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Comparison of Quality Requirements for Sterile Product Manufacture as Per Indian GMP and USFDA

Yogita P, N Vishal Gupta*, Natasha NS, Ashwini Nageen L, R Sudeendra Bhat

JSS College of Pharmacy, JSS University, Sri Shivarathreeshwara Nagar, Mysore – 570015, Karnataka, India.

ABSTRACT

The purpose of the present work was to make a detailed study of the Quality requirements for sterile product manufacture as per the regulatory authorities such as Indian GMP (Schedule M) and USFDA. The pharmaceutical companies are required to follow the quality management specifications as per different guidelines such as Indian GMP (Schedule M) and USFDA. Sterile pharmaceutical products are very critical and sensitive. The specific requirements of these products are that these products should be handled very carefully in predefined environmental conditions, by fully trained personnel. Medicinal drug products that do not meet the requirement to be sterile, non-pyrogenic can otherwise cause severe harm to life, threatening health risk to patient. Knowledge of the differences in the requirements of guidelines given by different international agencies is important to guarantee the quality products and their supply in due time for the designated market.The main aim is to study the quality requirements for sterile pharmaceutical product manufacture and to list down the similarities and differences as per the international regulatory requirements. The aspects that are taken into consideration are environmental parameters, buildings and premises, personnel, sanitation, equipment and sterilization.These guidelines focus on the parameters to be stressed on while manufacturing sterile pharmaceutical product and when these guidelines were compared, certain similarities and differences were observed. The requirements were broadly similar, and the differences found are detailed in this study.

Keywords: GMP, Schedule M, USFDA, Sterile.

Corresponding author
Email: vkguptajss@gmail.com

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INTRODUCTION

Sterile pharmaceutical products are very critical and sensitive. The specific requirements of these products are that these products should be handled very carefully in predefined environmental conditions, by fully trained personnel. Any failure in the set requirements directly affects the safety of the patient being treated. A lot of requirements have to be met to ensure that the aseptically manufactured product can be regarded sterile. Therefore certain aspects have to be taken into consideration during the manufacture of sterile pharmaceutical product. The aspects that were taken into consideration are as follows: Environmental parameters, buildings and premises, personnel, sanitation, equipment and sterilization [1].

The purpose of the present work is to make a detailed study of the Quality requirements for sterile product manufacture as per different regulatory authorities such as GMP (Schedule M), USFDA and compare them.

ENVIRONMENTAL PARAMETERS:

Indian GMP

Air Handling System (Central Air-Conditioning)

Air Handling Units for sterile product manufacturing areas shall be different from those for other areas. Critical areas, such as the aseptic filling area, sterilized components unloading area and change room conforming to Grades B, C and D respectively shall have separate air handling units. The filter configuration in the air handling system shall be suitably designed to achieve the Grade of air as given in Table 1. Typical operational activities for clean areas are highlighted in Tables 2 and 3.

For products which are filled aseptically, the filling room shall meet Grade B conditions “at rest” unmanned. This condition shall also be obtained with in a period of about 30 minutes of the personnel leaving the room after completion of operations.

The filling operations shall take place under Grade A conditions which be demonstrated under working of simulated conditions which shall be achieved by providing laminar air flow work stations with suitable HEPA filters or isolator technology.

For products, which are terminally sterilized, the filling room shall meet Grade C conditions at rest. This condition shall be obtainable within a period of about 30 minutes of the personnel leaving the room after completion of operations.

The minimum air changes for Grade B and Grade C areas shall not be less than 20 air changes per hour in a room with good air flow pattern and appropriate HEPA filters. For Grade A laminar air flow work stations, the air flow rate shall be 0.3 meter per second ± 20% (for vertical flows) and 0.45 meter per second ± 20% (for horizontal flows). Differential pressure between

areas of different environmental standards shall be at least 15 Pascal (0.06 inches or 1.5mm water gauge). Suitable manometers or gauges shall be installed to measure and verify pressure differential. The final change room shall have the same class or air as specified for the aseptic area. The pressure differentials in the change rooms shall be in the descending order from white to black. Unless there are product specific requirements, temperature and humidity in the aseptic areas shall not exceed 27 degree centigrade and relative humidity 55%, respectively.

