A Review on Parenteral Production Technology

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Abstract

The main objective of this paper is to facilitate the area planning, utilities, environmental control for production of parenteral. Compare to other dosage forms parenterals are efficient. This gives quick onset of action and provides a direct route for achieving the drug effect within the body. So by producing these under necessary requirements we can yield better economic and therapeutical performance.

Keywords: Area Planning, change rooms, environmental control, personnel flow.

Introduction

Parenteral preparations are sterile preparations containing one or more active ingredients intended for administration by injection, infusion or implantation into the body. They are packaged in either single-dose or multidose`` containers[1-3].Parenteral preparations may require the use of excipients such as solvents, substances to enhance solubility, suspending agents, buffering, agents, and substances to make the preparation isotonic with blood, stabilizers or antimicrobial preservatives. The addition of excipients is kept to a minimum. When excipients are used they do not adversely affect the stability, bioavailability, safety or efficacy of the active ingredient(s), or cause toxicity local irritation. There must be no incompatibility between any of the components of the dosage form.

Parenteral drugs are administered directly into the veins, muscles or under the skin or more specialized tissues such as the spinal cord. Circumvented the highly efficient first line body defense that is skin and mucus membrane.

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Thus they should be free from microbial contamination and should have high purity Preparations such as vaccines, human blood and products derived from human blood, peritoneal dialysis solutions, and Radioactive pharmaceuticals require special formulation, methods of manufacture, or presentation appropriate to their particular use and may not comply with certain parts of this monograph.

Types

There are four main forms of parenteral Preparations:

- Injections,
- Intravenous infusions (large volume parenterals),
- Powders for injections, and
- Implants.

Certain injections and intravenous infusions may be presented in the form of sterile concentrated solutions, which must be suitably diluted before use[4]

Facilities required for parenteral production

Parenteral may contain excipients preparations such as solvents, suspending agents, buffering agents, substances to make the preparation isotonic with blood, stabilizers, or antimicrobial preservatives. The addition of excipients should be kept to a minimum. When excipients are used, they should not adversely affect the stability, bioavailability, safety, or efficacy of the active ingredient(s), or cause toxicity or undue local irritation. There must be no incompatibility between any of the components of the dosage form.

Water for injections is used as the vehicle for aqueous injections. It should be freshly distilled by the process described under "Aqua pro Injection", be free from carbon dioxide, and comply with Test for bacterial endotoxins.

Sterilization at this stage may be omitted, provided that the solution or preparation is immediately sterilized upon finalization. For non-aqueous injections, fixed oils of vegetable origin are used as vehicles. Unless otherwise specified in the individual monograph, sodium chloride or other suitable substance(s), may be added to an aqueous solution for injection in order to render the preparation isotonic.[5,6]

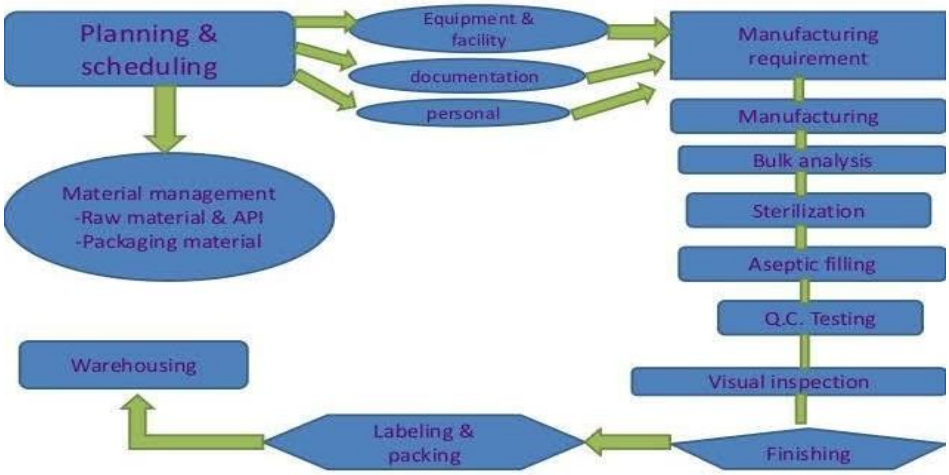

Fig 1: Overview of manufacturing process

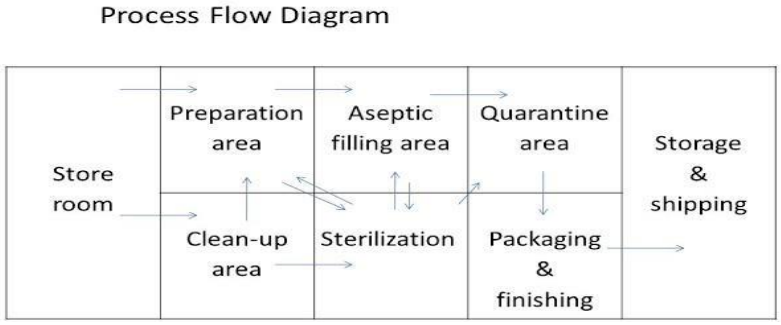

Fig 2: flow of materials

GMP Requirements for Sterile Products

- Specific points relating to minimizing risks of Contamination.
  - – Microbiological
  - – Particulate matter
  - – Pyrogen

