ANNAMACHARYA COLLEGE OF PHARMACY

(AUTONOMOUS)

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UNIT –V

Sanitation of manufacturing premises

Subject: Quality Control & Quality Assurance

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Sanitation of manufacturing premises

Sanitation

- Sanitation means promoting health through prevention of human contact with the hazards of wastes as well as proper disposal of sewage.

Guidelines for the maintenance of sanitation

- As per GMP guidelines says, sanitation is “any building used in the manufacture, processing, packing or holding of a drug product shall be maintained in a clean and sanitary condition”

Sanitation control procedures

- **Sanitation SOP**

Each processor should have and implement a written sanitation standard operating procedure (herein referred to as SSOP) or similar document that is specific to each location where Drug and drug products are produced. The SSOP should specify how the processor will meet those sanitation conditions and practices

- **Sanitation monitoring**

Each processor shall monitor the conditions and practices during processing with sufficient frequency to ensure, at a minimum, conformance with required conditions as follows,

- The manufacturing premises shall be cleaned and maintained in an orderly manner, so that it is free from accumulated waste, dust, debris and other similar material

- A validated cleaning procedure shall be maintained. The manufacturing areas shall not be used for storage of materials, except for the material being processed.
- It shall not be used as a general through fare

- A routine sanitation program shall be drawn up and observed, which shall be properly recorded and which shall indicate

a) specific areas to be cleaned and cleaning intervals

b) cleaning procedure to be followed, including equipment and materials to be used for cleaning

c) personnel assigned to and responsible for the cleaning operation.

- The adequacy of the working and in-process storage space shall permit the orderly and logical positioning of equipment and materials so as to minimize the risk of mix-up between different pharmaceutical products or their components to avoid cross contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps
- Production areas shall be well lit, particularly where visual on-line controls are carried out

- **Sanitation control records**

Each processor shall maintain sanitation control records that, at a minimum, document the monitoring and corrections

- **Relationship to HACCP plan**

Sanitation controls may be included in the HACCP (Hazard Analysis and Critical Control Point) plan

Hazard analysis critical control point

IMPORTANCE OF SANITATION

- Prevents contamination of products
- Cross contamination is avoided
- Provides health and safety to workers
- Improves product quality

Other measures need to be taken to maintain sanitation are,

- Regular pest control programme should be drawn up for stores, manufacturing and packaging areas. Services of a pest control agency may be employed.
- Manufacturing areas should not be used for other than manufacturing purposes
- Eating, chewing or smoking should not be allowed in manufacturing areas
- Manufacturing areas should not be used as general to store any personnel materials except processing materials

Records of sanitation

- Records of sanitation should be maintained in the form of log- book
- A separate log book should be maintained for each section

Example of sanitation report

PLANT	TEL/FAX
ADDRESS	CONTACT
INSPECTOR	DATE

PLANT OPERATION	SATISFACTORY	UNSATISFACTORY

Example 1. Inspection form.

Mix – ups and Cross contamination

Mix –up

- Mix –up is defined as “the contamination at unsafe levels of one product with another via inadequate plant and process design or human error”
- Most commonly occurs through labeling, receipting, line clearance type problems, human error

Risks with mix -up

- Causes cross contamination
- Causes poor personnel hygiene

Reasons for mix –up

- Improper cleaning and sanitation
- Time and temperature abuse
- Cartons of one product to another.
- Tablets of one product with another product which have different shape size or color.

- ✓ Close proximity of two products i.e size , shape & color etc;
- ✓ Pack in same color container
- ✓ Multiple products/packs handled in same area.
- ✓ Same apparatus or instrument used for multiple products.
- ✓ Improper labeling
- ✓ No identification code

Precautions for mix-up

- Handle the drug materials and products by proper air handling system
- Processing of sensitive drugs like Beta-lactum antibiotics, cytotoxic substances must be taken care.
- Proper labeling system should be adopted to avoid mix-up during production stages

