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(Review Article)

Comparison of Quality Requirements for Sterile Product Manufacture as per International Regulatory Agencies

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ABSTRACT

The present study deals with a brief overview of the quality requirements for sterile pharmaceutical product manufacture as per international regulatory requirements. The pharmaceutical companies are required to follow the quality management specifications as per different guidelines such as Indian GMP (Schedule M), WHO, US cGMP and MHRA. Parenteral products are intended to be non-pyrogenic too, additionally to the requirement to be sterile. 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. It is necessary to know the differences in the requirements of guidelines given by different international agencies. Knowledge of the differences in the requirements 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.

Key Words: Indian GMP, Schedule M, WHO, US cGMP, MHRA

INTRODUCTION

Sterile pharmaceutical products are very critical and sensitive products. These products by design are required to be free from living micro-organisms, pyrogens and unacceptable particulate matter.

Sterile products produced in staffed cleanrooms are subject to microbial contamination from the environment in which the process is carried out. The process may be adversely affected by the presence of microorganisms termed “adventitious,” (i.e., contamination incidental to the process) but also by contamination that is an unavoidable consequence of that process. Furthermore, there is no direct method to establish the source of contamination in aseptic processing environments. Contamination may be derived from the process, materials, equipment, operators, or the production environment, but could just as easily be introduced during sampling or the testing of samples. The sterility testing of samples from an aseptic process may be considered an entirely separate aseptic process, subject to the same types of adventitious contamination as the aseptic process itself. Nonetheless, contaminants found in samples taken from the production environment, whether for sterility or environmental monitoring, are routinely associated solely with the production environment and not considered adventitious contaminants introduced during the testing. As long as the background contamination rate in the sterility and environmental testing environments is sufficiently low, it can be assumed that all contamination is derived from the production area.

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. Aseptic processing involves more variables than terminal sterilization. Before aseptic assembly into a final product, the individual parts of the final product are generally subjected to several sterilization processes. For example, glass containers are subjected to dry heat sterilization; rubber closures are subjected to moist heat sterilization; and liquid dosage forms are subjected to sterile filtration. Each of these aseptic manufacturing processes requires thorough validation and control. Each process also could introduce an error that ultimately could lead to the distribution of a contaminated product. 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. A terminally sterilized drug product, on the other hand, undergoes a single sterilization process in a sealed container, thus limiting the possibilities for error.
Manufacturers should have a keen awareness of the public health implications of distributing a non sterile product. Poor CGMP conditions at a manufacturing facility can ultimately pose a life-threatening health risk to a patient[1-10].

ELEMENTS REQUIRED TO BE CONSIDERED IN PROCESSING OF STERILE PRODUCTS
The following elements are required to be considered in the processing of sterile pharmaceutical products:

- Only trained personnel should be allowed to process these products.
- Layouts and specifications of the manufacturing facilities and buildings should be such that it will help in creating and maintaining the quality, purity, identity and safety of the product being manufactured.
- Particulate (non-viable) and microbial (viable) environment should be monitored as per the regulatory guidelines.
- Utmost precautions should be taken about the quality of the air, water, steam and other gases used in the manufacturing process.
- Standard operating procedures should cover issues related to people, materials, material flow, equipment, solution preparation, environmental monitoring and control etc.
- Sanitation and sterilization processes should be pre-validated.
- System suitability studies (media fill) should be carried out at regular frequency.
- Production batches must be released by authorized person only after thorough scrutiny of all the documents related to the manufacturing of the batch.
- Concept of the "Quality Assurance" to be followed rather than "Quality Control" of the finished product.
- Use of LAF units of appropriate rating must be used where required.
- Environmental conditions control and monitoring is very important.

The industry should have a manual describing the Quality Requirements for sterile pharmaceutical manufacturing. The quality manual should outline the organization and format of documents used in the management as well as the roles and responsibilities of the personnel responsible for management of the Quality systems for sterile pharmaceutical manufacture and for management of the technical procedures. The quality manual should also document the administrative, organizational and scientific aspects of the work of the industry necessary for its proper management.
The documentation should be readily available in the industry and accessible to all relevant staff. It should be continuously reappraised and updated to ensure that changing circumstances are taken into account. Various factors, such as personnel, accommodation and environment, test methods, method validation, equipment, reference standards, sampling and the handling of test items contribute towards the accuracy and reliability of results and also determine to a large extent the uncertainty of the measurement[2-12].

GENERAL CONSIDERATIONS
The general consideration / requirements for the manufacturing of sterile products are discussed below [11-20]:

Indian cGMP
Sterile products, being very critical and sensitive in nature, a very high degree of precautions in the preparations are needed. Dampness, dirt and darkness are to be avoided to ensure aseptic conditions in all areas. Areas are classified into four grades namely A, B, C, and D.

WHO

The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in separate areas within a manufacturing site.
Sterile manufacturing areas are divided into four grades (A, B, C and D).
Manufacturing operations are divided here into two categories:

1) Those where the product is terminally sterilized, and
2) Those which are conducted aseptically at some or all stages.