General Requirements

- Production in clean areas
- Airlocks for entry
  - – Personnel entry.
  - – Material entry
- Separate areas for operations
  - – Component preparation
  - – Product preparation
  - – Filling
  - – Sealing etc.
- Level of cleanliness
- Filtered air
- Air classification: Grade A, B, C and D.
- Laminar air flow
  - – Air speed (horizontal versus vertical flow)
  - – Number of air changes
  - – Air samples
- Work station and environment
- Barrier technology and automated systems.[7,8]

Quantitative layout of parenteral manufacturing

WHO good manufacturing practices for sterile pharmaceutical products

1. General considerations
2. Quality control
3. Sanitation
4. Manufacture of sterile preparations
5. Sterilization
6. Terminal sterilization
7. Aseptic processing and sterilization by filtration
8. Isolator technology
9. Blow/fill/seal technology
10. Personnel
11. Premises
12. Equipment
13. Finishing of sterile products

General considerations

The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in separate areas within the clean area. [11,12]

Quality control

The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.

Samples taken for sterility testing should be representative of the whole of the batch but should, in particular, include samples taken from parts of the batch considered to be most at risk of contamination, for example:

• For products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work;

• For products that have been heat sterilized in their final containers, consideration should be given to taking samples from that part of the load that is potentially the coolest. [13]

Sanitation

The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with an approved written Programme. Where disinfectants are used, more than one type should be employed. Monitoring should be regularly undertaken to detect contamination or the presence of an organism against which the cleaning procedure is ineffective. Interactions between different cleaning materials should be validated. Appropriate cleaning validation should be carried out to ensure disinfectant residuals can be detected and are removed by the cleaning process.Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilized. Disinfectants and detergents used in Grade A and B areas should be sterile before use.A disinfectant programme should also include a sporicidal agent since many common disinfectants are ineffective against spores. The effectiveness of cleaning and disinfectant procedures should be demonstrated. Fumigation of clean areas may be useful for reducing microbial contamination in inaccessible places.

Manufacture of sterile preparations

Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate level of environmental cleanliness in the operational state to minimize the risks of particulate or microbial contamination of the product or materials being handled.

Clean room and clean-air device classification

Clean rooms and clean-air devices should be classified in accordance with ISO 14644

Classification should be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each grade is given in Table .

Terminally sterilized products

Components and most products should be prepared in at least a Grade D environment to ensure low microbial bioburden and particulate counts prior to filtration and sterilization. Where the product is at unusual risk of microbial contamination (e.g. because it actively supports microbial growth, must be held for a long period before sterilization, or is necessarily processed mainly in open vessels), the preparation should generally be done in a Grade C environment.

The filling of products for terminal sterilization should generally be done in at least a Grade C environment.

Where the product is at unusual risk of contamination from the environment (e.g. because the filling operation is slow, the containers are wide-necked or are necessarily exposed for more than a few seconds

before sealing), the filling should be done in a Grade A zone with at least a Grade C background.

The preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a Grade C environment before terminal sterilization[14,15]

Aseptic preparation

Components after washing should be handled in at least a Grade D environment. The handling of sterile starting materials and components, unless subjected to sterilization or filtration through a microorganism-retaining filter later in the process, should be undertaken in a Grade A environment with a Grade B background.

The preparation of solutions which are to be sterile-filtered during the process should be undertaken in a Grade C environment (unless a closed system is used, in which case a Class D environment may be justifiable). If not sterile-filtered (therefore an aseptic manipulation) the preparation of materials and products should be undertaken in a Grade A environment with a Grade B background.The handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, should be undertaken in a Grade A environment with a Grade B background.

The transfer of partially closed containers, as used in freeze-drying, before stoppering is completed, should be undertaken either in a Grade A environment with a Grade B background or in sealed transfer trays in a Grade B environment.

The preparation and filling of sterile ointments, creams, suspensions and emulsions should be undertaken in a Grade A environment with a Grade B background when the product is exposed and is not subsequently filtered.

Sterilization

Whenever possible products intended to be sterile should be terminally sterilized by heat in their final container. W here it is not possible to carry out terminal sterilization by heating due to the instability of a formulation or incompatibility of a pack type (necessary to the administration of the product, e.g. plastic eye-dropper bottles), a decision should be taken to use an alternative method of terminal sterilization following filtration and/or aseptic processing.

Sterilization can be achieved by the use of moist or dry heat, by irradiation with ionizing radiation (noting that ultraviolet irradiation is not normally an acceptable method of sterilization), by ethylene oxide (or other suitable gaseous sterilizing agents), or by filtration with subsequent aseptic filling of sterile final containers. Each method has its advantages and disadvantages. Where possible and practicable, heat sterilization is the method of choice. In any case the sterilization process must be in accordance with the marketing and manufacturing authorizations.

Terminal sterilization

Sterilization by heat: Each heat-sterilization cycle should be recorded by means of appropriate equipment of suitable accuracy and precision, e.g. on a time/ temperature chart with a suitably large scale. The temperature should be recorded by a probe situated at the coolest part of the load or loaded chamber, this point having been determined during the validation; the temperature should preferably be checked against a second independent temperature probe located at the same position. Sterilization records should be available for each sterilization run and should be approved as part of the batch release procedure. Chemical or biological indicators may also be used but should not take the place of physical controls.

