Tabulation of some formulation/Ingredients and their agent which cause spoilage

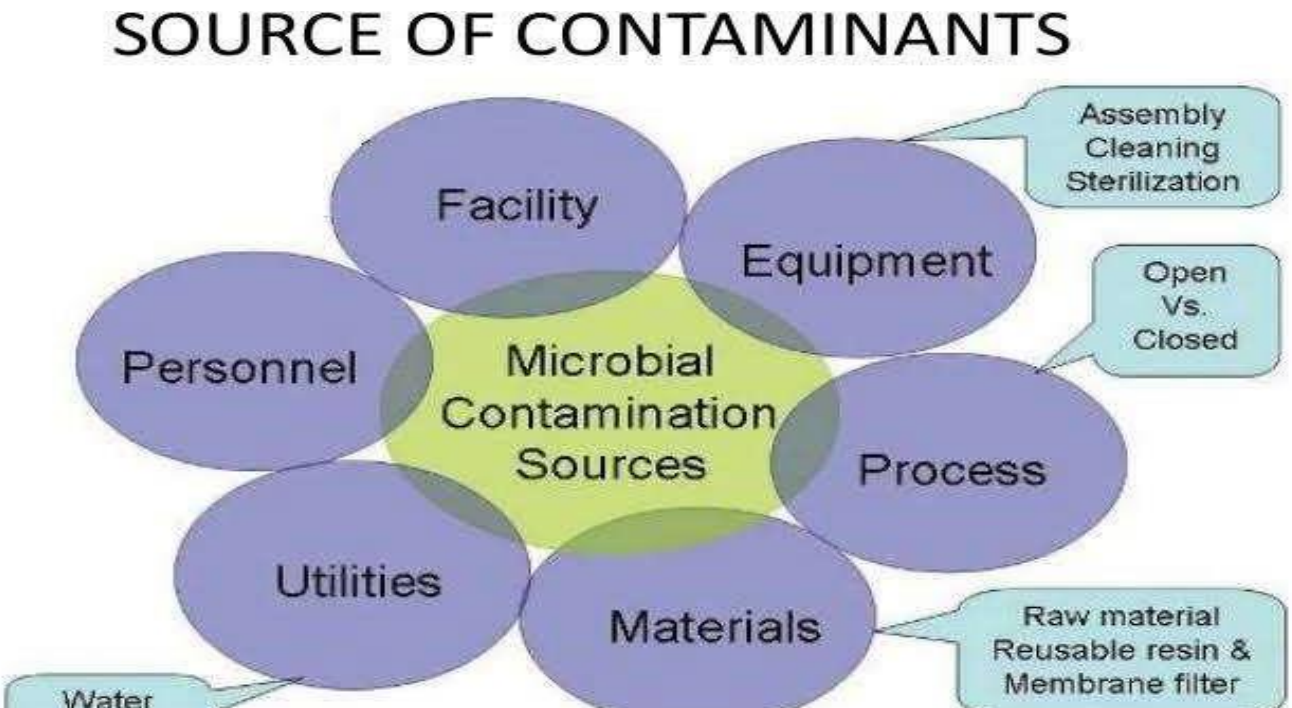
Formulation/Chemical compounds/Drugs	Contaminating species/agents
Polysaccharides (Agar, Starch,Cellulose)	Bacillus, pseudomonas, clostridia spp.
Proteins and Gelatin	Aspergillus spp. Penicillium spp.
Creams and emulsions	moulds
Aromatic compounds	Pseudomonas spp. Gram negative bacteria
Acetyl salicylic acid	Acinetobactor spp.
Syrup of Tolu	Penicillium spp.
Atropine eye drop	Corynebacterium spp.
Prednisolon tablet	Aspergillus spp.
Hydrocortison tablet	Clostridium herbarum

Rose-Hip preparation

Anaerobic bacteria

SOURCES OF CONTAMINATION

- Contaminants can gain entry into a production process stream from several sources such as, Personnel, Poor facility design, Incoming ventilation air, Machinery and other equipment for production, Raw material and semi-finished material, Packaging material, Utilities, Different media used in the production process as well as for cleaning and Cleanroom clothing.



Personnel

- Personnel who are supervising or performing drug manufacturing or control can be a potential source of microbiological contamination and a vector for other contaminants.

The main reasons for contamination from the personnel include:

- Lack of training
- Direct contact between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product
- Inadequate personnel cleanliness
- Access of unauthorized personnel into production, storage, and product control areas
- Inadequate gowning and personnel protective equipment, and
- Malpractices like eating food, drinking beverages, or using tobacco in the storage and processing areas.

Buildings and Facility

- The buildings and manufacturing facilities may also contribute to the contamination.