Table 1: Airborne particulate classification for manufacture of sterile products

Grade	At rest		In operation	
	Maximum No. of permitted particles per m^3 equal to or above			
	0.5µm	5µm	0.5µm	5µm
A	3520	29	3500	29
B	35200	293	352000	2930
C	352000	2930	3520000	29300
D	3520000	29300	not defined	not defined

Table 2: Types of operations to be carried out in the various grades for aseptic preparations

Grade	Types of operations for aseptic preparations
A	Aseptic preparation and filling
B	Background room conditions for activities requiring Grade A
C	Preparation of solution to be filtered
D	Handling of components after washing

Table 3: Types of operations to be carried out in the various grades for terminally sterilized products

Grade	Types of operations for terminally sterilized products
A	Filling of products, which are usually at risk
C	Placement of filling and sealing machines, preparation of solutions when usually at risk. Filling of product when usually at risk
D	Moulding, blowing operations of plastic containers, preparations of solutions and components for subsequent filling

The recommended frequencies of periodic monitoring shall be as follows:

- Particulate monitoring in air - 6 Monthly.
- HEPA filter integrity testing (smoke testing) - Yearly
- Air change rates - 6 monthly.
- Air pressure differentials - Daily.
- Temperature and humidity – Daily.

Recommended limits for microbiological monitoring of clean areas-in operation are as given in Table 4.

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Table 4: Recommended limits for microbiological monitoring of clean areas "in operation"

Grade	Air sample cfu/m^2	Settle plates (dia. 90mm. cfu/2hrs.)	Contact plates(dia. 55mm) cfu/plate	Glove points(five fingers) cfu per glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	--
D	500	100	50	--

USFDA

The air classification limits stated by USFDA are listed in Table 5.

Table 5: Air Classifications

Clean area classification(0.5µm particles/ft^3)	≥0.5µm particles/m^3	Microbiological active air action levels[c] (cfu/m^3)	Microbiological settling plates action levels[b,c] (diam.9mm; cfu/4hours)
100	3520	1[d]	1[d]
1000	35200	7	3
10000	352000	10	5
100000	3520000	100	50

a. All classifications based on data measured in the vicinity of exposed materials/articles during periods of activity.
b. Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels due to the nature of the operation or method of analysis.
c. The additional use of settling plates is optional.
d. Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.
Two clean areas are of particular importance to sterile drug product quality: the critical area and the supporting areas associated with it.

Critical Area – Class 100

This area is critical because an exposed product is vulnerable to contamination and will not be subsequently sterilized in its immediate container. To maintain product sterility, it is essential that the environment in which aseptic operations (e.g. equipment setup, filling) are conducted be controlled and maintained at an appropriate quality [2].

One aspect of environmental quality is the particle content of the air. Appropriately designed air handling systems minimize particle content of a critical area HEPA-filtered air should be supplied in critical areas at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations. The velocity parameters established for each processing line should be justified and appropriate to maintain unidirectional airflow and air quality under dynamic conditions within the critical area.

Supporting Clean Areas

Supporting clean areas can have various classifications and functions. Many support areas function as zones in which non sterile components, formulated products, in-process materials, equipment, and container/closures are prepared, held, or transferred. These environments are soundly designed when they minimize the level of particle contaminants in the final product and control the microbiological content (bioburden) of articles and components that are subsequently sterilized.

FDA recommends that the area immediately adjacent to the aseptic processing line meet, at a minimum, Class 10,000 standards under dynamic conditions.

Manufacturers can also classify this area as Class 1,000 or maintain the entire aseptic filling room at Class 100. An area classified at a Class 100,000 air cleanliness level is appropriate for less critical activities (e.g. equipment cleaning).

Clean Area Separation

An essential part of contamination prevention is the adequate separation of areas of operation. It is vital for rooms of higher air cleanliness to have a substantial positive pressure differential relative to adjacent rooms of lower air cleanliness. For example, a positive pressure differential of at least 10-15 Pascal (Pa) should be maintained between adjacent rooms of differing classification (with doors closed). When doors are open, outward airflow should be sufficient to minimize ingress of contamination, and it is critical that the time a door can remain ajar be strictly controlled.

Air change rate is another important clean room design parameter. For Class 100,000 supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable. Significantly higher air change rates are normally needed for Class 10,000 and Class 100 areas.

