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RESEARCH ARTICLE

GMP COMPARISION OF PARENTERAL DOSAGE FORM IN US, AUSTRALIA AND MALAYSIA

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ABSTRACT

GMP guidelines are not prescriptive instructions on how to manufacture products. They are sequence of general principles that must be observed during manufacturing. When a company is setting up its quality program and manufacturing process, there may be many ways it can fulfill GMP requirements. It is the company's responsibility to determine the most effective quality standards. Regulations for manufacturing Parenteral dosage form is very stringent, so it is necessary to understand the similarities and differences among GMP requirements for the manufacturing of Parenteral dosage form & general requirement which are used in manufacturing by the Regulated countries which will be beneficial to the pharmaceutical companies of both ROW countries & Regulated countries.

INTRODUCTION

GMP [1]

- GMP regulation are enforced by the FDA and primarily housed within the Federal Food, Drug and Cosmetic Act, 1940.
- Good Manufacturing Practices (GMP) is a set of regulations, codes and guidelines for the manufacturing and testing of active pharmaceutical ingredients, diagnostics, foods, pharmaceutical products and medical devices.
- GMP term that is recognized worldwide for the control and management of manufacturing and quality control testing of pharmaceutical products.
- Basic goal of these guidelines is safeguarding the health oe the patient as well as producing good quality medicines.
- The cGMP requirements were established to be flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures.
- The flexibility in this regulation allows companies to use modern technologies and innovative approaches to achieve higher quality through continuous improvement.
- GMP is referred to as “cGMP” mostly in the United States of America. The “c” in cGMP stands for “current” requiring companies to use technologies and systems that are up to date in order to comply with the regulations.

Definition [1]

- GMP is that part of Quality assurance which ensures that the products are consistently manufactured and controlled to the Quality standards appropriate to their intended use.
- "GMP" - A set of principles and procedures which, when followed by manufacturers for therapeutic goods, helps ensure that the products manufactured will have the required quality.

History of GMP[2]

1906- Pure Food and Drug Act
1938- Federal Food, Drug and Cosmetic (FD&C) Act: - Sulfanilamide tragedy
1941- Two Unrelated Events:- Insulin tragedy, Sulfathiazole tablet with Phenobarbital
1962- Kefauver-Harris Drug Amendments tragedy: - Thalidomide case
1963- GMPs for Drugs (28 CFR 6385)
1976- Medical Device amendments Tragedy
1978- cGMP for Drugs and Device (21 CFR 210-211 and 820)
1982- Tamper-Resistant Packaging Regulation Issued for OTC Products Tragedy
1987- Guidelines on General Principles of Process Validation

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1992- Generic Drug Enforcement Act
1996- Two Unrelated Events Proposed revision to US cGMP for Drugs and Biologics (21 CFR 210 211)
1997-Electronic Records Final Rule (21 CFR 11)
1998- Draft Guidelines
2001- ICH Q7A API Guidelines ICH's "Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredient (API)

Principles of GMP [3]

1. Step-by-step written procedure
2. Follow procedure
3. Document work
4. Validation work
5. Integrate productivity, quality and safety in to facilities and equipments
6. Maintain facilities and equipments
7. Define, Develop and Demonstrate job competence
8. Make cleanliness a daily habit
9. Build Quality in to the product
10. Conduct compliance and performance audits

Specific Requirements for Manufacturing Of Parentral Dosage Form In Us, Australia And Malaysia [4, 5]

GMP as per the Country

Table 1 Comparison of guideline

US	Australia & Malaysia
FDA (Food and drug administration) Guidance for Industry for Sterile Drug Products Produced by Aseptic processing – cGMP, September 2004	Guidelines to Good Manufacturing Practice for medicinal products for human use (Directive 91/356/EEC), Annex 1 Manufacture of Sterile Medicinal Products.

