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Comparative Study of Good Manufacturing Practice (GMPs) Requirements for Sterile Pharmaceutical Products in USA and INDIA

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ABSTRACT:

The objective of this work helps in bringing the awareness about the manufacturing requirements as per USFDA and India. The present study deals with a brief overview of the GMP requirements for sterile pharmaceutical product manufacture as per USA and India. 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 USFDA and India. Knowledge of the differences in the requirements is important to guarantee the quality products and their supply in due time for the designated market. 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.

Key Words: Indian GMP, Schedule M, US cGMP, USFDA

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INTRODUCTION [1-6]

Sterile pharmaceutical products are very critical and sensitive products. These products should be free from living micro-organisms, pyrogens and unacceptable particulate matter. Parenteral products are radically different from other dosage form in terms of standards of purity and safety. The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure.

There are two broad methods to produce a sterile drug product:

A. Terminal Sterilization
B. Aseptic Processing of sterilized unit components

A. Terminal Sterilization - The terminal sterilization process usually involves filling and sealing product containers under high quality environmental conditions designed to minimize microbial and particulate contamination of the product. This minimization of upstream bioburden reduces the challenge to the subsequent sterilization process. In most cases, the product, container, and closure have low bioburden, but are not sterile at the time of filling. The product is then subjected to a sterilization process in its final container.

There are various methods of terminal sterilization including:

- Moist heat sterilization
- Dry heat sterilization
- Steam sterilization
- Gas sterilization

B. Aseptic Processing - Aseptic processing presents a higher risk of microbial contamination of the product than terminal sterilization. In an aseptic filling process, the drug product, containers and closures are sterilized separately and then brought together under an extremely high quality environmental condition designed to reduce the possibility of a non-sterile unit. Aseptic processing involves more variables than terminal sterilization. Any manual or mechanical manipulation of the sterilized drug, containers, or closures prior to or during aseptic filling and assembly poses the risk of microbial contamination.

COMPARATIVE STUDY GMPs REQUIREMENTS FOR THE MANUFACTURING OF STERILE PRODUCTS ARE DISCUSSED BELOW [2-6]:

1. CLEAN AREA CLASSIFICATION

Production of sterile products should be carried out in a clean environment with a limit for the environmental quality of particulate and microbial contamination. Clean areas for the production of sterile products are classified into different grades discussed below:

TABLE 1: COMPARISON OF CLEAN AREA CLASSIFICATION [2-3]

Indian GMP	US cGMP
Grade A	Class 100
Grade B	Class 1000
Grade C	Class 10,000
Grade D	Class 100,000

Two clean areas are of particular importance to sterile drug product quality: the critical area and the supporting clean areas associated with it.

Critical Area (Class 100)

Activities conducted in such areas include manipulations (e.g., aseptic connections, sterile ingredient additions) of sterile materials prior to and during filling and closing operations.

Supporting Clean Areas

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.

Indian GMP:

TABLE 2: AIRBORNE PARTICULATE CLASSIFICATION FOR MANUFACTURE OF STERILE PRODUCT [2]

Grade	At rest			In Operation
	Maximum number of permitted particles per m^3 equal to or above			
	0.5 µm	5 µm	0.5 µm	5 µm
A	3520	29	3500	29
B	35,200	293	3,52,000	2,930
C	3,52,000	2,930	35,20,000	29,300
D	35,20,000	29,300	Not defined	Not defined

TABLE 3: TYPES OF OPERATION TO BE CARRIED OUT [2]

Grade	Types of operation for aseptic preparation
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

US cGMP:

TABLE 4: AIR CLASSIFICATION [3]

Clean Area Classification (0.5 µm particles/ft^3)	ISO Designation	≥ 0.5 µm particles/m^3
100	5	3,520
1000	6	35,200
10,000	7	352,000
100,000	8	35,20,000

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. A positive pressure differential of at least 10-15 Pascal should be maintained.

