



PRODUCTION OF PARENTERALS AND ASEPTIC AREA

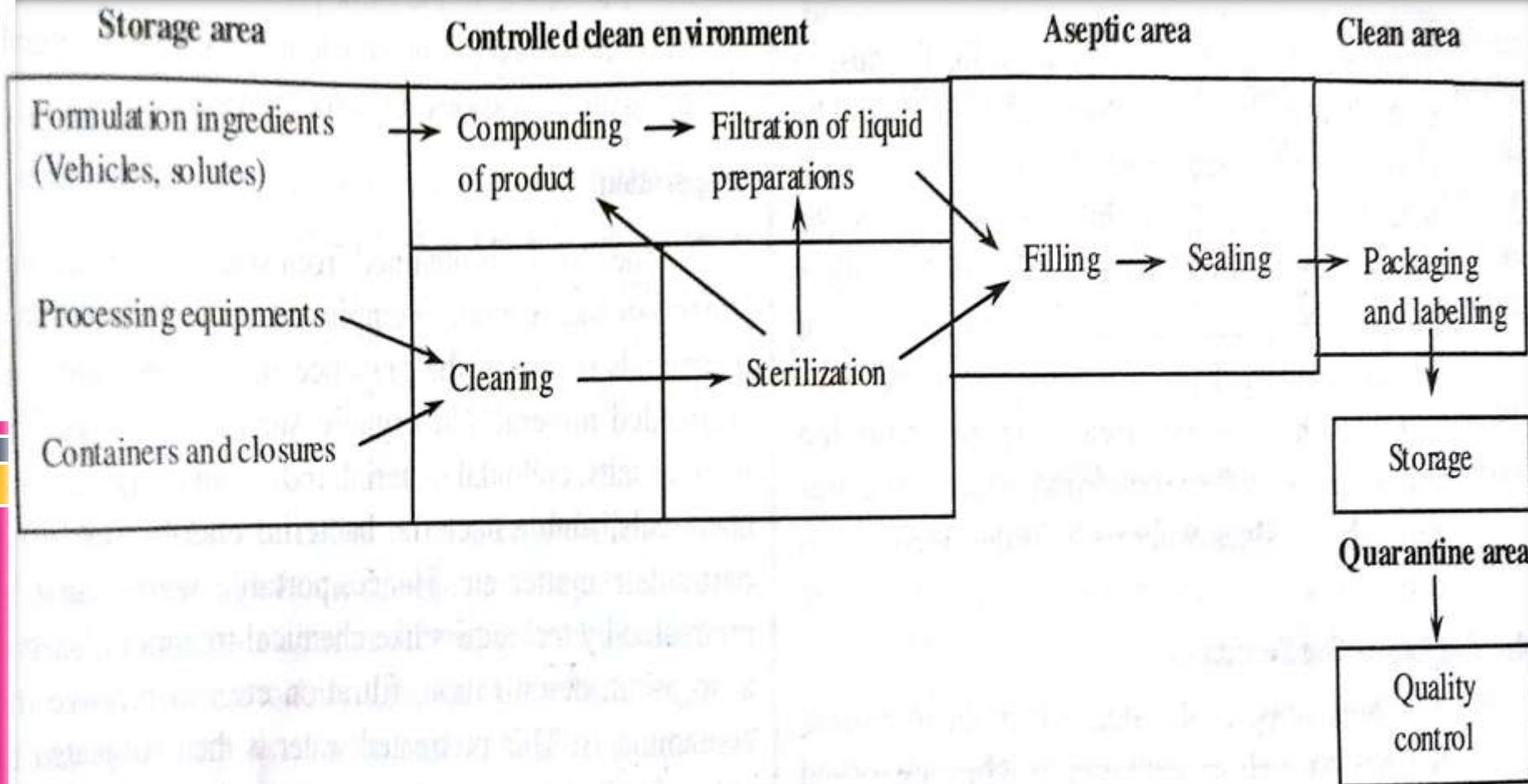
By
Sk.Sana Banu,
Third year,
Rao's college of pharmacy,
Nellore.



