GMP for Sterile Pharmaceutical Products

Part 2

Annex 6. TRS 961, 2011

World Health Organization

Sterile Production

Personnel

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

10.1 – 10.3

Sterile Production

- High standards of personal hygiene and cleanliness

10.4 – 10.7

- 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.

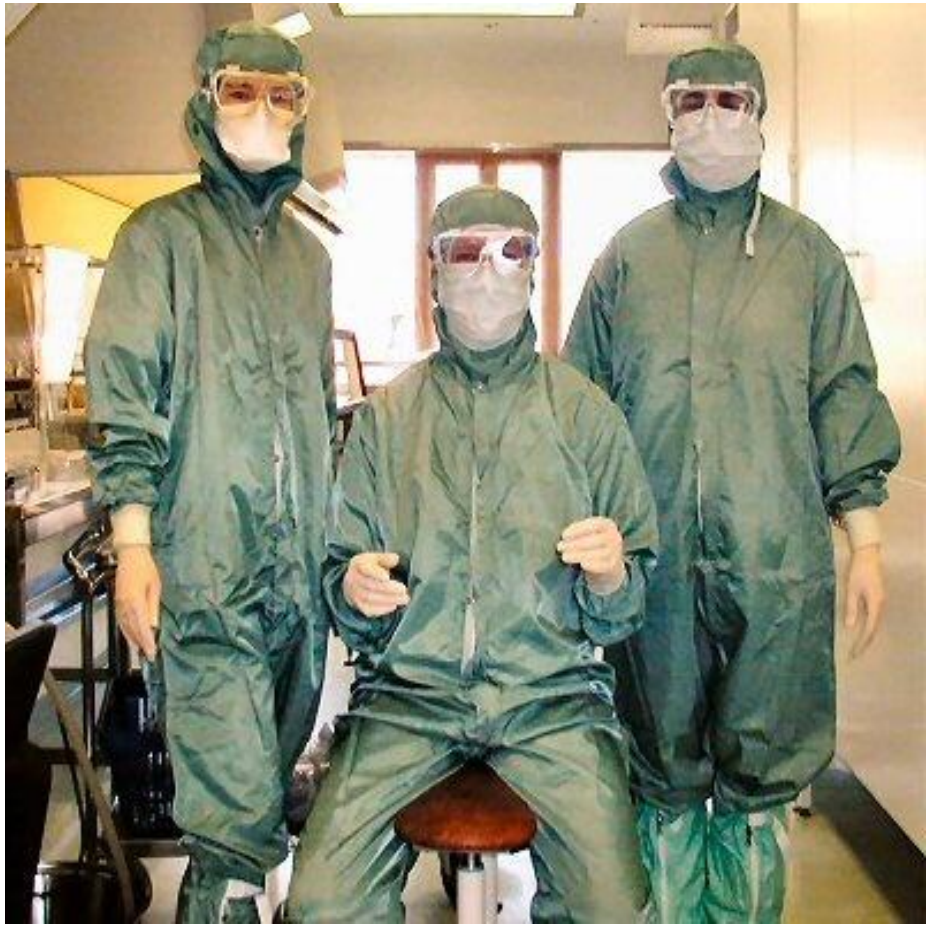
Sterile Production

	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

10.6, 10.8

Sterile Production

- 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



10.9

Sterile Production

Equipment

Sterile Production

- 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.

12.1 – 12.4

Sterile Production

- 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 more than 4 °C)

12.5 – 12.6

Sterile Production

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

4.21 – 4.23

Sterile Production

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)

4.24 – 4.25

Sterile Production

- 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

4.26

Sterile Production

- 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 action taken

4.27 – 4.29

Sterile Production

- 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

4.30

Sterile Production

- 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

4.31 – 4.35

Sterile Production

- 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 sterilizers

4.36 – 4.37

Sterile Production

Finishing of sterile products

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

13.1 – 13.4

Sterile Production

- Vials with missing or displaced stoppers rejected prior to capping
- Human intervention - appropriate technology to be used
- RABS and isolators may be beneficial
- 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

13.5 – 13.8

Sterile Production

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)