2. MICROBIAL MONITORING

TABLE 5: MONITORING PARAMETERS [2-3]

PARAMETER	INDIA	USA
Pressure differential B/N clean room	15 Pascal	10 – 15 Pascal
HEPA filter integrity testing	Yearly	Twice a year
Particulate monitoring in air	6 monthly	Each production shift
Air change rate	6 monthly	Each production shift
Air pressure differential	Daily	Each production shift
Time & temperature	Daily	Each production shift

Indian GMP:

TABLE 6: RECOMMENDED LIMIT FOR MICROBIAL MONITORING OF CLEAN AREA "IN OPERATION" [2]

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

US cGMP:

TABLE 7: MICROBIAL MONITORING [3]

Clean Area Classification	ISO Designation	Microbiological Active Air Action Levels (cfu/m^3)	Microbiological Settling Plates Action Levels (Dia. 90mm; cfu/4 hrs.)
100	5	1	1
1000	6	7	3
10,000	7	10	5
100,000	8	100	50

3. BUILDINGS & 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. 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.

US cGMP:

Adequate design features include seamless and rounded floor to wall junctions as well as readily accessible corners. 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.

4. 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.

US cGMP:

Appropriate training should be conducted before an individual is permitted to enter the aseptic manufacturing area. After initial training, personnel should participate regularly in an ongoing training program. Some of the techniques aimed at maintaining sterility of sterile items and surfaces include:

a) Contact sterile materials only with sterile instruments
b) Move slowly and deliberately
c) Keep the entire body out of the path of unidirectional airflow
d) Approach a necessary manipulation in a manner that does not compromise sterility of the product
e) Maintain Proper Gown Control

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

US cGMP:

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.

6. FILTRATION (MEMBRANE)

Indian GMP:

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

A second filtration using another 0.22 µ sterilizing grade cartridge/membrane filter shall be performed immediately prior to filling.

Gases coming in contact with the sterile product shall be filtered through two 0.22 µ hydrophobic filters connected in-series.

US cGMP:

Non-fiber releasing filter of 0.22 µ maximum mean porosity of 0.45 µ shall be used in the manufacture, processing, or packing of these injectable drug products

Use of asbestos containing filters requires U.S. FDA approval.

Membrane filters can be used to filter a compressed gas to meet an appropriate high-quality standard.

Use of hydrophobic filters, as well as application of heat to these filters where appropriate, prevents problematic moisture residues.

7. MANUFACTURING PROCESS

Indian GMP:

Manufacture of sterile products shall be carried out only in areas under defined conditions. 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
- Form/fill/seal technology
- Terminally sterilized products
- Sterilization

US cGMP:

- Blow-fill- seal technology
- Sterilization
- Aseptic processing isolators

A. Form-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.

B. Blow-Fill-Seal technology

BFS system is widely used & accepted by USFDA. This system is reported to achieve contamination rate below 0.1%. Blow, fill-seal units are machines in which containers are moulded / blown (pre-formed) in separate clean rooms, by non-continuous operations.

C. 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**.** Pressure differential, glove integrity, and protection of the transfer (i.e., entry, exit) ports are key elements for the isolators.

8. VALIDATION OF ASEPTIC PROCESSING & STERILIZATION

Indian GMP:

Equipment for critical processes like aseptic filling and sterilizers shall be suitably validated according to a written program before putting them to use. All the sterilization process shall be appropriately validated. The validity of the process shall be verified at regular intervals, but at least annually.

US cGMP:

A. Process Simulation:

1. Study design
2. Frequency & number of run
3. Duration of run
4. Size of run
5. Line speed
6. Environmental condition
7. Media
8. Incubation & Examination of Media-Filled unit
9. Interpretation of test result

B. Filtration efficacy

C. Sterilization of equipment, containers & closures:

1. Qualification & Validation
2. Equipment controls & Instrument Calibration

9. STERILITY TEST

Indian GMP:

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.

US cGMP:

Certain aspects of sterility testing are of particular importance, including control of the testing environment, understanding the test limitations, and investigating manufacturing systems following a positive test. The testing laboratory environment should employ facilities and controls comparable to those used for aseptic filling operations. The use of isolators for sterility testing minimizes the chance of a false positive test result.