Sterilization by moist heat:-Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator.

The reading of the independent temperature indicator should be routinely checked against the reading on the chart recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position throughout the sterilization period. There should be regular leak tests on the chamber when a vacuum phase is part of the cycle.

Sterilization by dry heat:- Sterilization by dry heat may be suitable for non-aqueous liquids or dry-powder products. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. If air is supplied it should be passed through a microorganism-retaining filter (e.g. a HEPA filter). Where sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins are required as part of the validation.

Sterilization by radiation:-Sterilization by radiation is used mainly for heat-sensitive materials and products. Many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has

been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilization.

Sterilization by gases and fumigants:-Sterilization by gases and fumigants should only be used for finished products where there is no suitable alternative.

Various gases and fumigants may be used for sterilization (e.g. ethylene oxide and hydrogen peroxide vapour). Ethylene oxide should be used only when no other method is practicable. During process validation it should be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material concerned. These limits should be incorporated in the specifications.

Aseptic processing and sterilization by filtration

The operating conditions should be such as to prevent microbial contamination.

In order to maintain the sterility of the components and the product during aseptic processing, careful attention needs to be given to:

- the environment;
- personnel;
- critical surfaces;
- container/closure sterilization and transfer procedures;
- the maximum holding period of the product before filling into the final container;
- The same filter should not be used for more than one working day unless such use has been validated.[16]

The filter should not affect the product either by removing ingredients from it or by releasing substances into it.

Isolator technology

The use of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbial contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for each zone can be realized. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from single-door to double-door designs to fully-sealed systems incorporating sterilization mechanisms.

Blow/fill/seal technology

Blow/fill/seal units are purpose-built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective Grade A air shower may be installed in at least a Grade C environment, provided that Grade A or B clothing is used. The environment should comply with the viable and non-viable limits at rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products which are terminally sterilized should be installed in at least a Grade D environment.

Because of this special technology, particular attention should be paid to at least the following:

•Equipment design and qualification;

• validation and reproducibility of cleaning-in-place and sterilization-in- place;

• background clean room environment in which the equipment is located;

• operator training and clothing;

•interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

Personnel

Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. As far as possible, inspections and controls should be conducted from outside such areas. All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive initial and regular training in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision. Staff who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.

Premises

All premises should as far as possible be designed to avoid the unnecessary entry of supervisory or control personnel. Grade A and 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 to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used. To reduce the accumulation

of dust and to facilitate cleaning, there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be carefully designed to avoid uncleanable recesses; sliding doors may be undesirable for this reason. Swing doors should open to the high-pressure side and be provided with self-closers. Exceptions are permitted based on egress and site environmental, health and safety containment requirements. False ceilings should be sealed to prevent contamination from the void space above them. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Sanitary pipes and fittings should be used and threaded pipe connections should be avoided. Sinks and drains should be avoided wherever possible and should be excluded from Grade A and B areas where aseptic operations are carried out. Where installed they should be designed, located and maintained so as to minimize the risks of microbial contamination; they should be fitted with effective, easily cleanable traps and with air breaks to prevent backflow. Any floor channels should be open and easily cleanable and be connected to drains outside the area in a manner that prevents the ingress of microbial contaminants. Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand-washing facilities should be provided only in the first stage of the changing rooms. There should not be a change of more than one grade between airlocks or passages and changing rooms, i.e. a Grade D passage can lead to a Grade C airlock, which leads to a Grade B changing room, which leads to a Grade B clean room. Changing rooms should be of a sufficient size to allow for ease of changing. Changing rooms should be equipped with mirrors so that personnel can confirm the correct fit of garments before leaving the changing room. Airlock 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 a time.

Finishing of sterile products

Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules, should be subject to 100% integrity testing. Samples of other containers should be checked f or integrity according to appropriate procedures. The container closure system for aseptically filled vials is not fully integral until the aluminum cap has been crimped into place on the stoppered vial. Crimping of the cap should, therefore, be performed as soon as possible after stopper insertion. As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment should be located at a separate station equipped with adequate air extraction.

Vial capping can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a Grade A air supply until the cap has been crimped. Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimize microbial contamination.

Area planing and environmental control

Area planning may be addressed by functional groups ground this critical area with particular attention given to maintaining cleanliness. The goal of the designer is to group manufacturing operations so that the flow to people, product, and components proceeds in the direction of successive steps of increasing cleanliness likewise, the flow of waste materials and products must be thoroughly separated from the flow of clean personnel and product in order to prevent contamination.

Functional groupings

Warehousing

- Basic warehousing functions include receiving, shipping, and in-process storage.
- Receiving areas include unpacking, sampling and incoming quarantine.
- Shipping includes quarantine prior to shipment.
- The storage of spare parts, air filters, change parts, water treatment chemicals, office supplier, laboratory supplies, janitorial supplies, uniforms, an so on may be handled as central storage or individually by department.
- Finished product and certain raw materials need special environmental storage conditions, such as, temperature and humidity control.
- The first and most basic warehouse function is received and holds incoming materials.