BUILDING AND PREMISES:

Indian GMP

The building shall be built on proper foundation with standardized materials to avoid cracks in critical areas like aseptic solution preparation, filling and sealing rooms. Location of services like water, steam, gases etc. shall be such that their servicing or repair shall not pose any threat to the integrity of the facility. Water lines shall not pose any threat of leakage to aseptic area.

The manufacturing areas shall be clearly separated into support, preparation areas, change areas and aseptic areas.

Operations like removal of outer cardboard wrappings of primary packaging materials shall be done in the de-cartooning areas which are segregated from the washing areas. Wooden pallets, fiberboard drugs, cardboard and other particle shedding materials shall not be taken inside the preparation areas.

In aseptic areas

Walls, floors and ceiling should be impervious, non-shedding, non-flaking and non-cracking. Walls shall be flat, and ledges and recesses shall be avoided. Wherever other surfaces join the wall (e.g. sterilizers, electric sockets, gas points etc.) these shall flush the walls. Walls shall be provided with a cove at the joint between the ceiling and floor and the flooring should be unbroken.

Ceiling shall be solid and joints shall be sealed. Light-fittings and air-grills shall flush with the walls and not hanging from the ceiling, so as to prevent contamination.

There shall be no sinks and drains in Grade A and Grade B areas. Doors shall be made of non-shedding material. These may be made preferably of aluminum or steel material. Doors mostly made of wood, shall open towards the higher-pressure area so that they close automatically due to air pressure.

Windows shall be made of similar material as the doors, preferably with double panel and shall flush with the walls. If fire escapes are to be provided, these shall be suitably fastened to the walls without any gaps. The furniture used shall be smooth, washable and made of stainless steel or any other appropriate material other than wood.

Change rooms with entrance in the form of air-locks shall be provided before entry into the sterile product manufacturing areas and then to the aseptic area.

The black change room shall be provided with a hand- washing sink. The sink and its drain in the un-classified (first) change rooms may be kept clean all the time. The specially designed drain shall be periodically monitored to avoid presence of pathogenic microorganisms. Change room doors shall not be opened simultaneously. An appropriate inter-locking system and a visual and/or audible warning system may be installed to prevent the opening of more than one door at a time. For communication between aseptic areas and non-aseptic areas, intercom telephones or speak-phones shall be used.

Material transfer between aseptic areas and outside shall be through suitable airlocks or pass-boxes. Doors of such airlocks and pass-boxes shall have suitable interlocking arrangements.

Personal welfare areas like rest rooms, tea room, canteen and toilets shall be outside and separated from the sterile product manufacturing area.

Animal houses shall be away from the sterile product manufacturing area and shall not share a common entrance or air handling system with the manufacturing area.

USFDA

Both personnel and material flow should be minimized to prevent unnecessary activities that could increase the potential for introducing contaminants to exposed product, containers-closures, or the surrounding environment. The number of personnel in an aseptic processing room should be minimized.

To prevent changes in air currents that introduce lower quality air, movement adjacent to the critical area should be appropriately restricted. The design of the equipment used in aseptic processing should limit the number and complexity of aseptic intervention by personnel.

Carefully designed curtains and rigid plastic shields are among the barriers that can be used in appropriate locations to achieve segregation of aseptic processing line. Use of double door or integrated sterilizer helps ensure direct product flow, often from a lower to a higher classified area. Airlocks and interlocking doors will facilitate better control of air balance throughout the aseptic processing facility. Material of construction of clean rooms ensures ease of cleaning and sanitizing.

Floors walls and ceilings should be constructed of smooth, hard surfaces that can be easily cleaned. Ceilings and associated HEPA filter banks should be designed to protect sterile materials from contamination. Processing equipment and systems should be equipped with sanitary fittings and valves. With rare exceptions, drains are considered inappropriate for classified areas of the aseptic processing facility other than Class 100,000 areas. It is essential that any drain installed in an aseptic processing facility be of suitable design.

Equipment should be appropriately designed to facilitate ease of sterilization. It is also important to ensure ease of installation to facilitate aseptic setup. The effect of equipment design on the clean room environment should be addressed. Horizontal surfaces or ledges that accumulate particles should be avoided. Equipment should not obstruct airflow and, in critical areas, its design should not disturb unidirectional airflow.

