Review Article

Environmental Control for Parenteral Production

***Parag V. Ingle[1], Vivekanand K. Chatap[1], N. M. Bhatia[2]**

1. Post Graduate, Department of Industrial Pharmacy, H. R. Patel Institute of Pharmaceutical Education and Research, Karwand Naka, Shirpur, Maharashtra, India.
2. Post Graduate, Department of Quality Assurance, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India.

ABSTRACT

Parenteral dosage form differs from other dosage form. Parenteral product directly enters into systemic circulation. Parenteral preparation should be free from any type of pyrogen, micro-organisms and particulate matter. Environmental control is a major concern in potential drug manufacturing. There is substantial evidence establishing a direct relationship between the level of environmental control and the final quality of the product. Environmental control zone groupings consist of sevean zones and environmental design concepts include personal flow, welding screens, employee services, warehousing, utilities, quality control, wall and floor treatment, glass bead sterilizer, change room, handwash station, apparel storage cabinet, shoes, air shower, air curtains, air tight door, pvc flap/swing doors, washer, laminar flow unit, sampling booth, filling suites, communication, pass box which control contamination and maintain aseptic condiation effectively. Effective monitoring of the conditions in the system must be carried out from time to time to ensure that the right conditions are being created for the manufacturing process. It is important to understand that the design and function of the pharmaceutical manufacturing area forms a significant part of Good Manufacturing Practices (GMP), these being the requirements by governmental agencies like the FDA, WHO, ISO. Good environmental monitoring program is one of the most important laboratory controls. Environmental monitoring programs, when appropriate, should include quantification of microbial content of room air, compressed gases, and surfaces. Personnel contamination control, cleaning and dispensing procedure plays important role in environmental monitoring with quality assurance test.

Keywords: Control of parenteral production, environmental control, environmental control for parenteral production, parenteral, parenteral production

Received 12 June 2014 Received in revised form 08 July 2014 Accepted 11 July 2014

***Address for correspondence:**
Parag V. Ingle,
Post Graduate, Department of Industrial Pharmacy, H. R. Patel Institute of Pharmaceutical Education and Research, Karwand Naka, Shirpur, Maharashtra, India.
E-mail: paragvingle@gmail.com

INTRODUCTION

Environmental control is a major concern in potential drug manufacturing. There is substantial evidence establishing a direct relationship between the level of environmental control and the final quality of the product; this is especially true in the case of potential drugs should provide a level of sterility assurance of 1 in 3000 units. This level is still under scrutiny; potentially, additional and more demanding standards could be imposed in the future. To achieve this level of sterility assurance, an adequate environmental control program (ECS) is to be designed.

A comprehensive environmental control system for an aseptic processing facility includes but is not limited to each production phase has specific environmental control requirements; therefore, knowledge of the product, materials and personnel flow is required for adequate design of each phase. Several environmental parameters are of concern when designing an aseptic processing facility, but the most important are those limiting the presence of airborne and surface viable and nonviable contamination. Classification of the environments by their

intended use helps to identify the critical nature of the environmental levels. The following classification applicable to aseptic processing environments [1-6].

Critical or level I

Those environments where sterile products, containers or closures are directly exposed to the environment and where the aseptic filling operation takes place.

Controlled or level II

Those environments located immediately adjacent to level I environments and areas used for the storage or holding of unexposed sterile materials.

Ancillary or level III

Those environments where intermediates and/or products, components or related materials are prepared or cleaned and a control of particulate matter and /or bioburden is desired.

Potential risk of cross-contamination of product or critical materials during the process.

Classify working areas in a potential production facility as follows;

Non classified- warehouse area for a raw materials and finished product.

Level III

Washing area for cleaning and preparation of product containers and accessories. Drug preparation area for the mixing, preparation and filtration of active drug ingredients.

Level II

Sterile containers holding area (stoppers, glass containers, caps, etc in bags or trays). Areas in the perimeter of level I such as the ones immediately outside of unidirectional airflow devices.