Areas in parenteral processing

- Different sectional areas required for sterile preparations are as follows:
 - Clean-up section
 - Compounding section
 - Aseptic section
 - Quarantine section
 - Packing and labeling section
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Layout of parenteral processing





Clean-up area

- The cleaning area has walls and ceilings made up of film coating materials is involved in ceiling of bottles, vials or ampoules.
- Air inside the clean area should be free from dust and microorganisms.
- This is ensured through high efficiency (95%) filters.
- Air existing in the clean area should be frequently replace (10-15 air changes per hour).



Compounding section

- This area contains stainless steel cabinets and counters and is involved in the actual compounding.
- Unlike aseptic area, maintenance of sterile conditions is not essential, but necessary measures should be adopted to control the dust generated from raw material during weighing and compounding.



Aseptic area

- In this area, strict control measures should be adopted to avoid contamination of the preparations.
 - The stainless steel counters and cabinets should be such that they should not allow dirt particles to accumulate.
 - Mixing and storage of the compounded preparations should be done outside the aseptic area.
 - The compounded preparations are then transferred to the aseptic area through pipelines where the filling operation is carried out.
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Quarantine section

- This area consists of a store where the in-process batches as well as approved batches are stored separately.
- This area has limited access and is under the control of a responsible person.
- Without the consent of the incharge, other personnel cannot enter into this particular area.

Packing and labeling section

- In this area, the batches are packed and labeled.
- Packing is carried out by packaging machines, while labels are obtained by over printing devices.
- At a time, only one product labels are printed.
- Parenteral packing plays a vital role in the production of sterile preparations.
- Packing should be carried out in such a manner that the sterility of the product is maintained.



Requirements 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.
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1. Site of premises

- Aseptic area should be designed at a site away from stairs, lift shafts, corridors and general manufacturing area 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 aseptic area.
- Store rooms should be adjacent to aseptic area where all sterile equipments and products can be stored.



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 overall effect of microorganisms can be reduced which ultimately results in minimal contamination.



3. Windows

- Large windows with transparent glass are suitable for aseptic area.
- These windows should remain closed and ventilation should be provided artificially by air filtration system.
- These type 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.
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5. Floors, walls and bench tops

The floor, walls and bench tops should be,

1. Easy to clean
 2. Smooth with no cracks and pores
 3. Impervious to cleaning agents like disinfectants etc
 4. Chemically resistant to solvents, dyes, strong acids or alkalies.
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Floor

- It should be made up of the following materials,
 - a) Terrazzo
 - b) Linoleum
 - c) plastics
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Contd...

(a) Terrazzo:

It is a mixture of cement and marble which is mostly used as flooring material in aseptic area.

Advantages:

- it can withstand harsh cleaning.
- The water used for cleaning purpose can be removed easily by sloping the floor towards the gully, which is present at one side of the aseptic room.



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Disadvantages:

- Expensive
 - Noisy, cold and gets slippery when wetted.
 - It gets easily attacked by acids.
 - It gets easily stained by dyes.
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Contd...

(b).Linoleum

Linoleum of heavy grade is best suited for flooring. It is available in the form of sheets and tiles.

Advantages:

- easy to clean
- Inexpensive

Disadvantages:

- Polished surfaces get slippery when wetted.
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Contd...

- **Plastics:**

Polyvinyl chloride of non-slip and matt-finish grade is ideally for aseptic area. The joints of sheets & tiles can be welded.

Advantages:

- Easy to clean
 - Inexpensive
 - Available in many colors
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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.
- b) **Glass paint** – this type of paint is applied on smooth plaster. These plaster walls get easily damaged.
- c) **Plastic laminate** – this type of material I 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** – 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 colors.



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Advantages:

1. low cost and less noisy compared to stainless steel.
2. Resistant to heat.
3. Resistant to reagents



Disadvantages:

- May get stained with dyes.

