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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.

KEY WORDS

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

INTRODUCTION:

Parenteral preparations are sterile, pyrogen-free liquids (solutions, emulsions, or suspensions) or solid dosage forms containing one or more active ingredients, packaged in either single-dose or multidose containers. They are intended for administration by injection, infusion, or implantation into the body.

The dosage form for conveying a drug by means of injection through the skin or mucous membranes. 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. 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.

FACILITIES REQUIRED FOR PARENTERAL PRODUCTION:

PRODUCTION:

Parenteral preparations may contain excipients 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.

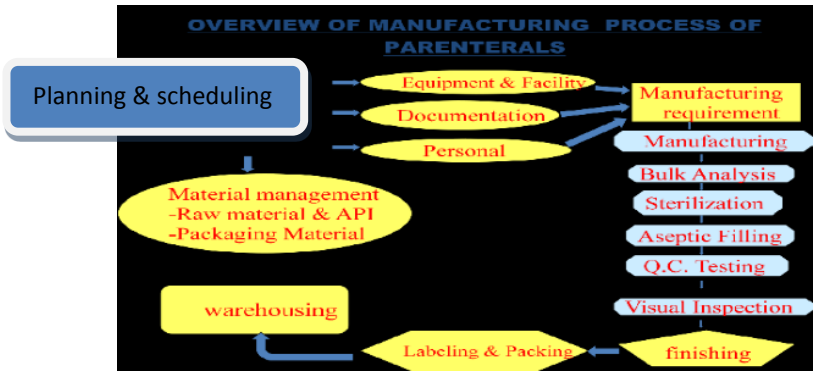

Figure: 1 Overview of manufacturing process

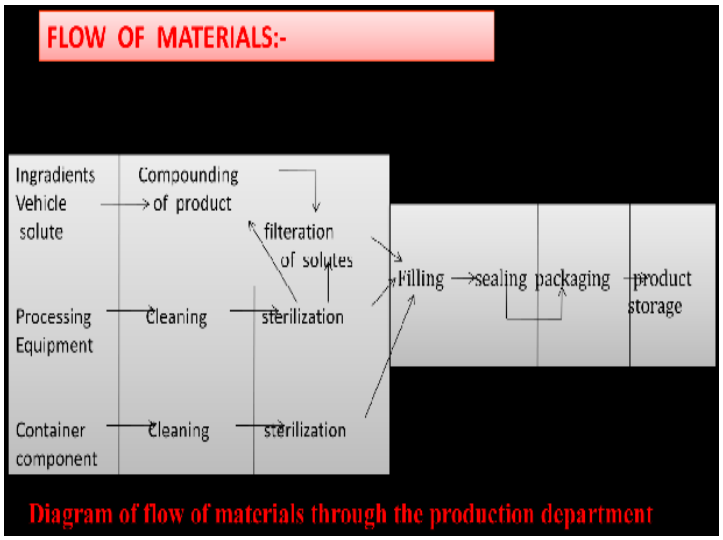

Figure: 2 Flow of materials

Types of sterile products processing:

1 Terminally sterilized

→ prepared, filled and sterilized

2 Sterilized by filtration

3 Aseptic preparations

Manufacture of sterile preparations:-

1. Terminally sterilized: - usually involves filling and sealing product containers under high-quality environmental conditions. Products are filled and sealed in this type of environment to minimize the microbial and particulate content of the in-

process product and to help ensure that the subsequent sterilization process is successful. In most cases, the product, container, and closure have low bio-burden, but they are not sterile. The product in its final container is then subjected to a sterilization process such as heat or irradiation.

2. Sterilization by Filtration:-

- Previously sterilized container are taken.
- Filters having nominal pore size 0.22 µm or less are used for filtration
- Remove bacteria and moulds but Not viruses & Mycoplasmas
- Double filter layer or second filtration
- No fiber shedding or asbestos filters
- Filter integrity testing

3. Aseptic Preparation: - In an aseptic process, the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together. Because there is no process to sterilize the product in its final container, it is critical that containers be filled and sealed in an extremely high-quality environment Before aseptic assembly into a final product, the individual parts of the final product are generally subjected to various sterilization processes. Any manual or mechanical manipulation of the sterilized drug, components, containers, or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control.

Note: - In area occupied by personal, the air must be exchanged with the frequent intervals. Fresh outside or recycled air must be first filtered to remove particulate matter and then HEPA filters are used to get CLASS-100 air systems.

