How to Use Environmental Monitoring Data as an Indicator of Aseptic Process Quality

Amanda Curtis
ValSource, Inc.

Introduction – Amanda Curtis

- Microbiology consultant with ValSource
- Bachelor's degree in microbiology from Purdue University
- >15 years experience between clinical and pharmaceutical micro
- Focus on ATMPs and aseptic manufacturing
- Coauthor on:
  - Global Sterile Manufacturing Regulatory Guidance Comparison & Assessment Tool (2nd Ed). (PDA, 2024)
  - PDA TR 70 "Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities" (In progress)

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Agenda

- Introduction to the Value and Limitations of EM Data
- How to Interpret and Communicate EM Data to Stakeholders – A Case Study

Introduction to the Value and Limitations of Environmental Monitoring Data

What Does EM Data Tell Us?

Environmental Monitoring: The monitoring of a controlled environment

EM Does:

- Assess effectiveness of contamination controls (ex. cleaning and disinfection)
- Identify problems in a facility or area
- Identify trends and individual events
- Gather data to support root cause analysis
- Evaluate the aseptic processing environment
- Demonstrate that the area is in or out of a state of control

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- Prove product sterility or non-sterility

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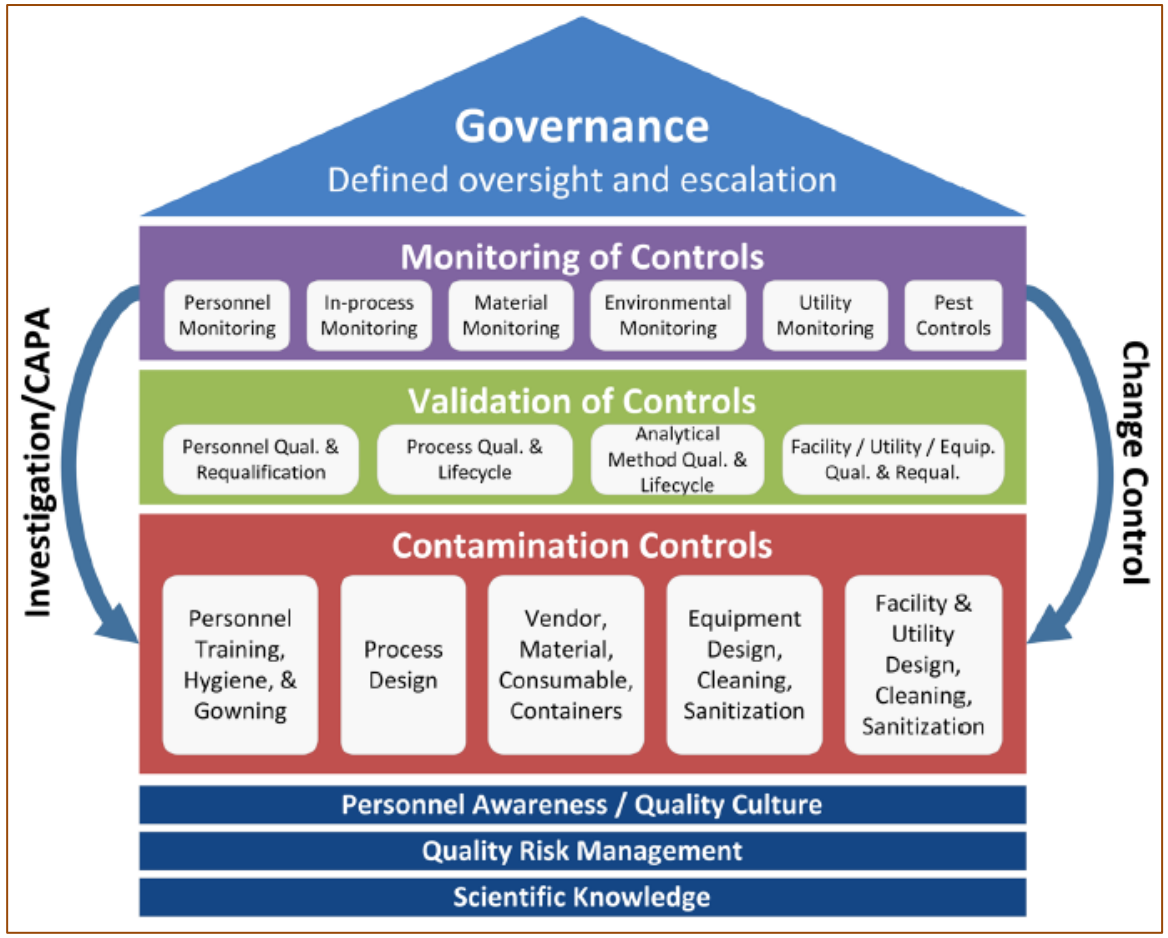

Figure 3.0-1 from PDA TR 90[1]

