GMP for Sterile Pharmaceutical Products

Part 1

Annex 6. TRS 961, 2011

World Health Organization

Sterile Production

Objectives

- To review basic GMP requirements in the manufacture of sterile pharmaceutical products
- To review air classifications for activities related to the manufacture of sterile products
- To review the different types of sterilization methods
- To review quality assurance aspects in the manufacture and control of sterile products
- To consider current issues applicable in your country

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GMP Requirements for Sterile Products

- Additional rather than replacement
- Specific points relating to minimizing risks of contamination
  - *microbiological*
  - *particulate matter*
  - *pyrogens*

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General Considerations for sterile products

- Production in clean areas
- Enter and exit through airlocks (personnel, equipment, material)
- Air supplied through filters (e.g. HEPA)
- Various operations in separate areas of appropriate grades
- Two categories of operations:
  - terminally sterilized products; and
  - aseptically prepared products

1.1 – 1.3

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Premises

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Premises

- Appropriate design. Avoid unnecessary entry of supervisory or control personnel. Observe operations from outside Grade A and B areas
- All exposed surfaces smooth, impervious and unbroken and allow repeated application of cleaning agents and disinfectants
- No uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment, also at doors. (No sliding doors. Swing doors open to the high-pressure side and be provided with self-closers
- False ceilings sealed to prevent contamination from above

11.1 – 11.4

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- No recesses, unsealed openings and surfaces that are difficult to clean for pipes and ducts and other utilities – sanitary type

Sinks and drains:

- avoided wherever possible
- excluded from Grade A and B areas
- where installed - designed, located and maintained
- effective, easily cleanable traps and with air breaks
- open floor channels that are easily cleanable. No ingress of microbial contaminants

11.5 – 11.6

Sterile Production

- Changing rooms
  - designed as airlocks
  - provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing
  - flushed effectively with filtered air
  - final stage to be the same grade as the area into which it leads
  - hand-washing facilities in the first stage
  - sufficient size
  - equipped with mirrors
- Not more than one grade between areas

11.7

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- Airlock doors interlocked - with visual and/or audible warning
- Filtered air supply to maintain a positive pressure and an airflow
- Effective flushing of the area
- Pressure differential of approximately 10–15 Pascals between areas
- Protection of the zone of greatest risk
- Decontamination of the facilities and the treatment of air leaving a clean area may be necessary for some operations
- Demonstrate suitable airflow patterns

11.8 – 11.10

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- A warning system to indicate failure in the air supply
- Indicators of pressure differentials fitted between areas
- Pressure differentials regularly recorded and failure alarmed
- Restrict unnecessary access to critical filling areas, e.g. Grade A filling zones, by means of a physical barrier

11.11 – 11.12

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Sanitation

- Particularly important to clean frequently and thoroughly - SOP and programme
- Disinfectants: Rotated; regular monitoring (contamination and effectiveness); storage
- Sterile disinfectants in Grade A and B areas
- Cleaning validation
- Use sporicidal agent also
- Fumigation may be useful

3.1 – 3.4

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Area classification and activities in these areas

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- Classify clean areas - required characteristics of the environment
- Each operation in appropriate level of cleanliness
- Areas classified according to ISO 14644
- Includes determination of the number of sample locations, calculation of sample size and evaluation of classification from the data obtained
- Also used as the basis for monitoring clean areas for airborne particles

4.1 – 4.2

Sterile Production

Four grades of clean areas:

Grade A	Grade B	Grade C	Grade D
Local zone for high-risk operations	Background environment to Grade A	Less critical steps	Less critical steps
Unidirectional airflow		Product is not directly exposed	Product is not directly exposed
Speed of 0.36–0.54 m/s			

4.3

- Lower velocities accepted in closed isolators and glove boxes.