Warehouse space is usually of greater height than production areas, is less rigidly controlled from an environmental and sanitation stand point, and usually

has a relatively high density of flammable materials. Thus a separate but adjoining area separated by a firewall is usually the best arrangement[17]

Wall & floor treatment: The design of filling areas or more generally, controlled environment areas involves attention to many seemingly minor details. The basic cleanlability requirement includes smooth, cleanable walls, floors, ceilings, fixtures, and partition exposed columns, wall studs, bracing, pipes, and so on are unacceptable. The need for cleanability also eliminates the open floor system commonly used in the microelectronics industry for laminar airflow rooms. The goal of the designer, when creating the details for the architectural finishes and joining methods, is to eliminate all edges or surfaces with in the room where dirt may accumulate.

All inside walls must be finished; common methods of finish are block, plaster, or gypsum board. Concrete block walls are sturdy and easily constructed. The porosity of concrete block walls can be reduced by coating with block filler prior to painting. But even filled concrete block walls have a surface texture that is not conductive to cleaning. Painted concrete block walls are particularly susceptible to peeling if they are subjected to moisture as from leakage or rain on the backside.Use of ceramic-faced block can overcome the surface finish problems of concrete block. Epoxy paint is normally used to increase the durability and impermeability of the surface.When gypsum board is used, an epoxy point system is normally employee to create a surface that is resistant to cleaning compounds.

Gypsum board is not an acceptable surface for use in powder-filling operations without incorporating an additional surface coating or vapor barrier. By itself, gypsum is susceptible to vapor barrier. By itself, gypsum is susceptible to vapor migration which presents problems in a low humidity controlled area.

To overcome the surface weaknesses of most walls, various heavy coverings are available.A few spray on and brush on coatings have provide a much harder and more durable surface than gypsum, but are still relatively economical to install and do not present the installation difficulties of vinyl sheeting.

The use of modular systems has increased substantially in the last few years that provide a much harder and more durable surface than gypsum, but are still relatively economical to install and do not present the installation difficulties of vinyl sheeting.

The use of modular wall systems has increased substantially in the last few years because they arrive at the construction site prefinished and are much faster. Selection of floor materials poses a particularly difficult problem since they must be durable, and easily cleaned and sanitized. To achieve good floor results, the application must be matched to the particular characteristics of the floor system.

Hardeners may be added to concrete to increase to surface hardness by as much as a factor of 3, greatly improving the floor's resistance to scratching and dusting and are available in colors to improve the appearance of the floor.

A sealed concrete floor is therefore not acceptable for use in controlled areas within a parental filling plant because of the potential for cracking of the soil beneath the concrete when laid as a coating over a cured concrete surface. The plants in many parenteral plants are constructed of epoxy terrazzo.

Finally, the floor is sealed with several coats of urethane to protect the surface finish. The result is a very attractive floor that is extremely impact and abrasion-resistant. A third general type of floor is composed of large sheets vinyl or polyvinylchloride laid on a concrete base floor and "welded" together with heat or sealed at the seams with cement. Selection of compatible material-handled equipment whets and for floors will reduce floor damage. All floors in areas where water can accumulate should toward one or more drain points.

Lightning fixtures

Lighting fixtures should be reduced flush with the ceiling. Since most lighting fixtures are not tightly sealed, the diffuser should be sealed integrally with the ceiling, and the lamps changed from outside the room. Either recessed or surface mounted fixtures can be used. Special "wash- down" fixtures are well sealed, but protrude obtrusively into the room and have clips and sealing lips which are difficult to sanitize. Areas having a full HEPA ceiling obviously cannot accommodate recessed lighting fixtures. In these areas, fixtures are of a special "teardrop" shape which minimizes disruption to the laminar airflow pattern.

Change rooms

Personnel access to all controlled areas should be through change rooms. Change rooms concepts and layouts vary from single closet size rooms to expensive multi-room complexes.

Entrance to a change area is normally through vestibules whose doors are electrically interlocked so that both cannot be opened simultaneously, thus maintaining the necessary air pressure differential to prevent the entry of airborne contamination. Upon entry into the change room wash sinks are provided for scrubbing hands and forearms. Although commercial hands are often used, they may create undesired airflow patterns and may circulate particular

laden air. Special filtered driers are available to minimize the creation of particulate contamination. Further control may be achieved by using filtered and heated compressed air for drying to reduce further particular potential. In some facilities, a foamed type of alcohol is dispensed on the hands, which then evaporates. This is used to eliminate need for tap water and sinks in the gowning rooms, since these can be a potential source of contamination. After hands are dry, garments are taken from dispensers and donned while moving across a dressing bench. As a final gowning step, aseptic gloves are put on and sanitized. Exit from the change room to the controlled area is, like entrance, through an interlocked vestibule. Depending on the degree of disrobing required, separate gowning facilities facilities may be provided for men and women.

Separate "degowning" rooms are provided where the clean room garments can be discarded prior to leaving the controlled zone.