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
▸ Conformity to standards
▸ Work station and environment
▸ Barrier technology and automated systems.

Space requirements:-

[QUANTITATIVE LAYOUT OF PARENTERAL MANUFACTURING]

Function	Area	
	Square meter	Percentage
Production	11,094	45.1
Warehouse	7,606	30.9
Utility	1,716	4.1
Quality control	1,716	7.0
Administration	1,018	4.1

Maintenance	1,014	4.5
Employee services	1,014	4.1
Security	39	0.9
Total	24,607	100.0

Table: 1 space requirements

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.

Administrative areas:-

Administrative area planning requires careful analysis of the direct and indirect administrative requirements of a particular plant.

Successively higher levels of supervision are usually provided successively larger office areas. Some offices are individual, while some are grouped in an “open area concept”.

The relative location of administrative areas demands particular attention. For the necessary to maintain production, a close proximity is desirable. Any other support offices should be separated from the production area because, production area contaminations can be related to people. The reduction of numbers of people will reduce the challenge to the plant cleanliness. Many of the “fringes” normally associated with administrative areas-plants, flowers, closets, outside windows are potential contamination sources. Finally the traffic of visitors, vendors, employment application, and so on, who are not particularly acquainted with pharmaceutical discipline can be reduced.

Requirements are related more to the relationship between the plant and the company or corporate headquarters. These indirect administrative requirements will usually include functions not directly related to plant operation,

such as company or corporate management and staff functions.

Environmental control zone grouping:-

1st. Zones as per the c GMP:-

- Zone 7:- Filling line
- Zone 6:- Filling area
- Zone 5:- Weighing, mixing & transfer area.
- Zone 4:- Clean area
- Zone3:-General production
- Zone 2:- Warehouse
- Zone 1:- Exterior

1st. Zones as per Gazette of India

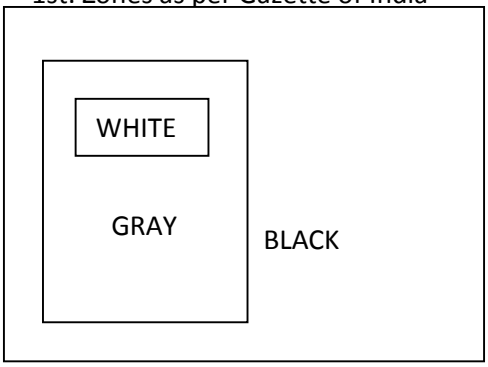

Figure: 3 environmental control zone groups

ZONES AS PER GAZZETE OF INDIA:

- White zone:-Final step (filling of parenteral)
- Grey zone:-weighing, Dissolution & filtration.
- Black zone:-Storage, Worst area from contamination view point
  - **a)** Have a per-cubic-particle count of not more than 100 in a size range of 0.5 micron and larger through the entire work area upstream of the work piece.
  - **b)** Be supplied at the point of use as specified in section 212.77.

The layout of the plant must be carefully developed in coordination with the needs of the HVAC system.

Zone-7:-filling line:-

The walls of the filling area are the last physical barrier to the ingress of contamination, but within the filling area a technique of contamination control known as laminar flow may be considered as the barrier to contamination.

Zone-6:-filling area:-

Zone 6 is a distinct zone of the controlled environment area for an aseptic filling process but may not be distinct zone for non-aseptic filling processes.

