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# Environmental Monitoring

## Requirements and Trending

# Speaker Lineup

**Jacqueline Esqueda, PharmD, BCSCP, RPH**

Vice President of Regulatory and Quality Compliance

Eagle Analytical Services

# Learning Objectives

1. Explain the purpose of environmental monitoring as part of a contamination control strategy for sterile compounding environments.
2. Define the requirement for nonviable, viable, and environmental control monitoring in pharmaceutical compounding.
3. Apply a risk-based approach to sampling location selection using ISO classification, compounding activities, material flow, critical sites and cleaning difficulty.
4. Define documentation requirements for an environmental monitoring program.
5. Evaluate environmental monitoring data using action levels, microbial identification, historical trends, and contamination risk to determine whether the environment remains in a state of control.
6. Describe appropriate responses to environmental monitoring excursions or upon identification of adverse trends.

# Abbreviations

- CAPA – corrective and preventive action
- CFU – colony forming unit
- CNSP – compounded nonsterile preparation
- COA – certificate of analysis
- CRR – contamination recovery rate
- CSP – compounded sterile preparation
- DP – designated person
- GFT – gloved-fingertip testing
- HD – hazardous drug
- ISO – International Standards Organization
- MEA – malt extract agar
- MFT – media-fill test
- RABS – restricted access barrier system
- SDA – sabouraud dextrose agar
- SOP – Standard Operating Procedure
- TSA – tryptic soy agar
- USP – United States Pharmacopeia

# Definitions

- Adverse trends – a drift from normal or a repeated pattern; may not always be associated with an excursion.
- Critical zone – the area in which containers, closures, and product are exposed to the environment.
- Dynamic operations – conditions in which personnel and equipment are performing or simulating routine/normal operations; should reflect largest normal of personnel present and the highest complexity of compounding.
- Viable – the ability to multiply, grow, or exhibit properties of a living organism.

# What is Environmental Monitoring?

- Program for the collection, evaluation, and trending of environmental data from classified spaces used for compounding.

# Purpose of Environmental Monitoring

- Provides information
  - Environmental control
  - Effectiveness of engineering controls
  - Personnel
  - Effectiveness of cleaning and disinfection program
  - Potential routes of contamination

# Importance of Environmental Monitoring

- Patient safety

- Regulatory requirement
  - Insanitary Conditions per Section 501(a) of the FD&C Act
  - USP <797> Pharmaceutical Compounding – Sterile Preparations

*"…a drug is deemed to be adulterated if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health…"*

