# PhEn-602

Notes # 6

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# Unidirectional Flow Clean Rooms & Air Velocity

- Parenteral Drug Association – guidance on air velocity
- Topic A:  Airflow Velocity How often tested?
- Problem Statement: **When do velocity measurements have to be taken?**
- Recommendation
  Airflow velocity measurements should be taken during operational and performance qualification studies.  Frequency of routine monitoring should be at least annually.  HEPA filters in critical areas should be tested semi-annually.  More frequent measurements may be appropriate if other measures of clean room quality indicate a significant deviation.

# Unidirectional Flow Clean Rooms Velocity Testing

- Airflow pattern studies should be repeated when any changes are made that might have an impact on the velocity measurements outside validated acceptance criteria (i.e., changes to air handling systems, aseptic processing equipment, HEPA filters). Evaluation of such impact should be made following applicable change management procedures. Airflow measurements can be area or line-specific.

- Rationale for Recommendation
  Airflow velocity is measured to ensure adequate airflow to protect exposed product, product contact packaging components, and product contact surfaces. It is also measured to ensure there have been no significant changes to the HVAC system. **Airflow criteria are established during qualification studies.**

# Unidirectional Flow Clean Rooms Velocity Testing

- During qualification, airflow pattern tests/smoke studies should be performed to establish the acceptable velocity range.
  - Where is velocity measured?
    - **Filter face?**
    - **6” down?**
    - **Work level?**
  - For homework

# Clean Rooms and Controlled Environments

- **FDA Aseptic guidelines:** section 4, Buildings and Facilities: “Clean area control parameters should be supported by microbiological and particle data obtained during qualification studies. Initial cleanroom qualification includes, in part, an assessment of air quality under as-built, static conditions. It is important for area qualification and classification to place most emphasis on data generated under dynamic conditions (i.e., with personnel present, equipment in place, and operations ongoing). An adequate aseptic processing facility monitoring program also will assess conformance with specified clean area classifications under dynamic conditions on a routine basis”.

# FDA Aseptic Guidelines Class of Clean Room

- **Supporting Clean Areas**
- Supporting clean areas can have various classifications and functions. Many support areas function as zones in which nonsterile components, formulated products, in-process materials, equipment, and container/closures are prepared, held, or transferred. These environments are soundly designed when they minimize the level of particle contaminants in the final product and control the microbiological content (bioburden) of articles and components that are subsequently sterilized.

# FDA Aseptic Guidelines Class of Clean Room

- **Supporting Clean Areas**
- The nature of the activities conducted in a supporting clean area determines its classification. ***FDA recommends that the area immediately adjacent to the aseptic processing line meet, at a minimum, Class 10,000 (ISO 7) standards (see Table 1) under dynamic conditions***. Manufacturers can also classify this area as Class 1,000 (ISO 6) or maintain the entire aseptic filling room at Class 100 (ISO 5). An area classified at a Class 100,000 (ISO 8) air cleanliness level is appropriate for less critical activities (e.g., equipment cleaning).

# FDA Aseptic Guidelines Class of Clean Room

**FDA Aseptic Guidelines from 1987**

**Controlled Area:**

"A controlled area is one in which unsterilized drug product, in-process materials or containers/closures are prepared..... acceptable air quality if it has a per-cubic-foot particle count of not more than 100,000 in a size range of 0.5 micron and larger (Class 100,000) when measured in the vicinity of the exposed articles during periods of activity.

# Clean Rooms and Controlled Environments

- **Pharmaceutical:**
  - A controlled* area where personnel are required to be in a minimal amount of gowning. E.g.: Packing hall. Typical gowning consists of coat, hat and shoe covers