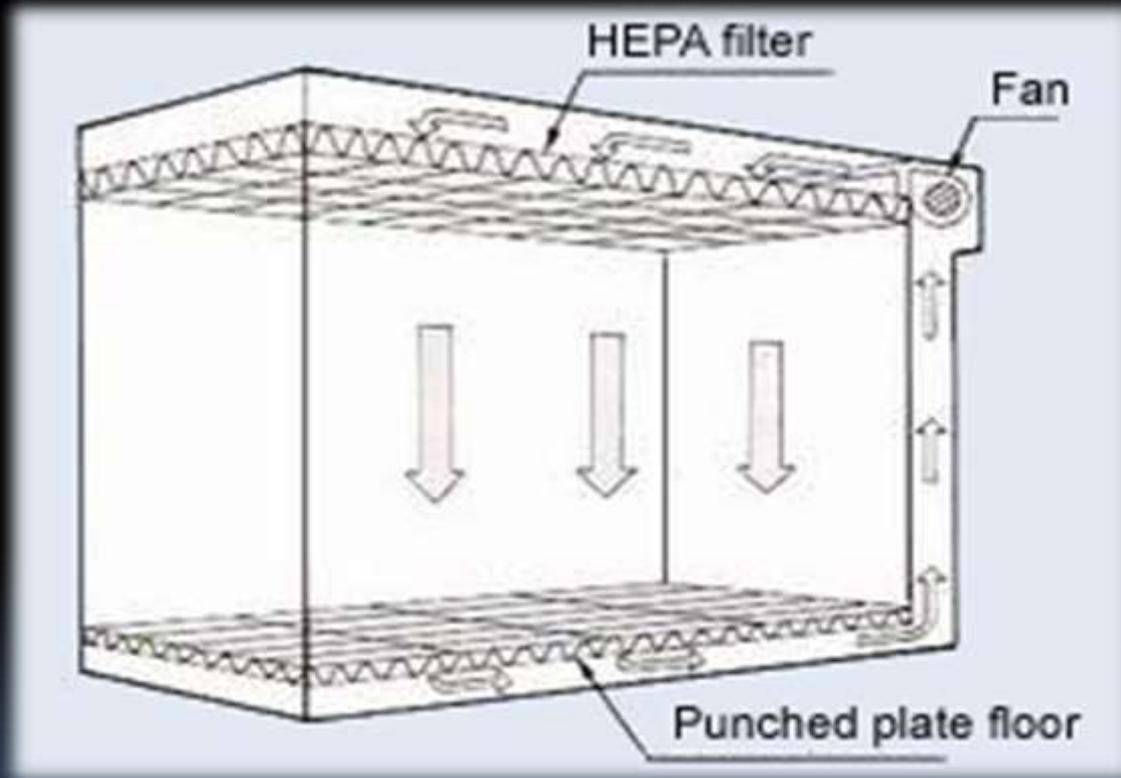


Types of laminar flow systems

laminar air flow systems are generally of three types.

1. Vertical flow system
 2. Horizontal flow system
 3. Wall to floor flow system
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1. Vertical flow system