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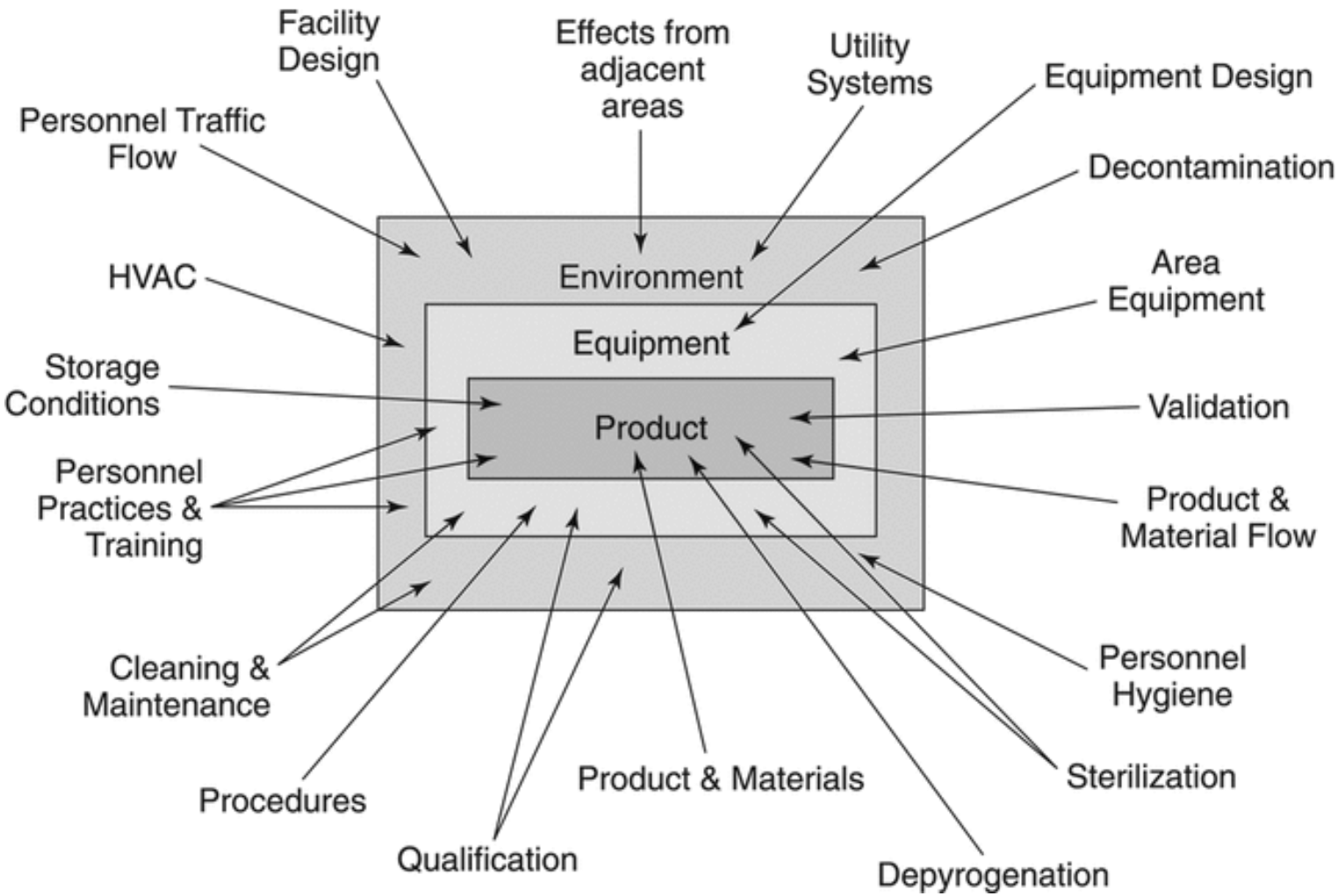
# Influences on Sterile Products

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# Environmental Monitoring Frequency

| Sampling Type | Category 1 | Category 2 | Category 3 |
|---|---|---|---|
| Nonviable Particulate Counts | Semiannually | | |
| Viable Air Sampling | Semiannually | | Monthly[1] |
| Viable Surface Sampling[2] | Monthly | | Weekly +<br>Per Batch (PEC) |
| Personnel Monitoring (GFT) | Semiannually | | Quarterly |
| Differential Pressure,<br>Temperature and Humidity | Daily/Continuous | | |

[1] Must be completed 30 days prior to the commencement of Category 3 CSP compounding.
[2] Collected from the DCA upon media-fill test completion.

# Nonviable Particulate Counts

- ISO Classifications based on particles

| ISO Class | Limit<br>Particles ≥ 0.5 µm/m³ |
|---|---|
| 5 | 3,520 |
| 7 | 352,000 |
| 8 | 3,520,000 |

- Vector for microbial contamination
- Safety concern in injections and ophthalmics
- Effectiveness of controls
  - ACPH, HEPA filters, processes

- Typically performed by certifier
  - Dynamic operations (simulated)
    - Proximity to critical sites
    - Representative
  - Documentation (certification report)
    - Reviewed by DP
    - Include # personnel present