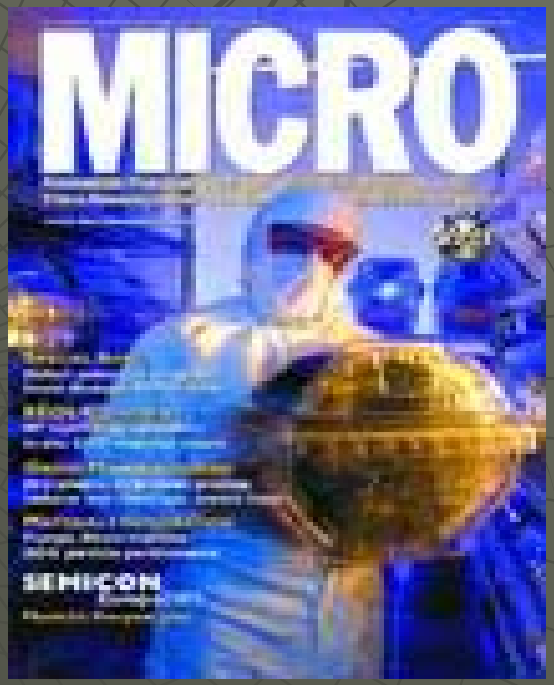
*controlled term is used generically. It is different from the controlled area referenced in the 1987 Aseptic guidelines.

- **Pharmaceutical with local monitoring:**
  - A pharmaceutical area that has at least some portions designed as Class 100,000 at rest.

# Clean Rooms and Controlled Environments

- **Pharmaceutical also called "Controlled Not Classified"**
  - Often designed as EU Grade D

# Microbiological Considerations & Environmental Monitoring



# Lesson Objectives:

- Discuss sources of micro-contaminants
- Discuss regulatory requirements
- Identify types of microbiological sampling in the clean room
- Discuss sampling equipment used
- Discuss environmental monitoring program

# Reference Documents

- USP, <1116>, “Microbiological Evaluation of Clean Rooms and Other Controlled Environments”
- FDA, 1987. Guideline on Sterile Drug Products Produced by Aseptic Processing.
- FDA, 2002. Draft Guideline on Sterile Drug Products Produced by Aseptic Processing
- European Commission Good Manufacturing Practices: Medicinal Products for Human and Veterinary Use

# Microbiological Considerations

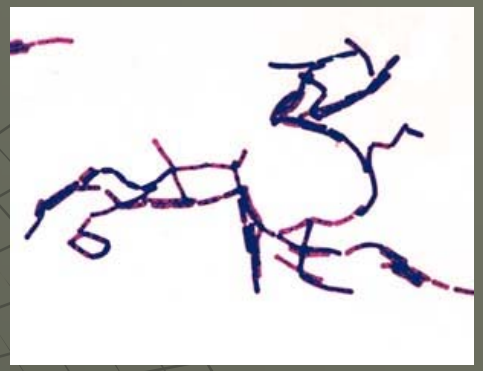
- FDA Aseptic Guidelines: first document to establish general micro limits
- USP and EU GMP's provide more specific limits for micro-contaminants in the *Clean Room* in three areas:
  - Airborne
  - Surface
  - Personnel

# Microbiological Considerations

- People are often the only source of micro-organisms or viable particulates in the clean room
- Micro-organisms are continually dispersed from people in the room
- Testing for microorganisms in the “as-built” or “at rest” state is of little value.

# Microbiological Considerations

- Other sources of microbial contamination:
  - Water
  - Gases
  - Raw materials



- Important to monitor micro levels in these systems as well as air
  - Will not be discussed in PhEn-602

# Microbiological Considerations

- Unit of measure is colony forming unit (cfu) (Viability?)
- FS 209E and ISO 14644-1 do not contain any specific limits for microbial contaminants
- ISO: Developing new standards for Micro limits in clean rooms

# Critical Areas

- Critical Areas (sites, zones, surfaces) are identified as those areas where sterilized product or container and/or closures are exposed to the environment
  - Critical sites, zones, surfaces should be monitored most rigorously
  - Class 100 areas (EU Grade A)
  - Organisms recovered from critical areas should be identified to genus and species for possible investigation

# Critical Area Examples:

- Room air in areas with product or container exposure
  - Path of any open containers
- Manufacturing equipment surfaces
  - Component loading areas
  - Filling Stations
- Storage containers
- Gloved hands
- Aseptic connections

# Non-Critical Area Examples:

- Areas that do not come in contact with the sterilized product or container/closures.
  - Class 10,000 and 100,000 (C, D)
  - Monitoring becomes less rigorous as the classification number increases

# Non-Critical Area Example

- Class 100,000 Areas
  - “Non-sterile” portion of changing areas. Example: washrooms
  - Preparation of bulk solutions prior to sterile filtration
  - Preparation of components prior to sterilization