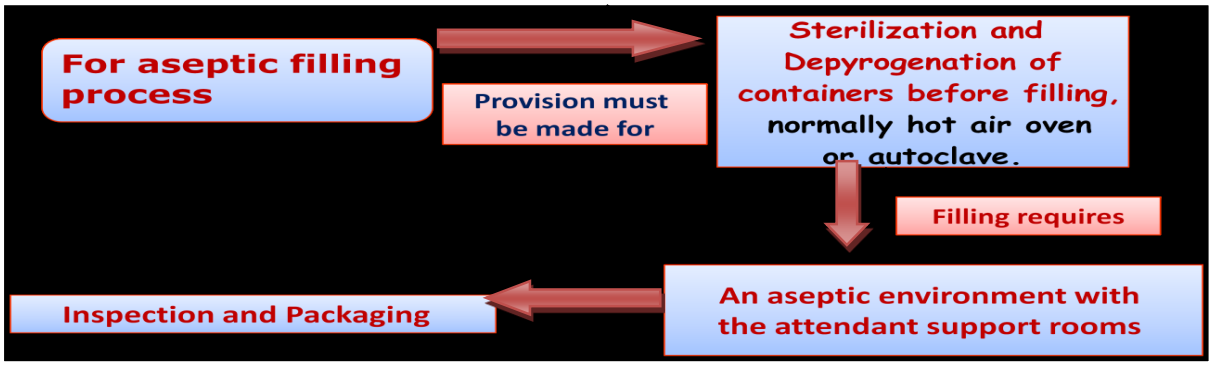

Figure: 4 Aseptic filling

Non asepting filling, followed by terminal sterilization, normally requires less rigid environmentalcontrol.

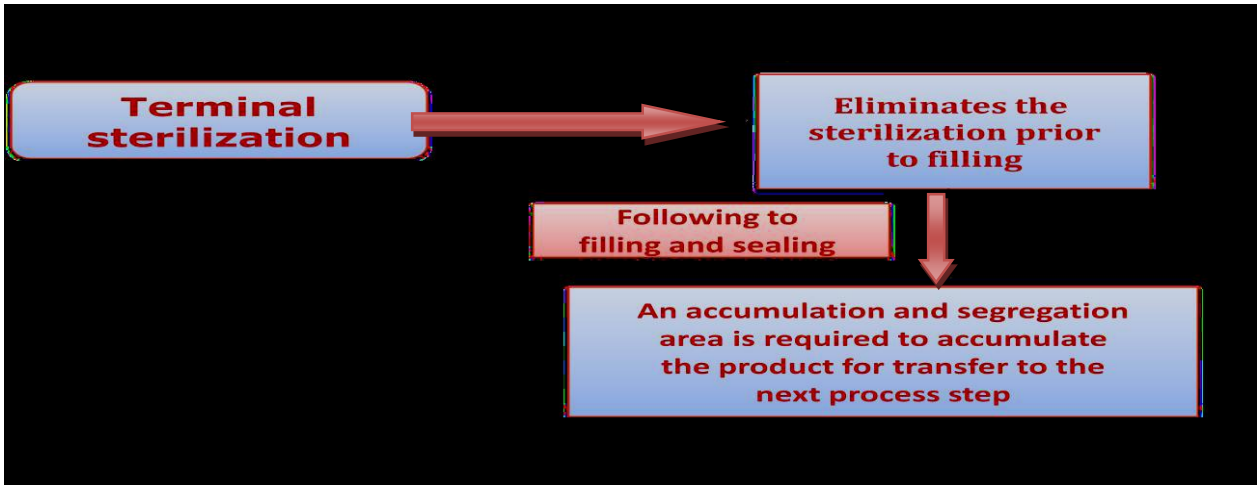

Figure: 5 Non aseptic filling

Zone-5:-weighing, mixing, and transfer area:-

Zone5 encompasses those activities of "weighing, mixing, filling or transfer operations" addressed by c GMP section 212.81 which are not handled as zone 6 but which require a controlled environment.

Zone-6:-clean area:-

Activities in these may include washing and preparations of equipment or accumulation and sampling of filled product.

Zone-3:-general production and administration area:-

The third zone of environmental control is formed by the periphery of the general production area. Openings into the area are usually well sealed and large enough for only essential material-handling equipment and personnel.

Zone-2:-plant exterior:-

The environmental with in which a plant located is first environmental control zone. It is a base point from which to work in determining the requirements for the various control barriers.

Management actions to control zone 1 might include the maintenance of sterile areas around the facility where weeds, insects and rodents are controlled or eliminated.

2. 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 with in 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.

3. 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.

4. 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.