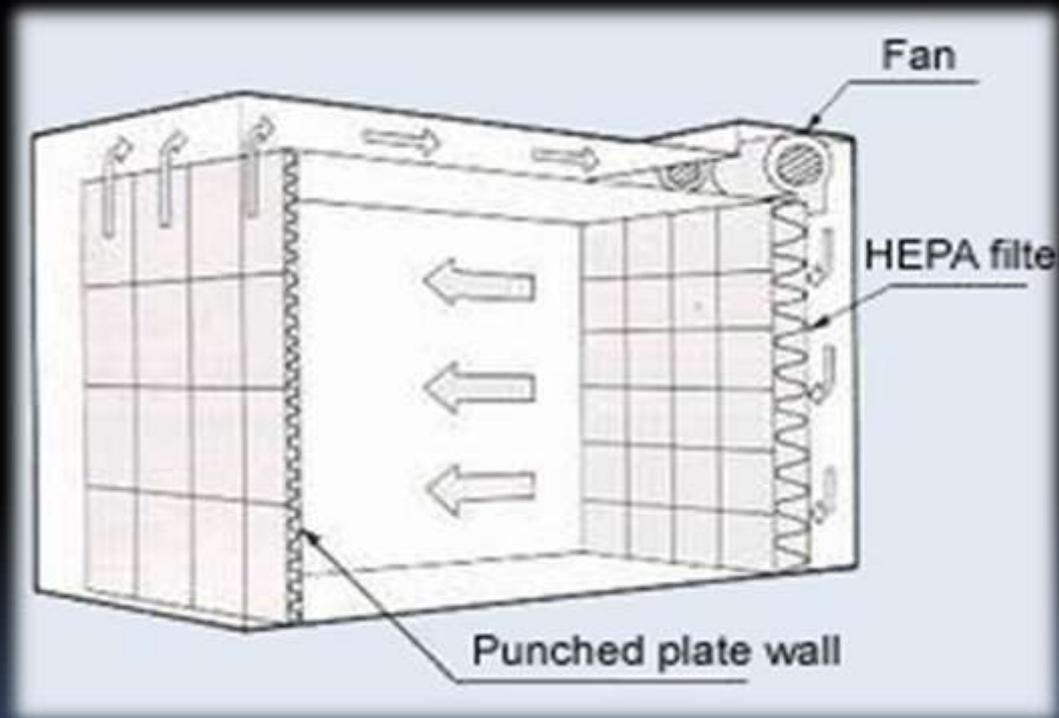
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- This system consists of false floor & ceiling
 - The air is filtered through pre-filters, electrostatic filters and HEPA filters in sequence
 - These 3 filters are placed in false ceiling
 - From the false floor, a small portion of filtered air is recirculated in to false ceiling through a recirculation duct
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Contd...

- **Advantages:**
- The operating area is provided with exhaust filters which remove the remaining portion of the air. This provides protection to the operator.
- It is more preferable when compared to horizontal flow systems.
- **Disadvantages:**
- It is an expensive system as it requires double installation of HEPA filters.

2. Horizontal flow system



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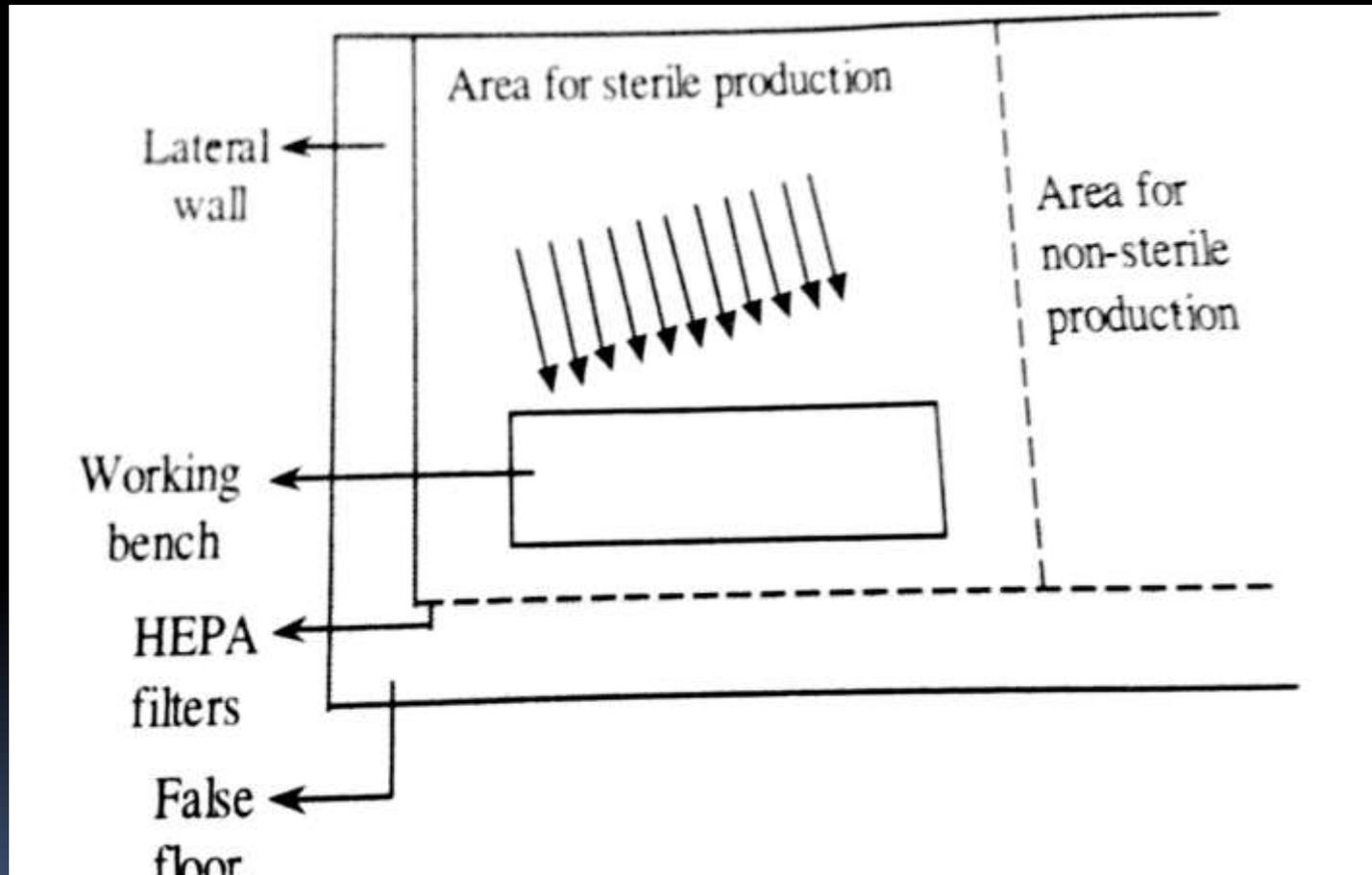
- The air is filtered through prefilters, HEPA filters which are placed in lateral walls.
- Air is recirculated through punched plate wall or recirculation duct.
- Achievement of complete sterile conditions is not possible because the airflow is not focused on working area