# Microbiological Considerations

## 1987 FDA Aseptic Guideline Limits:

- **Controlled areas: (Class 100,000 areas)**
  - **"with regard to microbial quality, an incidence of no more than 25 colony forming units per 10 cubic feet is acceptable."**
- **Critical areas: (Class 100 areas)**
  - **"air should also be of a high microbial quality….no more than 1 colony forming unit per 10 cubic feet is considered attainable and acceptable".**

# FDA Aseptic Guidelines: Clean Room Class

| TABLE 1 - Air Classifications | CDER Aseptic Guidelines - 2004 | | | |
|---|---|---|---|---|
| Clean Area Classification (0.5 micron particles/$ft^3$) | ISO Designation | G.T. or equal to 0.5 micron (particles/$m^3$) | Microbiological Active Air Action Levels ($cfu/m^3$) | Microbiological Settling Plates Action Levels (diam. 90mm, cfu/4 hours) |
| 100 | 5 | 3,520 | 1 | 1 |
| 1,000 | 6 | 35,200 | 7 | 3 |
| 10,000 | 7 | 352,000 | 10 | 5 |
| 100,000 | 8 | 3,520,000 | 100 | 50 |

# Microbiological Considerations

- EU Limits for Microbial Contaminants
  - Differs for Grades A, B, C, D
  - No requirements for the “at rest” state
  - Requirements for
    - Airborne
    - Surfaces
    - Personnel Gowns
    - Personnel Gloves
  - EU has limits for surfaces contained in Class 100,000 areas. FDA & USP do not

# Microbiological Considerations

- EU Limits for Microbial Contaminants
  - Airborne:
    - Grade A: less than 1 cfu/cubic meter
    - Grade B: less than 10 cfu/cubic meter
    - Grade C: less than 100 cfu/cubic meter
    - Grade D: less than 200 cfu/cubic meter

# Microbiological Considerations

- USP Limits for Microbial Contaminants
  - Controlled areas: (Class 100,000 areas)
  - Class 10,000 Areas (sometimes referred to as “sub-critical” areas)
  - Critical areas: (Class 100 areas)

# Microbiological Considerations

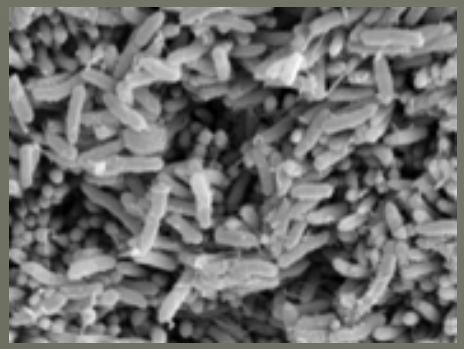
- USP Limits for Microbial Contaminants
  - Requirements for
    - Airborne
    - Surfaces
    - Personnel Gowns
    - Personnel Gloves

# USP Airborne Viable Limits

| Room Classification | cfu/$m^3$ | cfu/$ft^3$ |
|---|---|---|
| Class 100 | <3 | <0.1 |
| Class 10,000 | <20 | <0.5 |
| Class 100,000 | <100 | <2.5 |

**Note: These limits are consistent with the 1987 FDA guidelines for Class 100, and Class 100,000 areas**

# USP Surface Limits



| Class | cfu/contact plate (24-30cm$^2$) |
|---|---|
| 100 | 3 (including floor) |
| 10,000 | 5<br>10 (floor) |

# USP Limits for Personnel

| Class | cfu/contact plate Gloves | cfu/contact plate Garb |
|---|---|---|
| 100 | 3 | 5 |
| 10,000 | 10 | 20 |

# USP Limits for Personnel

- No limits for personnel in Class 100,000 areas
- Microbial monitoring of personnel is not required for Class 100,000 areas

# Environmental Monitoring

- **Environmental Control:**

  Steps taken through facility design and construction, testing and validation, personnel practices and cleaning and sanitization to limit micro-organisms in the clean room.

