CHAPTER 1

REGULATORY REQUIREMENTS FOR PHARMACEUTICAL PLANTS

1.1 Introduction

When we design a pharmaceutical plant we need to understand and follow the basic regulatory requirements for the construction of a pharmaceutical plant. These requirements are mainly divided into two categories namely -

- Requirements related to good manufacturing practices currently followed in pharmaceutical industry. These are elaborately describe in the various international cGMP guidelines.
- Requirements related to Factories Acts and Rules, which is a Central Act and the rules described separately by each state in India, for this work we have referred the rules specified by the state of Maharashtra.
- In addition to these, there are specific rules and regulations related to following activities which should be referred separately by the reader e.g.,
  - Regulation related to water and air pollution.
  - Regulation related to handling and storage of inflammable materials etc.

1.2 Regulatory Requirements Related to Current Good Manufacturing Practices in Pharmaceutical Industry

The cGMP requirements are described in the various guidelines which deal mainly in the following categories, e.g.,

(a) Requirements related to surroundings.
(b) General requirements for pharmaceutical plants.
(c) Requirements related to various departmental areas in the plant and
(d) Requirements related to special products. e.g., sterile products.

We will briefly deal with these guidelines below:

(a) Requirements Related to Surroundings of the Plant

Part I of schedule-M of Drugs and Cosmetics Act- 1940 states the requirements in the following words- "The factory building(s) for manufacture of drugs shall be so situated and shall have such measures as to avoid risk of contamination from external environment including open sewage, drain, public lavatory or any factory which produces disagreeable or obnoxious odour, fumes, excessive soot, dust, smoke, chemicals or biological emissions."

Only Indian cGMP guidelines specifically talk about "surroundings" of pharmaceutical plant. All other international guidelines talk in terms of "General Requirements" and "different plant areas." In the next section, we will review the "General Requirements" related to pharmaceutical plants.

Comment

Many countries have industrial zone concepts, i.e., a particular type of industry planned by design in a particular part of the country, province or even city. When deciding this, the basic requirements of the industry are taken into account and hence selection of location for the organization is simplified.

Presently in India also such industrial zones are coming up e.g., Information Technology industry is coming up in Hyderabad, Bangalore, and Pune etc. Similarly pharmaceutical industry is coming up in places like Baddi in Himachal Pradesh, more similar pharmaceutical zones are expected come in more places in India.

Some of the major points to be considered in these cases are - Land cost, water sources, supply of electric power, extremes of climate like – heavy rain, extremes of temperature, earthquake proneness, transport facilities for material

and men, Availability of trained or skilled man power, Labour and industrial legislations, cost of living, etc.

(b) General Requirements for Pharmaceutical Plants

After reviewing the leading international cGMP guidelines, we can summarize the same in the following points.

1. Pharmaceutical plants must be located, designed, constructed, adapted and maintained to suit the operations to be carried out.
2. Their layouts and design must aim to minimize the risk of errors and permit effective cleaning and maintenance, in order to avoid cross-contamination, built up of dust or dirt and in general any adverse effect on the quality of the product and safety of the personnel.
3. The Canadian guidelines are similar to above 1 and 2 but adds one point or "Orderliness" in the plant and specifically talks about preventing contamination of drug and addition of extraneous materials to the drug. It also talks about regular maintenance of the plants to prevent deterioration of the premises and finally says that the –"Ultimate objective of all endeavours is product quality."

Comment

Pharmaceutical plants must be designed so that they must meet following requirements. They should be easy to clean, maintain and operate. These factors must be taken into account while designing the plant layout and detailed exercises should be carried out for men and materials movement, considering the manufacturing flow charts of the products to be manufactured. Zigzag movements of men and materials should be avoided as far as possible.

Avoiding cross contamination and mix-ups is the main idea in designing the pharma plants and working out their layouts. Layouts include equipment, subsection, section, department etc. Equipment or workstation is the basic unit of operation e.g., a compression m/c for tablets, a sifter, a capsule filling m/c etc. For avoiding cross contamination and mix-ups the flow of materials is to be considered as primary aspect and other aspects like, storage of intermediate materials at different stages of processing and packing and also the separation of air handling unit must be considered to avoid contamination of materials.

Manufacturing plants must be situated in such an environment which protect all the manufacturing processes by minimizing the risk of contamination of R.M. /P.M. / Intermediate and finished products.

Comment

Protecting manufacturing processes in plant from contamination involves control on the environment. A careful planning of HVAC system must be done to avoid contamination. Following points must be considered while doing this e.g., segregation and clearly defining the scope of individual air handling unit so that only one product is being exposed in that area at any time of operation.

Duct and filter cleaning procedures must be well defined and documented. The HVAC system details must be worked out very critically, these include details like,

- Temperature
- Humidity
- Differential pressure
- Air changes per hour
- Class of air etc.

Even SOPs related to movement of men from one workstation to other workstation must be clearly defined. The seven zone concept of area planning may be worth considering while planning the layouts of pharmaceutical operations. The Dholka plant of Cadila Pharmaceuticals Ltd., was pioneer in this area.