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- Disadvantage:
 - During the handling of materials like antineoplastic drugs, this system fails to provide protection to the operator.
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3. Wall to floor system





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- The filtered air enters from the lateral wall with an inclined flow towards the floor.
- This system offers high aseptic conditions.

Advantage:

- The system is portable.

Disadvantage:

- It is expensive.
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Sources of contamination and methods of prevention

- Contamination, in broad sense, is the presence of minor unwanted particulate matter called contaminants in atmosphere, physical body, work station etc.
- Right from production to packaging almost every sector of pharmaceutical industry comes across contamination.

The most common sources of contamination fall into the following three main categories:

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- Atmospheric contamination
 - Fluid contamination
 - Transfer contaminants

1. Atmospheric contamination

- Atmospheric conditions during manufacturing as well as during storage affects the quality of final preparation.
- Atmosphere in and around the industrial area contains potential contaminants like dust, silica etc and gases like CO_2 , water vapor etc.
- Besides the above mentioned contaminants, microorganisms like *P.aeruginosa*, *A.niger* etc.
- These contaminants may get incorporated into the end product either during the process of manufacturing or during purification.

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Prevention:

- Prior to its entry into the working area, the air should be initially passed through a suitable prefilter then treated with an electrostatic precipitator and finally through HEPA filters.
- Periodic removal of air-borne dust settled on walls, floors and ceilings is essential.



2. Fluid contamination

- Besides serving as the most common solvent in pharmaceutical industry, water also serves as the greatest solvent in pharmaceutical industry.
 - Although, it is deprived of most of the contaminants yet it contains pyrogens and traces of sulphates, chlorides and carbonates of Ca, Mg and Na.
 - Therefore, usage of water for washing the machineries and working areas may leave traces of these contaminants.
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Prevention:

- Almost all of the pharmaceutical operations should be carried out using purified water obtained upon deionization, distillation, ion-exchange, reverse osmosis, filtration or other similar processes.
 - For the preparation of parenterals, water for injection, sterile water for injection or bacteriostatic water for injection must be employed.
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3. Transfer contaminants

- Transfer contaminants refer to the contaminants sourced from personnel and wheels of trolleys used for transport of goods.
- Personnel working in aseptic areas, if suffering from cold, allergies, dermatological conditions or any similar illness carry multiple microorganisms which upon expulsion into atmosphere via sneezing, coughing, talking etc., can lead to contamination.
- For example, atmospheric dust particles may get entangled with the fibres of the clothes which can get dislodged due to body movements and lead to contamination.