- **Environmental Monitoring:**

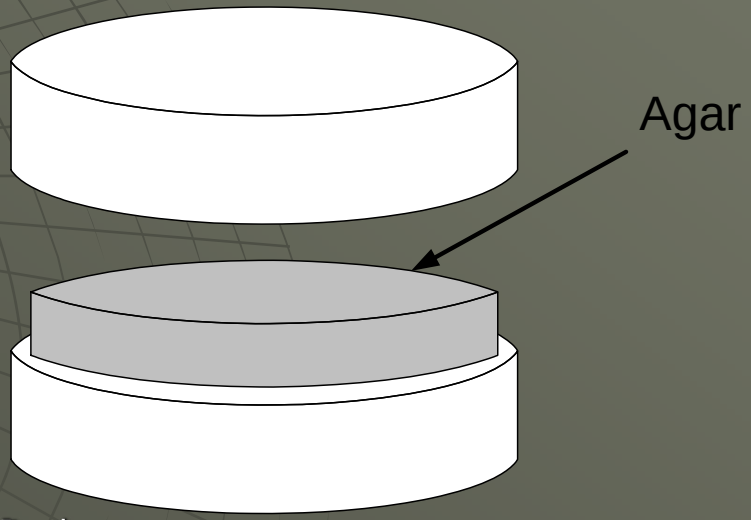
  Routine microbiological monitoring provides a series of snapshots of the microbiological profile of a controlled environment. Routine monitoring ensures that systems continue to provide an environment of consistent quality.

# Environmental Monitoring

- EM Objectives
  - Monitor the effectiveness of the cleaning and sanitization
  - Monitor effectiveness of gowning and training of personnel in aseptic areas
  - Provide information for trending and to identify excursions from normal operating parameters
  - Verify that we continue to maintain an environmentally controlled system as initially established in the validation of the clean room

# Environmental Monitoring

- Agar:
  - Jelly-type material
  - Nutrients added to support microbiological growth