5. Manufacturing plants should be so constructed that they can always be kept in clean and sanitized conditions.

Comment

The vacuum cleaning lines laid down in plants with connections at suitable points may be a fast and easy method of cleaning. These can at least be planned for major corridors and if well planned with a powerful central vacuum system other workstations may also be connected to this. The dry dust may be collected by this way at few selected points in the plants, eliminating physical transfer of collected dust from the plant. Suitable trash collection systems may also be planned. Trash collection points may be planned in each section or subsection. Each such trash collection point may have recycled plastic bags put in a suitable wire meshed containers and these bags may be collected along with collected trash at least twice in a shift of 8 hours or whenever required.

Sanitization SOP and records must be in place and followed.

Sanitization SOPs should be clearly described for different areas e.g., corridors, engineering service areas, wash places, change rooms, linen rooms, non-sterile processing areas, primary and secondary packaging areas

and sterile processing areas. Aseptic operations areas must have vacuum cleaners made up of at least S.S.304 and fitted with additional HEPA filters. The people doing sanitation work in aseptic areas must be specifically trained in entry and exit from the aseptic area, and method of handling sanitation equipment and other materials like detergents and disinfectants etc for this purpose substances like cresol with soap, (Lysol) which are highly caustic and can result into physical accidents because of its contact to skin or eye etc people must be trained in safety procedures for using such materials and methods of dealing with accidental injuries by such caustic substances.

U.S.F.D.A. consider the role of sanitary supervisor as one of the important positions and its detailed job description is demanded by F.D.A. inspectors during their plant audits, hence well experienced and suitably qualified people should be put in charge of this position. Records of sanitary work carried out as per laid down SOPs must be maintained.

6. Manufacturing plants should always be kept in a good state of repair. It should be so designed, so that the maintenance operations can be carried out without affecting the product quality. Separate service lanes may be provided.
7. SOPs and records should be kept for cleaning, maintenance, disinfection and sanitization.
8. Plants should be maintained in order with reference to –
    - Electric supply
    - Lighting
    - Temperature
    - Humidity
    - HVAC

You should have specifications and records of maintenance about the above mentioned points.

Comment

A detailed SOP and relevant records should be maintained for building maintenance. The maintenance activities should cover following areas at the minimum.

(i) Wall and ceiling surfaces. No peel off of paint is permissible; and such situation must be immediately repaired, this is to be considered as one of the main source of material contamination in the processing or other areas.

(ii) Brocken tiles or surfaces can result in accumulation of dust and dirt and also a potential source of physical accidents. Material trolleys can get toppled or material can fall from the trolleys and fall down on the surfaces and needs to be rejected.

(iii) Routine painting of the facility is a must to maintain the facility, always production worthy.

(iv) Plumbing damages, drain chocking, leaking taps and pipe joints must always be immediately repaired and kept in good working conditions.

(v) Electrical wiring and operating switches should be repaired, if found out of order, immediately.

(vi) Doors and windows must always be closed properly. Whenever you have provided interlocking systems, they must always be functioning properly.

(vii) All the lights in all the areas must be working whenever required. Burnt out lamps and tubes must be immediately replaced.

(viii) HVAC systems must always be in working condition and desired levels of environment conditions in terms of temp, humidity, air changes and class of air must be maintained.

(ix) Lawns outside the plants must be hygienically maintained periodic services of a qualified and trained horticulturist may be sought. Many a times neglected lawn becomes a big and unwanted source of insects creating a nuisance to the plant maintenance.

There are only some of the points which are considered regarding facility maintenance. Ideally a detailed maintenance manual should be prepared covering all related SOPs and recording system. Such SOPs should be followed and records maintained.

9. Plants should be so constructed that they avoid the entry of crawling and flying insects, pests, rodents and other Animals and Birds. A pest and insect control programme should always be in place. Toxic baits should be carefully controlled and used in such a way that they should not present a hazard to product or materials.

Comment

Eliminating pests, crawling and flying insects, rodents, birds etc., is a measure problem faced by plant people. It is always advisable to take care of preventive measures during construction of the plant only. e.g. All doors opening outside must be tight closing so that no space remains open at the side or bottom of closing shutter in closed condition. Rubber gaskets may be useful at appropriate position, PVC strips, air curtains and insecticutors may

be provided. Warehouses may be provided with spine surfaces at the potential areas where accidently entered birds are likely to sit. Birds can not sit on such surface because they will get hurt.

10. Steps should be taken to prevent the entry of unauthorized people. Particularly no unauthorized person is allowed in the area of production, stores and quality control departments.

Comment

Modern pharmaceutical plants should provide small meeting room in the reception or office area, where outside persons can meet the plant people and have discussions; this avoids entering of people who do not need to enter the plant, and still their work can be done. A SOP and record should be in place, where an outsider is required to enter the plant area.

11. Waste materials should be continually removed from the premises and written sanitation procedures available, detailing schedules, methods, materials and equipment. Responsibility should be assigned in writing. Cleaning and disinfection should be on going on a regular basis and must include change rooms, wash rooms toilets and refreshment areas.