Level I

Sterile or aseptic filtration. Sterile product filling area. In general, all areas under unidirectional airflow devices (laminar air flow) [7].

ENVIRONMENTAL CONTROL ZONE GROUPINGS

Zone 1. Plant Exterior

The environment within which a plant is located is the first environmental control zone. A zone that can be controlled through planning and management. Planning may involve choosing a location that is free of objectionable airborne contaminants. Management actions to controls zone 1 might include the maintenance of "sterile" area around the facility where weeds, insects and rodents are controlled or eliminated [2,3,8-10].

Zone 2. Warehousing

The second environmental control zone provides minimal protection for materials and product. Large openings are required for easy access (truck, doors etc.), this barrier may be only marginally effective against insects, rodents and birds. Control of airborne contaminants is often little more than rough air intake filters. Storage of final product may require temperature control in the warehouse [2,3,7,8,11].

Zone 3. General Production and Administration Area

The third zone of environmental control is formed by the periphery of the general production area [2,4,7,8].

Zone 4. Clean Area

Production areas immediately proceding or following a controlled environment area in the production flow are often controlled as an area intermediate between a general production area and a controlled environment area [2,7,8].

Zone 5. Weighing, Mixing, and Transfer Area

Those activities of "weighting, mixing, filling or transfer operations" addressed by cGMP section 212.81 which are not handled as zone 6 but which require a controlled environment [2,7,8].

Zone 6. Filling Area

Distinct zone of the controlled environment area for an aseptic filling process but may not be a distinct zone for non aseptic filling processes. The proposed cGMP defines and requires controlled environment area for any weighing mixing, filling, or transfer operation [2,12,13].

Zone7. 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 last barrier to contamination [2,13].

DESIGN CONCEPTS

Personnel Flow

Personnel flow paths from zone to zone must be such that access to higher levels of cleanliness is only through change rooms,

gowning areas, locker rooms, or higher levels of cleanliness is only be required to prepare the personnel for the cleaner area. 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 a common corridor is usual. However, highly traveled personnel corridors are inefficient and unsafe paths for moving materials, particularly if heavy forklifts are required [2,14].

Welding Screens

Protect employees against welding bash, sparks and the harmful transmission of ultraviolet light. Mandor welding screens are constructed from 25mm so steel framework lilted with 300mm wide x 3mm thick high grade welding quality, green PVC strips, complete with angle support feet and castors. All screens are purpose made to suit individual requirements and available up to a maximum size of 2000mm square [2,15,16].

Employee Services

The general problem associated with cafeteria (food of services) facilities is sanitation. With respect to sanitation, the presence of food creates a potential rodent and insect problem. Restroom facilities are usually considered in conjunction with locker rooms. For small plants, restroom / locker room combinations may be adequate. Storage must also be provided for the employee clothing. Employee safety and health services are necessarily located in or near the production area [2,17,18].

Warehousing

Temperature control in summer months often consists of nothing more than exhaust fans or evaporative coolers, and winter heating may be by ceiling-mounted unit heaters. A first consideration is to prevent contamination while unloading materials. The warehouse must be adequate in size and must be flexible enough to hold materials in an indefinite status if necessary. It is normal to have multiple types of warehousing areas or facilities. Finished products and certain raw materials need special environmental storage conditions, such as, temperature and humidity control. The first and most basic warehouse function is to receive and hold incoming materials. Warehouse space is usually of greater height sanitation stand point has usually have a relatively high density of flammable materials [2,16,19].

Utilities

Exposed overhead piping is not acceptable from cleanliness or contamination standpoint since it collects dirt is difficult to clean and may leak. Major utility distribution services should be located outside of clean areas. The choice of location for utilities can have important ramifications for the entire plant because of the amount or lengths of piping and wiring in over under and around critical productions areas [2,7,8].

Quality Control

Quality control serves several functions and therefore may be located in one or several locations [17,18].