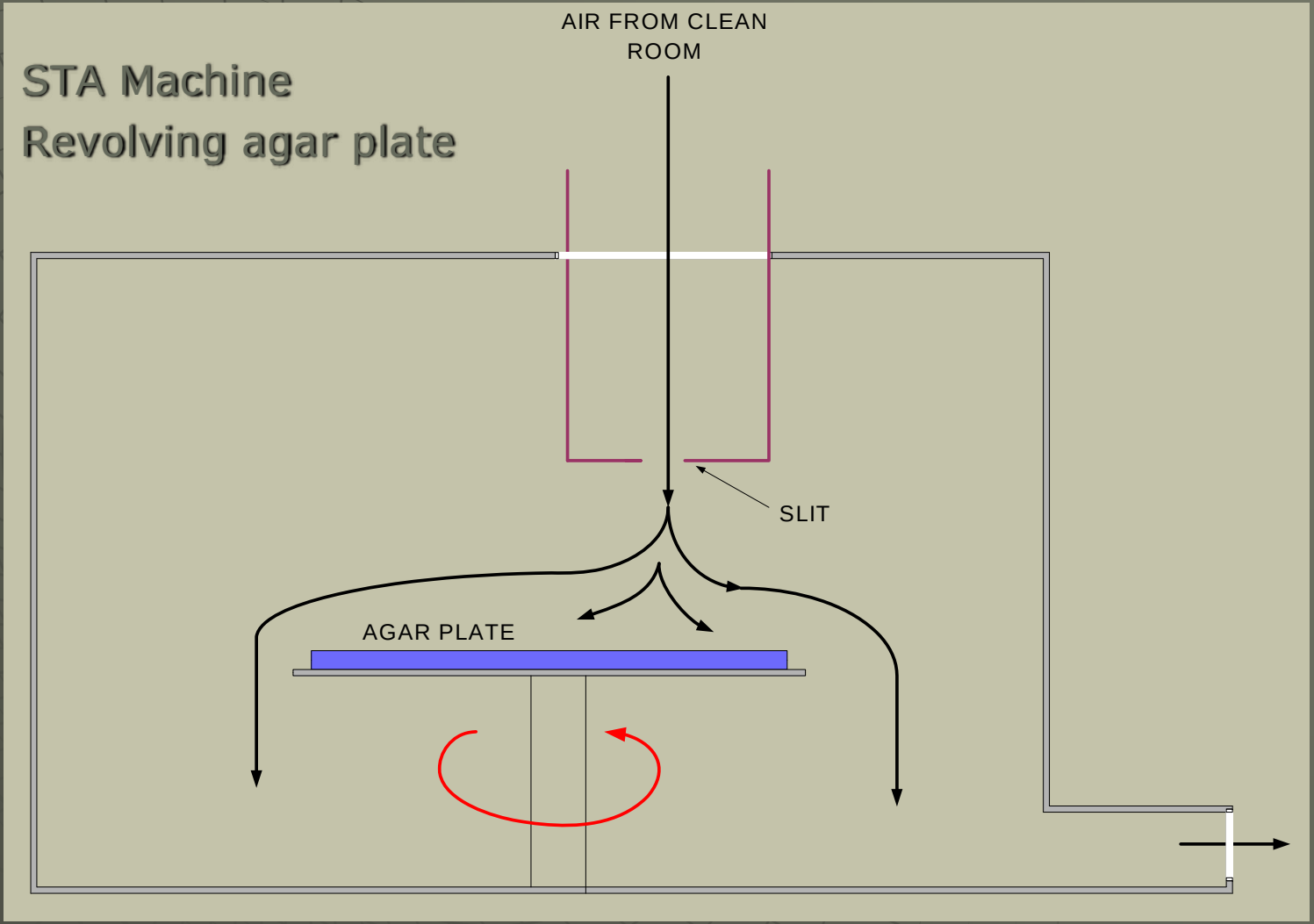
# Environmental Monitoring

- Airborne Viables are measured:
  - Volumetric (i.e. cfu/$m^3$)
  - Settling plate (i.e. measured in cfu per unit time collected)
    - 1 cfu/4 hr. period, for a 90 mm settling plate, is requirement for a Grade A room).

# Environmental Monitoring

- Airborne Viables
  - Volumetric sampling typically done by sampling a specific volume of air per unit time.
  - Slit to Agar (STA) sampler typically used

# Environmental Monitoring



# Environmental Monitoring

- Devices Used for Monitoring Air:


# Environmental Monitoring

- Air through STA slit travels at a high velocity
  - Forced to turn 90 degree so particles leave the air stream and impact the agar surface
  - When incubated at a suitable temperature, for specific period of time, microbe carrying particles will grow to form a colony
  - Count the colonies to obtain a count.

# Environmental Monitoring

- STA samples typically 30–180 liters per minute approximately
  - We can determine how many liters of air are sampled.
  - Knowing the counts and the volume, we can obtain the cfu/$m^3$

# Slit to Agar (STA) Sampler

- Change out plate every 60 minutes
  - Microbiologist gowns and enters fill room every hour
- Colonies are “seen” as dots in the contact plate
  - Different colors, clear or translucent
- Incubate at different temperatures
  - First two days at 30 - 35 C
  - Next five days at 20 - 25 C
  - Total of five to seven days for incubation
- Various types of spores may be present
- Mold, if present will grow in a large formation covering most of the plate.
  - Individual colonies would lie underneath the mold
    - reverse the plate to see them.

# Environmental Monitoring

- Airborne Viable- Settling plate
  - Petri dish left in room for a specific period of time.
  - Can correlate number of micro-organisms deposited onto the settling plate to # particles deposited onto an open product container
    - Proportional areas.

# Environmental Monitoring

- **Surface Viables**: Measured in cfu per contact plate.
  - Contact Plates often used: RODAC (Replicate Organisms Detection and Counting)
  - Agar is pushed onto the clean room surface to be sampled
  - Then incubate to obtain count per plate

# Environmental Monitoring

- RODAC plates are appropriate for flat surfaces
  - Can obtain CFU per plate, or CFU per unit area (per sq inch)

# Environmental Monitoring

**Other methods of surface sampling including uneven surfaces:**

- Cotton Swabs
  - Rub surface to be sampled, then pass over an agar plate.
  - Plate then incubated and counted
- Contact Strips & Slides
  - Strips are removed from containers
  - Applied to the surface to be sampled
  - Incubate, then count

# Environmental Monitoring

## Sampling Personnel

- Sample gloves – Fingers tips pressed against an agar plate
- Garments/gowns:  Press plate or contact strip against the clothing. Best done as they exit the clean room.
  - Could sample at various locations on the body
- Initial qualification sampling more in-depth than routine sampling

# EM & FDA Expectations

- FDA expects firms to have a thorough Environmental Monitoring program
  - For critical areas, clear action and alert limits must be specified
  - SOP's must establish frequency of sampling, and type of sampling to be performed, for each type of clean room
  - Trending must be performed
  - Deviations from normal results must be documented on an investigation report
  - Excursions must be explained
  - Corrective action must be taken if applicable