Comment

You should have detailed SOP and records for handling and managing waste materials, trash and scrap etc. All such materials coming out from the processing area should be certified before it moves to waste material collection centre. This is to avoid accidental entry of undesired material.

12. Adequate Lighting:

Comment

CFR211.44 gives only one line guideline and states that "Adequate lighting shall be provided in all area." Regulatory guidelines do not make any comment on the intensity of light required in various operational areas. But there are certain industry norms for specific critical areas in the plant they are as follows:

(i) Visual inspection areas for ampoules and vials or similar sterile products → 100foot candle

(ii) Visual inspection areas for liquid oral Bottles or similar non sterile products → 50 to 80 foot candles

(iii) Packaging line in packaging department → 50 foot candles

(iv) Visual inspection of tablets/capsules Or automatic, semiautomatic inspection Belts → 50 to 80 foot candles

(v) Other operational areas in plant → 50 foot candle

Such light intensity should be checked at operational height in the department.

(c) Regulatory Related To Various Departmental Areas

The regulatory requirements related to various departmental areas cover following points.

The regulatory guidelines cover requirements related to the following departments. viz.,

(i) Storage and weighing areas
(ii) Production areas
(iii) Q.C areas
(iv) Sterile – products areas
(v) Ancillary areas covering following :
  (a) Rest, refreshment rooms and smoking areas.
  (b) Change rooms and storing of linen, toilets and washrooms.
  (c) Maintenance workshops.
  (d) Animal houses.
  (e) Now let us briefly look at the regulatory requirements regarding the above mentioned departmental areas.

(i) Storage and Weighing Areas

- Storage area should be of sufficient capacity to allow orderly storage of the various categories of materials and products; starting and packaging material, intermediates, bulk and finished products, products in quarantine and released, rejected, returned or recalled products.
- 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 condition are required (temp and humidity) there should be provided, checked and monitored.

Comment

Storage capacity should be calculated based on following information.

(i) Types of formulation being handled and their volumes per day, week, month etc.
(ii) Inventory to be carried of R.M, P.M and F.G at the plant.

(iii) Specific large volume inventory items to be kept e.g.,

(a) Bottles (Glass or plastic) Here the inventory may be required large, depending upon the suppliers production runs.

(b) Sugar, where large volumes of syrup based liquid orals are prepared.

(c) Other formulation based solvents like glycerin, liquid sorbitol, I.P.A, Methylene chloride etc.

(iv) Special products to be stored e.g., sterile drug powders of antibiotics and other of similar substances.

(v) Active and other substances which are required to be stored in special conditions such as

- Low temp. (Cool area or cold and refrigerated storage etc.)
- Low humidity

(vi) Primary packaging materials.

(vii) Printed packaging materials.

(viii) Separate suitable and sufficient storage area for returned, recalled, rejected goods etc.

Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

Comment

All receiving and dispatch bays must have an extended weather protection for the goods vehicles standing in front of the receiving or dispatch bay. This protects the materials from rain, storm etc. This can be of permanent nature or it can also be of temporary nature. Temporary shelter protections can be created as and when the goods vehicle arrives at the bay. Such temporary shelters are now available readymade, which are fixed at the opening side of the bay and can be folded or unfolded as per need. Such protections either temporary or permanent should have sufficient length and also have enough protection from other two sides also. This should not be considered only as a legal requirement but should be treated as important requirement during the plant design. The receiving and dispatch bays should have provisions for vacuum cleaner and may be other suitable cleaning systems. This is required for the cleaning of external surfaces of the containers of materials received at the receiving bay. The warehouse management should be able to prove that the available cleaning system is

able to take care of the cleaning needs. A SOP should be in place and concerned people must be trained. These people should also be able to explain the system to the inspecting authorities.

- Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

Comment

Identification of materials is one of the major cGMP requirements. The R.M /P.M received may go on changing its identity without having any change in its physical appearance. e.g. A material received may have following changes in identity like

- Material received
- Material sampled
- Material under test
- Material approved
- Material rejected etc.

The ware house should be provided with specific areas either by permanent segregation or by temporary segregation for the above categories of materials and no unauthorized person should be allowed to make any change in this situation.

- There should normally be a separate sampling area for starting materials (e.g., raw and packaging materials) If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross contamination.

Comment

Warehouse should be provided with separate areas for sampling and dispensing of following categories of materials.

(i) Active non sterile substances (general category)
(ii) Active non sterile substances (β- lactam and other specific / sensitive materials.)
(iii) In active raw materials.
(iv) Liquids and semisolid materials either active or inactive.
(v) Sterile powder substances. **
(vi) Highly toxic, poisonous or hazardous materials.
(vii) Primary packaging materials.

A SOP clearly defining the area and sampling and dispensing procedure must be in place and records of such activities carried out should be made in chronological fashion in a log book. (This should include Date and Time also.)

** Normally sampling of sterile powder e.g., antibiotics are carried out in either Q.C labs or in production areas. This always have problem regarding time slots being made available for sampling. The author feels that a beginning should be made to create a separate class 100/ 10000 area in ware housing area for sampling and managed by the Q.C unit.

