PREMISES

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INTRODUCTION

- In an industry, manufacturing operations must be carried out under clean and hygienic conditions because of the nature of the products being manufactured.
- Special care must also be taken to prevent contamination of the products.
- Therefore, the location, design, construction and layout of premises is a vital part of Good Manufacturing Practices.
- Premises refers to the buildings and facilities where pharmaceutical processing is done.
- These places must comply with cGMP requirements.

INTRODUCTION

- There should be defined areas for the following activities:-
- Receipt, identification, sampling, and quarantine of incoming materials
- Sampling of intermediates
- Storage of rejected materials before disposition
- Storage of released materials
- Production areas
- Packaging and labelling areas
- Laboratory operations

1. LOCATION

- Premises must be located in a site that is of suitable size to house all the different departments.
- The following factors are to be considered while selecting the location:-
- Nature of manufacturing and testing performed
- Magnitude of the operation in terms of daily production levels
- Number of products that will be processed
- Storage space required for raw material, in-process and finished goods
- Availability of power, water, labour workforce and closeness to transport hubs.
- Climatic condition and hygiene levels in surrounding

1. LOCATION

- According to Schedule M of the D & C Act,
- The building used for the factory shall be so situated and shall have such measures as to avoid the risk of contamination from external environment including open sewage, drains, public lavatories or which produces disagreeable or obnoxious odours, fumes, dust, smoke, chemical or biological emissions.

2. DESIGN & CONSTRUCTION

- The building used must be designed, constructed and maintained in a manner that permits drug production under hygienic conditions.
- Construction and layout of the building must allow for a sequential and logical flow of the production process and movement of the personnel and materials.
- It must also permit regular cleaning, repair and maintenance work without harming product quality.
- The following factors are considered:-
- General requirements
- Ancillary areas
- Storage areas
- Weighing areas
- Production areas
- Quality control areas

GENERAL REQUIREMENTS

- **LIGHTING –** lighting levels should be adequate to permit operators to do their work properly, accurately and attentively. Lighting of production and packing areas should enable good vision. Suitable lighting level requirements for specific areas should be mentioned.
- **ELECTRICITY** - Continuity of electrical supply is essential for different purposes and backup systems should be available in the event of failure.
- **SEWAGE** – Sewage, and trash shall be disposed in a sanitary manner
- **TOILETS & WASHING** – adequate facilities should be provided and equipped with hot and cold water, soap, detergents, air driers etc.
- **UTILITIES** – adequate ventilation, air filtration, and exhaust systems should be provided.

ANCILLARY AREAS

- Rest and refreshment rooms should be separate from other areas.
- Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users.
- Toilets should not directly communicate with production or storage areas.
- Maintenance workshops should be separated from production areas.
- Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.
- Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

STORAGE AREAS

- Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.
- Storage areas should be designed or adapted to ensure good storage conditions.
- In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.
- Receiving and dispatch areas should be separated and protected.

STORAGE AREAS

- Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel.
- There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.
- Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.
- Highly active (controlled) materials or products should be stored in safe and secure areas.
- Printed packaging materials are considered critical to the conformity of the medicinal products to its labeling and special attention should be paid to the sampling and safe storage of these materials.

WEIGHING AREAS

- Weighing of the starting materials and of the final yield should be done in separate areas.
- Weigh room design depends on the type of processing that will take place in the process area.
- Weight room is viewed as the entry point to manufacturing and the transition point for materials coming from the warehouse and entering process areas, so specific criteria will determine the best location.
- Weighing of hazardous materials and sterile materials should also be done in separate areas.

PRODUCTION AREAS

- Dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitizing materials or biological preparations to minimise the risk of a serious medical hazard.
- The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.
- Premises should preferably be laid out in such a way that the production areas is connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
- Positioning of equipment and materials in proper and logical manner to minimise the risk of confusion between different medicinal products or their components, to avoid cross contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

PRODUCTION AREAS

- Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.
- Pipe work, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.
- Drains should be of adequate size, and designed and equipped to prevent back flow.

PRODUCTION AREAS

- Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.
- Effective ventilation with air control activities should be allowed.
- Production areas should be regularly monitored during production and non-production periods to ensure compliance.
- Packaging areas should be specifically designed and should be avoid the cross – contamination.
- Production areas should be well – lit.