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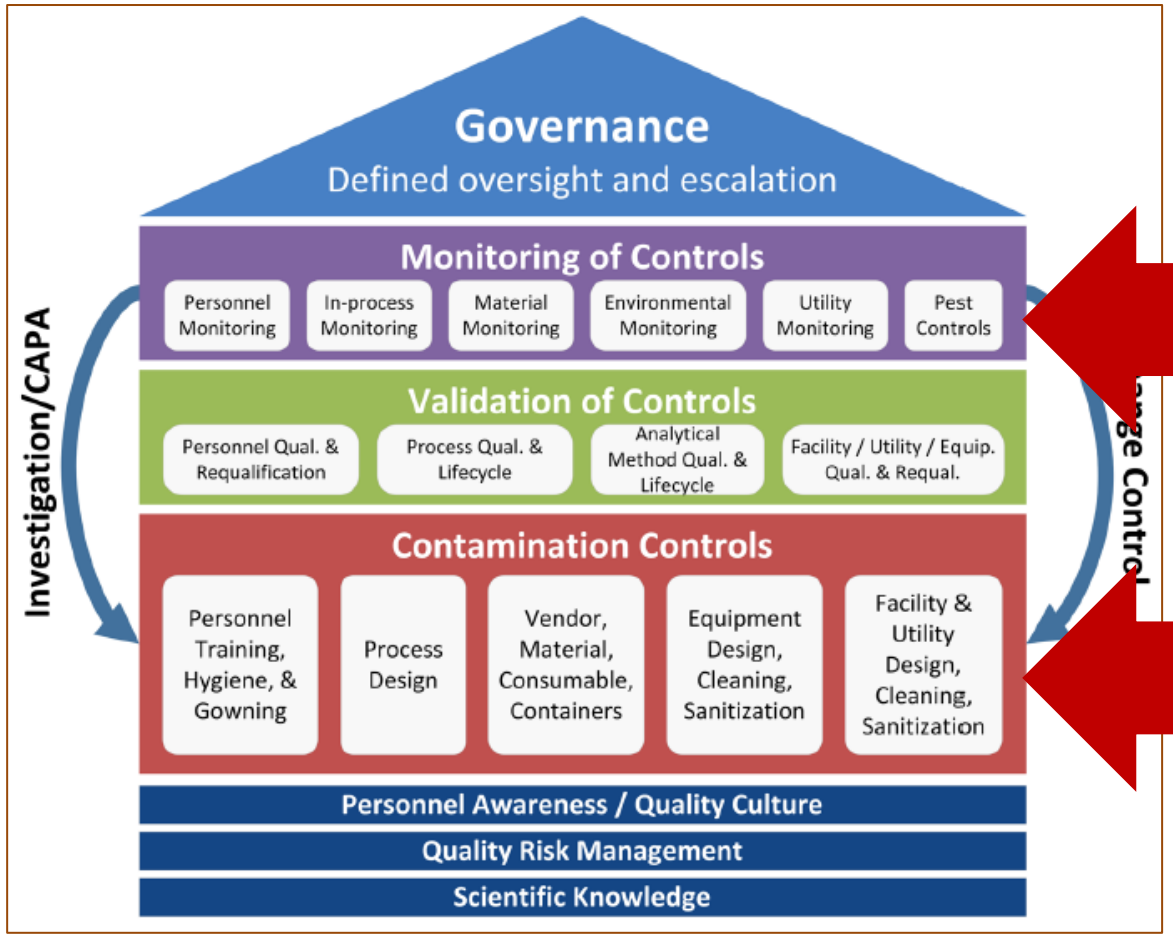

Monitoring of Controls

Contamination Controls

Figure 3.0-1 from PDA TR 90[1]

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Reasons EM Does Not Have a 100% Recovery Rate[2]:

1. Microbiology is not chemistry

- Microorganisms are stressed/damaged and not actively growing in a cleanroom
- Microorganisms can be slow growers (ex. *C. acnes*)[3]
- Natural microorganism variability