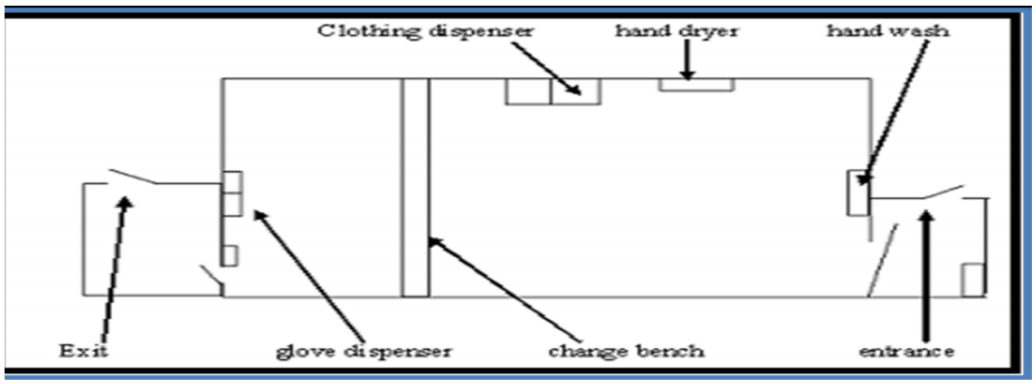

Fig 3: Change room

Personnel flow

The movement of personnel should be planned during the design of individual plant areas. Each individual production area may have a smooth and efficient personnel flow pattern, a discontinuous or crowded pattern may develop when several individual production area plants are combined. The separation of people and products is greatly facilitated by the use of the third dimension. Security concerns about personnel flow may include minimizing access to controlled substances and minimizing the personnel traffic in or near work areas where controlled substances are handled.The flow of material and personnel through corridors are inefficient and unsafe paths for moving materials, particularly if heavy forklifts are required.

Parenteral plants, like any other plant have visitors and the degree of access to be granted must be determined. A glassed mezzanine or balcony provides absolute solution yet may give an excellent view of the processes, but may not be adaptable for single-floor layouts.

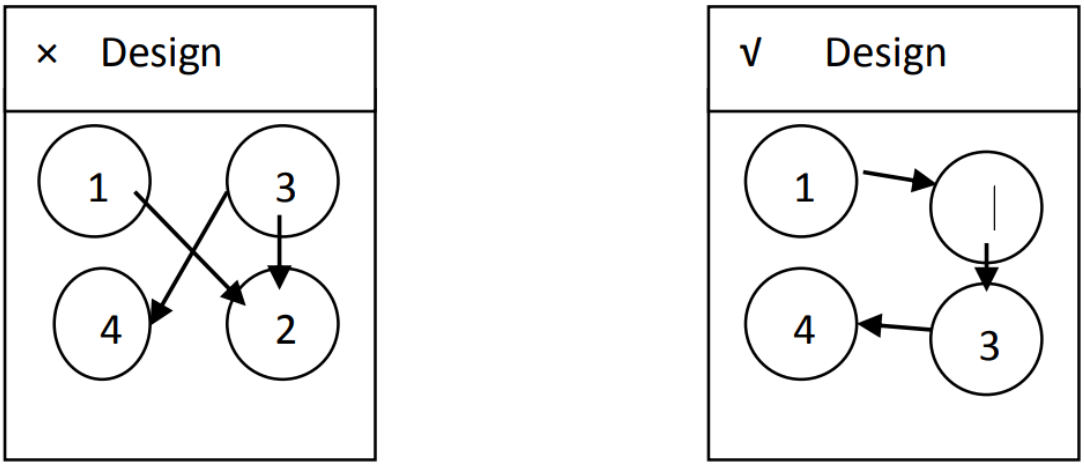

Fig 4: personal flow

Discontinuous and crowded flow patterns can decrease production efficiency, increase security problems, and increase the problems of maintaining a clean environment. Personnel flow path from zone to zone must be such that access to higher level of cleanliness is only through change rooms, gowning rooms, locker rooms, or other areas as may be required to prepare the personnel for the cleaner area.

Utilities and utility equipment location

Utilities

Piping system in particular, must be initially and often periodically cleaned and serviced. Exposed overhead piping is not acceptable from a cleanliness or contamination standpoint since it collects dirt, is difficult to clean and may leak. Buried or concealed pipe may require unacceptable demolition for cleaning or repair. Whenever possible, major utility distribution services should located outside of clean areas. The actual utility connections are distributed within the plant, building codes usually require that their distribution systems be exposed and not buried with-in walls or ceilings.

Utilities equipment location

Public utilities require space for metering. In addition to meeting, electrical power system require for switchgear and transformers. Water systems usually require treatment to ensure consistent quality. Plant generated utilities typically require steam boilers, air compressors, and distillation, the typical "boiler room" approach. Although a central location minimizes distribution problems and minimizes service distribution distances. Proper equipment maintenance is difficult in foul weather, especially winter. Heavy equipment may damage the roof- structure, particularly if the equipment location requires numerous penetrations through the roof which, coupled with equipment vibration, will invariable lead to leakage. A mezzanine equipment platform eliminates the problems of operation in a harsh environment and roof loading.

Materials

The selection of materials for a piping system depends on the product tube handled, the product purity desired, material cost, and installation cost.