- Segregation should be provided for the storage of rejected, recalled, and returned materials or products.

Comment

Depending upon the volumes expected to be handled and the material is likely to stay in ware house following areas should be planned in a segregated fashion. e.g.,

- Rejected materials
- Returned materials
- Recalled materials
- Highly active material, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.

Comment

Expected formulations to be made in the plant should be carefully studied for the materials to be used and their volumes required to be handled and stored, in the following categories namely:

(i) Highly active materials

(ii) Narcotics

(iii) Dangerous drugs/ Technical poisons like pesticides and herbicides

(iv) Explosive materials

(v) Poisons (e.g., pot. cyanide etc.)

Suitably secured areas of suitable sizes at appropriate places should be provided in the design of stores and ware houses.

- Printed Packaging Materials are considered critical to the conformity of the pharmaceutical product to its labeling and special attention should be paid to the safe and secure storage of these materials.

Comment

Storage of printed packaging materials must be segregated and have the rooms lockable, along with the storage cupboards also lockable. The main problem comes for the storage of carton which are printed and requires relatively large volumes for storage as compared to the labels, which are generally stored in the pigeon hole cupboards. Lockable big areas may be also provided with wire mesh segregation can be thought of for storage of printed cartons.

Printed and unprinted foils can be stored on solid rods slightly inclined upwards to avoid damage of sides of the rolled foils.

Relatively clean areas (say class 10000) may be provided for sampling of primary packaging materials. (M.H.R.A. inspector had asked for such a facility in one of the audit, which the author has faced in the year 2004.)

- Storage areas should be clean and dry and maintain acceptable temperature and humidity limits.
- Specials storage areas such as cold rooms or low humidity rooms should be provided for materials that require these conditions. The environment should be continuously monitored and equipped with alarms to alert personnel in case of failures, so that alternative arrangements can be made.

Comment

Volumes handled and normal period of storage should be considered while providing the storage area for materials required to be stored at low temp. and low humidity.

- Warehouses that are not computer controlled should provide separate areas clearly demarcated and preferably physically separated for following categories of materials – sampling, quarantine, raw, packaging intermediate, finished products,

rejected, recalled and returned materials or products. Areas must be restricted to authorized personnel only.

- Computer controlled warehouses must have a system which gives equivalent security.

Comment

Warehouses should be provided with sufficient spaces for office work, computer room etc. Depending upon the activity following areas should be considered.

(i) Cabin for warehouse manager and other senior people who will be sitting in this area.

(ii) Office for ware house (one or more)

(iii) Office record rooms / Stationary storage

(iv) Computer room. etc.

- Warehouses should be secured against theft and the important medicines and raw materials should be locked in separate secured areas.

Comment

Dispensing (or weighing) area should be provided as discussed earlier.

- **Weighing Areas**

  The weighing of starting materials and the estimation of yields by weighing should be usually carried out in separate weighing areas designed for that use, e.g., with provision for dust control.

(ii) Production Areas

In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials. e.g., (penicillin) or biological preparations (e.g., live micro organisms) the production of certain other products such as some antibiotics, hormones, cyto toxic substances, highly active pharmaceutical products should not be conducted in the same facilities.

Comment

Formulation wise production areas are any way separate in the same building but if we plan to handle sensitive products, the areas should be preferably in separate buildings which are sufficiently apart and the normal wind direction should be from non sensitive to sensitive products facilities.

1. The HVAC and water system should be separate.
2. The people working in these areas must not have free access to other areas.
3. Uniforms used by people in sensitive product areas must be laundered separately, preferably after decontaminating (or desensitizing).
4. The exhausted air from sensitive product area should be first decontaminated / desensitized by suitable scrubbing method (e.g., pH 8 solution of NaOH for β-Lactum etc). A provision for air sampling after scrubbing should be available to confirm no sensitive material is passed in the atmosphere.
5. Except senior supervisory staff all people working in the area should be separate. Facilities for restroom, snacks and dining should also be separate. The main idea behind this is, all possible care should be taken to avoid cross contamination.

- The manufacture of technical poisons, such as pesticides and herbicides should not normally be allowed in premises used for manufacture of pharmaceutical products. In exceptional cases, the principle of campaign working in some facilities can be accepted provided that specific precautions are taken and the necessary validations are made.

Comment

Campaign working is accepted only in exceptional cases. In such cases following points should be kept in mind.

(i) SOP and records for decontamination and sanitization should be in place and followed.

(ii) Cleaning, sanitization and decontamination procedures must be fully validated. This should be considered for both, facilities and equipment used. In short, everything which comes in contact with such materials like technical poisons such as pesticides and herbicides must be decontaminated before the manufacture of other products start in the same area. Such procedures carried out must be put on record.

- Premises should preferably laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to sequence of the operations and to the requisite cleanliness levels.

Comment

While designing the production areas flow diagrams of material movement as per the progression of the process and also the men movement should be considered to avoid zigzag movement of materials and men both. Such designed facilities should be easy to operate clean and maintain.