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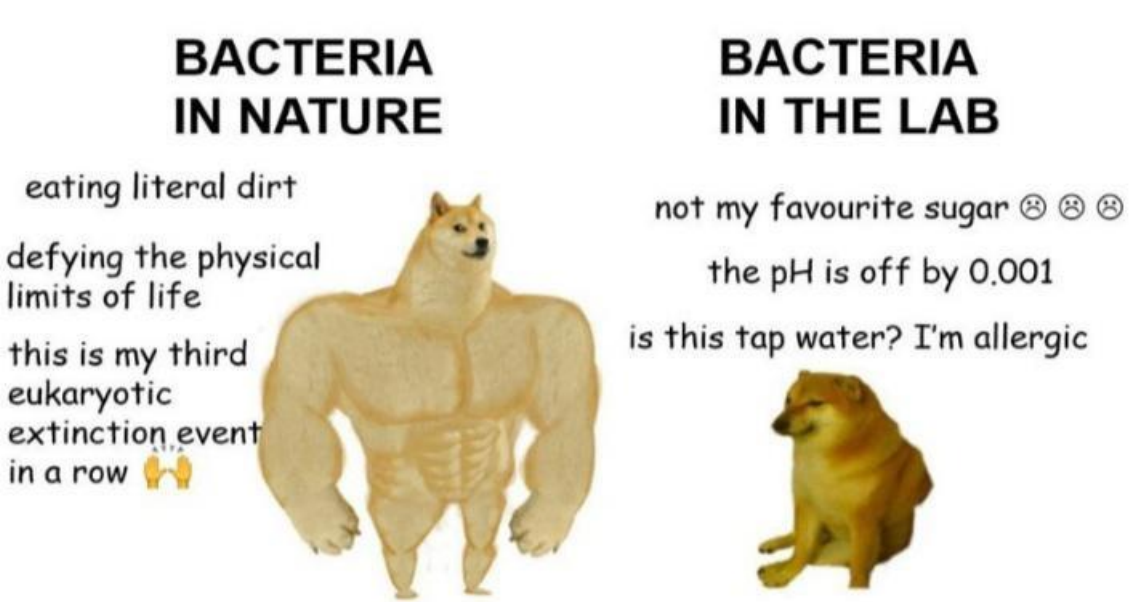
Reasons EM Does Not Have a 100% Recovery Rate[2]:

1. Microbiology is not chemistry
2. **Traditional growth-based methods don't recover everything present[4]**

- Traditional growth media supports the growth of <0.1% of bacterial species in the world
- Not everything grows on TSA!
- Growth-based methods have been shown to recover 10 to 10,000 times fewer bacteria than direct microscopic methods in soil and water samples
  - 1 CFU does not necessarily equal 1 cell



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1. Microbiology is not chemistry
2. Traditional growth-based methods don't recover everything present[4]
3. Contamination is not uniform. Sampling locations in the wrong spots won't detect it.
4. **Limitations and variation in EM sampling methods, techniques, and equipment**

What Does EM Data Tell Us?

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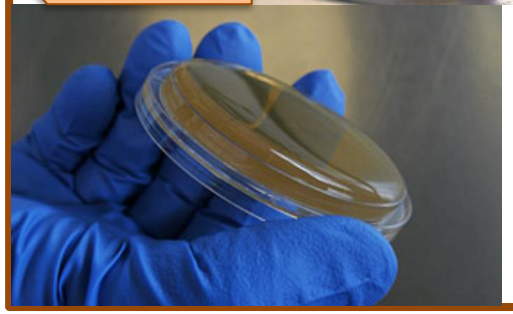
Recovery varies up to ±3-fold

Recovery is ~ ¼ that of active methods

Recovery rate: 0-56%

Recovery rate: 0-80%



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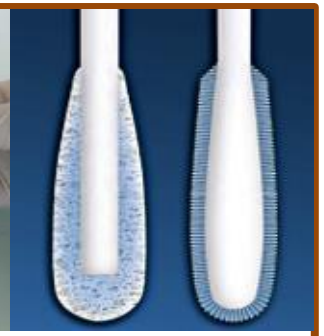