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Prevention:

- Personnel should be well trained and periodically evaluated in the principles of aseptic processing and techniques to be employed before participating in the preparation of sterile products.
- Apart from gown, the personnel area also required to put on face mask, head cap, gloves, foot covers and even goggle to ensure complete coverage of all skin areas.
- The entrance of most of the working areas is equipped with air blowers that aid in removing any loose dirt, lint from uniform of the operators.



Contd...

- Those mechanical parts of the equipments that come in contact with the parenteral products should be demountable which enables their easy cleaning and sterilization.
 - All the apparatus and their carriers being carried to the aseptic areas should be sterilized by suitable methods.
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Requirements for aseptic area

- Conditions to be maintained in aseptic area are as follows,
 1. Environmental control
 2. Traffic control
 3. General cleaning
 4. Clean rooms
 5. Cleaning of air
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Environmental control

- The environmental control maintained is different for different areas.
 - Stringent environmental control is required before and during the processing of parenterals to assure an area free from contamination and where there is no accumulation of dust particles, lint, viable microorganisms etc.
 - Production environment is constantly monitored and evaluated to assure that the required aseptic conditions are maintained.
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- Various evaluation tests are available to evaluate the environmental control.
 1. Particle count
 2. Slit to agar (STA) sampler
 3. Rodac plates
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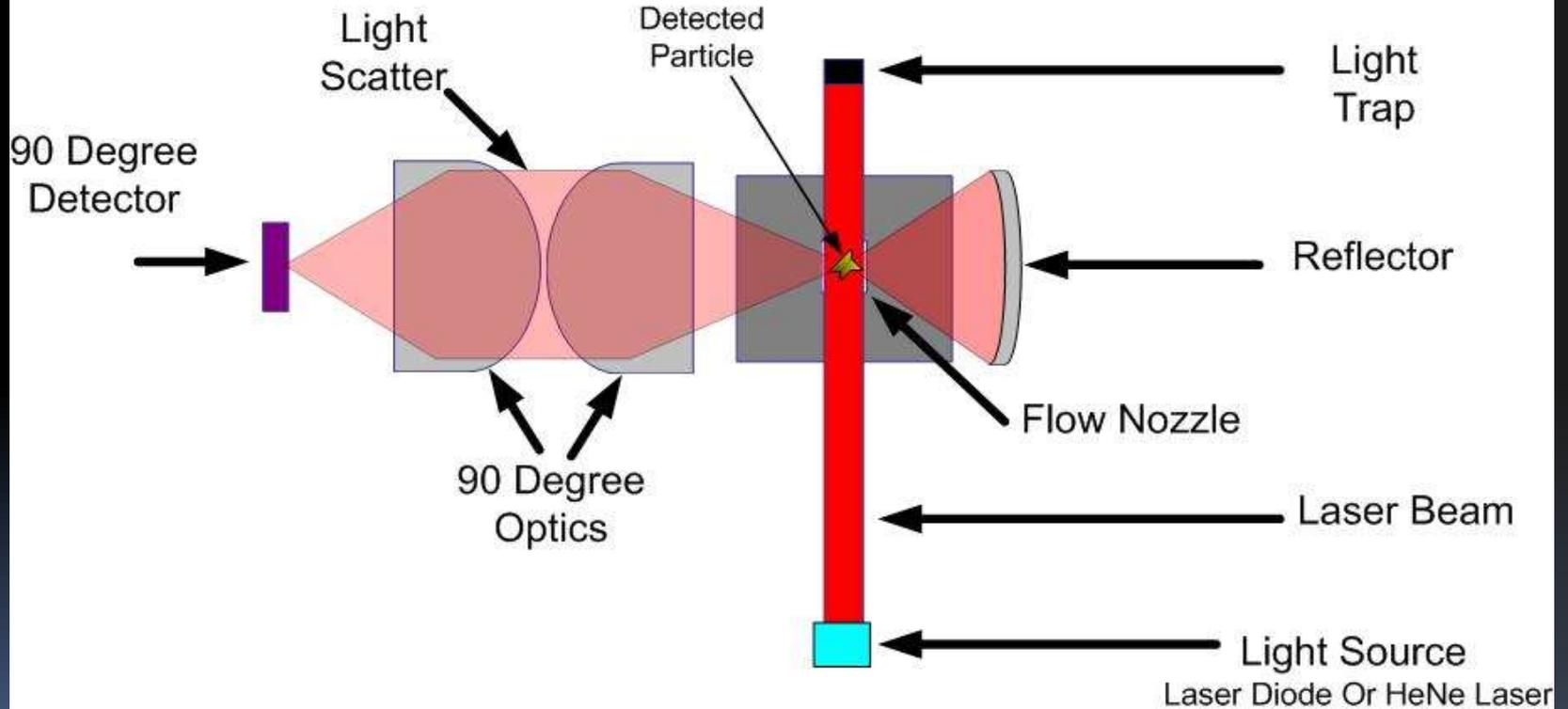