Wall and Floor Treatment

The design of filling areas or more generally, controlled environment areas involves attention to many seemingly minor details. The basic clean ability requirement includes smooth, cleanable walls, floors, ceilings, fixtures and partitions. Exposed columns, wall studs, bracing, pipes and so on are unacceptable. A potential filling facility is cleaned on a very frequent basis, usually by washing all surfaces in the room with a detergent and a disinfectant to control microbial growth [2,18].

Walls

All inside walls must be fished; 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. A final problem with block walls is the tendency to crack along joints due to the inevitable movements of building structures. A plaster was all requires a good substantial base such as a block or concrete wall or wire-reinforced gypsum board and has moderate resistance to movement creaking. Gypsum board is an economical alternative to plaster. Vinyl sheeting is used to cover the walls [2,18,19].

Floors

The floors in many potential plants are constructed of epoxy terrazzo. Terrazzo

floors are usually installed over bare concrete floors that have been previously etched with acid and have all of the creaks and joints coated with an elastomer. General type of floor is composed of large sheets of vinyl or polyvinylchloride laid on a concrete base floor and "welded" together with heat or sealed at the seams with cement. All floors in areas where water can accumulate should be sloped toward one or more drain points [15,18,19].

Air Curtains

Air curtain creates an invisible barrier of air generated by high efficiency direct driven fans that compress the air inside the unit and release the air through a directional nozzle with a pressure [20].

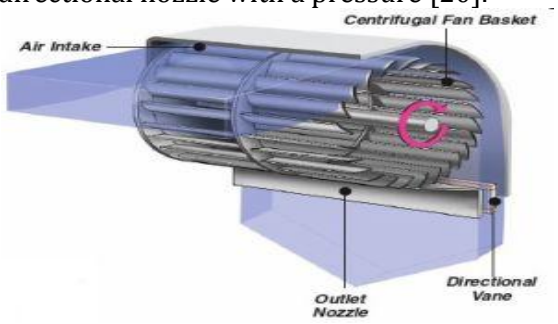

Figure 1: Air Curtain

Change Rooms

Maintaining the necessary are pressure differential to prevent the entry of airborne contamination. Upon entry into the change room, wash sinks are provided for scrubbing hands and forearms. Automatic or foot-operated controls for water and soap eliminate hand contact with contaminated surfaces. After hands are dried by hot air blowers. As a final growing steps, aseptic gloves are put on and sanitized [2,14,18].

Handwash Station

Handwash station is designed for food, beverages, pharma companies. Where human touch to the product increases the chances of contamination. The product is fabricated out of 304 grade stainless steel. The station is provided with auto taps, soap dispensers, towel, hand sanitizer liquid dispensers and waste bins [18,21,22].

Apparel Storage Cabinet

These garment cubicles are designed to perfection and are dimensionally accurate with U.V. germicidal tube to ensure keeping the garments completely free from bacterial contamination [2,17-19].

Figure 2: Handwash Station

Figure 3: Apparel Storage Cabinet

Figure 4: shoes

Air Shower

Air showers that provides an ideal way to minimize the contaminants taken up by the individuals, entering or leaving a controlled area. These showers use concentrated air flows to lift off the contamination. These are designed to deliver jets of pressurized air at a velocity of 20-22m/s, in which an individual simply stands in or walks through a specially constructed air chamber. To remove the particulate matters an efficient scrubbing action is necessary. Removing all the particles not smaller than 0.3 micron in size [2,15,20].

Figure 5: Air Shower

Air Tight Door

Air tight doors are designed to prevent air leakages in critical applications like air handling rooms of air conditioning, humidification, ventilation systems & diverse fields of industries. A easy replaceable gasketing arrangement is provided. The doors are spray painted with itching metal primer & paint of any colour shade of customer choice. These door are available in single/double shutter [2,18,19].

Figure 6: Air Tight Door

PVC Flap/Swing Doors

Purafil's transparent, flexible swing-doors are equipped with complete outer steel frame with rounded eged overlapping flaps, made out of clear transparent, flexible venyl sheets of doors are provided with top and bottom hinge-bearings. These doors can be made to suit requirements up to 3000mm width and 3000mm hight and are custom-built. The standard size of doors available is 2000 mm x 2050 mm, 3 mm thickness. They have a push-opening and self-closing with spring action [17-19].