PERSONNEL:

Indian GMP

The manufacture shall be conducted under the direct supervision of competent technical staff with prescribed qualifications and practical experience in the relevant dosage and / or active pharmaceutical products.

Personnel for Quality Assurance and Quality Control operations shall be suitably qualified and experienced. Written duties of technical and Quality Control personnel shall be laid and following strictly.

Number of personnel employed shall be adequate and in direct proportion to the workload. The licensee shall ensure in accordance with a written instruction that all personnel in production area or into Quality Control Laboratories shall receive training appropriate to the duties and responsibility assigned to them. They shall be provided with regular in-service training.

This section covers garments required for use by personnel working only in aseptic area. Outdoor clothing shall not be brought into the sterile areas. The garments shall be made of non-shedding and tight weave material. The clothing and its quality shall be adopted to the process and the work place and worn in such a way as to protect the product from contamination. Garments shall be single piece with fastenings at cuffs, neck and at legs to ensure close fit. Trouser legs shall be tucked inside the cover boots. Suitable design of garments shall either include a hood (head-cover) or a separate hood which can be tucked inside the over-all. Pockets, pleats and belts shall be avoided in garments. Zips (if any) shall be of plastic material.

Only clean, sterilized and protective garments shall be used at each work session where aseptic filtration and filling operations are undertaken and at each work shift for products intended to be sterilized, post-filling. The mask and gloves shall be changed at every work session in both instances.

Gloves shall be made of latex or other suitable plastic materials and shall be powder-free. These shall be long enough to cover wrists completely and allow the over-all cuff to be tucked in. The footwear shall be of suitable plastic or rubber material and shall be daily cleaned with a bactericide. Safety goggles or numbered glasses with side extension shall be used inside aseptic areas.

Garment changing procedures shall be documented and operators trained in this respect. A full size mirror shall be provided in the final change room for the operator to verify that he is appropriately attired in the garments. Periodic inspection of the garments shall be done by responsible staff [3].

USFDA

Appropriate training should be conducted before an individual is permitted to enter the aseptic manufacturing area. Fundamental training topics should include aseptic technique, clean room behavior, microbiology, hygiene, gowning, patient safety hazards posed by a non sterile drug product, and the specific written procedures covering aseptic manufacturing area operations.

After initial training, personnel should participate regularly in an ongoing training program. Supervisory personnel should routinely evaluate each operator's conformance to written procedures during actual operations. After initial gowning, sterile gloves should be regularly sanitized or changed, as appropriate, to minimize the risk of contamination.

Personnel should not directly contact sterile products, containers, closures, or critical surfaces with any part of their gown or gloves.

Rapid movements can create unacceptable turbulence in a critical area. Such movements disrupt the unidirectional airflow, presenting a challenge beyond intended clean room design and control parameters. The principle of slow, careful movement should be followed throughout the clean room.

Also, operators should refrain from speaking when in direct proximity to the critical area.

Prior to and throughout aseptic operations, an operator should not engage in any activity that poses an unreasonable contamination risk to the gown. The gown should provide a barrier between the body and exposed sterilized materials and prevent contamination from particles generated by, and microorganisms shed from, the body. The Agency recommends gowns that are sterilized and non shedding, and cover the skin and hair (face-masks, hoods, beard/moustache covers, protective goggles, and elastic gloves are examples of common elements of gowns).

Written procedures should detail the methods used to don each gown component in an aseptic manner. An adequate barrier should be created by the overlapping of gown components (e.g. gloves overlapping sleeves). If an element of a gown is found to be torn or defective, it should be changed immediately. Gloves should be sanitized frequently.

There should be an established program to regularly assess or audit conformance of personnel to relevant aseptic manufacturing requirements. An aseptic gowning qualification program should assess the ability of a clean room operator to maintain the quality of the gown after performance of gowning procedures. It is recommended that this assessment shall include microbiological surface sampling of several locations on a gown (e.g. glove fingers, facemask, forearm and chest).

Periodic requalification will provide for the monitoring of various gowning locations over a suitable period to ensure consistent acceptability of aseptic gowning techniques. Annual requalification is normally sufficient for those automated operations where personnel involvement is minimized and monitoring data indicate environmental control.