- Examples
  - Hair, paint/caulk, fibers, skin, residue, dirt, debris

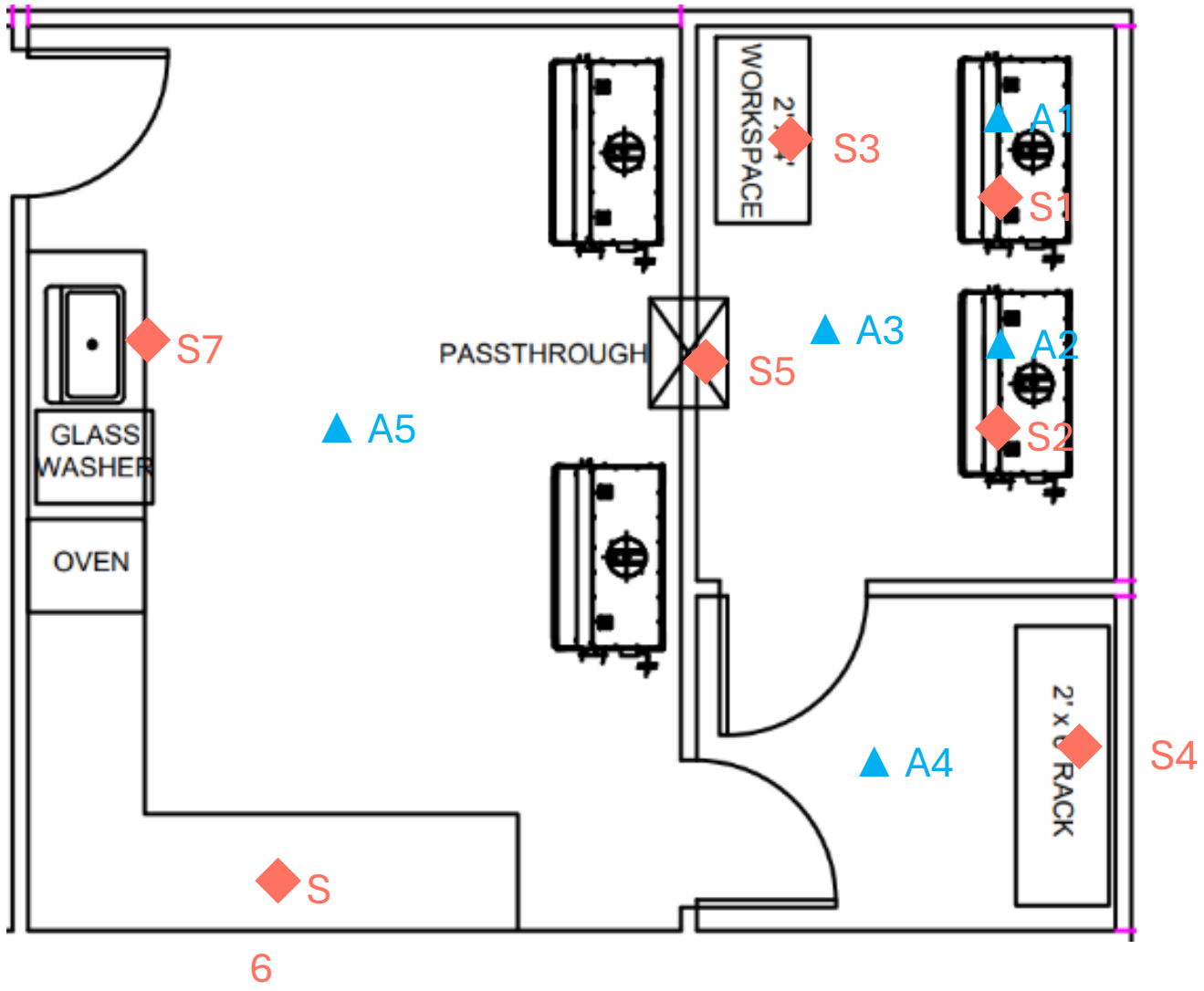
# Sampling Locations

- All ISO-classified areas
- Defined in SOPs
  - Include sampling diagram
- Risk-based
  - Highest risk to CSP
  - Highest personnel activity
  - High touch areas
  - Difficult to clean areas

- Examples
  - PEC and equipment within PEC
    - Near DCA (≈ 1 ft)
  - Staging and storage areas
  - Pass-through chambers
  - RABS
  - High touch areas
    - Pumps, keyboards, light switches, door handles, door plates, etc.
  - High traffic areas
  - Near PECs, pass-through chambers, and sinks
  - Areas of stagnant or turbulent air (outside of the PEC)
  - Areas within and around doors