Washer Selection

Tunnel washers have a higher throughput than a single washer would reduce the washing time to about 40 minutes. Three to four washers can do the work of five washers in the same time. The employees are free to do other tasks [9,19,20,22].

Figure 7: Shoes

Figure 8: PVC Flap/Swing Doors

Figure 9: Tunnel Washers

Glass Bead Sterilizer

Glass bead sterilizer is a common method for chair-side sterilization of small hand instruments [9,16].

Portable Laminar Flow Unit

A handy clean air unit designed for maximum portability and rapid installation at low cost. In smaller labs, purafil portable laminar flow unit can be used to control contamination [2,23].

Biological Safety Cabinet

Biological safety cobinets are designed to provide personnel/environmental safety and product protection in application involving biological agents [2,19,24,25].

Sampling Booth

The purafil dispensing/sampling/weighing booths allow to obtain delimited areas of clean and sterile air, through a unidirectional and descendant air filtered flow. Due to lower pressure in the working area possibility of cross contamination with other products is avoided. The main applications are dosing and weighing of raw material, sampling antibiotics handling, hormones, cytostatics etc. Either powders or liquids [2,19,22,24,26].

Figure 10: Glass Bead Sterilizer

Figure 11: Biological Safety Cabinet

Figure 12: Sampling Booth

Filling Suites

The filling area being the most highly controlled plant environment and the most critical site for potential product contamination. It is a logical starting point for designing a plant layout. The filling suite is often called the "sterile core." The space should be maintained under full laminar airflow and be rated at class 100 or better [2,22,24,27-29].

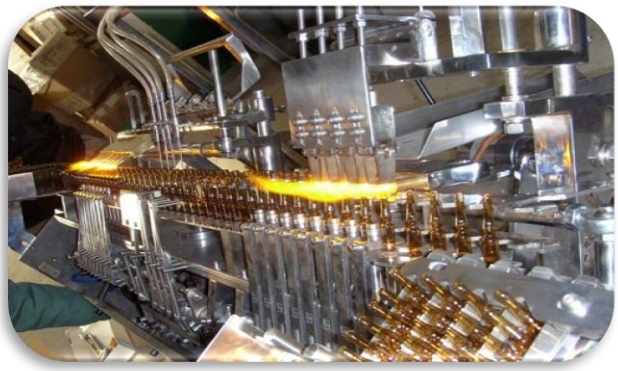

Figure 13: Ampoules Filling and Sealing Suites

Communication

Communication in a controlled area is usually via membrane plates mounted in windows, telephones, intercoms, or computer keyboards. Special intercoms which are sealed and cleanable and require a minimum of hand contact are often the best means of communication [2,14].

Pass- Throughs

Pass box minimizes entry of contaminants and also cross contamination into the clean rooms. A pass-thru (dedusting unit) air lock that permits the pickup of material, components, products and to from a clean room area [2,18,19,30].

Catering Facilities

Drinking, smoking, eating activity do not carried out in aseptic area for that separate catering facility available outside the plant. Which control ants and food contamination in parenteral plant properly [18,19].

Figure 14: Pass Box

Figure 15: Catering Facilities

ENVIRONMENTAL MONITORING

Effective monitoring of the conditions in the system must be carried out from time to time to ensure that the right conditions are being created for the manufacturing process. It is important to understand that the design and function of the pharmaceutical manufacturing area forms a significant part of Good Manufacturing Practices (GMP), these being the requirements by governmental agencies like the FDA. Good environmental monitoring program is one of the most important laboratory controls. Environmental monitoring programs, when appropriate, should include quantification of microbial content of room air, compressed gases and surfaces (equipments, floors, walls, protective garments, etc.). Air monitoring and surface monitoring are plays important role in environmental monitoring (2-4,31,32).