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- Number of air changes important to achieve class B, C and D
  - Consider size of the room, equipment and personnel
- Installed filter leakage tests for HEPA filters (ISO 14644-3)
  - every 6 months - but not exceeding 12 months
  - aerosol selected should not support microbial growth
  - aerosol composed of a sufficient number or mass of particles
- HEPA filter patching is allowed - patch sizes and procedures in accordance with ISO 1822-4

4.4 – 4.5

Sterile Production

Clean room and clean-air device classification

- Clean rooms and clean-air devices should be classified in accordance with ISO 14644
- **Classification** is clearly differentiated from operational process environmental **monitoring**
- The maximum permitted airborne particle concentration for each grade is given in the next slide

4.6

Sterile Production

Maximum permitted airborne particle concentrate: maximum permitted number of particles per m3 greater than or equal to the tabulated size

At rest[a]			In operation[b]	
Grade	**0.5 µm**	**5.0 µm**	**0.5 µm**	**5.0 µm**
A	3 520	20	3520	20
B	3 520	29	352 000	2900
C	352 000	2900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

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For classification purposes

Grade	ISO Class	Particle size
A	ISO 4.8	Particles ≥ 5.0 µm
B	ISO 5	Both particle sizes
C	at rest - ISO 7 in operation - ISO 8	
D (at rest)	ISO 8	

- Sample 1m3/location

4.6.2

- ISO 14644-1 (*2*) methodology, based largest particle size

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For classification purposes (2)

- Calculate sample volume (ISO 14644-1 (*2*) clause B.4.2. – for Grade C in operation and Grade D at rest - volume per location at least 2 litres and the sample time not less than 1 minute
- Portable particle counters with a short length of sample tubing
- Isokinetic sample heads used in unidirectional airflow systems
- "In operation" classification during normal operations, simulated operations or during media fills as worst-case simulation

4.6.2 – 4.6.4

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Clean room and clean-air device monitoring

4.7 .1

- Routine monitoring during operation and simulated operations
- Locations based on a formal risk analysis study and the results obtained during the classification
- **Grade A** - particle monitoring (full duration – from equipment assembly and during critical processing)
- Frequency and sample size cover all interventions, transient events. System deterioration to be captured and alarms triggered
- Expected higher levels of ≥ 5.0 µm particles at the point of fill when filling is in progress, due to the generation of particles

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Clean room and clean-air device monitoring

- Similar system be used for Grade B zones
- Sample frequency may be decreased
- Consider effectiveness of the segregation between the adjacent Grade A and B zones
- Grade B zone should be monitored at a frequency and with a sample size such that changes in levels of contamination and any deterioration of the system would be captured and alarms triggered if alert limits are exceeded

4.7.2

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Airborne particle monitoring systems

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Airborne particle monitoring systems:

- Independent particle counters;
  - a network of sequentially accessed sampling points connected by manifold to a single particle counter;
  - multiple small particle counters
  - combinations of systems
- Appropriate system for the particle size considered
- Consider length of tubing and the radii of any bends
- Be aware of any risk presented by the materials used in the manufacturing operation (e.g. live organisms or radiopharmaceuticals)

4.7.3

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- Sample size in automated systems - sampling rate
- Conditions “at rest” in the absence of the operating personnel after a short “clean-up” or “recovery” period of about 15–20 minutes
- The “clean-up” or “recovery” test to demonstrate a change in particle concentration by a factor of 100 (see ISO 14644-3)
- Grade A “in operation” maintained in the zone immediately surrounding the product
- Particle counts needed: “at rest” and “in operation” classification AND monitored periodically “in operation” at critical locations
- Locations and sample sizes (monitoring) based on risk

4.7.4 – 4.7.6

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- Monitoring in Grade C and D areas in operation - based on quality risk management
- Requirements and alert/action limits determines, and “clean-up period” should be attained
- Temperature and relative humidity dependent product and operations
- Examples of operations to be carried out in the various grades are given in the next slide

4.7.7 – 4.7.9

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Examples of operations to be carried out in the various grades

Grade	Terminally sterilized product	Aseptically prepared product
A	Filling of products when unusually at risk	Aseptic preparation and filling
C	Preparation of solutions when unusually at risk. Filling of products	Preparation of solutions to be filtered
D	Preparation of solutions and components for subsequent filling	Handling of components after washing

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- Control and monitor microbiological cleanliness of Grades A – D
- Surfaces and personnel should be monitored after critical operations.
- Frequent in aseptic operations
- Also after validation of systems, cleaning and sanitization.
- Use settle plates, volumetric air and surface sampling (e.g. swabs and contact plates)
- Review results again when reviewing batch documentation for finished product release