- The adequacy of working and in process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion 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.

Comment

Pharmaceutical plant designers should consider following points.

(i) All equipment placed in the plant should be such that it can be easily and conveniently approachable for operation, cleaning and maintenance.

(ii) A service passage may be provided from behind the equipment wherever possible, processing part of the equipment and electro mechanical part of the equipment may be separated by S.S. partition. This may be possible in case of big blenders; F.B.Ds etc.

(iii) The flow diagram should show where the in-process materials are required to be stored. Depending upon the volumes of such materials and normal time of the storage area should be planned. Neglecting these things during planning may result in accumulation of materials in processing area, resulting in danger of cross contamination and mix-ups.

- Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces, (walls, floors and ceilings) should be smooth and free from cracks and open joints should not shed particulate matters and should permit easy and effective cleaning and if necessary disinfection.

- Pipe work, light fittings, ventilation points and other services should be designed and fixed to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purpose, they should be accessible from outside the manufacturing areas.

Comment

Service pipe lines like, different types of waters (Raw, Potable , Purified, Soft, W.F.I) steams (plant steam and purified steam) other gases etc should preferably be drawn from outside the processing area, if possible from top or service ceiling floor and dropped down at the points of use through closed, seamless, S.S. conduits. All such lines must be marked with direction of low and contents inside. International guidelines may be needed for identifying the contents for different gases and other solvents etc. But my personal view is that, since every one working in the area may not be fully aware of such markings hence plain word-writing is still preferable.

- Drains should be of adequate size and equipped to prevent back-flow.

  Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and disinfection. If drains are connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent back-siphorage.

Comment

Open channels, even though shallow, may still be covered with light wet, easily removable and cleanable, preferably transparent cover of suitable size.

- Potable water shall be supplied under conditions of positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations set forth in 40CFR part 141or any relevant country's requirements. Water not meeting such standards shall not be permitted in potable water system.

Comment

Additionally advantages may be taken of chilled water lines available for cooling the potable water if so desired.

- Production areas should be effectively ventilated, with air-control facilities (e.g., temp, humidity, filtration etc.) appropriate to products handled, to the operations under taken, and to the external environment. These areas should be regularly monitored

during production and non-production periods to ensure compliance with their design specification.

Comment

These days, normally the HVAC system is installed above the ceiling of the processing area, and ducts of supply are dropped from the top and returns are taken from bottom of the room through closed systems embedded within the room walls. Scope of each HVAC system and U.R.S requirements must be clearly discussed before the finalization of the HVAC system for each processing area. The U.R.S should consider at least following points in this regard.

(a) Types of products to be handled in the area.

(b) No. of people working in the area.

(c) Heat generated by equipment in operation.

(d) Temp and humidity requirements.

(e) No. of air changes per hour.

(f) Differential pressure desired.

(g) Class of air required to be maintained as per cGMP requirement (e.g., class 100, 10000, 100000 etc.)

- In case where dust is generated (e.g., during sampling, weighing, mixing and processing operations, packaging of dry products) specific provisions should be made to avoid cross-contamination and facilitate cleaning.

Comment

Separate, effective dust collection systems must be provided, plant design should consider these points. So that appropriate openings in ceiling or in walls may be provided during construction of the plant itself.

- Equipment for adequate control over air pressure, micro-organisms, dust, humidity and temperature shall be provided when appropriate for manufacture, processing, packing or holding of a drug product.
- Air filtration systems, including pre filters and high efficiency particulate matter air filters, shall be used when appropriate or air-supplies to production areas. If the air is re circulated to production areas, measures shall be taken to control re circulation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.

- Air handling systems for the manufacture, processing and packing of penicillin (and other β-Lactam products) shall be completely separate from those for other drug products for human use.
- Premises for packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups or cross contamination.

Comment

Normally primary packaging and secondary packing must be separated. Following areas may be considered in this as primary packaging.

(a) Strip sealing and blister packaging of tablets and capsules.
(b) Dry syrup filling
(c) Liquid oral bottle filling
(d) Ointment / Cream tube filling and sealing etc.

- In-process controls may be carried out within the production areas provided they do not carry any risk for the production.

Comment

Every production department should have a separate I.P.Q.C lab, following areas may be considered.

(i) Tablet compression area.
(ii) Capsule filling area.
(iii) Strip sealing and blister packing area.
(iv) Liquid filling area.
(v) A non-sterile room in injection department for I.P.Q.C of filled ampoules/vials. This is in addition to what the operators are doing at the point of fill.

- Production areas should be well lit, particularly where visual-online controls are carried out.

(iii) Quality Control Areas

- Quality control laboratories should be separated from production areas. Areas where biological, micro-biological or radioisotope tests are employed should be separated from each other.
- Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross contamination. There should be adequate suitable

storage space for samples, reference standards (if necessary, with cooling) and records.