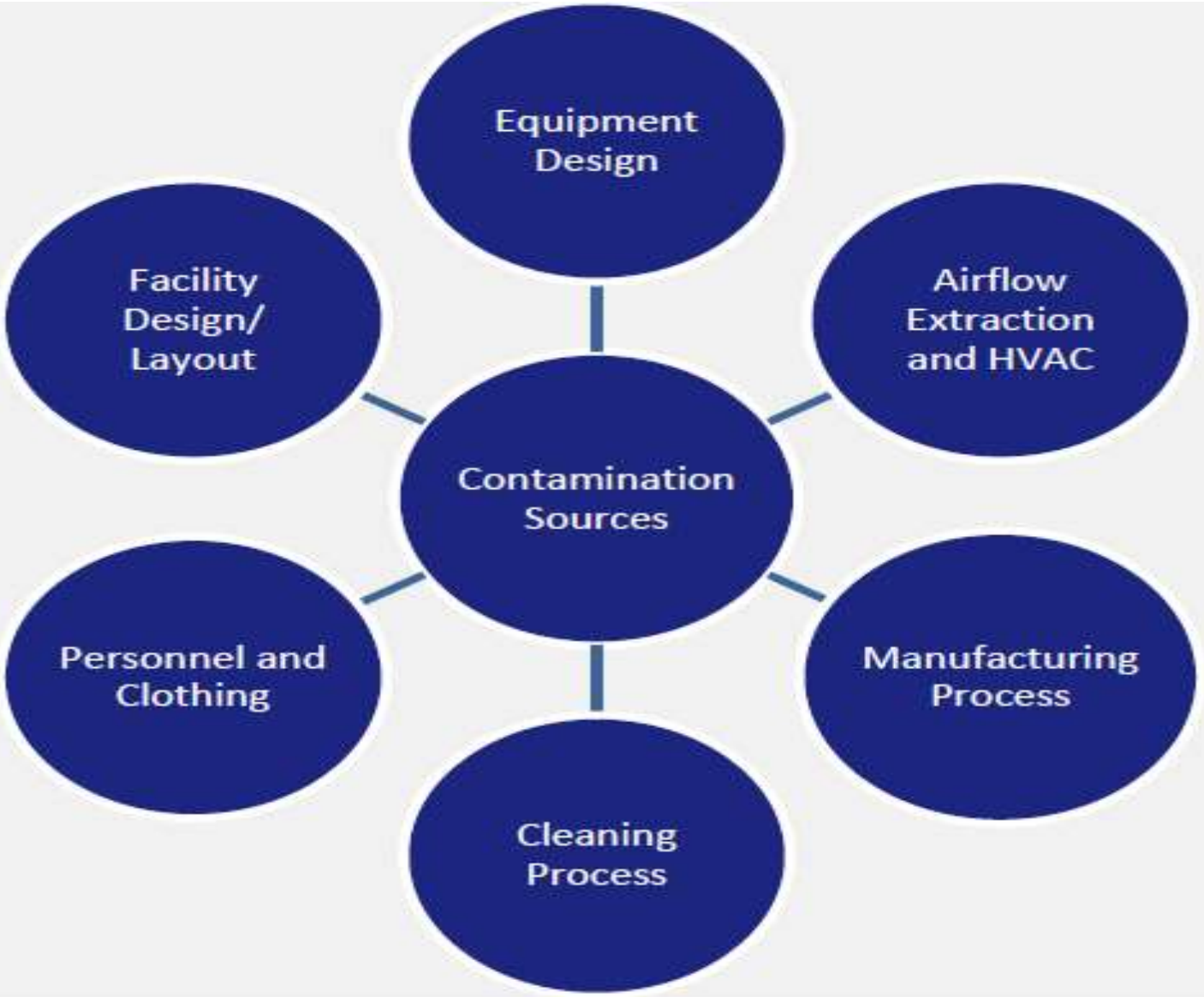
Cross contamination

- Cross-contamination is the contamination of a starting material, intermediate or finished product with another starting material or product.

It is presence of some material which is not desired. It may not always be visibly seen.

Eg. Fine dust of one product into another product.
Fine black particles of dust into processing

Sources of contamination



TYPES OF HIGHLY CROSS CONTAMINATED PRODUCTS

The products which are more likely to prone to cross contamination include:

- Highly sensitive materials.
- Biological preparations.
- Hormones.
- Cytotoxics.

MATERIALS:

- ✓ Improper handling of materials can lead to spillage on ground & cause contamination.
- ✓ Broken materials can leak out and pose a contamination danger.
- ✓ Dusty uncontrolled activities can contaminate processing environment.

PEOPLE:

- People working in the processing area are a powerful source of contamination.