PERSONNEL CONTAMINATION CONTROL

It is very important to implement measures that will prevent or minimize contamination from personnel. These measures should include:

1. Action of operating personnel for critical areas and comprehensive audiovisual training of personnel.

2. Routine verification of manufacturing proceduresd periodic retesting and retraining of personnel and constant supervision of personnel activity.

3. Proper selection of clean room garments and proper gowning techniques (18,33).

CLEANING AND DISINFECTION PROCEDURES

Cleaning and disinfection procedures are an important part of the environmental control program. The objective is to remove debris and materials that have been deposited or settled on surfaces and reduce or eliminate the microorganisms present on equipment, walls, floors and ceilings within the aseptic environment (34).

Selection of adequate cleaning and disinfecting agents

1. Surfactant or detergent activity of the cleaning agent and compatibility with treated surfaces.
2. Compatibility with treated surfaces and stability and reactions in the presence of organic matter and shelf life and elimination of spore formers and disinfectant effectiveness against specific strains.
3. Safety and water used for the preparation of cleaning and disinfectant solutions.

CONTROL OF CONTAMINATION

The environmental control system in a potential drug manufacturing facility is primarily designed to prevent and control contamination from reaching the product at specific stages during the manufacturing process. Contamination can be defined as the presence of any undesirable element in a process or product. For critically controlled of environments, the sources of product contamination are personnel air, equipment and materials used in manufacturing.

Air as a Source Contamination

Two main groups: Those in solid phase and those in liquid phase. In the solid phase there are such contaminants as soils of all types minerals, vegetable fibers, synthetic materials, all the biological materials (e.g., skin cells, hair, and bacteria), fumes from incomplete combustion, and vapors from

oxidation of metals. Contaminants in the liquid phase can include sprays of all kinds, condensed vapors, and chemicals vapors.

Equipment and Materials Used in Manufacturing as Source of Contamination

Equipment with parts in motion gives off particles and if not properly shielded, these particles could end up in a critical area. Inadequate disinfection of equipment surfaces also will be a significant factor in not maintaining the bioburden levels required in a critical environment. Materials can be a source of contamination by them.

Purpose

1. To demonstrate that environment quality is consistently within specified levels.
2. To provide a timely and sensitive warning if the environmental quality or its control.

Proper Role of Environmental Monitoring in Aseptic Processing

Environmental monitoring has always played an indispensable role in aseptic processing. EM was practiced using many of the same methods still in use today. Settling plates, contact plates, personnel monitoring and active air sampling were all features of aseptic processing (2,33).

QUALITY ASSURANCE TEST

cGMP AND FDA Guidelines on frequencies and types of monitoring for Aseptic Dispensing Facilities (2, 17-19,33,35-37)

3.1 Sessional Tests (record duration of session)

Finger dabs in critical zones (e.g. LAFC/Isolator) in the operational state. Settle plates in critical zones (e.g. LAFC/Isolator/Transfer Devices) in the operational state. (a)Glove integrity test/ visual inspection of glove and sleeve assembly.

3.2 Daily Tests

Record pressure drop across filter, isolator pressure differential and airflow rate. Record pressure drop across HEPA filter (LAFC) and record pressure differential between aseptic rooms and adjacent areas and Alarm test (isolators).

3.3 Weekly Tests

Settle plates at test sites in the background environment and change facility in the operational state. User pressure decay test (all isolators) and microbiological surface samples in LAFC/ Isolator, transfer devices and background environment.

3.4 Monthly Tests

Airborne viable organisms in LAFC/isolator, transfer devices, background environment and change facility in the operational state.

3.5 Monthly Tests

Airborne particle count in LAFC/isolator, transfer devices, background environment and change facility in the operational state. Air change rate in aseptic rooms and air velocity in LAFC and inlet air velocity into controlled work zone for laminar air flow isolators and volume flow rate in turbulent flow isolators and operator aseptic transfer tests for all operators.

3.6 Annual Tests

Integrity and efficiency of all HEPA filters.

