GMP for Sterile Pharmaceutical Products

Part 2

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Sterile Production

Personnel

Many of the activities to ensure that quality sterile products are manufactured, are dependent on people, their actions and behaviour.

People can be the biggest source of contamination

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Sterile Production

Personnel

- Minimum number present in clean areas
- Inspections and controls conducted from outside clean areas
- All to receive initial and regular training
- Manufacture, hygiene, microbiology
- Staff who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed

All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive initial and regular training in disciplines relevant to the correct manufacture of sterile products, including hygiene and 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

منخرط

صارم

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Sterile Production

- High standards of personal hygiene and cleanliness
- Report any conditions and periodic health checks
- Changing and washing procedure
- Gowning and quality appropriate for the process and work area
- No outdoor clothing into changing rooms to Grade B and C rooms and no wrist-watches, cosmetics and jewellery worn
- Grade A/B area - clean sterile garments at each work session
- Gloves regularly disinfected during operations. Masks and gloves changed at least every working session; wear sanitized goggles. نظارات

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The clothing required for each grade is as follows:

	Gowning	
D	Cover hair, beard and moustache.	Wear protective clothing and appropriate shoes or overshoes. Prevent contamination from outside the clean area
C	Cover hair, beard and moustache.	Wear one-piece jumpsuit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes. Shed virtually no fibres or particulate matter
B and A	Headgear enclosing hair, beard and moustache The headgear tucked into the neck of the suit. Wear a facemask to prevent shedding of droplets.	Wear one-piece jumpsuit, gathered at the wrists and with a high neck. Sanitized goggles Wear sterilized, non-powdered gloves of appropriate material and sterilized or disinfected footwear. Trouser-bottoms tucked inside the footwear and garment sleeves into the gloves. Shed no fibres or particulate matter and should retain particles shed by the body

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- Cleaning of clothing – ensure not to gather additional particulate contaminants that can later be shed
- Separate laundry facilities
- No damaged fibres
- SOP for washing and sterilization

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Equipment

Mixing vessel

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- Conveyor belts – not through different areas of cleanliness
- Equipment should be effectively sterilized
- Work carried out outside the clean area where possible
- Equipment taken apart for maintenance re-sterilized after complete reassembly, wherever possible
- Maintenance in a clean area, clean instruments and tools should be used and the area should be cleaned and disinfected again, where appropriate, before processing recommences, if the required standards of cleanliness and/or asepsis have not been maintained during the maintenance work.

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- Equipment and utilities subject to validation and planned maintenance
- Return to use should be approved
- Water-treatment plants and distribution systems
  - Designed, constructed and maintained
  - Operate within their designed capacity
- Water for injection
  - Appropriately produced, stored and distributed (prevents the growth of microorganisms, e.g. by constant circulation at a temperature above 70 °C or not r C)

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Processing

- Take precautions to minimize contamination during all processing stages, including the stages before sterilization
- Normally no preparations with live microorganisms in areas used for the processing of other pharmaceutical products
- Vaccines consisting of dead organisms or of bacterial extracts
- Demonstrate and validate the effective decontamination of the live microorganisms
- Validation of aseptic processing

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Validation of aseptic processing – Media Fill

- Includes process simulation test (media fill) – appropriate medium
- based on dosage form, selectivity, clarity, concentration and suitability for sterilization
- Imitate routine aseptic manufacturing steps, actions, interventions, worst case situation, shift change
- Part of validation - three consecutive satisfactory simulation tests
- Repeated at defined intervals and after any significant modifications (e.g. HVAC, equipment, process) heating,

(HVAC) = ventilation and air-conditioning system

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- The number of containers used for media fills appropriate
  - Small batch of product - equal the size of the product batch
- Target zero growth and the following applies:
- < 5000 units — 0 contaminated units
- 5000–10 000 units — 1 contaminated unit - investigation and consideration of a repeat media fill
  2 contaminated units - revalidation following investigation;
- > 10 000 units — 1 contaminated unit - investigation
  2 contaminated units - revalidation following investigation

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- Investigate intermittent incidents of microbial contamination
- Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill
- Validation must not compromise the processes
- Water sources, water-treatment equipment and treated water should be monitored regularly for chemicals, biological contamination and contamination with endotoxins
- Water complies with the specification
- Records maintained of the results and of any

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- Activities during operations kept to a minimum
- Movement of personnel controlled and methodical - avoid excessive shedding of particles and organisms
- Personnel excluded from Grade A zones as far as possible
- Temperature and humidity controlled and monitored - appropriate

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- Minimal number containers and materials present
- No recontamination of components, bulk-product containers and equipment after final cleaning process
- Interval between the washing and drying and the sterilization and use - as short as possible. Validated time limits
- Time between the start of the preparation of a solution and its sterilization or filtration through a bacteria-retaining filter as short as possible. Maximum time set for each product
- Use filtered gas to purge a solution or blanket a product

Any gas that is used to purge a solution or blanket a product should be passed through a sterilizing filter.

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- Bioburden monitored before sterilization - working limits
- Bioburden assay on each batch (aseptically and terminally sterilized products)
- Level of endotoxins monitored when needed
- All solutions passed through a microorganism-retaining filter immediately before filling
- Components, bulk-product containers, equipment, and any other articles required in a clean area where aseptic work is in progress, should be sterilized and wherever possible
- Passed into the area through double ended s

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Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules, should be subject to 100% integrity testing. Samples of other containers should be checked f or integrity according to appropriate procedures

Finishing of sterile products

- Validated closing methods
- Glass and plastic ampoules subjected to 100% integrity testing
- Crimping of aluminium cap asap after stopper insertion
  - Others - appropriate procedures.
- Crimping equipment location; adequate air extraction
- Capping as an aseptic process/clean process

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Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimize microbial contamination

- Vials with missing or displaced stoppers rejected prior to capping
- Human intervention - appropriate technology to be used
- RABS and isolators may be beneficial(RABS= Restricted access barriers and isolators)
- Containers sealed under vacuum tested
- Filled containers of parenteral products individually inspected - suitable and controlled conditions - illumination and background
- Operators: regular eyesight checks, frequent breaks
- May use validated equipment
- Results recorded

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Summary

- Key points here include the role of operators
- Operator gowning, actions, health and hygiene
- Appropriate use of equipment
- Equipment finishing, cleaning, maintenance
- Qualification of equipment
- Cleaning validation
- Appropriate closure of dosage units
- Media fill (validation)

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