QUALITY CONTROL AREAS

- QC labs should be separate from production areas.
- Areas where biological, microbiological, test methods are employees should be separated from each other.
- Should avoid cross contamination or mix-ups.
- Adequate storage space for samples, reference standards, solvents, reagents and records.
- Separate air supply to laboratory areas.
- Separate room for the instruments used in the laboratory to prevent electrical interferences or contact with moisture.

3. SANITATION

- All areas must be cleaned regularly and cleaning records must be maintained.
- Wastes from manufacturing areas must be disposed in keeping with regulations of Environmental Pollution Control Board. Wastes should be disposed in a safe manner.
- Any waste that are inflammable, or toxic must be stored in a segregated area while awaiting disposal.
- Restrooms, toilets and refreshment area must be located far from manufacturing areas 3.1 Sanitation of Sterile Areas
- Must be cleaned and sanitized often
- Regular monitoring to detect presence of contaminating microorganisms.
- Cleaning procedures should be validated and the cleaning agents used should be sterilized before use.
- For spaces that are inaccessible, fumigation should be used.
- Occasional cleaning with a sporicidal agents to clean any microbial spores present.

4. MAINTENANCE

- CFR 9 211 states that “ any building used in the manufacture, processing, packing or holding of a drug product shall be in a good state of repair.” Facility maintenance includes a check on :-
- Spoilage of plaster
- Peeling off of paints
- Ceiling leakages
- Water, steam, gases pipeline leakage
- Loose or broken tiles
- Improper closing of doors, windows, electrical wiring or fitting
- Missing tube lights A detailed checklist may be prepared, during routine inspection of the facilities and identified deficiencies should be rectified immediately and maintained.

4.1 Maintenance of Sterile Areas

- The sterile manufacturing areas should be maintained as per the written SOP for cleaning and disinfection.
- Cleanliness of air is defined by number of airborne particles in diameter per unit volume of air. The number of particles serves as a parameter for early detection of environmental deterioration.
- Air cleanliness is classified into 4 types :- Grade 1, Grade 2, Grade 3, Grade 4
- Grade 4 has the number of airborne particles whereas the Grade 1 has the lowest number of airborne particles.
- Cleaning of filling and sealing areas should be Grade C or higher. Personnel entry to these areas should limited.
- Direct support areas also should be cleaned under Grade C or higher. The number of airborne particles and micro-organisms should be monitored on a regular basis when in production & non-production.

4.1 Maintenance of Sterile Areas

- Weighing and preparation areas are usually conducted under Grade C
- Heating, Ventilation, & Air Conditioning (HVAC) systems –air in clean areas should be controlled by designing, instituting and managing HVAC systems. Maintains atmospheric conditions at appropriate levels.
- Temperature and RH – should be appropriately established, controlled, monitored, and maintained throughout the processing as both the parameters have a direct impact on materials and products, comfort of personnel, and microbial contamination.
- Sterile area should be cleaned & disinfected according to SOP's and the performance should be recorded.
- Cleaning and disinfectant agents should be evaluated confirmed by quality. Their efficacy should be assessed and validated. Agents used in Grade A or B areas should be filtered or treated to ensure sterility and prevent internal microbial contamination.

4.1 Maintenance of Sterile Areas

- When cleaned or disinfected, surfaces that come in direct contact with pharmaceutical products should be free of the cleaning and disinfecting agents after cleaning and disinfection.
- If sporicides or fungicides are used, the type, usage, procedures should be predetermined and specified in writing.
- Expiration dates should be established for disinfectants.
- Disinfection should not precede cleaning.
- The chemical properties of cleaning agents and disinfectants on facility and equipment surfaces, should be assessed prior to their selection.
- Air- secure constant airflow from area of higher to lower cleanliness level in order to maintain environmental conditions.
- Pressure difference areas of different cleanliness levels should be defined, monitored and controlled.
- Continuous monitor of pressure difference is recommended and install an alarm to enable detection of any pressure difference.