To protect exposed sterilized product, personnel should to maintain gown quality and strictly adhere to appropriate aseptic techniques. Written procedures should adequately address circumstances under which personnel should be retrained, requalified, or reassigned to other areas.

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SANITATION:

Indian GMP

There shall be written procedures for the sanitation of sterile processing facilities. Employees carrying out sanitation of aseptic areas shall be trained specifically for this purpose.

Different sanitizing agent shall be used in rotation and the concentrations of the same shall be as per the recommendations of the manufacturer. Records of rotational use of sanitizing agents shall be maintained.

Distilled water freshly collected directly from the distilled water plant or water maintained above 70 degree centigrade from the re-circulation loop shall be used for dilution of disinfectants. Alternatively, distilled water sterilized by autoclaving or membrane filtration shall be used. The dilution shall be carried out in the "white" change room.

Where alcohol or isopropyl alcohol is used for dilution of disinfectants for use as hand sprays, the preparation of the same shall be done in the bulk preparation area and diluted solution membrane filtered into suitable sterile containers held in aseptic area.

Diluted disinfectants shall bear the label "use before", based on microbiological establishment of the germicidal properties. The solutions shall be adequately labeled and documents maintained.

Formaldehyde or any other equally effective fumigant is recommended for the fumigation of aseptic areas or after major civil modifications. Its use for routine purpose shall be discouraged and an equally effective surface cleaning regime shall be followed along with the SOP.

USFDA

The suitability, efficacy, and limitations of disinfecting agents and procedures should be assessed. The effectiveness of these disinfectants and procedures should be measured by their ability to ensure that potential contaminants are adequately removed from surfaces.

To prevent introduction of contamination, disinfectants should be sterile, appropriately handled in suitable (e.g. sterile) containers and used for no longer than the predefined period specified by written procedures. Routinely used disinfectants should be effective against the normal microbial vegetative flora recovered from the facility. Many common disinfectants are ineffective against spores. For example, 70 percent isopropyl alcohol is ineffective against *Bacillus* spp. spores. Therefore, a sound disinfectant program also includes a sporicidal agent, used according to a written schedule and when environmental data suggest the presence of spore forming organisms.

Disinfection procedures should be described in sufficient detail (e.g. preparation, work sequence, contact time) to enable reproducibility. Once the procedures are established, their adequacy should be evaluated using a routine environmental monitoring program. If indicated, microorganisms associated with adverse trends can be investigated as to their sensitivity to the disinfectants employed in the clean room in which the organisms were isolated.

Methods for monitoring the microbiological quality of the environment include:

a. Surface Monitoring

Environment monitoring involves sampling various surfaces for microbiological quality.

For example, product contact surface, floors, walls, and equipment should be tested on a regular basis. Touch plates, swabs, and contact plates can be used for such tests.

b. Active Air Monitoring

Assessing microbial quality of air should involve the use of *Active* devices including but not limited to impaction, centrifugal, and membrane (or gelatin) samplers. Each device has certain advantages and disadvantages, although all allow testing of the number of organisms per volume of air sampled.

Manufacturers should be aware of a device's air monitoring capabilities, and the air sampler should be evaluated for its suitability for use in an aseptic environment based on collection efficiency, cleaning ability, ability to be sterilized, and disruption of unidirectional airflow.

Because devices vary, the user should assess the overall suitability of a monitoring device before it is placed into service. Manufacturers should ensure that such devices are calibrated and used according to appropriate procedures.

c. Passive Air Monitoring (Settling Plates)

Another method is the use of passive air samplers, such as settling plates (Petri dishes containing nutrient growth medium exposed to the environment). Because only microorganisms that settle onto the agar surface are detected, settling plates can be used as qualitative, or semi-quantitative, air monitors.

Their value in critical areas will be enhanced by ensuring that plates are positioned in locations posing the greatest risk of product contamination. As part of methods validation, the quality control laboratory should evaluate what media exposure conditions optimize recovery of low levels of environmental isolates.

Exposure conditions should preclude desiccation (e.g., caused by lengthy sampling periods and/or high airflows), which inhibits recovery of microorganisms.