# Environmental Monitoring

## Environmental Control vs. Monitoring

### Environmental Control

**Steps taken in the facility/clean room design construction, operation, personnel behaviors, and cleaning and sanitization to limit the presence of micro-organisms in the clean room environment.**

# Environmental Control Requires:

- Providing/maintaining:
  - Appropriate sterile air flow and air changes
  - Effective sanitization and disinfection
  - Appropriate controls of temperature and relative humidity (RH)
  - Equipment cleaning and sterilizing
    - Especially important
  - Appropriate training and re-training of operators/personnel

# Environmental Monitoring

## Environmental Control vs. Monitoring

Environmental Monitoring:

**Routine microbiological monitoring program that provides a series of snapshots of the microbiological profile of a controlled environment. Routine monitoring ensures that systems continue to provide an environment of consistent quality.**

# “Alert” Level

- Warning of a potential problem
- Exceeding the alert level signals a potential drift from normal operating conditions
  - Should define the alert level based on history
  - Excursions may or may not require action, but they do require that the situation be closely monitored
  - Frequent alert level excursions will require action

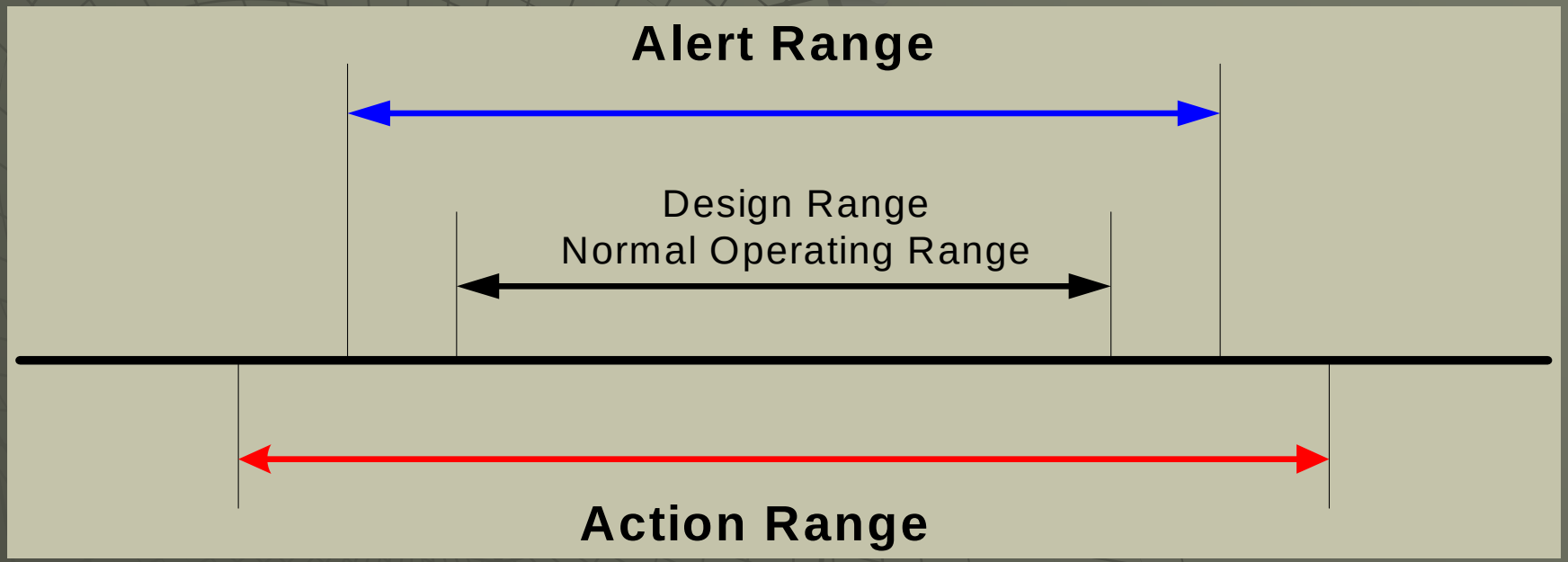
# “Action” Level

- Exceeding the action level signals a drift from normal operating conditions
  - Excursions beyond the action level will require some type of investigation and/or **action**
  - The investigation will result in some sort of **action**
  - The action will depend on the frequency of the excursion, the usage of the room, the activity in the room, etc.