Sterility test includes following:

A. Microbiological laboratory controls

B. Sampling and Incubation

C. Investigation of Sterility positives

1. Identification of organism in sterility test
2. Record of laboratory tests and deviations
3. Monitoring of production area environment
4. Monitoring Personnel
5. Product Presterilization Bioburden
6. Production record review

10. WATER SYSTEM

TABLE 8: TYPES OF WATER AS PER PHARMACOPOEIA [5-6]

USP	IP
Potable water	Purified water
Purified water& Water for injection	Water for injection
Sterile water for injection & inhalation	Water for injection in bulk
Sterile water for irrigation	Sterile water for injection
Water for Haemodialysis	
Sterile Bacteriostatic water for injection	

TABLE 9: SIGNIFICANT DIFFERENCES OF REQUIREMENTS ON PURIFIED WATER FOR PHARMACEUTICAL [5-6]

USP (US cGMP)	IP (Schedule "M")
Purified Water is water obtained by distillation, ion-exchange treatment, reverse osmosis, or other suitable process. It is prepared from water complying with the regulations of the U.S. Environmental Protection Agency (EPA) with respect to drinking water. It contains no added substances.	Purified Water is prepared by distillation, by means of ion exchange or by any other appropriate means from suitable potable water that complies regulations (standard specified by bureau of Indian standard).

TABLE 10: SIGNIFICANT DIFFERENCES OF REQUIREMENTS ON WFI [5-6]

USP (US cGMP)	IP (Schedule "M")
Water for injection intended for use in the preparation of parenteral solution, where used for the preparation of parenteral solution subjected to final sterilization, use suitable means to minimize microbial growth.	Water for injection is water intended for use in the preparation of medicines for parenteral administration.

TABLE 11: SPECIFICATION WATER ACCORDING TO USP AND IP [5-6]

	IP		USP	
	Purified Water	**WFI**	**Purified Water**	**WFI**
P^H	-	-	5.0 to 7.0	**5.0 to 7.0**
Cl	Comply with Test	Comply with Test	Comply with Test	**Comply with Test**
SO_4	Comply with Test	Comply with Test	Comply with Test	**Comply with Test**
NH_4	Comply with Test	Comply with Test	Comply with Test	**Comply with Test**
Ca	Comply with Test	Comply with Test	Comply with Test	**Comply with Test**
Nitrate	Comply with Test	Comply with Test	Comply with Test	**Comply with Test**
TOC	NMT 0.5 mg / L	NMT 0.5 mg / L	NMT 500 ppb	**NMT 500 ppb**
Solid	-	-	-	**-**
Conductivity	Comply with Test	Comply with Test	< 1.25 µS/cm	**< 1.25 µS/cm**
Heavy metals	Comply with Test	Comply with Test	Comply with Test	**Comply with Test**
Bacterial Endotoxin	NMT 0.25 EU/ml	NMT 0.25 EU/ml	NMT 0.25 EU/ml	**NMT 0.25 EU/ml**
CO_2	-	-	-	**Comply with Test**
Bacteria	**-**	**-**	**100 cfu/ml**	**10 cfu/100 ml**

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 & water system. USFDA more focus on and have strict GMP regulation on clean area classification, microbial monitoring, validation aspects and personnel training.

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REFERENCES

1. Food and Drug Administration - Sterile Drug Process Inspection (http://www.ccv.com.ve/SalasLimpias/FDA_SterileDrug ProcessInspections.pdf). Accessed 26 September 2013.
2. Schedule M, Part I-A, Specific Requirements for Manufacture of Sterile Products, Parenteral Preparations and Sterile Ophthalmic Preparations (http://cdsco.nic.in/html/GMP/ScheduleM(GMP).pdf). Accessed 26 September 2013.
3. Guidance for Industry for Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice (http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070342.pdf). Accessed 1 November 2013.
4. 21 CFR 211 - Current Good Manufacturing Practice In Manufacturing, Processing, Packing or Holding of Drugs; Current Good Manufacturing Practice For Finished Pharmeceuticals (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=211). Accessed 27 September 2013.
5. Indian Pharmacopoeia 2010.
6. United State Pharmacopoeia 30 - NF 25.