EQUIPMENT:

Indian GMP

The special equipment required for manufacturing sterile products includes component washing machines, steam sterilizers, dry heat sterilizers, membrane filter assemblies, manufacturing vessels, blenders, liquid filling machines, powder filling machines, sealing and labeling machines, vacuum testing chambers, inspection machines, lyophilizers, pressure vessels etc. suitable and fully integrated washing sterilizing filling lines may be provided, depending upon the type and volume of activity.

Unit-sterilizers shall be double-ended with suitable inter-locking arrangements between the doors. The effectiveness of the sterilization process shall be established initially by biological inactivation studies using microbial spore indicators and then at least once a year by carrying out thermal mapping of the chamber. Various sterilization parameters shall be established based on these studies and documented. For membrane filters used for filtration, appropriate filter integrity tests that ensure sterilization shall be carried out before and after filtration.

Filling machines shall be challenged initially and then at periodic intervals by simulation trials including sterile media fill. Standard Operating Procedures and acceptance criteria for media fills shall be established, justified and documented. Special simulation trial procedures shall be developed, validated and documented for special products like ophthalmic ointments.

The construction material used for the parts which are in direct contact with products and the manufacturing vessels may be stainless steel 316 or Boro-silicate glass (if glass containers) and the tubing shall be capable of being washed and autoclaved.

On procurement, installation qualification of each of the equipment shall be done by engineers with the support of production and quality assurance personnel. Equipment for critical processes like aseptic filling and sterilizers shall be suitably validated according to a written program before putting them to use. Calibration status of equipment gauges shall be adequately documented and displayed [4].

USFDA

Under the CGMP regulations, equipment must be qualified, calibrated, cleaned, and maintained to prevent contamination and mix-ups. The CGMP regulations place as much emphasis on process equipment as on testing equipment while most quality systems focus only on testing equipment.

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MANUFACTURING PROCESS

Indian GMP

Manufacture of sterile products shall be carried out only in areas under defined conditions.

Bulk raw materials shall be monitored for bio-burden periodically. Bio-burden of bulk solution prior to membrane filtration shall be monitored periodically and a limit of not more than 100 cfu per ml is recommended.

The time between the start of the preparation of the solution and its sterilization or filtration through a micro-organism retaining filter shall be minimized. There shall be a set maximum permissible time for each product that takes into account its composition and method of storage mentioned in the Master formula record.

Gases coming in contact with the sterile product shall be filtered through two 0.22µ hydrophobic filters connected in-series which shall be tested for integrity. Gas cylinders shall not be taken inside aseptic areas. Washed containers shall be sterilized immediately before use. Sterilized containers, if not used within an established time, shall be rinsed with distilled or filtered purified water and re-sterilized.

Each lot of finished product shall be filled in one continuous operation. In each case, where one batch is filled in using more than one operation, each lot shall be tested separately for sterility and held separately till sterility test results are known.

Special care shall be exercised while filling products in powder form so as not to contaminate the environment during transfer of powder to filling machine-hopper.

a. Form-Fill-Seal Technology or Blow, Fill-Seal Technology

Form-Fill-Seal units are specially built automated machines in which through one continuous operation, containers are formed from thermoplastic granules, filled and then sealed. Blow, fill-seal units are machines in which containers are moulded/ blown (pre-formed) in separate clean rooms, by non-continuous operations.

Form-Fill-Seal/Blow, Fill-Seal machines used for the manufacture of products for terminal sterilization shall be installed in at least Grade C environment and the filling zone within the machine shall fulfill Grade A requirements.

b. Terminally sterilized products

Preparation of primary packaging material such as glass bottles, ampoules and rubber stoppers shall be done in at least Grade D environment. Where there is unusual risk to the

product from microbial contamination, the above operation shall be done in Grade C environment. All the process used for component preparation shall be validated.

Filling of products requiring terminal sterilization shall be done under Grade A environment with a Grade C background.

Preparation of solutions, which are to be sterilized by filtration, shall be done in Grade C environment, and if not to be filtered, the preparation of materials and products shall be in a Grade A environment with Grade B in background.

c. Filtration (membrane)

Solutions for Large Volume Parenterals shall be filtered through a non-fiber releasing, sterilizing grade cartridge/membrane filter of nominal pore size of 0.22µ for aseptic filling whereas 0.45µ porosity shall be used for terminally sterilized products.