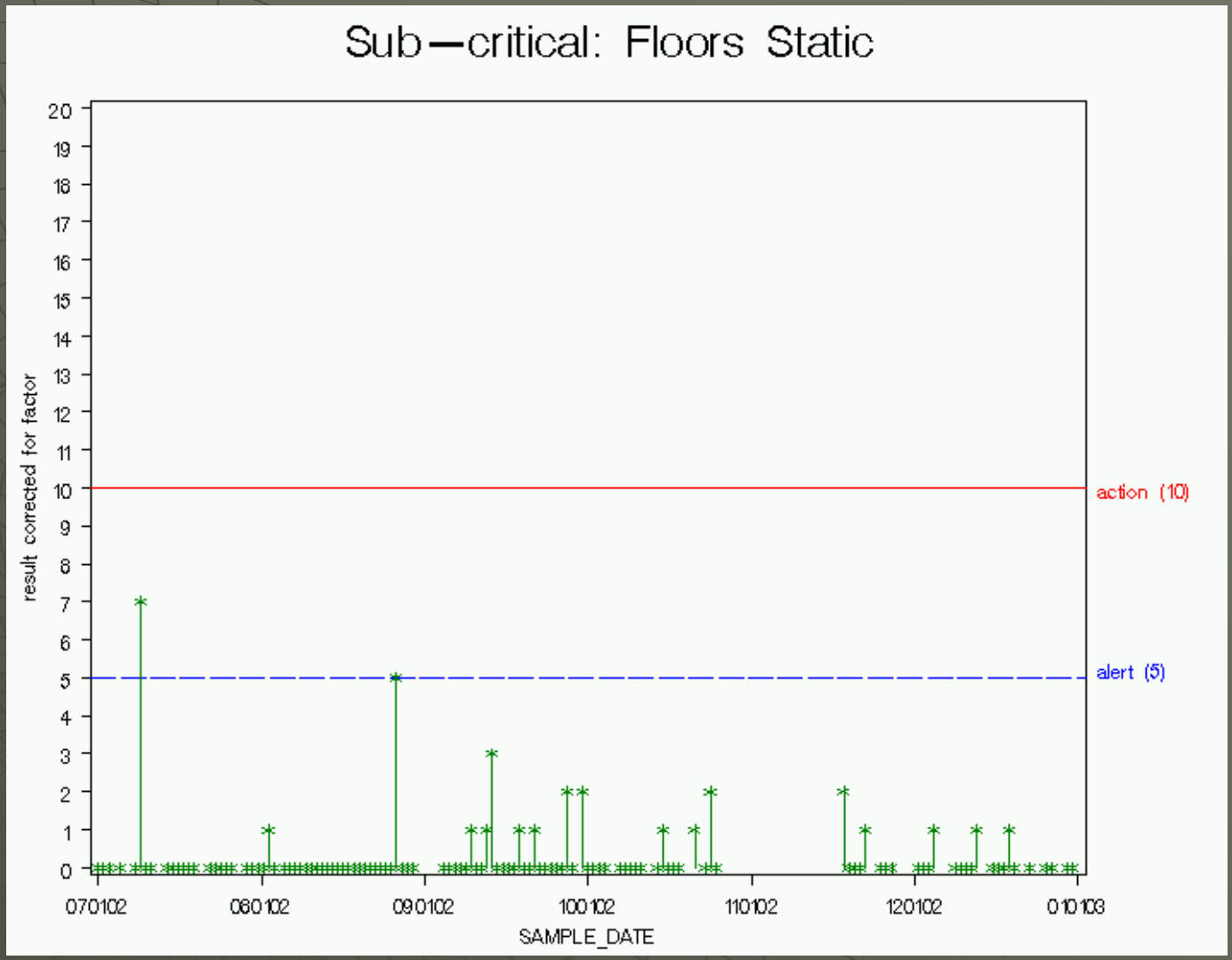
# Environmental Monitoring

- There should be a “cushion” between the design and operating level of the clean room, and the alert and action levels.
- There should be a “cushion” between the alert level and action level.
- For less critical areas, such as controlled areas, alert and action levels **may be** equivalent

# “Alert” and “Action” Levels



# Example: "Alert" and "Action" Levels



# Example: Classification Levels within an Aseptic Facility