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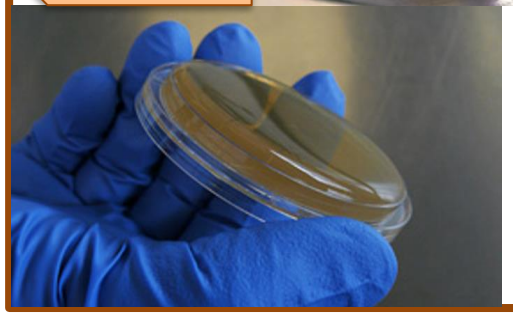
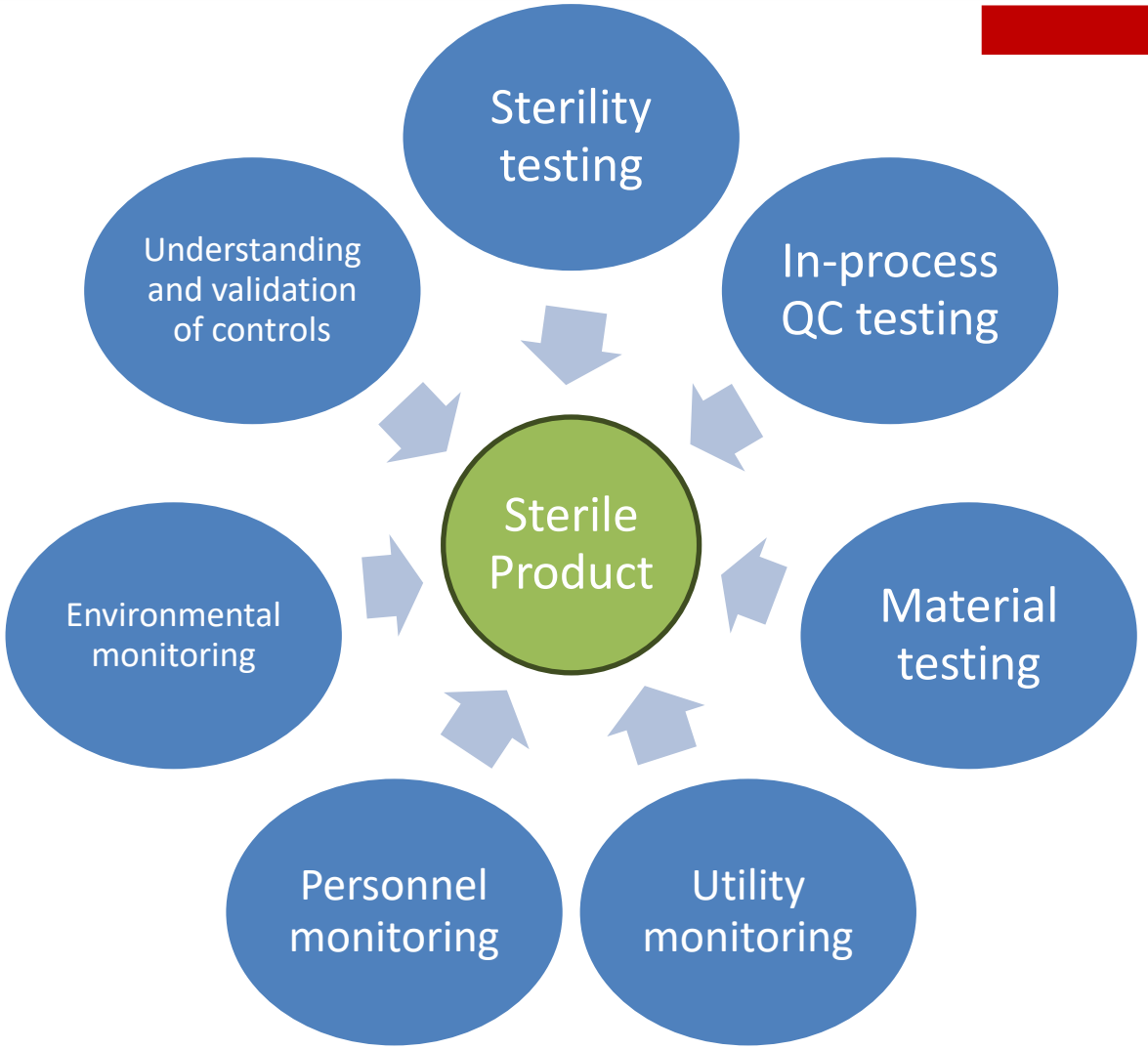


Factors that can affect viable recovery:

- Sampling time
- Sampling volume (active methods)
- Sampler design and calibration (active methods)
- Type of swab used[5]
- Sampling technique
- Surface material
- Types of microorganisms present
- Plate handling post-sampling
- Incubation conditions

What Does EM Data Tell Us?



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How to Interpret and Communicate an Adverse Trend to Stakeholders – A Case Study

Case Study: Background

Company contacted us because they were having sterility failures that impacted numerous lots of multiple commercial products. Sterility positives were ID'd as a wide range of microorganisms, including sporeformers.

While investigating those, they had found some issues and gaps that they wanted us to come in and help address:

- Review and evaluate disinfectant efficacy study (DET or DES) results and assess current cleaning and disinfection program
- Evaluate current room classifications
- Evaluate gowning program

As part of my initial information request, I requested the last couple years of EM trend reports[2,6,7].

Why EM Trend Reports?

The Asks:

- Review and evaluate disinfectant efficacy study results and assess current cleaning and disinfection program
- Evaluate current room classifications
- Evaluate gowning program

1. EM trend reports can give you a quick overview of the state of control in a facility or area…but only if they’re done well.
2. EM trend reports can pinpoint specific areas in a facility where issues are occurring.
3. EM speaks to effectiveness of the cleaning and disinfection program, which is directly related to the DET point