A second filtration using another 0.22µ sterilizing grade cartridge / membrane filter shall be performed immediately prior to filling. Process specifications shall indicate the maximum time during which a filtration system may be used with a view to precluding microbial build-up to levels that may affect the microbiological quality of the Large Volume Parenterals.

The integrity of the sterilized filter shall be verified and confirmed immediately after use by an appropriate method such as Bubble Point, Diffusive Flow or Pressure Hold Test.

d. Sterilization

Sterilization by Autoclaving:

Before any sterilization process is adopted, its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load pattern to be processed shall be demonstrated by physical measurements and by biological indicators, where appropriate.

All the sterilization process shall be appropriately validated. The validity of the process shall be verified at regular intervals, but at least annually. The sterilizer shall be double ended to prevent mix-ups.

Periodic bio-burden monitoring of products before terminal sterilization shall be carried out and controlled to limits specified for the product in the Master Formula. The use of biological indicators shall be considered as an additional method of monitoring the sterilization. These shall be stored and used according to the manufacturer‘s instructions. Their quality shall be checked by positive controls. If biological indicators used, strict precautions shall be taken to avoid transferring microbial contamination from them. There shall be clear means of differentiating “sterilized” and “un- sterilized” products. Each basket, tray or other carrier of

products or components shall be clearly labeled with the name of the material, its batch number, and sterilization status. Indicators shall be used, where appropriate, to indicate whether a batch (or sub-batch) has passed through the sterilization process.

Sterilization records shall be available for each sterilization run and may also include thermographs and sterilization monitoring strips. They shall be maintained as part of the batch release procedure.

Sterilization by dry heat:

Each heat sterilization cycle shall be recorded on a time/temperature chart of a suitable size by appropriate equipment of the required accuracy and precision. The position of temperature probes used for controlling and/or recording shall be second independent temperature probe located in the same position. The chart shall form a part of the batch record. Container mapping may also be carried out in the case of Large Volume Parenterals [5].

Chemical or biological indicators may also be used, but shall take the place of physical validation. Sufficient time shall be allowed for the load to reach the required temperature before measurement of sterilization time commences. This time shall be separately determined for each type of load to be processed.

After the high temperature phase of a heat sterilization cycle, precautions shall be taken against contamination of sterilized load during cooling. Any cooling fluid or gas in contact with the product shall be sterilized unless it can be shown that any leaking container would not be approved for use. Air inlet and outlets shall be provided with bacterial retaining filters.

The process used for sterilization by dry heat shall include air- circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Air inlets and outlets should be provided with micro-organism retaining filters. Where this process of sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins would be required as part of the validation process.

Sterilization by moist heat:

Both the temperature and pressure shall be used to monitor the process. Control instrumentation shall normally be independent of monitoring instrumentation and applications; these shall be validated to ensure that critical process requirements are met.

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 shall be frequent leak tests done on the chamber during the vacuum phase of the cycle.

The items to be sterilized, other than products in sealed containers, shall be wrapped in a material which allows removal of air and penetration of steam but which prevents re-

contamination after sterilization. All parts of the load shall be in contact with the sterilizing agent at the required temperature of the required time.

No Large Volume Parenteral shall be subjected to steam sterilization cycle until it has been filled and sealed. Care shall be taken to ensure that the steam used for sterilization is of a suitable quality and does not contain additives at a level which could cause contamination of the product or equipment.

Product Containers and Closures

All containers and closures intended for use shall comply with the pharmacopoeial and other specified requirements and shall be rinsed prior to sterilization with Water for Injection according to written procedure.

The design of closures, containers and stoppers shall be such as to make cleaning, easy and also to make airtight seal when fitted to the bottles. It shall be ensured that containers and closures chosen for a particular product are such that when coming into contact they are not absorbed into the product and they do not affect the product adversely. The closures and stoppers should be of such quality substances as not to affect the quality of the product and avoid the risk of toxicity.

Glass Bottles

Glass bottles made of USP Type-I and USP Type-II glass shall only be used. Before use, USP Type-II bottles shall be validated for the absence of particulate matter generated over a period of the shelf life of the product and shall be regularly monitored after the production, following statistical sampling methods. USP Type-III glass containers may be used for non-parenteral sterile products such as Otic Solutions and should not be reused.