# Sampling Diagram

- Viable air ▲
- Viable surface ◆



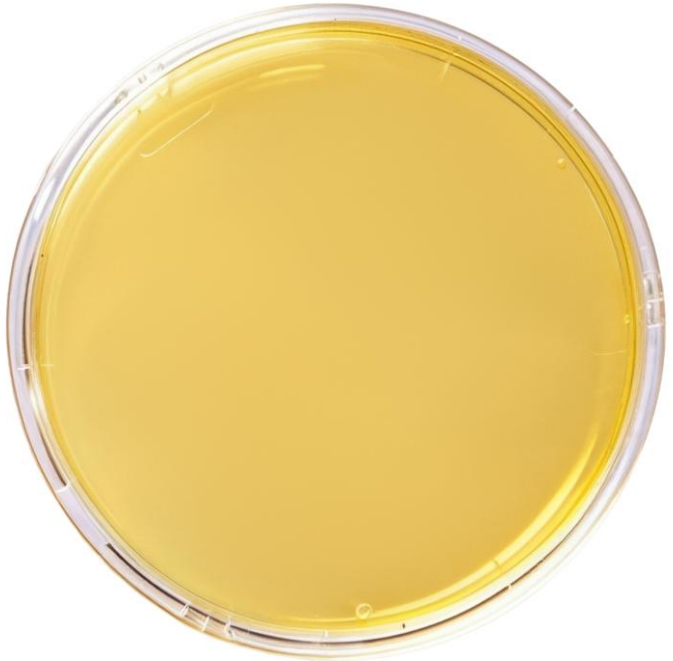
# Media Plate Options

- Types
  - Contact plates
    - Convex surface
    - Ideal for surface sampling and personnel monitoring
  - Settle plates
    - Ideal for air sampling and gloved-fingertip testing
- Media
  - TSA: general microbial growth media
  - SDA/MEA: fungal growth media
- Sterile (irradiated) vs aseptically processed
  - Inspect upon receipt
- Wrapping
  - Triple: facilitates transfer process across ISO-classified areas
- Storage temperature
  - Refrigerated vs room temperature
- Locking lid design
- Neutralizing agents
  - Required for surface sampling

# Media Plates

## CONTACT PLATES

## SETTLE PLATES



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# Viable Air Sampling

- Dynamic operations

- Impaction air sampling
  - Volume: 1,000 L (1 m3)
  - Media
    - Single (TSA)
    - Dual (TSA + TSA or TSA + SDA/MEA)
  - Oriented towards the airflow
  - Calibrated NLT annually

- Incubation
  - Invert plates
    - Prevents condensation
  - Temperature and duration
    - 30° to 35°C for NLT 48 hours
    - 20° to 25°C for NLT 5 days
  - Document on log

- Evaluate results
  - Alert/action limits
  - Adverse trends
  - Microbial identification

# Impaction Viable Air Samplers

**SINGLE HEAD**

**DUAL HEAD**

# Viable Air Sampling

- Handle media carefully to prevent contamination
- Sampling head should be autoclaved or sanitized in accordance with manufacturer's recommendation
- Ensure proper volume of air is collected


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# Viable Air Sampling Action Limits

| ISO Classification | CFU/$m^3$ |
|---|---|
| 5 | > 1[1] |
| 7 | > 10 |
| 8 | > 100 |