They cause contamination from two sources:

- By their indiscipline activities in the processing area.
- Infectious nature of skin or other body parts.

MANUFACTURING AREAS:

- Manufacturing areas are classified in categories based on expected cleanliness such as aseptic filling area, other sterile operation areas, non- sterile processing areas, corridors, change rooms etc;
- If proper pressure difference is not maintained between the areas then there is chance for entry of air from unclean area to clean area which result in contamination of materials.
- If packaging lines are not well segregated, it can lead to accidental mix-ups of materials from two adjacent lines.

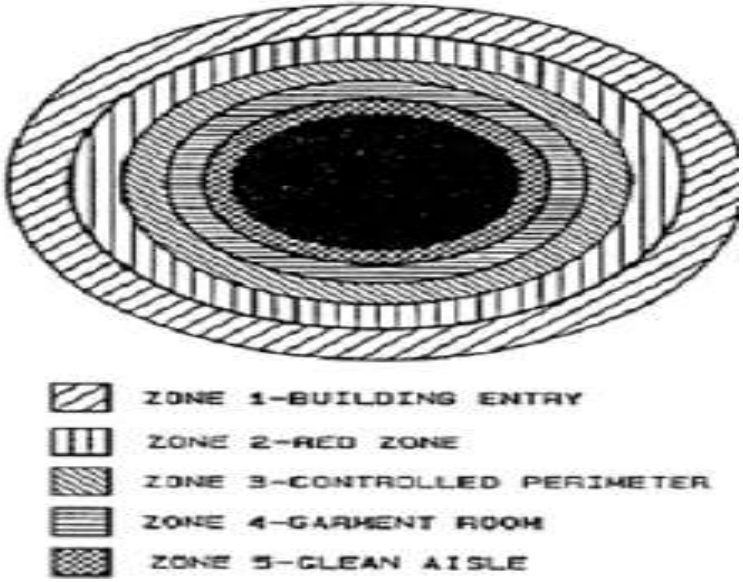
MACHINES AND OPERATIONS:

- Equipments which are not in use for long time, if not maintained clean cause contamination.
- Discharge of exhausted dust, smoke fumes , gases from any equipment or operation can cause contamination.

CONTROLLING OF CROSS CONTAMINATION AND MIX-UPS:

- Exhaust system with proper air filtration and dust collection should be placed where heavy dust is generated.
- Separate air handling units should be provided for each work-station activities.

- Depending upon nature of products being handled different rooms should be maintained at different pressure.
- A pressure difference of 1.5 mm of water guage in the adjacent rooms is recommended.
- Isolation between processes prevents cross contamination; separate rooms, air showers, door interlocks
- “Onion” concept: cleanest areas are inside, have to pass through successively cleaner areas to reach these areas.



- Packaging lines in the central packaging areas should be well segregated. A partition of at least 1.2 to 1.5 meters is recommended in two adjacent packaging lines.

Problems with cross contamination

- Affects product stability and Quality
- Deteriorates the product
- Reduces safety and efficacy to patients
- Increases market recall

Reasons for cross contamination

- Poorly designed air handling system and dust extraction systems
- Poorly operated and maintained air handling system and dust extraction systems
- Inadequate procedures and training for personnel and equipment

Control measures for cross contamination

- Dedicate the facility to the manufacture of a single formulation of product
- Utilize a closed manufacturing system where the product is not exposed to the immediate room environment
- Perform area line clearance according to approved procedures
- Use cleaning status labeling on all equipment and materials used within the manufacturing facility

Cont.,

- External contaminants can be removed by filtration of supply air to retain the required cleanroom classification
- Internal contaminants can be removed by displacing airflow
- Personnel training and clothing