Clean Area Classification

Table 2 Comparison of clean area classification

US	Australia & Malaysia
Class 100	Grade A
Class 1,000	Grade B
Class 10,000	Grade C
Class 1,00,000	Grade D

US

Table 3 Air Classification in US

Clean Area Classification ($0.5\ \mu m$ particles/ft^3)	ISO Designation	≥0.5µm particles/m^3
100	5	3,520
1000	6	35,200
10,000	7	352,000
100,00	8	35,20,000

Australia & Malaysia

Table 4 Particulate Classification for Manufacture of Sterile Products in Australia & Malaysia

Grade	Maximum number of permitted particles per cubic meter equal to or above			
	At rest		In Operation(a)	
	0.5 µm	5 µm	0.5 µm	5 µm
A	3,520	20	3,520	20
B	3,520	29	3,52,000	2,900
C	3,52,000	2,930	35,20,000	29,000
D	35,20,000	29,000	Not defined	Not defined

Table 5 Types of Operation to be carried out for Terminally Sterilized in Australia & Malaysia

Grade	Operations for terminally sterilized products
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Table 6 Types of Operation to be carried out for Aseptic Preparation in Australia & Malaysia

Grade	Operations for aseptic preparations
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

Microbial Monitoring

US

Table 7 Microbial monitoring in US

Clean area classification	ISO Designation	Microbial 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

Australia & Malaysia

Table 8 Microbial monitoring in Australia & Malaysia

Grade	Air sample cfu/m3	Settle plates (diameter 90mm) cfu/4 hours	Contact plates (diameter 55 mm) cfu/plate	Glove print 5 fingers cfu/glov
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Environmental Monitoring

Table 9 Environmental Monitoring Parameters

Parameters	US	Australia & Malaysia
HEPA filter integrity testing	Twice a year	Twice a year
Particulate monitoring in air	Each production shift	6 monthly
Air change rate	Each production shift	Each production shift
Air pressure –differential	Each production shift	Each production shift
Time & Temperature	Each production shift	Each production shift
Air change rate	Class 1,00,000: NLT 20 air change per hour Class 100 & 10,000: Higher air change rate	Grade B, C & D: NLT 20 air change per hour
Pressure differential between clean rooms	10-15 Pascal	10-15 Pascal

Buildings & Facilities

US

- Adequate design features include seamless and rounded floor in 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 product sterile materials from contamination. Clean rooms also should not contain

unnecessary equipment, fixtures or materials.

Australia & Malaysia

- 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.
- To reduce accumulation of dust and to facilitate cleaning there should be no un-cleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment.
- Doors should be designed to avoid those un-cleanable recesses; sliding doors may be undesirable for this reason.
- False ceilings should be sealed to prevent contamination from the space above them.
- Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.
- Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains.
- Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

Filtration Membrane

Table 10 Comparison of filtration process

US	Australia & Malaysia
Filter should be Non-fibre releasing and USFDA approved asbestos containing filters are used. Filter should be of 0.22µ and maximum mean porosity of 0.45 µ shall be used in the manufacture, processing, or packing of these injectable drug products.	Sterile filter having nominal pore size of 0.22 micron (or less). Fibre-shedding characteristics of filters should be minimal.

Personnel

US

- 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 behaviour, microbiology, hygiene, gowning, patient safety hazards posed by a non sterile drug product, and the specific written procedures covering aseptic manufacturing area operations.

Australia & Malaysia

- Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.
- All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products. This training should include reference to hygiene and to the basic elements of microbiology.
- When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.
- The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.

Sanitation

Table 11 Comparison of Sanitation process

US	Australia & Malaysia
• The suitability, efficacy and limitation of disinfecting agents and procedures should be assessed. • The effectiveness of these disinfectants and procedures should be assessed by their ability to ensure that potential contaminants are removed from surfaces.	• Disinfectants and detergents should be monitored,for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilized. • Disinfectants and detergents used in Grades A and B areas should be sterile prior to use. • Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

Equipments

US

- Under the cGMP regulation, equipment must be qualified, calibrated, cleaned and maintained to prevent contamination and mix up. The CGMP regulation place as much emphasis on process equipment as on testing equipment while most quality systems focus on testing equipment.
- Equipment used in manufacturing sterile products may include the following:

Production equipments

1. Aseptic processing
2. Capping Equipments
3. Post fill Visual Inspection
4. Sterilizers
5. Lyophilizer
6. Isolators
7. Blow-fill-seal(BFS) Technology

Container-closure processing equipment

E.g. stopper washer, glassware dehydrogenation equipment

Support system/material system related equipment

E.g. WFI system and related equipment

Australia & Malaysia

- A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilized.
- Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity.
- Water for injections should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C.
- All equipment such as sterilizers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved.