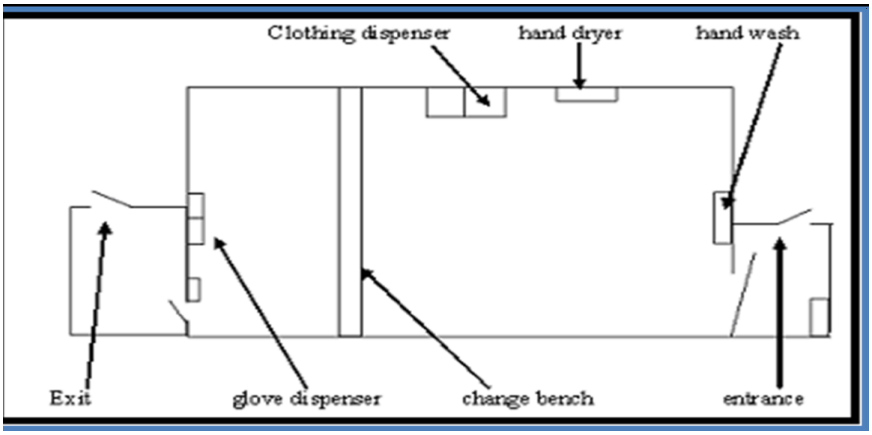

Figure: 6 Change room

5. 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.

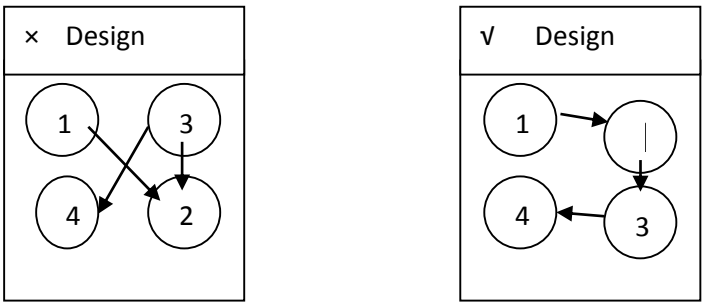

Figure: 7 personnel flow

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.

6. 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 with in 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:

1. 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.

2. 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.

3. 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.

4. 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:

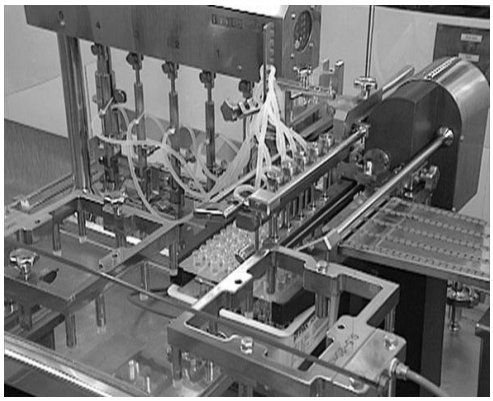

Figure: 8 Syringe Filling Machine

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:-

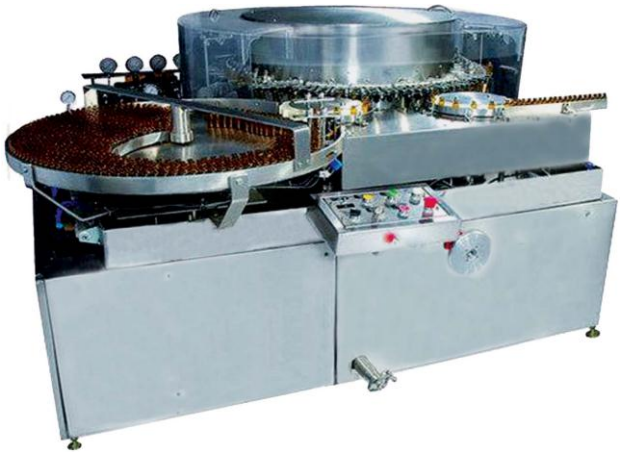

Figure: 9 Ampoule washing machine

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)
6th wash	-	Compressed Air

Vial Filling Machine:-

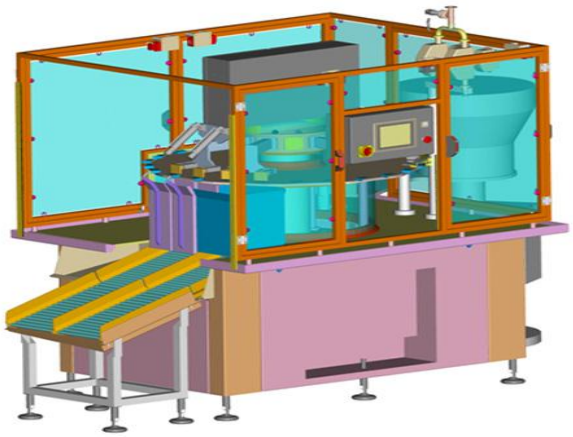

Figure: 10 Vial filling machine

- 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.

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.

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