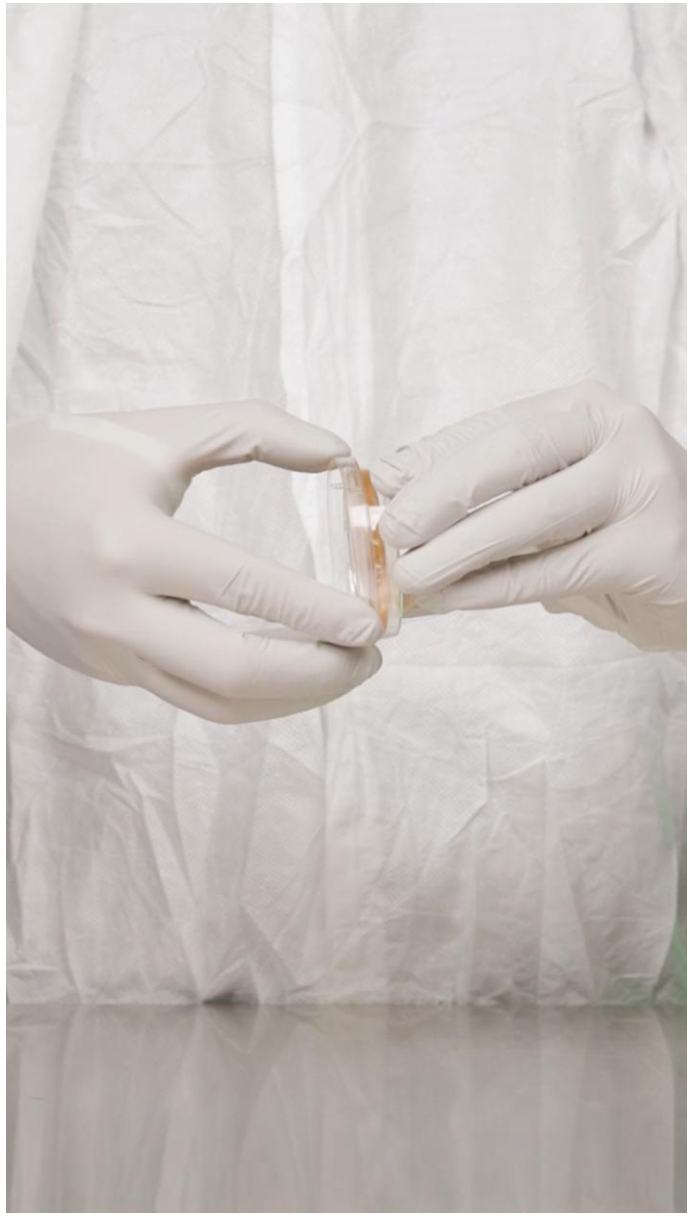
[1] *Best practice: ≥ 1*

# Viable Surface Sampling

- Contact plates/swabs
  - Media + neutralizing agent (e.g., lecithin and polysorbate 80)
    - Single (TSA)
    - Dual (TSA + TSA or TSA + SDA/MEA)
- Schedule
  - Dynamic operations
    - After compounding
      - Each batch
      - Shift
  - Before cleaning and disinfection
- Incubation
  - Invert plates
    - Prevents condensation
  - Temperature and duration
    - 30° to 35°C for NLT 48 hours
    - 20° to 25°C for NLT 5 days
  - Document on log
- Evaluate results
  - Alert/action limits
  - Adverse trends
  - Microbial identification

# Surface Sampling

- Use rolling motion to press media onto surface
- Handle media carefully to prevent contamination
- Clean the sampled area with sterile 70% IPA



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# Viable Surface Sampling Action Limits

| ISO Classification | CFU/m³ |
|---|---|
| 5 | > 3[1] |
| 7 | > 5 |
| 8 | > 50 |

[1] *Best practice: ≥ 1*

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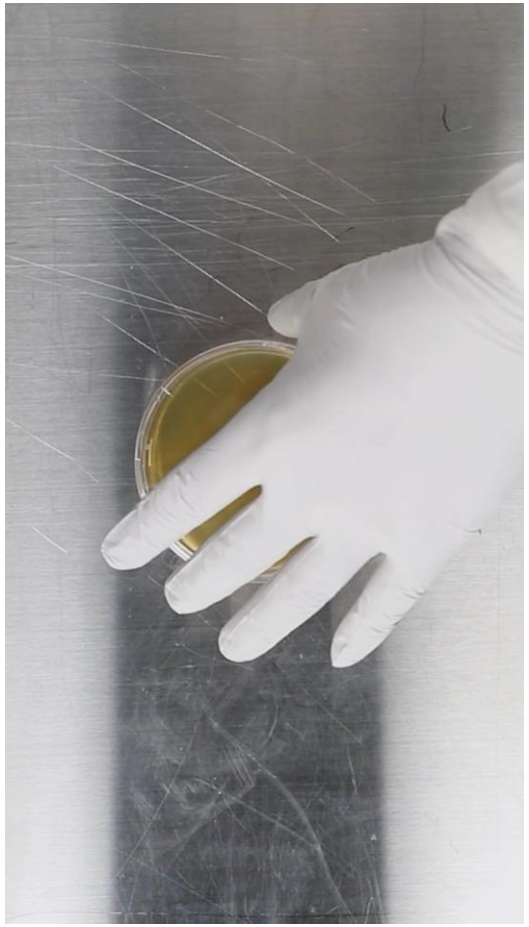
# Personnel Monitoring