Leak detection test (e.g. Helium Test (all isolators).

KI discus operator protection test.

Calibration of gauges and critical equipment (e.g. automatic dispensing systems).

Process simulation tests for aseptic processes.

cGMP AND FDA Guidelines on action levels for monitoring of Aseptic Dispensing Facilities (18,19,35,37)

The source document for each of the tests is referenced and if clarification is required, these documents should be consulted.

1. **Non-viable particle counts** Maximum permitted number of particles/m^3 equal to or above.
2. **Pressure differentials**
   >10 Pa between classified area and adjacent area of lower classification.
   > 15 Pa between classified and unclassified area.
3. **Airflow velocity**
   Horizontal LAFC 0.45 to 0.1 m/s.
   Vertical LAFC 0.30 to 0.05 m/s.
   Safety cabinet inward air flow > 0.4m/s.
   Downward air flow 0.25 - 0.5m/s.
   Laminar air flow isolators 0.3 - 0.6m/s.
4. **Air change rate**
   Aseptic room: > 20 air changes per hour.
   Clean support room: > 20 air changes per hour.
5. **Operator protection factor**
   Safety cabinet: OPF > 1 x 105.

6. Settle plates
Diameter 90mm, 4hr exposure.
7. Active viable air sampling
Operational:- cfu/m3 (average value).
8. Finger dabs
Glove print 5 fingers, cfu/glove (average value) <1 (in critical workzones).
9. Surface samples
Diameter 55mm plate (surface area $25cm^2$)/surface swabs.
Operational:- cfu/$25cm^2$ (average value).
10. Operator aseptic transfer tests
Zero growth.
11. Process simulation tests
Zero growth.
Actions when results deviate from action levels
I. Physical tests
1. When the results of physical testing are out with action levels. The responsible pharmacist must be informed and test repeated.
2. A satisfactory repeat test should be confirmed in duplicate.
3. If the repeat test is still out with the action level, this may indicate a problem such as a blocked HEPA filter, a leak in the isolator, a hole in the glove system, etc., and further action must be taken to identify and rectify the problem.
4. All corrective actions taken and subsequent results must be fully documented [18,35].
II. Microbiological tests
1. The action taken will depend on the type, extent and duration of the observed contamination.
All abnormal results must be reported to the responsible pharmacist.
2. Isolated incidents often require no more than close monitoring of the results of subsequent tests or a repeat test and examination of the control systems.
3. Repeated levels of contamination greater than action levels may require an increase in the frequency of testing, observation of operator technique, investigation of cleaning procedures etc.
4. Gross contamination in any test requires immediate action.
5. All corrective actions taken and subsequent results must be fully documented [6,10,18,35,38].

CONCLUSION
Effective monitoring of the conditions in the system must be carried out from time to time to ensure that the right conditions are being created for the manufacturing process. It is important to understand that the design and function of the pharmaceutical manufacturing area forms a significant part of Good Manufacturing Practices (GMP), these being the requirements by governmental agencies like the FDA, WHO, ISO. Good environmental monitoring program is one of the most important laboratory controls. Environmental monitoring programs when appropriate should include quantification of microbial content of room air, compressed gases and surfaces. Personnel contamination control, cleaning and dispensing procedure plays important role in environmental monitoring with quality assurance test like cGMP and FDA guidelines on frequencies and types of monitoring for aseptic dispensing facilities. cGMP and FDA guidelines on action levels for monitoring of aseptic dispensing facilities actions when results deviate from action levels then physical tests and microbiological tests require.