- The design of the laboratories should take into account the suitability of construction materials, prevention of fumes, and ventilation. Separate air-handling units and other provisions are needed for biological, micro-biological and radioisotope laboratories.
- A separate room may be needed for instruments to protect them against electrical interference, vibrations, contact with excessive moisture and other external factors or where it is necessary to isolate the instruments.

Comment

In addition to the point written above designing of the quality control labs should consider following area

- Office for Q.C. /Q.A. staff
- Library and conference room
- Stores for glassware, chemicals, microbial media, stationary etc.
- Control samples room.
- Records room.
- Strong room for storage of government original documents like various licenses etc.
- Change rooms for Q.C. /Q.A. staff with wash facility.
- Any other areas

(iv) Sterile Products Area

In addition to the general requirements for the facilities, sterile-products manufacturing areas should give attention to following points:

- All premises should as far as possible designed to avoid the unnecessary entry of supervisory or control personnel. Grade “B” areas should be designed so that all operations can be observed from outside.
- In clean areas all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents and disinfectants used.
- To reduce the accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting

ledges, shelves, cupboard and equipment. Doors should be carefully designed to avoid uncleanable recesses; sliding doors are undesirable for this reason.

- False ceilings should be sealed to prevent contamination from space above them.
- Pipes and ducts should be installed so that they do not create recesses that are difficult to clean.
- Sinks and drains should be avoided where ever possible and should be excluded from areas where aseptic operations are carried out. Where installed they should be designed, located and maintained so as to minimize the risk of microbial contamination, they should be fitted with effective, easily cleanable traps with air break to prevent back flow. Any floor channel should be open and easily cleanable and be connected to drains outside the area in a manner that prevents ingress of microbial contamination.
- Changing rooms should be designed as airlocks and used to provide separation of the different stages of changing, so minimizing microbial and particulate contamination of protective clothing. They should be effectively flushed with filtered air. The use of separate changing rooms, for entering and leaving clean areas is sometimes desirable.
- Hand washing facilities should be provided only in the first stage of changing rooms, not in areas where aseptic work is done. The final stage of the changing room should in the at rest state, be the same grade as the area into which it leads.
- Air lock doors should not be opened simultaneously. An interlocking system and a visual and / or audible warning system should be operated to prevent the opening of more than one door at time.
- A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent room of different grades should have a pressure differential of 10-15 pascals (General Guidelines) particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which the product are exposed clean components which contact the product are exposed.

The various recommendation regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials e.g., pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.

- It should be demonstrated that air flow patterns do not present a contamination risk e.g., care should be taken to ensure that air flows do not distribute particles from a particle generating person, operations or machine to a zone of higher product risk.
- A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.
- In addition to above points discussed from various regulatory guide lines following points must also be considered. These are discussed in "Annex-1" of orange guide under the title of "Manufacturing of sterile medicinal products."
- The manufacturer of sterile products should be carried out in clean areas, entry to which should be through air locks for personnel and / or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.
- The various operations of component preparation product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are divided into two categories, firstly those where the product is terminally sterilized, and secondly those which are conducted aseptically at some or all stages.
- Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risk of particulate or microbial contamination of the product or material being handled.

In order to meet "In Operation" conditions these areas should be designed to reach certain specified air cleanliness levels in the "at rest" occupancy state. The "at rest" state is the condition where the installation is complete with production equipment installed and operating but with no operating personnel present. The "In Operation" state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

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

***Grade A*:** The local zone of high risk operations e.g., filling zone, stopper bowls, open ampoules and vials making aseptic connections. Normally such conditions are provided by a laminar-air-flow work station. Laminar air flow systems should provide a homogeneous air speed of 0.45 met/sec. ±20% (i.e. 72 to 108 feet /min) (Guidance Value) at the working position.

***Grade B*:** In case of aseptic preparation and filling the background environment for grade A zone.

***Grade C and D*:** Clean area for carrying out less critical stages in manufacturing of sterile products.

The airborne particulate classification for these grades is given in the following table.

Grade	At Rest (b)		In Operation(c)	
	Maximum permitted number of particles /m3			
	0.5µm	5 µm	0.5 µm	5 µm
A	3500	0	3500	0
B (a)	3500	0	350000	2000
C (a)	350000	2000	3500000	20000
D (a)	3500000	20000	Not defined	Not defined

(a) In order to reach B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate filters such as HEPA for grade A, B and C.

(b) The guidance given for maximum permitted number of particles in the "at rest" condition corresponds approximately to US federal standard. 209E and the ISO classifications as follows:

Grades A and B - Corresponds to class 100, M3.5, ISO5

Grade C - Corresponds to class 10000, M5.5, ISO7

Grade D - Corresponds to class 100000, M6.5, ISO8

(c) The requirement and limit for this area will depend on the nature of the operations carried out.

Examples of operations to be carried out in the various grades are given in the table below.