Carbon steel

Carbon steel pipe, manufactured according to ASTM standard A53 of A106 is commonly available in various schedules or wall thicknesses. The standard schedule is number 40. Common uses include water, compressed air, oil, nitrogen, steam and steam condensate.

Copper

Copper is commonly used for water and compressed air piping because of easy installation. Either type of K or type L, tubing is available in annealed form, making it more flexible. Copper has a smooth surface finish compared to that of carbon steel and is relatively resistant to corrosion. Copper loses strength rapidly at higher temperatures and is not recommended for steam use.

Type 304 Stainless Steel

It contains approximately 18% chromium and 8% nickel, being nonmagnetic and non-harden able. Type 304 is a good general purpose alloy for pharmaceutical applications where pitting corrosion is not a problem.

Type 316 Stainless Steel

It is similar to type304 except that type 316 has 2- 4% higher nickel content. 2% less chromium and has 2-3% molybdenum.

The molybdenum gives type 316 improved resistances to pitting corrosion as compared to type 304 and slightly improved general corrosion resistance.

Both type 304 and 316 stainless steel are susceptible to intergranular corrosion adjacent to welded areas

Type 316L piping is typically used for distribution of water for injection, clean steam, deionized water, compressed air to be used in controlled environmental areas and or product transfer piping.

Plastics

Plastic piping has been used in drain lines and chemical treatment systems. Additionally, some companies have used poly vinyldene fluoride (PVDF) piping for dematerialized water. This poly fluroplastic has an advantage in that a system is constructed by thermal fusion of the joints rather than welding.

Surface finish

Surface finish specifications after refer to 3-A sanitary standards. According to these standards a product contact surface should be polished to a number 4 finishes, a finish obtained by polishing with a 150-grit sanding belt. In addition to mechanical polishing, electro polishing has been used to improve further the surface finish of stainless steel.

The electro polished surface exhibits somewhat better corrosion resistance than mechanically polished surfaces.

Joining techniques

Piping system can be joined by threading, welding or clamping. Threaded connections are common for non-electrical applications where iron pipe may be used. Sanitary tubing is welded by using an automatic fusion welding machine that fuses the two sections of tubing together, using an electric current and a purge of inert gas on the inside of the tubing to yield a high quality weld. The quality of the weld is checked internally by

the use of a video boroscope.Following the welding, the piping is passivated with nitric acid to form an oxide layer on the inside of the pipe, thereby providing increased corrosion resistance.

Valuing

A typical ball valve as ported ball that is rotated 90° to regulate flow. A diaphragm valve, control flow by compressing a diaphragm against a wire placed across his direction flow. A number of new valves came into the market recently to deal with the limitations of existing valves. One of the best is pinch valve. The pinch valve is a cylindrical valve that is modulated by pinching the inner tubing wall of the valve.

Utility services connection arrangements

Utilities must be carefully connected to avoid stagnant areas and to avoid difficult to clean areas just as would be done for the utility distribution system. To minimize contamination potential, typical utility arrangements and typical service connections should be defined during planning. Utilities can be arranged so that the service connections enter a room vertically upward, horizontally, and vertically downward, with various advantages and disadvantages. Vertical upward service connections, with connections under machinery, create a very neat appearance, a low full unobstructed machine access, and require only short connection lengths. Horizontal service connections are often used in single level facilities to avoid floor excavation during equipment relocation or utility maintenance. Horizontal service do limit machine access, create some congestion, and may necessarily be longer than vertical service connections. Vertical downward services create a visually cluttered appearance and may restrict access to the working surface of equipment. This type of connections may also be undesirable if laminar flow coverage of the equipment is necessary.

7. Engineering and maintenance:-From an engineering stand point, even a location outside the plant can serve well if access to the production area by engineers for field wok is not too difficult often particularly in small or less complex plants, maintenance or other plant service functions such as utilities or combined with engineering, making an in-plant location desirable. Although often associated with engineering, maintenance is a unique and distinct function. Maintenance responsibilities cover all areas of the plant and can generally be grouped into two categories:

Plant maintenance and production maintenance.

Production maintenance is a direct production support function and includes all the routine and recurring operating maintenance work. Production maintenance facilities are usually minimal, often only a place to store a tool box, and seldom have more than a small workbench.

Plant maintenance operations, in contrast, are more diverse. They vary from heavy maintenance on production equipment to cosmetic work on the building exterior and often include plant service functions such as sanitation, ground sweeping, or waste disposal.

Facilities required are extensive and mostly include provisions for equipment cleaning. Disassembly major rebuilding of equipment and painting. These operations can present a contamination risk to pharmaceutical operations and must be isolated.

Although maintenance requires access to all parts of a plant, it must be located to be able to receive and handle cumbersome and bulky groups.

An absolute must is that the plant maintenance shop be located so that its personnel have easy access to major plant utilities and service equipment.

Types of containers

Ampoules: They are intended for single use only; ampoules are opened by breaking the glass at a score line on the neck. Because glass particles may become dislodged during ampoule opening, the product must be filtered before it administered. Because of their unsuitability for multiple-dose use, the needs to filter solutions before use and other safety considerations have markedly reduced ampoule use.

Vials: are glass or plastic containers are closed with a rubber stopper and sealed with an aluminum crimp.