- Requirement
  - Initial GFT in triplicate for personnel garbing and gloving qualification
    - Best practice: include other sites of sterile garb that may breach ISO 5
  - Ater media-fill test
    - Semiannually or quarterly dependent on compounding Category
    - Annually for personnel who do not compound
- Scope
  - Garbing and gloving qualification applies to all personnel entering the cleanroom
- Best practice
  - After every batch

# Gloved-Fingertip Testing

- **DO NOT SANITIZE GLOVES PRIOR TO SAMPLING**
- Use a separate device for each hand
- Roll the fingertip and thumb over the agar surface with light pressure
  - Do not split or damage the media



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# Gloved-Fingertip Testing Action Limits

| Timing | CFU (both hands) |
|---|---|
| After garbing | > 0 |
| After media-fill test | > 3[1] |
| [1] *Best practice: ≥ 1* | |

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# Contamination Recovery Rates

- Percent of samples with growth
- Useful in identifying adverse trends

| ISO Classification | Active Air | Settle Plate[1] | Contact Plate/Swab | Glove/Garment |
|---|---|---|---|---|
| Isolator/ Closed RABS | < 0.1 % | < 0.1 % | < 0.1 % | < 0.1 % |
| 5 | < 1 % | < 1 % | < 1 % | < 1 % |
| 7 | < 5 % | < 5 % | < 5 % | < 5 % |
| 8 | < 10 % | < 10 % | < 10 % | < 10 % |

[1] 4-hour exposure

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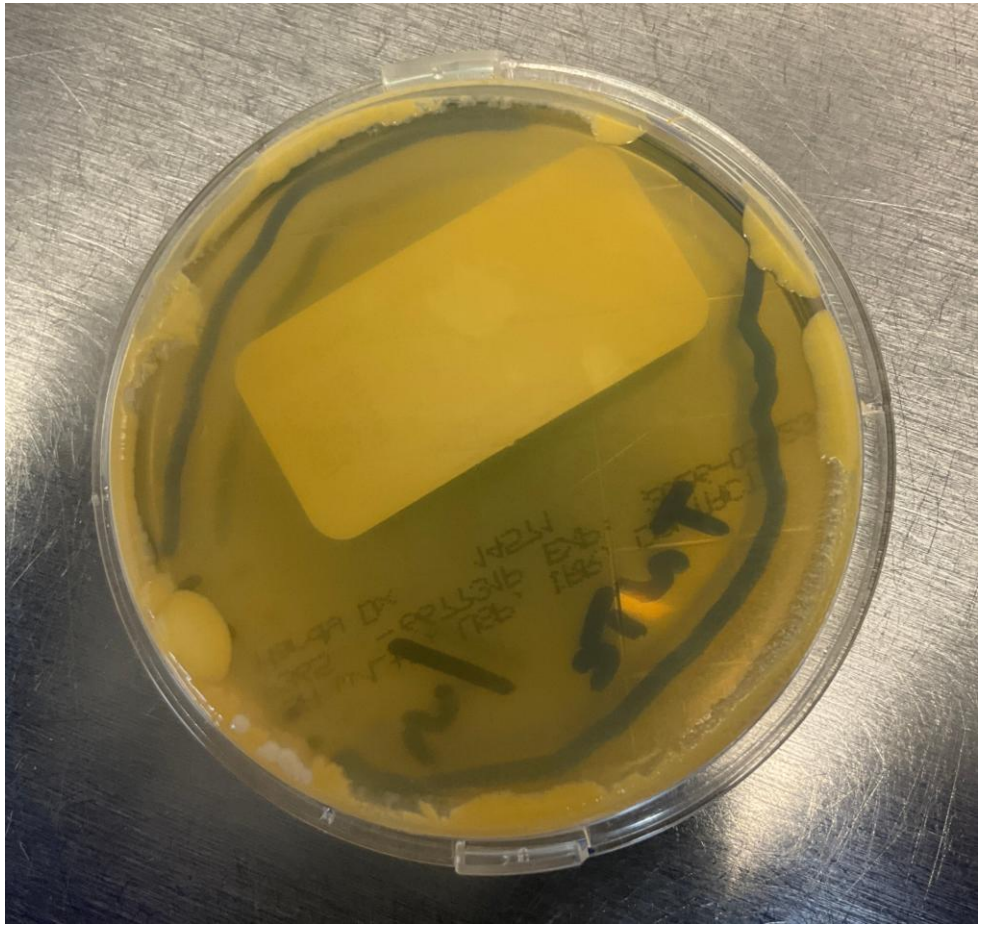
# Sample Handling