Grade	Examples of operations for terminally sterilized products
A	Filling of products, when unusually at risk.
C	Preparation of solutions, when unusually at risk filling of products
D	Preparations of solutions and components for subsequence filling

Grade	Examples of operations for aseptic preparations
A	Aseptic preparation and filling
C	Preparations of solutions to be filled
D	Handling of components after washing

The particulate conditions given in the table for the "at rest" state should be achieved in unmanned state after a short "clean-up" period of 15 to 20 minutes, (Guidance value) after completion of operation. The particulate conditions for Grade A in operation given in the table should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always possible to demonstrate conformity with particular std. of the point of fill when filling is in progress, due to generation of particle or droplets from the product itself.

- In order to control the particulate cleanliness of the various grades in operation, the areas should be monitored.
- In order to control the microbiological cleanliness of the various grades in operations the areas should be monitored.

When aseptic operation is performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling. (e.g., swab or contact plates) Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations.

Additional microbiological monitoring is also required outside production operations e.g., after validation of systems, cleaning and sanitation.

Recommended limits for microbiological monitoring of clean areas in operation.

	Recommended limits for microbial contamination (a)			
Grade	Air sample CFU /m3	Settle plates (dia-90mm) CFU/4 hours(b)	Contact plates (dia -55 mm) CFU /plate	Glove-print 5 fingers CFU/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	NA
D	200	100	50	NA

Notes: (a) These are average values

(b) Individual settle plates may be exposed for less than 4 hours.

Appropriate alert and action limits should be set for the results of particulate and microbial monitoring. If these limits are exceeded operating procedures should prescribe corrective action.

(v) Ancillary Area

(a) ***Rest, Refreshment Rooms and Smoking Areas:*** Rest and refreshment rooms should be separate from other areas. Refreshment areas may be declared as smoking areas.

Comment

These days entire plant declared as “non-smoking areas”. But some senior audit persons and even company executives are smokers. For them one or more smoking room may be provided in the plant at the suitable places where they can go and smoke such rooms may be provided with suitable exhaust system and sitting arrangement.

Refreshment rooms are part of the dining hall.

Rest rooms are generally not provided in the plant however such rooms should be provided. These areas should be used for resting after lunch/dinner till the employee finish their lunch break. In the absence of such area unhealthy practice of using lawns or change rooms or canteens itself is followed. This practice can be avoided by providing suitable rest rooms. The plant management should however see that these areas are not misused.

(b) ***Change Rooms and Storing of Linen:*** Facilities for changing and storing of clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. (Also ref. to factory's Act requirements) Toilets should not communicate directly with production or storage area. These areas should be well ventilated.

(c) ***Maintenance Work Shops:*** Maintenance work shops should if possible be separated from production areas, whenever parts and tools are stored in the production areas these should be kept in rooms or lockers reserved for that use.

(d) ***Animal Houses:*** Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

1.3 Regulatory Requirements Related to Factories Act - 1948 of India and the Maharashtra Factories Rules, 1963

While designing a factory premises the regulations related factories act and rules must be considered along with the F.D.A. regulations. These regulations may slightly vary from country to country but more or less they are similar in nature. They take care of requirements related to health and safety of the people working in such premises, along with other requirements. Following is a brief summary of the requirements specified in "The factories Act, 1948" of India and "Maharashtra Factories Rules-1963."

We describe these regulations in two parts namely –

(A1) Regulations related to health as per Factory's Act - 1948 of India.

(A2) Regulations related to health Maharashtra Factory's Rules - 1963

(B1) Regulations related to safety Factory's Act – 1948 of India.

(B2) Regulations related to safety Maharashtra Factory's Rules - 1963

(A1) Regulations Related to Health: (As per Factories Act- 1948)

1. Effective drainage system must be provided in the factory building.
2. Effective arrangement shall be made in every factory for the treatment of waste and effluent due to the manufacturing process carried on there in, so as to render them innocuous for their disposal.
3. Effective and suitable provision shall be made in every factory for securing and maintaining in every work room-
   (a) Adequate ventilation by the circulation of fresh air, and
   (b) Such a temperature as will secure to workers there in reasonable conditions of comfort and prevent injury to health.
4. Every factory premises must take effective measure to prevent inhalation of dust and fumes by the employees. Suitable dust/fumes extraction systems must be installed.
5. No room in any factory shall be over crowded to an extent injurious to the health of the workers employed there in. The law recommends a minimum of 4.2 cubic meters of space for every worker employed there in.
6. In every part of a factory where workers are working or passing there shall be provided and maintained sufficient and suitable lighting, natural, artificial or both.
7. In every factory effective provision shall be made to prevent glare and formation of shadows which may result in eye-strain or the accident to any worker.

   In every factory effective arrangement shall be made to provide and maintain at suitable points conveniently situated for all workers employed there in a sufficient supply of wholesome drinking water.

   In every factory where in more than 250 workers are ordinarily employed provision shall be made for cooling drinking water during hot weather by effective means and for distribution there of .

8. In every factory
   - Sufficient latrine and urinal accommodation of prescribed types shall be provided conveniently situated and accessible to worker at all times while they are in the factory.

- Separate enclosed accommodation shall be provided for male and female workers.
- Such accommodation shall be adequately lighted and ventilated.
- The floors and internal walls up to a minimum height of 90 cms of latrines and urinals shall be laid in glazed tiles or otherwise finished to provide a smooth polished impervious surface.