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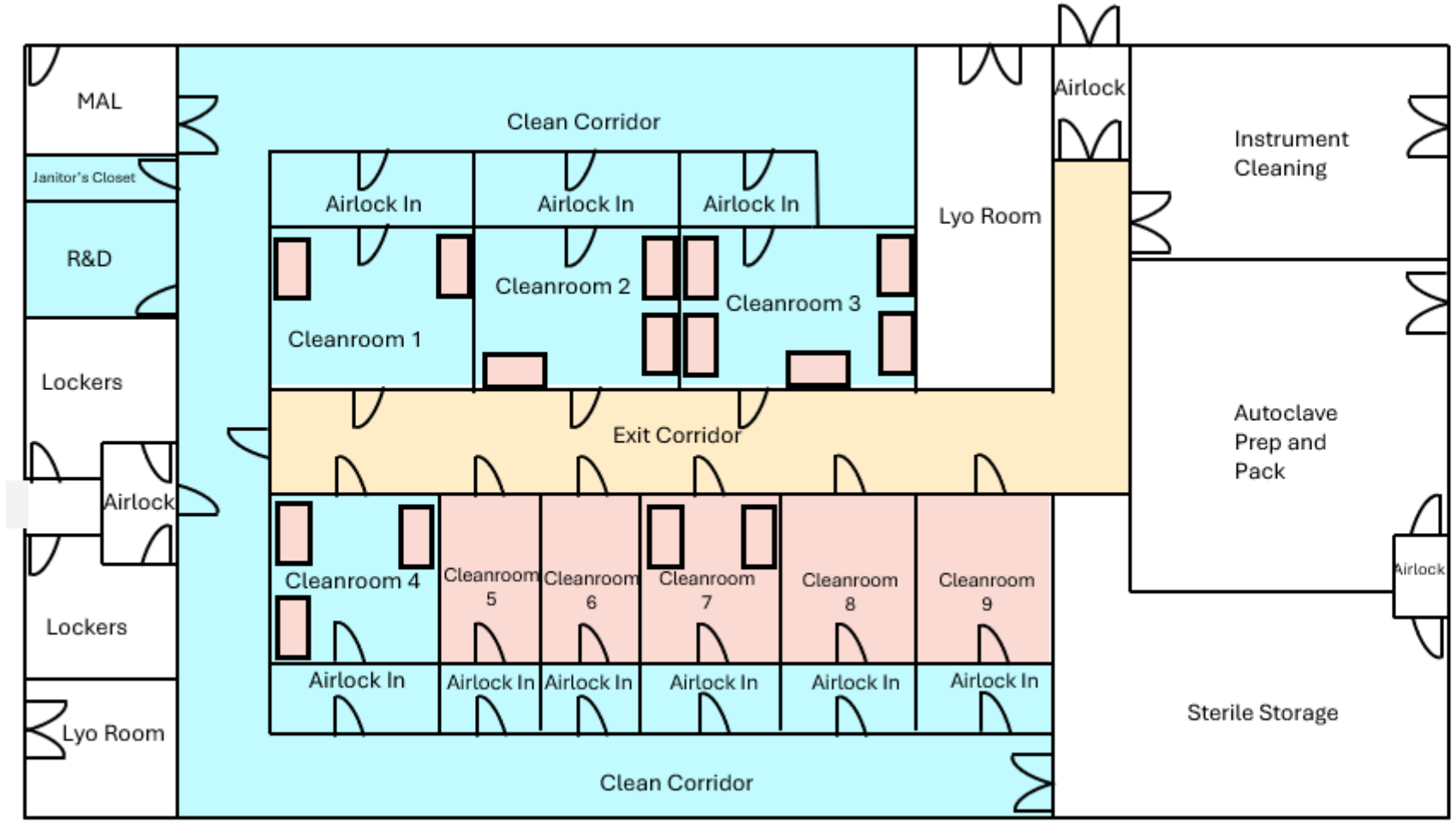
Red Flag #1: No EM trend reports