The main reasons of contamination due to facility issues include:

- Insufficient size and inadequate organization of the space leading to selection errors like mix-ups or cross contamination between consumables, raw materials, in-process materials, and finished products
- Inadequate filth and pest controls
- Rough floors, walls and ceilings
- Lack of air filtration systems
- Improper lighting and ventilation
- Poorly located vents, and drains
- Inadequate washing, cleaning, toilet, and locker facilities to allow for sanitary operation, cleaning of facilities, equipment, and utensils; and personal cleanliness.

Equipments

- The equipment and utensils used in processing, holding, transferring and packaging are the common source of pharmaceutical contamination.

The main reasons for contamination from the equipment include:

- Inappropriate design, size, material leading to corrosion and accumulation of static material and/or adulteration with lubricants, coolants, dirt, and sanitizing agents
- Improper cleaning and sanitization
- Design preventing proper cleaning and maintenance
- Improper calibration and irregular service, and
- Deliberate use of defective equipment

Materials

- The raw materials used for production can be a potential source of contamination.

The main reasons for contamination from the raw materials include:

- Storage and handling mistakes causing mix-ups or selection errors
- Contamination with microorganisms or other chemicals
- Degradation from exposure to excessive environmental conditions such as heat, cold, sunlight, moisture, etc.
- Improper labelling
- Improper sampling and testing, and
- Use of materials that fail to meet acceptance specifications.

Manufacturing Process

- There are various opportunities for contamination of raw material, intermediates or packaging materials throughout the manufacturing process.

The main reasons for contamination during manufacturing process include:

- Lack of dedicated facilities to manufacture a single product
- Inappropriate cleaning in-between batches to minimize the amount of product changeovers
- Use of an open manufacturing system exposing the product to the immediate room environment
- Inappropriate zoning
- Absence of an area line clearance according to approved procedures following each cleaning process and between each batch, and
- Lack of cleaning status labelling on all equipment and materials used within the manufacturing facility

To minimize the risks of manufacturing contamination

- Manufacture products in a campaign, with the appropriately qualified cleaning processes and checks performed in-between batches to minimize the amount of product changeovers
- Utilize a closed manufacturing system. This is where the product is not exposed to the immediate room environment (and vice versa)
- Perform an area line clearance according to approved procedures following each cleaning process and between each batch/campaign
- Zone the facility and
- Use Cleaning Status labelling on all equipment and materials used within the manufacturing facility

HVAC System

- HVAC stands for Heating, Ventilating, and Air Conditioning
- A poor HVAC system can be a potential source of microbes growth and a transportation mode for dispersing contaminants throughout the manufacturing facility.

The main reasons of contamination due to HVAC issues include:

- Accumulations of organic material in or near HVAC air intakes
- Ineffective filtration of the supply air
- Insufficient magnitude of pressure differentials causing flow of reversal
- Erroneous ratio of fresh air to recirculated air
- Inability to access ventilation dampers and filters from outside the manufacturing areas, and
- Non-directional airflow within production or primary packing areas

Assessment of microbial contamination and spoilage

1. **Physical and chemical changes:**

- It is the changes of different pharmaceutical formulations indicate microbial contamination and spoilage
- Change in viscosity, pH, emulsion stability and loss of surface activity of formulation indicates microbial spoilage.
- Measurement of oxygen consumption of the product can indicate the degree of oxidative attack and microbial growth

Sterility test

- **Testing** which confirms that products are free from the presence of viable microorganisms.
- Claim to be **sterile** or free from viable microorganisms.
- Test is conducted by competent and experienced personnel in an adequately clean room with laminar flow cabinet facilities.
- All injectables and ophthalmic preparations are sterile hence, these preparations are tested by the sterility test.

Assessment of viable microorganisms in non-sterile products

- Non-sterile products are tested for viable microorganisms for detection of pathogens and total viable counts.
- In microbiological terms, pharmaceutical products can be divided into two groups: sterile and non-sterile.
- Non-sterile drugs must satisfy the appropriate microbiological purity criteria which are included in pharmacopoeial monographs.
- Pharmacopoeial studies are prepared specifically with a view to ensuring that the medicinal product is therapeutically effective and safe for the patient.

Estimation of pyrogens

- Pyrogen a substance, typically produced by a bacterium, which produces fever when introduced or released into the systemic circulation.
- The lipopolysaccharides and lipoproteins which comprises a major part of the cell wall og Gram –ve bacteria are called endotoxins which are the most commonly called pyrogens
- To test the pyrogens presence, two tests are used

1. **RP Test (Rabbit Pyrogen Test)**
2. **LAL Test (Limulus Amoebocyte Lysate Test)**