- Clean and disinfect
  - Packaging
  - Hands
- Inspect media before use
- Do not clean or disinfect surface before sampling
- Use aseptic technique when removing and replacing lid to ensure media is not contaminated
- Clean sampled area after sampling
- Label base of the plate
- Ship cool (not frozen) overnight



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# Incubation Requirements

- Two incubators
  - 30° to 35°C
  - 20° to 25°C
- Trained staff
  - Incubation and enumeration
- Documentation
  - SOP (incubation and enumeration)
  - Incubation log
  - Temperature monitoring
    - Daily or continuous

# Incubation Log

- Minimum requirements
  - Sample description
    - Name of person evaluated, if applicable
    - Sampling location
  - Sampling date/time
    - Name of person collecting sample
  - Name of person collecting sample
  - Incubation dates
  - Media information
    - Lot number, expiration date, type, manufacturer, etc.
  - Starting temperature per interval
  - Result (CFU)
    - Evaluator name and date

# Evaluate Results

- Evaluate results
  - Alert/action limits
  - Contamination recovery rate
  - Adverse trends
    - PEC, room, person, process

- Investigate excursions and adverse trends
  - Microbial identification
    - Helps determine source (e.g., human, water, soil, etc.)
  - Potential causes

# Trending

- Timing
  - Immediate/ongoing
  - Short term: monthly or quarterly
  - Long term: annually
- Data
  - Location/room/shift
  - ISO Class
  - Sample type (air, surface)
  - Microorganism
  - Personnel

- Trending rules
  - Repeated alerts at same location
  - Multiple alerts in same room
  - Increase over time
    - CRR
  - Pattern
  - Sustained recoveries over alert
  - Microorganism
    - Repeat
    - Atypical
    - Spore
  - Personnel, process, etc.
  - Across adjacent rooms
  - After event

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# Temperature, Relative Humidity, and Differential Pressure

- Temperature
  - 20°C or cooler
  - Operator comfort
- Relative humidity
  - 60% or below
- Differential pressure
  - NonHD: ≥ 0.020-inch water column
  - HD: -0.03 to -0.01-inch water column
- Frequency
  - Manual: document daily
  - Continuous
    - Review daily
      - Compounding days

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# Investigation

- Document excursion or identified trend
- Define activity at time of occurrence, affected location(s), personnel involved, etc.
- Investigate
  - Personnel practices: garbing, gloving, material transfer, cleaning/disinfection, sampling technique, etc.
  - Logs: differential pressure, temperature and humidity, cleaning/disinfection
  - Facility and equipment: engineering controls, HEPA-filters, materials of construction, design
  - Workflow
  - Microorganisms recovered
- Additional sampling
- Impact assessment to CSP(s)
- Identify root cause/likely root cause and implement CAPA

# CAPA

- Document and implement corrective and preventive action

- Perform effectiveness check

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# Thank You

Jacqueline Esqueda

Eagle Analytical Services

800.745.8916