Red Flag #2: Disconnect between Production and QC

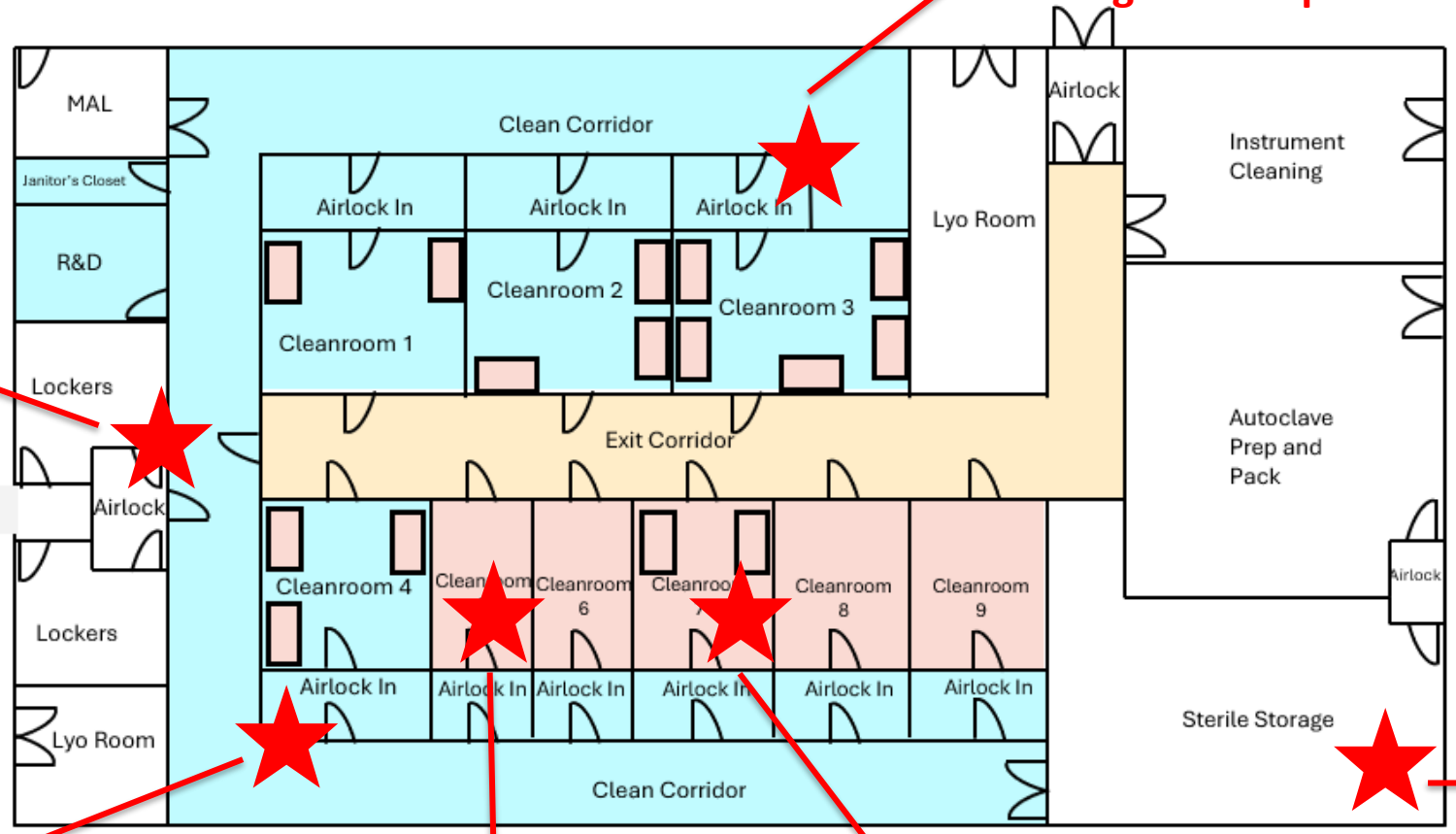
Case Study: Background



Case Study: Background

Red Flag #3: Poor facility design

Material and personnel flow through same space at same time



Grade A

Grade B

Grade C

CNC → Grade B. Skipped Grades D and C

Use of sliding doors with no interlock that remained open

Grade A cleanrooms

Grade A BSCs in Grade A cleanrooms

"Sterile storage" in a CNC space with no airlock or separation from Grade B

Case Study: How EM Data Was Presented to Production

Date	Location	Site	EM Type	CFU	ISO Class	Action Lev	Microorganism	EM Acceptable?
1/31/2022	CR 5	2	Air	1	5	Yes	Fungus isolated	No
2/6/2022	A/L 2	1	Air	5	7	No	*Staphylococcus epidermidis*	Yes
	A/L 2	1	Air	5	7	No	Staphylococcus capitis	
2/6/2022	CR 2	25	Surface	1	7	No	Micrococcus luteus	Yes
2/6/2022	CR 1	3	Air	1	7	No	Micrococcus luteus	Yes
2/1/2022	CR 6	25	Surface	3	5	Yes	Fungus Isolated	No
2/6/2022	CR 6	1	Surface	1	5	No	Staphylococcus epidermis	Yes
2/6/2022	CR 2	BSC Left	Surface	1	5	No	Staphylococcus haemolyticus	Yes
2/6/2022	CR 2	BSC Right	Surface	1	5	No	Micrococcus luteus	Yes
2/6/2022	CR 3	12	Surface	1	7	No	Fungus isolated	Yes
2/11/2022	Clean Corridor	7	Surface	1	7	No	Fungus isolated	Yes
2/15/2022	CR 5	14	Surface	1	5	No	Bacillus species not anthracis	Yes
	CR 5	21	Surface	1	5	No	Bacillus species not anthracis	Yes
2/23/2022	A/L 4	1	Air	1	7	No	Bacillus species not anthracis	Yes
2/23/2022	CR 2	2	Air	1	7	No	Acinetobacter species	Yes
2/23/2022	A/L 2	1	Air	3	7	No	*Streptococcus sanguinis*	Yes
2/25/2022	CR 9	12	Surface	20	5	Yes	Acinetobacter baumanii	No
	CR 9						Calcoaceticus complex	
3/1/2022	A/L 5	1	Air	1	5	Yes	Staphylococcus epidermidis	Yes
3/2/2022	CR 5	BSC Outside	Surface	1	5	No	Micrococcus luteus	Yes
3/3/2022	A/L 5	1	Air	1	7	no	Staphylococcus epidermidis	Yes
3/4/2022	CR 6	1	Surface	1	5	No	Bacillus species not anthracis	Yes
3/4/2022	Clean Corridor	15	Surface	3	7	No	Coryneform bacteria	Yes
	Clean Corridor						Dermabacter species	
3/15/2022	CR 7	4	Surface	1	5	No	Bacillus species not anthracis	Yes
3/23/2022	CR 4	BSC Left	Surface	1	5	No	Staphylococcus hominis	Yes
4/12/2022	A/L 4	3	Surface	1	7	No	Bacillus species not anthracis	Yes
4/12/2022	CR 4	3	Air	1	7	No	Staphylococcus capitis	Yes
4/13/2022	Clean Corridor	5	Surface	1	7	No	Bacillus simplex	Yes
4/21/2022	A/L 4	4	Surface	1	7	No	Staphylococcus epidermidis Bacilus species not anthracis	Yes