5. UTILITIES

- Building must be supplied with adequate light, water, power supply and ventilation and must be fitted with systems to maintain the temperature and humidity of different areas at desired levels
- Arrangements to protect against the entry of pests, insects, rodents
- Fittings, ducts, pipes and ventilation points must be designed in such a way that they do not produce difficulty in cleaning.
- Sensitive drug manufacturing areas must be air-conditioned to achieve optimum temperature and humidity conditions
- All areas must receive filtered air
- Lighting facilities – visual inspection areas should be brightly lit, light sensitive drug manufacturing requires amber lighting provisions.
- Water system – shall be installed to provide water of the quality required for the drug product. Portable water for washing and cleaning whereas distilled water for testing and manufacturing can be used

5. UTILITIES

- Flooring shall be smooth, have no creak and crevices and be in such a way as not to permit any accumulation of dust.
- The wall of the room in which manufacturing operations are carried out shall have a height of six feet from the floor, smooth and water proof and also be capable of cleaning. Plastic, epoxy or polyester coating with carried up walls base or raised floor.
- Space for offices, aisles and toilets should be adequately given.
- Rooms must be sized only after fully understanding what goes into the room, and the process that takes place between the four walls.
- Availability of public transport should also be considered.

6. ENVIRONMNETAL CONTROL

- Environmental control is essential to the manufacture of a quality product.
- Control the level of microorganisms and air-borne particles.
- Evaluate the efficacy of cleaning, disinfection, and decontamination procedures.
- Environmental monitoring can be of two types:- microbiological control and particle control.
- SOP’s for implementing any type should be established and implementation outcome should be recorded.
- Program should be developed by assessing and examining properties of the substance being monitored, frequency of monitoring, sampling locations etc
- Optimal number and locations of monitoring points should be determined for individual processing areas.

6. ENVIRONMNETAL CONTROL

- Devices for collecting air borne particles should be calibrated.
- Size of the area to be sampled should be determined based on the shape and surface condition of monitoring targets and locations.
- Culture medium used for monitoring should be tested for the absence of cell growth inhibitory substance.
- Gases that may directly contact pharmaceutical products, primary containers, surfaces should be periodically inspected and controlled to ensure the absence of micro-organisms.
- For adequate maintenance, monitoring data routinely obtained should be analyzed to detect any trends in changes in the environmental conditions and establish specific limits.
- Even if changes in the environmental conditions do not deviate, any future deviations should be predicted and the causes investigated to maintain the quality of the environment at an appropriate level.

7. CONTAMINATION CONTROL

- Contamination is the “ undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during production, sampling, packaging, or repackaging, storage or transport.
- Common sources – dust, skin, hair, microorganisms, grease, chemicals and particulate matter.
- Types – functional and nuisance contaminants
- Functional contaminants – which has detrimental effect on product or processes.
- Nuisance contaminants – which does not have functional affect on product or processes.
- Five major classes of pharmaceutical contaminants – particles, metallic ions, chemicals, bacteria, airborne molecular contaminants

7.1 CLEAN ROOM STRATEGY

- Clean room refer to a controlled environment where level of contamination is kept very low to meet requirements specified in terms of number of particles per cubic meter.
- To achieve this, air enters the clean room through High Efficiency Particulate Air (HEPA) filters that remove particles greater than or equal to 0.3 micron in size.
- Typical flow rate – 90-100 ft/mint
- Two types of air – vertical and horizontal laminar flow
- Elements of a Clean Room :- adhesive floor mats, gowning area, air pressure, air showers, service bays, double door pass through, static control
- Adhesive floor mats – placed at every entrance to pull off and hold dirt.

- Gowning area – between clean room and plant. Supplied with filtered air from HEPA filters.
- Air pressure – high pressure in the clean room causes a low flow of air out of the doors and blow air borne particle back to the dirtier hallway.
- Air shower – located between gowning room and clean room. High velocity air jets blow off particles from the outside of the garments.
- Service bay – semi clean area for storage materials and supplies.
- Double door pass through – may have a supply of positive pressure filtered air with interlocking devices that prevent both the doors to open at same time.

7.2 WATER

- Unacceptable contaminants are found in water
- Removed by reverse osmosis and ion exchange systems
- Solid particles are removed by sand filtration
- Bacteria are removed by sterilizing using UV radiation
- Organics like plant and faecal materials are separated by carbon bed filtration. 7.3 CHEMICAL PROCESSING
- Chemicals used should be of 99.9%.
- Inside of containers should be cleaned.
- Use containers that do not dissolve the chemicals
- Use particulate free labels

7. 4 CROSS – CONTAMINATION

- Contamination of a starting material, intermediate, or finished product with another.
- Manufacture product in the dedicated areas.
- Prevent re-entry or re-circulation of untreated air.
- Use protective clothing
- Regular testing for presence of residues
- Protect premises with air-locks, air extraction systems and pressure differentials.
- Airlocks – the barrier which separates two controlled areas
- Pressure differential – use of low airflow with high pressure.