Plastic Containers

Pre-formed plastic containers intended to be used for packing of Large Volume Parenteral shall be moulded in-house by one-continuous operation through an automatic machine.

Entry to the area where Blowing, filling and sealing (plugging) operations are undertaken, shall be through a series of airlocks. Blowers shall have an air supply which is filtered through 0.22µ filters.

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USFDA

a. Aseptic processing isolators

Aseptic processing using isolation systems separate the external clean room environment from the aseptic processing line and minimize its exposure to personnel [6].

There are two types of aseptic processing isolators:

Closed isolators employ connections with auxiliary equipment for material transfer.

Open isolators have openings to the surrounding environment that are carefully engineered to segregate the inner isolator environment from the surrounding room via overpressure.

Turbulent flow can be acceptable within closed isolators, which are normally compact in size and do not house processing lines. Other aseptic processing isolators employ unidirectional airflow, avoiding any turbulence or stagnant airflow in the area of exposed sterilized materials, product, and container closures. The air handling system should be capable of maintaining the requisite environmental conditions within the isolator.

Isolators that include an open portal should be designed to ensure complete physical separation from the external environment. A positive air pressure differential adequate to achieve this separation should be employed and supported by qualification studies. Positive air pressure differentials from the isolator to the surrounding environment have largely ranged from approximately 17.5 to 50 Pascal's.

The appropriate minimum pressure differential established by a firm will depend on the system's design and, when applicable, its exit port. Air balance between the isolator and other direct interfaces (e.g., dry heat tunnel) should also be qualified.

The positive pressure differential should be coupled with an appropriately designed opening to the external environment to prevent potential ingress of surrounding room air by induction.

Induction can result from local turbulent flow causing air swirls or pressure waves that might push extraneous particles into the isolator. Local Class 100 protection at an opening is an example of a design provision that can provide a further barrier to the external environment. The interior of the isolator should meet Class 100 standards. The classification of the environment surrounding the isolator should be based on the design of its interfaces, as well as the number of transfers into and out of the isolator. A Class 100,000 background is commonly used based on consideration of isolator design and manufacturing situations.

Blow-fill- seal technology: BFS technology is an automated process by which containers are formed, filled, and sealed in continuous operation. This manufacturing technology includes the economies in container closure processing and reduced human intervention and is often

used for filling and packaging ophthalmic, respiratory care products, and, less frequently, injectables.

As with any aseptic processing operation, it is critical that product contact surfaces be sterile. A validated steam-in-place cycle, or equivalent process, should be used to sterilize the equipment path through which the product is conveyed. In addition, any other surface that represents a potential contamination risk to the sterile product should be sterile.

The classified environment surrounding BFS machinery should generally meet Class 100,000 or better, standards, depending on the design of the BFS machinery and the surrounding room. HEPA-filtered or sterile air provided by membrane filters should be used during the steps when sterile products or materials are exposed. Air in the critical area should meet Class 100 microbiological standards during operations. A well-designed BFS system should also normally achieve Class 100 airborne particle levels. Only personnel who have been qualified and appropriately gowned should enter the classified environment surrounding the BFS machinery.

BFS equipment design typically calls for use of specialized measures to reduce particle levels that can contaminate the exposed product. In contrast to non-pharmaceutical applications using BFS machinery, control of air quality (i.e. particles) is critical for sterile drug product manufacture. Particles generated during the plastic extrusion, cutting, and sealing processes should be controlled. Provisions for carefully controlled airflow can protect the product by forcing generated particles outward while preventing any ingress from the adjacent environment.

CONCLUSION

All guidelines should be considered and they must be used in a rational sense for practical use.

All the aspects of quality requirements for sterile product manufacture as per different guidelines were observed in certain aspects like in the frequencies for environmental monitoring between Indian GMP and USFDA guidelines, regarding the requirements of building and premises, importance of personal hygiene, methods for monitoring the microbiological quality of the environment, requirements for equipment with written procedures, etc.

All the aspects mentioned have to be taken into consideration to avoid false positive results and during the comparison it has been found that, all the guidelines focussed on high quality requirements for the manufacturing process for sterile pharmaceutical products.

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