MHRA

The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials. Manufacturing operations are divided into two categories; firstly those where the product is terminally sterilized, and secondly those which are conducted aseptically at some or all stages.

ENVIRONMENTAL PARAMETERS

Indian cGMP

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.

WHO

For the manufacture of sterile pharmaceutical preparations, four grades are distinguished here, as follows:
Grade A: The local zone for high-risk operations, e.g. filling and making aseptic connections. Normally such conditions are achieved by using a unidirectional airflow workstation.
Grade B: In aseptic preparation and filling, the background environment for the grade A zone.
Grades C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products. In order to reach the B, C and D air grades, the number of air changes should be appropriate for the size of the room and the equipment and personnel present in it.

USFDA

The air classification limits stated by USFDA are listed in Table 4.
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.
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.
Clean Area Separation
An essential part of contamination prevention is the adequate separation of areas of operation.
To maintain air quality, it is important to achieve a proper airflow from areas of higher cleanliness to adjacent less clean areas.

MHRA

Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station.
Grade B: For aseptic preparation and filling, this is the background environment for the grade A zone.
Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

BUILDING AND PREMISES

Indian cGMP

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.
In aseptic areas
Walls, floors and ceiling should be impervious, non-shedding, non-flaking and non-cracking. Flooring should be unbroken and provided with a cove both at the junction between the wall and the floor as well as the wall and ceiling.

WHO

All premises should, as far as possible, be designed to avoid the unnecessary entry of supervisory or control personnel. Grade A/B areas should be designed so that all operations can be observed from outside.

False ceilings should be sealed to prevent contamination from the void space above them. Airlock doors should not be opened simultaneously.

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.

MHRA

In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.

PERSONNEL

Indian cGMP

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.

WHO

Only the minimum number of personnel required should be present in clean areas. This is particularly important during aseptic processes. Inspections and controls should be conducted from outside such areas as far as possible.

USFDA

To ensure maintenance of product sterility, it is critical for operators involved in aseptic activities to use aseptic technique at all times.

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.

MHRA

Same as that recommended by WHO. The description of clothing required for each grade is same as specified by WHO.

SANITATION

Indian cGMP

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.

WHO

Monitoring should be regularly undertaken in order to detect the contamination or the presence of an organism against which the cleaning procedure is ineffective. In view of its limited effectiveness, ultraviolet light should not be used as a substitute for chemical disinfection. Where disinfectants are used more than one type should be employed.

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.

MHRA

The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.

EQUIPMENT

Indian cGMP

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, lyophilisers, pressure vessels etc. suitable and fully integrated washing sterilizing filling lines may be provided, depending upon the type and volume of activity.

WHO

A conveyor belt should not pass through a partition between a grade A or B clean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilized.

Whenever possible, equipment used for processing sterile products should be chosen so that it can be effectively sterilized by steam or dry heat or other methods.

Equipment fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. Equipment that has to be taken apart for maintenance should be re-sterilized after complete reassembly, wherever possible.

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.

MHRA

Same as that recommended by WHO.

MANUFACTURING PROCESS

Indian cGMP

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.

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.

- Blow/fill/seal technology
- Terminally sterilized products
- Filtration (membrane)
- Sterilization

WHO

- Terminal sterilization
- Isolator technology
- Blow/fill/seal technology

USFDA

- Aseptic processing isolators
- Blow-fill- seal technology

MHRA

- Isolator technology
- Blow/fill/seal technology
- Terminally sterilised products
- Aseptic preparation
- Sterilization

ENVIRONMENTAL PARAMETERS

Comparison of Indian GMP (Schedule M), WHO, US cGMP, MHRA guidelines:

A general harmonisation in requirements for the clean rooms (particulate matter, microorganisms) between GMP (schedule M), MHRA and USFDA does not yet exist. The comparison between different agencies regarding environmental parameters are made and listed in the following table 5.

CONCLUSION

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. All the guidelines were broadly similar except for environmental factors and some were more detailed than the other.

Table 1: Airbone 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	Asceptic 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: Maximum permitted airborne particle concentration for each grade.

	Maximum permitted No. of particles per m^3 equal to or greater than the tabulated size			
	At rest		**In operation**	
Grade	**0.5µm**	**5.0µm**	**0.5µm**	**5.0µm**
A	3520	20	3520	20
B	3520	29	352000	2900
C	352000	2900	3520000	29000
D	3520000	29000	NOT DEFINED	NOT DEFINED

Table 4: 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

Table 5: Comparison of various grades described in various guidelines.

Sl. No.	**USFDA**	**GMP/WHO/MHRA**
1	Class 100	A and B
2	Class 10,000	C
3	Class 1,00,000	D

Table 6: Comparison of airborne particulate classification as per different guidelines.

		GMP	WHO/MHRA
	Grade	5µm	
AT REST	A	29	20
	B	293	29
	C	2930	2900
	D	29300	29000
IN OPERATION	A	29	20
	B	2930	2900
	C	29300	29000
	D	NOT DEFINED	NOT DEFINED

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