Sterilization Technique

Table 12 Comparison of Sterilization technique

US	Australia & Malaysia
Sterilization by Dry heat	Sterilization by Dry heat
Sterilization by Moist heat	Sterilization by Moist heat
Sterilization by Filtration	Sterilization by Heat
Steam Sterilization	Sterilization by Radiation
Sterilization by Radiation	Sterilization by Ethylene Oxide
Sterilization by Ethylene Oxide	
Lyophilisation	

Containers/Clousers

US

Glass container

- Pre sterilization preparation of glass containers usually involves a series of washes and rinse cycle. These cycles serve an important role in removing foreign matter.
- Subjecting glass containers to dry heat generally accomplishes both sterilization and depyrogenation. Validation of dry heat sterilization and depyrogenation should be include appropriate heat distribution and penetration studies as well as the use of worst case process cycle, container characteristics (e.g. mass), and specific loading configuration to represent actual production runs.

Plastic Containers

- Plastic containers are used for parenteral products also should be non-pyrogenic. Where applicable, multiple WFI rinses also should be effective in removing pyrogen from containers.
- Plastic containers can be sterilized with an appropriate gas, irradiation, or other suitable means.

Rubber closures

- Rubber closure (e.g. stoppers and syringe plungers) can be cleaned by multiple cycles of washing and rising prior to final steam or irradiation sterilization.
- At minimum, the initial rinses for the washing process should employ at least purified water, USP, of minimal endotoxins content, followed by final rinses with WFI for parenteral products.
- A potential source of contamination is the siliconization of rubber stoppers. Silicon used in the preparation of rubber stoppers should meet appropriate quality control criteria and not have an adverse effect on the safety, quality, or purity of the drug product.

Australia & Malaysia

Glass container

- While plastic dominates primary and secondary packaging materials for most types of pharmaceutical dosage forms, glass remains the primary packaging material of choice for parenteral products at this time. Glass vials and bottles are manufactured by moulding while ampoules, cartridges, pre-filled syringe barrels and vials are manufactured from tubing glass.

Table 13 Types of Glass containers

Type	General description	Type of test
I	Borosilicate glass	Glass grains
II	Treated soda-lime glass	Surface Etching
III	Soda-lime glass	Surface glass

Plastic Containers

- Plastic containers for aqueous solutions for parenteral infusion are manufactured from one or more polymers, if necessary with additives.
- They usually have a part that allows them to be suspended and which will withstand the tension occurring during use.

Rubber Closures

- Rubber closures for containers for aqueous parenteral preparations for powders and for freeze-dried powders are made of materials obtained by vulcanization (cross-linking) of macromolecular organic substances (elastomers), with appropriate additives.
- Rubber closures may be classified in 2 types:

Type I closures

They are those which meet the strictest requirements and which are to be preferred.

Type II closures

They are those which are having mechanical properties suitable for special uses and cannot meet requirements.

Validation of aseptic processing and sterilization

Table 14 Validation of aseptic processing and sterilization

US	Australia & Malaysia
a) Process Stimulation • Study design • Frequency & number of run • Duration of run • Line speed • Environmental condition • Media • Incubation & Examination of Media-filled unit • Interpretation of test result Sterilization of equipment, containers & closure • Qualification & Validation • Equipment controls & Instrumental calibration	**a.** Process Simulation Normally process simulation tests should be repeated twice a year per shift and process. It includes:- • Media fill • Aseptic manufacturing rocess & further steps Water source & Water treatment equipment **b.** Container, Component & Equipment validation **c.** Microbiological contamination **d.** Bio-burden monitoring

Manufacturing Process

Table 15 Comparison of manufacturing process

US	Australia & Malaysia
Blow-fill-seal technology Aseptic processing isolators Form-fill-seal technology Sterilization	Blow-fill-seal technology Aseptic processing isolators Sterilization

Table 16 Comparison of Blow-fill-seal technology

US	Australia & Malaysia
The classified environment surrounding BFS machinery should meet class 100,000 or better. A well-designed BFS system should normally achieve class 100 airborne particle levels	For terminally sterilized product it should be installed in at least a grade D environment. For aseptic production it shall be installed in at least Grade C environment with an effective grade A & B.

BFS system is widely used & accepted by USFDA. This system is reported to achieve contamination rate below 0.1%.

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CONCLUSION

All the above mentioned aspects have to be taken into consideration to avoid false positive results. During the comparison it was found that, all the guidelines mainly focus on high quality requirements for the sterile pharmaceutical products manufacturing process. All the guidelines were mostly similar except for clean area classification, microbial monitoring, environmental monitoring, manufacturing process, validation aspects. It has been concluded that US has more stringent GMP regulation for sterile product manufacturing compared to Australia and Malaysia.

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