1. Particle count

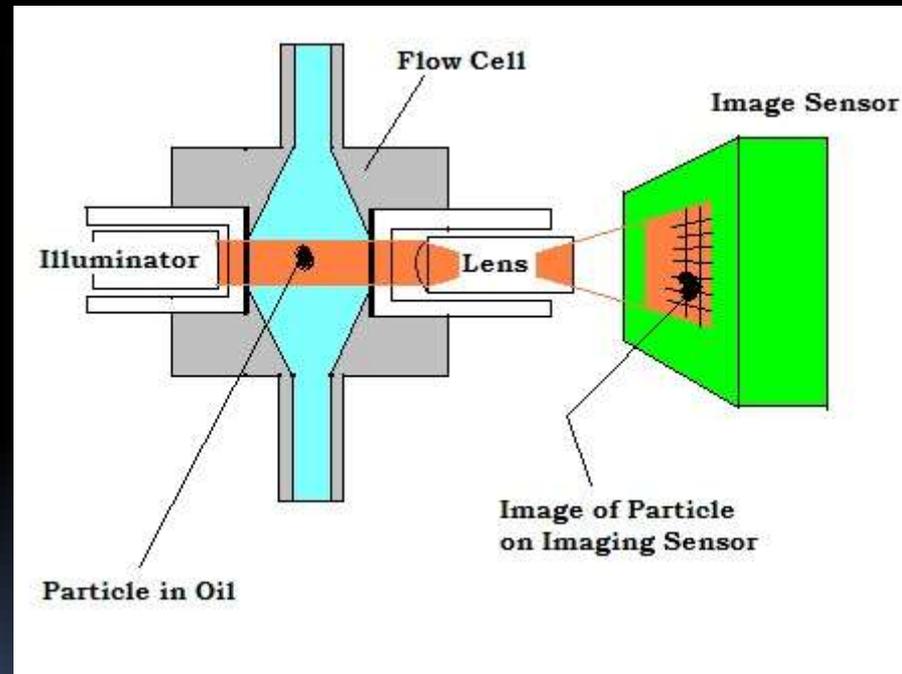
- The number of particles in a volume of air sample is measured by particle measuring systems which not only count the particles but also provide size distribution details based on the magnitude of light scattered by the particles.
- this instrument although detects all forms of particulate matter but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

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Top Down View of Particle Counter



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2. Slit to Agar (STA) Sampler

- This device consists of a rotating agar plate comprising of a slit through which measured amount of air is accumulated by applying vacuum.
- This air comes in contact with the surface of the agar plate.
- Viable microorganisms stick to the surface of the agar plate and start growing in the form of colonies that are counted as colony forming units (CFUs).

Slit to agar sampler



3. Rodac plates

- These plates consists 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.

Rodac plates



A white card with a torn top edge and a red background behind it. The words "Thank you" are written in a dark blue cursive font. To the right of the text, a fountain pen nib is visible, with three blue dots trailing off to the right.

Thank you ...