4.8

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Microbial limits

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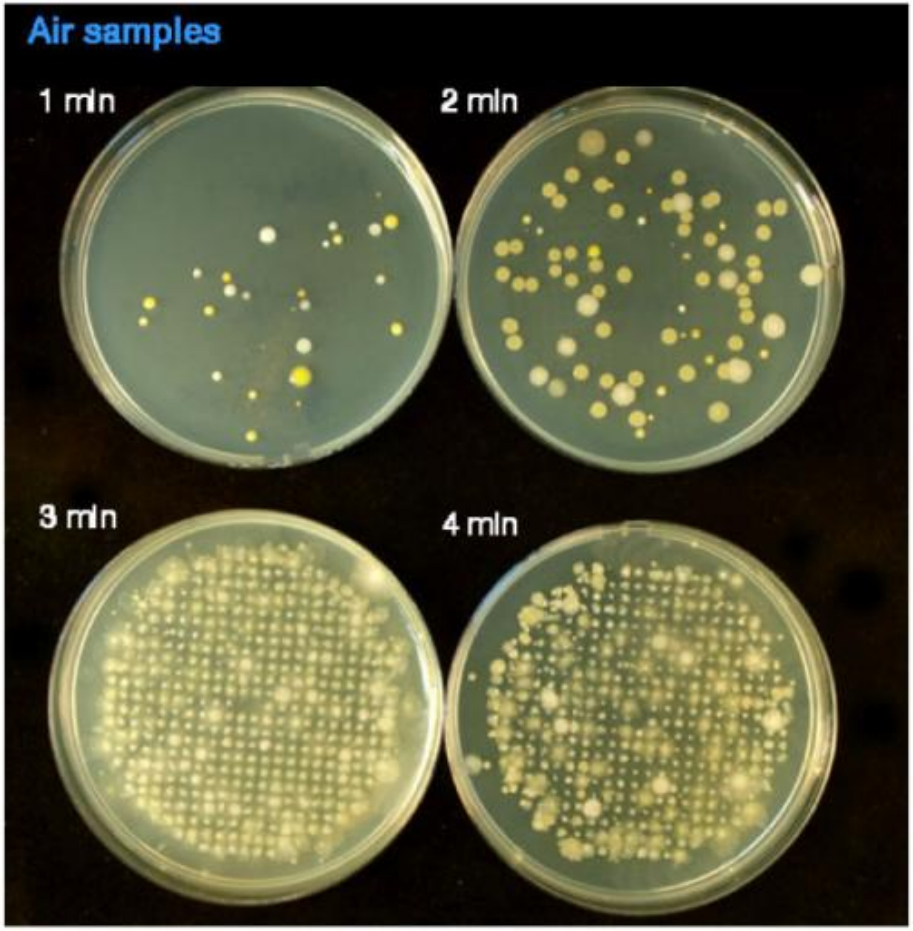
- Establish levels of detection for microbial contamination
- Alert and action limits
- Monitoring trends in environmental cleanliness
- Limits expressed in colony-forming units (CFU)
- Recommendations in the next slide – these are not intended to be specifications, but are for information only



4.9

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Recommended limits for microbial contamination[a]

Grade	Air sample Cfu/m3	Settle plates (diameter 90mm – Cfu/4h b	Contact plates (diameter 55mm Cfu/plate)	Glove print (5 fingers) (CFU/ glove)
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

a These are average values.

b Individual settle plates may be exposed for less than 4 hours

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- Alert and action limits (for particles and microbiological monitoring)
- In case of trend (alert limits) or exceeding action limits - investigation and corrective actions as per SOP
- Validation runs (e.g. aseptic media fills or others types of process simulations) to show processing hold times and a maximum fill duration

4.10 – 4.11

- Appropriate process area environment and a time limit based on the microbial contamination (bioburden) found

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Terminally sterilized products

Grade	Activity
A	Filling of products at unusual risk of microbial contamination
C	Preparation of products at unusual risk of microbial contamination
C	Filling of products for terminal sterilization
C	Preparation and filling of ointments, creams, suspensions and emulsions before terminal sterilization
D	Preparation of components and most products

4.12 – 4.15

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Aseptic preparation

Grade	Activity
D	Components after washing
A	handling of sterile starting materials and components
C	Preparation of solutions to be sterile-filtered
A	Aseptic manipulation (no filtration)
A	Handling and filling of aseptically prepared products
A	Handling of exposed sterile equipment
A	Transfer of partially closed containers (e.g. freeze-drying) and Preparation and filling of sterile ointments, creams, suspensions and emulsions

4.16 – 4.20

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Summary and important points

- Appropriate design, finishing, maintenance and cleaning of premises important
- Area classification and monitoring
- Particulate matter (non-viable) and viable
- Specified activities in defined classified areas