9. In every factory there shall be provided a sufficient number of spittoons in convenient places and they shall be maintained in a clean and hygienic condition.

(A2) Regulations Related to Health (As per the Maharashtra Factories Rules – 1963)

Following are some of the important guidelines given the state-rules, which are to be followed along with the requirements specified in the factories Act – 1948.

1. The quantity of drinking water to be provided for the workers in every factory shall be at least 5 liters a day per worker employed in the factory and such drinking water shall be readily available at all times during working hours.
2. During 1st March to 30th November every year the cooled drinking water shall be supplied in every canteen, lunch room, and rest rooms and also at conveniently accessible points throughout the factory. At least one such point shall be provided on each floor, if the factory has more than one floor. At least one water point (also called 'water centre') should be provided for each 150 workers or part there of employed at any one time in the factory. If the number of workers are more than 450 then you should have 3 water centres plus one additional for every 450 or part there of thereafter.
3. Where females are employed, there shall be at least one latrine for every 25 females.

   Where males are employed, there shall be at least one latrine for every 25 males.

   Where the number employees in each category exceed 100, it shall be sufficient to have one latrine for 25 employees in each category up to first 100 and one for every 50 thereafter.
4. There shall be at least one urinal for every 50 male workers or part there of employed at a time; where the number exceeds 500, it shall be

sufficient if there is one urinal for every 50 males to the first 500 and one for every 100 or part there of thereafter.

(B1) Regulations Related to Safety (As per Factories Act – 1948)

1. All floors, steps, stairs, passages and gang ways shall be of sound construction and properly maintained and where it is necessary to ensure safety, steps, stairs, passages and gang ways shall be provided with substantial hand-rails.
2. Safe means of escape for all people in the event of fire is required (Two separate stair cases should be provided to have safe passage of people in case one is obstructed because of fire.)

(B2) Regulations Related to Safety (As per Maharashtra Factories Rules – 1963)

1. Protection from lightening shall be provided for
   (a) Building in which explosion or highly flammable substances are manufactured used handled or stored.
   (b) Storage tanks containing oils, paints or other flammable liquids.
   (c) Buildings, tall chimneys or stacks where flammable gases, fumes, dust or lint are likely to be present.
2. Large quantities of flammable liquids shall be stored in isolated adequately ventilated building of fire resisting construction or in storage tanks. Preferably underground and a distance from any building as required in the petroleum Rules-1976.
3. Important points related to fire safety:
   - Suitable fire exits should be provided.
   - Iron rung ladders or spiral stair cases shall not be used on exit staircases. Fire resistant doors or roller shutters shall be provided at appropriate places along the escape routes to prevent spread of fire and smoke, particularly at the entrance of lifts or stairs where tunnels or flue effect may be created including an upward spread of fire.
   - All exits shall provide continuous means of engross to the exterior of a building or to an exterior open space leading to a street.
   - Exit shall be so located that the travel distance to reach at least one of them on the floor shall not exceed 30 meters. Exit door ways shall open outward, that is away from the room but shall

not obstruct the travel along any exit. The minimum width of an internal staircase shall be 100 cms. The maximum height of a riser shall be 19 cms and the number of risers shall be limited to 12 per flight. Hand rails shall be provided with a minimum height of 100 cms and shall be firmly supported.

- In every factory adequate provision of water supply for firefighting shall be made.

4. *Washing facilities:* These shall be provided and maintained in every factory for the use of employed persons adequate and suitable facilities for washing with necessary means of cleaning and the facilities shall be conveniently accessible. Facilities such as latrines and urinals shall be conveniently located near the rest or lunch rooms.

   If female workers are employed, separate washing facilities shall be provided and so enclosed that the interior are not visible from any place where person of other sex, work or pass.

5. *Ambulance Room:* The ambulance room or dispensary shall be separate from the rest of the factory and shall be used only for first-aid treatment and rest. It shall have a floor area of at least 24 sq.meters and smooth, hard and impervious walls and floor and shall be adequately ventilated and lighted by both natural and artificial means.

6. *Canteens:* The occupier of every factory where in more than 250 workers are ordinary employed, shall provide adequate canteen facility.

   The dining hall shall accommodate at a time at least 30 percent of workers working at that time. The floor area of the dining hall, excluding the area occupied by the service counters and any furniture except tables and chairs, shall be not less than one square meter per person to be accommodated.

7. *Minimum height in rooms:* The height in every room in the building shall not be less than 3.75 meters from the floor level to the lowest part of the roof.

8. *Floor area per person:* There shall be at least 1.1 sq. meter of floor area for every person employed.

9. *Creche*s: In every factory where in more than thirty women workers are ordinarily employed there shall be provided and maintained suitable room or rooms for the use of children under the age of six years of such women.

Such rooms should have a height of minimum 3.75 meters and a minimum of 2 sq. meters area should be provided per child.

Such rooms should be adequately lighted and ventilated.

Ordinarily a suitable fenced and shady open air play ground shall be provided for the older children.