REFERENCES
1. Ansel, Pharmaceutical Dosage Forms; Third Edition; 2007, 242-264.
2. Potdar, Hand Book of Quality Assurance; Third Edition; 2009.
3. Institute of Environmental Sciences, Cleanroom Housekeeping—Operating and Monitoring Procedures, IES-RP-CC018.2, IES, Mt Prospect, IL, 1992.
4. Scott Sutton., The Environmental Monitoring Program In a GMP Environment., Journal of GXP Cmpliance., 14(3); 2010,22-30.
5. FDA, Guidance for Industry: Stehle Drug Products Produced by AseptiC Processing-Current Good ManufactUring Practice, 2004.
6. USP, Chapter 1116 "Microbiological Control and Monitoring Environments Used for the Manufacture of Healthcare Products," Pharm Forum., 33(3); 2007.
7. Brian Wiseman, P.E., Room Pressure for critical environments, ashrae journal., 2003, 34-39.
8. Kenneth E.Avis, Herbert A. Liaberman and Leon Lachman, Pharmaceutical Dosage form: Parenteral Medication; Second Edition., Replika Press Pvt Ltd. Volume 2; 2005, NewYork, 235-316.

9. Leon Lachman, Herbert A. Liaberman, Theory and Practice of Industrial Pharmacy, Third Edition; Varghese Publishing House;1987, Bombay,619-680.
10. Anonymous, "Microbiological Evaluation and Classification of Clean Rooms and Clean Zones," Pharmacopeial Forum., 18 (5); 1992, 4042–4054.
11. R.M.Mehta, Pharmaceutic II, first edition, Vallabh prakeshan ;2005, Delhi, 223-249.
12. ISO, ISO 14644-1 Cleanrooms and Associated Controlled Environments - Part 1: Classification of Air Cleanliness, 1999.
13. Federal standard 209 E: Clean room and work station requirements: Controlled Environment.
14. A. Bhatia, A Basic Design Guide for Clean Room Applications, 2012, 1-58.
15. Pharma info.net.
16. Pharmaceutical science by Remington. 21st Edition, vol.1, 814-828.
17. www.isoguideline
18. U.S. Food & Drug Administration (FDA) Home.
19. www.cgmp.com
20. www.pharmamachines.com
21. Drugs & Cosmetics Act 1940.
22. www.GMP.online.coms
23. Ichiya Hayakawa , Shuji Fujii , Kwang Young Kim., Design Theory for a Laminar Flow-Type Clean Room and Image Processing on Remotely Detected Particulates. Aerosol Science and Technology., 1987, 47-56.
24. B. Venkateswara Reddy, B.Rasmitha Reddy, K.Navaneetha, V.Sampath Kumar., A review on parenteral production technology., IJPBS. 3(1); 2013, 596-610.
25. ISPE Pharmaceutical Engineering Guides, Sterile Manufacturing Facilities. Volume 3., 1999.
26. American Journal of Hospital Pharmacy., 38(8),1144-114710. Dispensing for pharmaceutical students.
27. D. W. Cooper, "Cleaning Aseptic Fill Areas," Pharmaceutical Technology, 20(2); 1996, 52,54,56,58,60.
28. Sandhya chaurasia, Sneha golani, Nishi prakash jain, Manoj Goyal, Sofiya Verma., Comprehensive review on aseptic fill/finish manufacturing as per regulatory guidelines. Journal of Current Pharmaceutical Research, 5(1); 2011, 19-27.
29. Keith Weseli and Michael DiGiovanni., Case Study: Parenteral Facility Upgrade Project with Fill Line Install., PHARMACEUTICAL ENGINEERING; 2008, 24-32.
30. Joseph D. Nally., Good manufacturing practices for pharmaceuticals. Six Edition, 37-113.
31. www.whqlibdoc.who.org
32. www.dwscientific.co.uk
33. D. L. Tolliver, ed., Handbook of Contamination Control in Microelectronics: Principles, Applications, and Technology, Noyes, Park Ridge, NJ, 1988.
34. James Agalloco,Validation of Pharmaceutical Processes,Third Edition; 2008, 27-44.
35. www.springerlink.com
36. D. W. Cooper, "Sterility Assurance for Cleanroom Wipers," to appear in Journal of the Institute of Environmental Sciences., 1996.
37. www.fda.gov.
38. D. M. Carlberg, Cleanroom Microbiology for the Non-Microbiologist, Interpharm, Buffalo Grove,IL., 1995.