Advantages over ampoules:

- They can be designed to hold multiple doses (if prepared with a bacteriostatic agent).
- It is easier to remove the product.
- They eliminate the risk of glass particle contamination during opening.

Prefilled syringes -These designed for quickest administration and maximum convenience. Drugs administered in an emergency (e.g., atropine, epinephrine) may be available for immediate injection when packaged in prefilled syringes.

Infusion solutions are divided into two categories: small volume parenteral (SVP), those having a volume of 100 ml; and large volume parenteral (LVP), and those having a volume of 100 ml or greater. Infusion solutions are used for the intermittent or continuous infusion of fluids or drugs.

List of Equipments (as per schedule-M)

The following equipment's is recommended:

a) Manufacturing area

1. Storage equipment for ampoules, vials bottles and closures.
2. Washing and drying equipment.
3. Dust proof storage cabinet

4. Water still.
5. Mixing and preparation tanks or other containers.
6. Mixing equipment where necessary.
7. Filtering equipment.
8. Hot air sterilizer.

b) Aseptic filling and sealing rooms

9. Benches for filling and sealing.
10. Bacteriological filters.
11. Filling and sealing unit under laminar flow work station.

c) General Room.

12. Inspection table.
13. Leak testing table.
14. Labeling and packing benches.
15. Storage of equipment including cold storage and refrigerators if necessary.

An area of minimum sixty square meters partitioned into suitable sized cubicles with air lock arrangement, is recommended for the basic installation.

Equipments

Sterile Garment Cabinet

- Made up of Stainless steel.
- Ensure a clean storage space by making use of UV disinfectant and heating through IR lamps.
- These cabinets may be designed in horizontal air flow system and clean air through HEPA filters.

Syringe Filling Machine

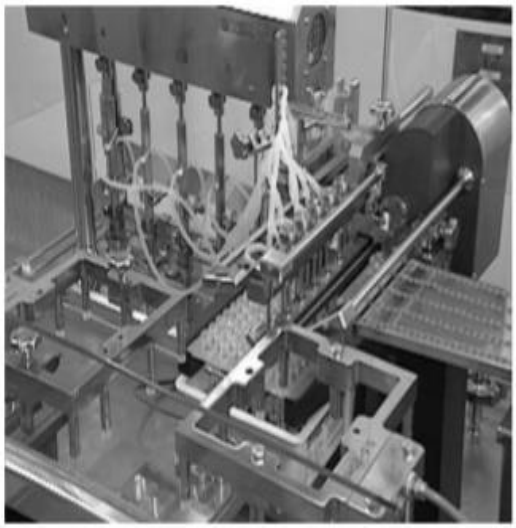

Fig 5:Syringe Filling Machine

Characteristics

- Barrier isolators
- In-process check weighing
- Filling: rotary piston pumps.
- Volume: 0.2 to 29 ml
- All types of syringe including glass, plastic can be filled.
- Filling Rate: 300 to 600 syringes in a minute.

Ampoule Washing Machine

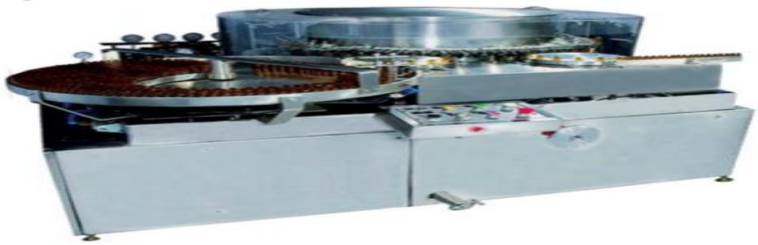

Fig 6:Ampoules Washing Machine

Process

- Water is sprayed onto the ampoules.
- Turned to an angle of 180 degree with their mouth downward to remove water.
- Finally the ampoules are filled with compressed air to remove residual water.
- Certain machines have a high temperature zone meant for killing any bacteria.

Washing cycle

1st wash - Recycled Water (WFI)
2nd wash - Compressed Air
3rd wash - DM Water
4th wash - Compressed Air
5th wash - Water for Injection (WFI)
6thwash - Compressed Air

