Enlist different secondary routes of parenteral preparations.
10. Define isotonicity. Give its significance in parenterals preparation.

69

11. Define parenteral preparations. State their disadvantages.
12. What is sterile water for injection? How is it differs from water for injection.*
13. Define parenteral preparations. Give its advantages.
14. Classify parenteral preparations.*
15. Draw a neat labelled diagram of different environmental control zones in parenterals.
16. Classify Plastics.
17. What is class 100 area?*
18. What are pyrogens? State different actions of pyrogens on humans.
19. Describe in brief intravenous route of administration.

70

5 Marks

1. What are pyrogens? State different actions of pyrogens. What are different sources of pyrogens and add note on elimination of pyrogens from various sources.
2. Add note on vehicles used in parenterals.
3. Write a note on HVAC system.
4. Give the construction and design of HEPA filters.
5. Discuss in detail about different components of HEPA filter.
6. State and classify different types of glass. Add a note on powder glass test.
7. Why powdered glass test performed over type - II glass? Explain in brief powdered glass test.
8. Discuss sterility test in detail.
9. Classify plastics. Explain evaluation of plastic containers used for injectable preparations.
10. Discuss in brief primary routes of administration for parenterals.

71

11. Discuss validation of HEPA filters by hot and cold DOP test.
12. Discuss any one method used for preparation of water for injection.
13. Explain parenteral emulsions with one example.
14. Describe form, fill and seal technology for sterile products with the help of diagram.
15. Explain parenteral suspensions with one example.*
16. Why is amber colored glass containers used in pharmaceuticals? Discuss type-I and type-II glasses. Add a detail note on Pyrogen test.

72

10 Marks

1. Define parenterals. Discuss the different evaluation tests for parenterals.
2. What are pyrogens? Give different actions of pyrogens. State and explain different sources of pyrogens. How will you eliminate pyrogens from these different sources? Add a detailed note on pyrogen test.*
3. What are class 100 and class 10000 areas? Add a note on HEPA filters. Discuss in detail sterility test.
4. Discuss in detail various parenteral vehicles. Add a note on preparation of water for injection.
5. Define parenterals. Classify it and add detail note on parenteral emulsion and suspension.

73

- Write your answers to the point.
- Underline important words/specifications/wherever needed.
- Attempt questions according to your comfort.
- Always save last 10 min. of exam to review your answer sheet.
- Present your answer sheet neatly.

74