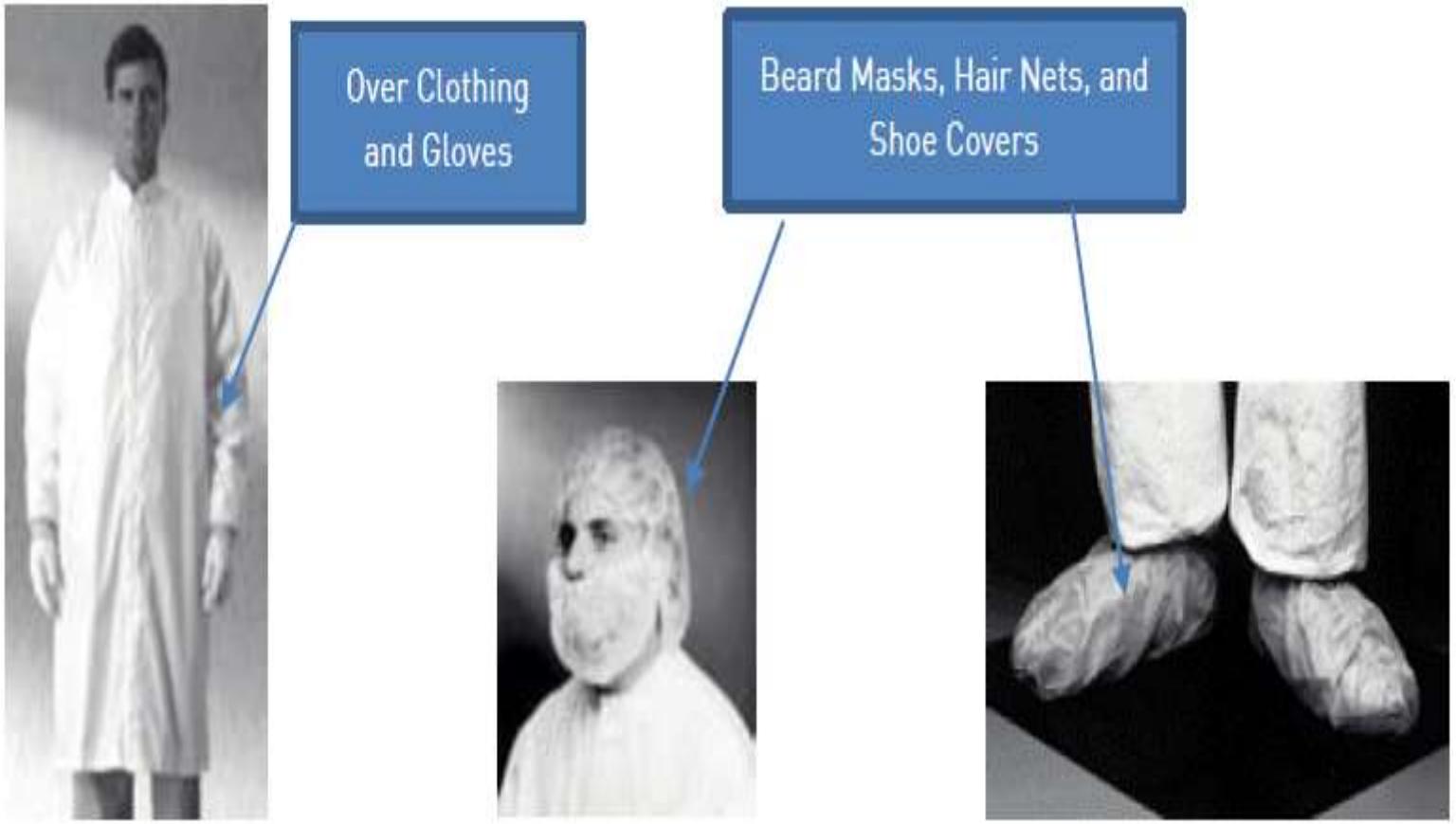
Prior to and during employment, all personnel should undergo the relevant GMP and cleaning training, and be periodically assessed for competency

Cont.,

- The importance of gowning should be implicit and competency of gowning/de-gowning procedures should be clearly documented and routinely monitored particularly in sterile situations via microbiological testing.
- Personnel should wear appropriate clothing to the duties they perform and the environment they work in. These include,

1. Personnel protective equipment (PPE)
2. Clean body coverings (refer to Basic GMP Gowning)
3. Cleanroom clothing (appropriate for each cleanroom classification), which can withstand repeated wear and laundering with minimal deterioration (refer to Cleanroom Gowning)

Basic GMP gowning



Cleanroom gowning

Cont.,

- Appropriate footwear (e.g. steel-capped shoes and shoe covers)must be wored, which is provided by the company

- Street clothing and shoes must not be worn within GMP areas

- Direct contact should be avoided between the operator and starting materials, primary packing materials and intermediate and finished products