Vial Filling Machine

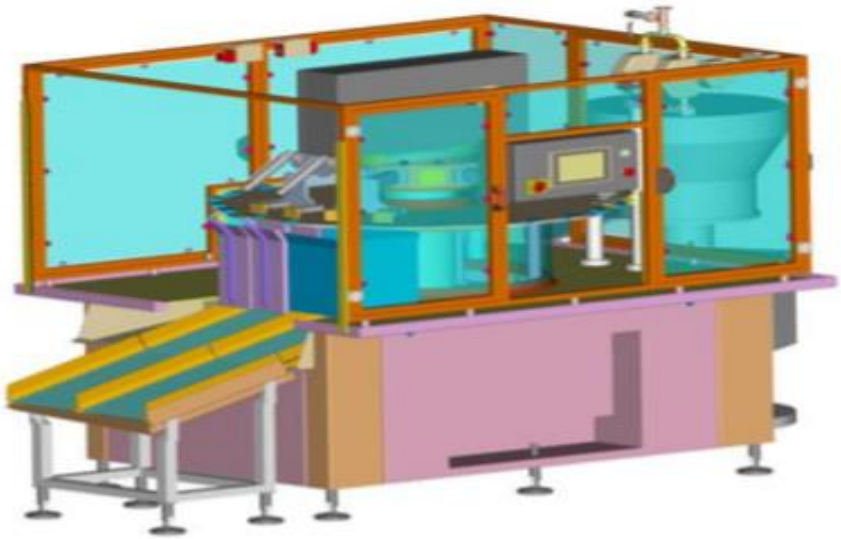

Fig 7: Vial Filling Machine

Vial filling machine

- Fill vials and bottles.
- Liquids, viscous material and suspensions and powders.
- Unique patented system for filling liquid products in sterile conditions.
- Global solution: preparation and sterilization of components, handling, sterile filling, process control and vial laser etching.
- More than 15 years of proven reliability in sterile filling.

Process

- The machine comprises of an intake section which loads the vials.
- Transferred through an intermittent transport section.
- Liquid filling section which fill the vials with predetermined quantity.
- Finally the filled and rubber stoppered vials are released and discharged.

Main Advantages

- Vial is closed and protected throughout the process.
- Vial is opened in the final filling stage in a controlled environment with horizontal laminar flow.
- No need for dry heat tunnel sterilization as it is carried out in an autoclave.
- Sterilization and depyrogenation combined with a HWFI washing cycle and an autoclave cycle. No need for a dry heat tunnel.

SIP System

- For in-line sterilization of various processing equipments.
- Handling various biological solutions and mixtures requires cleaning and sterilizing

these equipments from time to time as they are susceptible to contamination.

- Proper SIP integration with pharmaceutical equipment is very important for the overall success of the operation[18].

Conclusion

The parenteral route of administration is the most effective route for the delivery of the active pharmaceutical substances with narrow therapeutic index, poor bioavailability especially for those drugs, prescribed to unconscious Patients.

The present article describes that area planning, facilities, design, construction and manufacturing of sterile products. It is more impartment to produce good quality of parenteral. Parenterals are the pyrogen free liquids these are manufactured and stored according to cGMP guidelines. Proper area, environmental control, personnel observation will gives excellent parenteral products and attain their described therapeutic effect.

References

1. Rathod S, Deshpanden SG: Design and evaluation of liposomal formulation of pilocarpine nitrate. In J Pharm Sci 2010;72:155-60.
2. Samad A, Sultana Y, Aqil M: Liposomal Drug Delivery Systems: An update review. Curr Drug Deliv 2007;4:297-305.
3. azonano.com (Parenteral Drug Delivery III: Novel Parenteral Products, Devices, and Insulin).
4. Patel RP: Niosomes: An Unique Drug Delivery System. Pharmainfo.net. 2007.
5. Shahiwala A, Misra AN: Studies in topical application of niosomally entrapped nimesulide. J Pharm Pharmaceu Sci 2002;5:220-25.
6. Tamizharasi S, Dubey A, Rathi V, Rathi JS: Development and characterization of niosomal drug delivery of Gliclazide. J Young Pharm 2009;1:205-09.
7. Sutton D, Nasongkla N, Blanco E, Gao J: Functionalized micellar systems for cancer targeted drug delivery. Pharm. Res 2007;24:1029-46.
8. Doijad RC, Manvi FV, Swati S, Rony MS: Niosomal drug delivery of Cisplatin: Development and characterization. Indian Drugs 2008;45:713-18.
9. smail AA, Sanaa A, Gizawy E, Fouda MA, Donia AM: Influence of a niosomal formulation on the oral bioavailability of acyclovir in rabbits. AAPS PharmSci Tech 2007;8:1-7.
10. Roopa K, Mamatha GC, Subramanya G, Udupa N: Preparation, characterization and tissue disposition of niosomes containing Isoniazid. Rasayan J Chem 2008;1:224-7
11. Torchilin VP: Micellar nanocarriers: pharmaceutical perspectives. Pharm Res 2007;24:1-16
12. Müller R.H, Jacobs C and Kayer O: Nanosuspensions for the formulation of poorly soluble drugs. In: F Nielloud, G Marti-Mestres (ed). Pharmaceutical emulsion and suspension. New York, Marcel Dekker, 2000; 383-407.
13. Malakar J., Basu A. and Ghosh A: Nanosuspension: A Nano-Heterogeneous Carrier for Drug Delivery System. International Journal of Pharmaceutical and Biological Archives 2012; 3(1):4-13.
14. Talegaonkar S, Azeem A, Farhan J.Pathan S and Khan Z: Microemulsions: A Novel Approach to Enhanced Drug Delivery, Recent Patents on Drug Delivery & Formulation 2008; 2: 238-257
15. Brahmankar D.M: Biopharmaceutics and Pharmacokinetics. Vallabh prakashan, 2nd edition 2017
16. Zamboni WC: Liposomal, nanoparticle and conjugated formulation of anticancer agents. Clin Cancer Res 2005;11:8230-3.
17. Mamot C, Drummond DC, Hong K, Kirlotin DB, Park JW: Liposome based approaches to overcome anticancer drug resistance. Drug Resist Update 2003;6:271-79.

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