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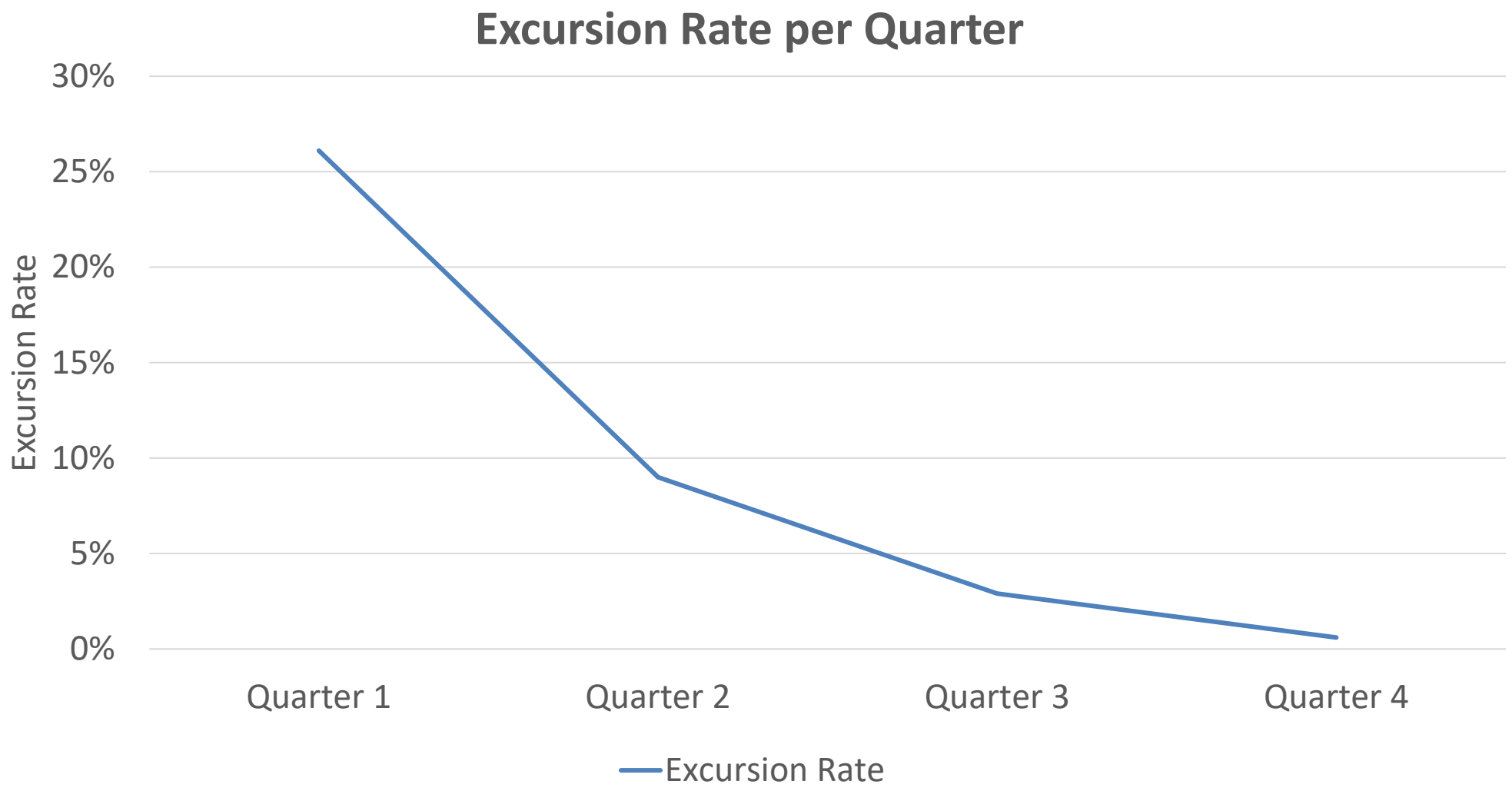

Examples of Adverse Trends

"Adverse trend" does not (just) mean 3 or more excursions in a row! Can also be:

- Consecutive growth results[6]
- Increased contamination recovery rates[2,6]
- Increasing numbers of excursions (action or alert)[6,8]
- Consecutive excursions from alert levels[6,8]
- Regular but isolated action excursions that may have a common cause[8]
- Changes in microbial flora type and numbers and predominance of certain organisms[6,8]

> iv. Changes in microbial flora type and numbers and predominance of specific organisms. Particular attention should be given to organisms recovered that may indicate a loss of control, deterioration in cleanliness or organisms that may be difficult to control such as spore-forming microorganisms and moulds.
>
> Annex 1, 9.11.iv[8]

Visual Presentation of Data

Human brains are better at detecting visual patterns than computers are![9,10,11,12]

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Data Point	Result (CFU)
1	0
2	1
3	0
4	2
5	1
6	1
7	2
8	3
9	1
10	1
11	1
12	2
13	2
14	3
15	3
16	4
17	3
18	4
19	4
20	5

Action: 5 CFU

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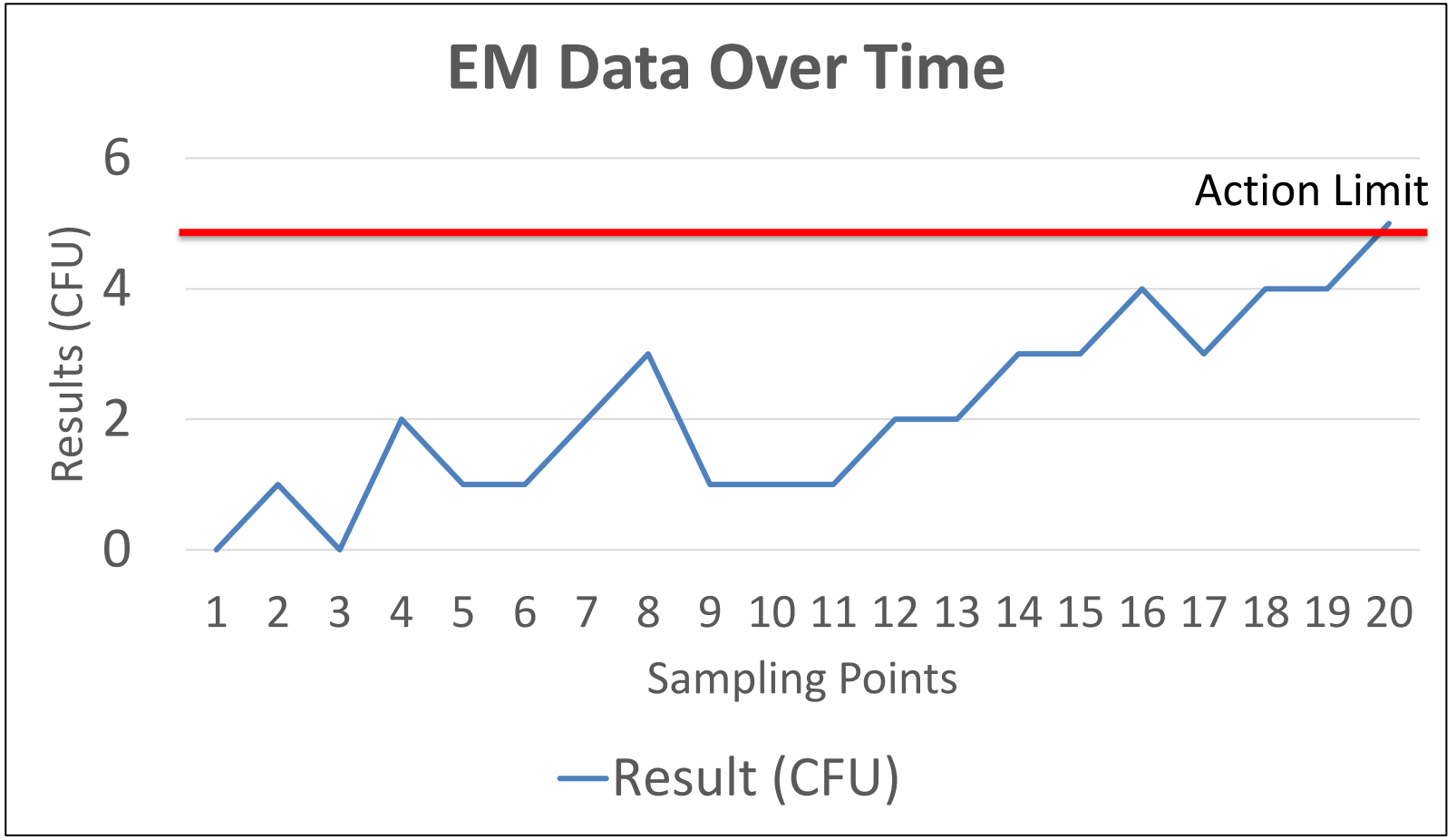
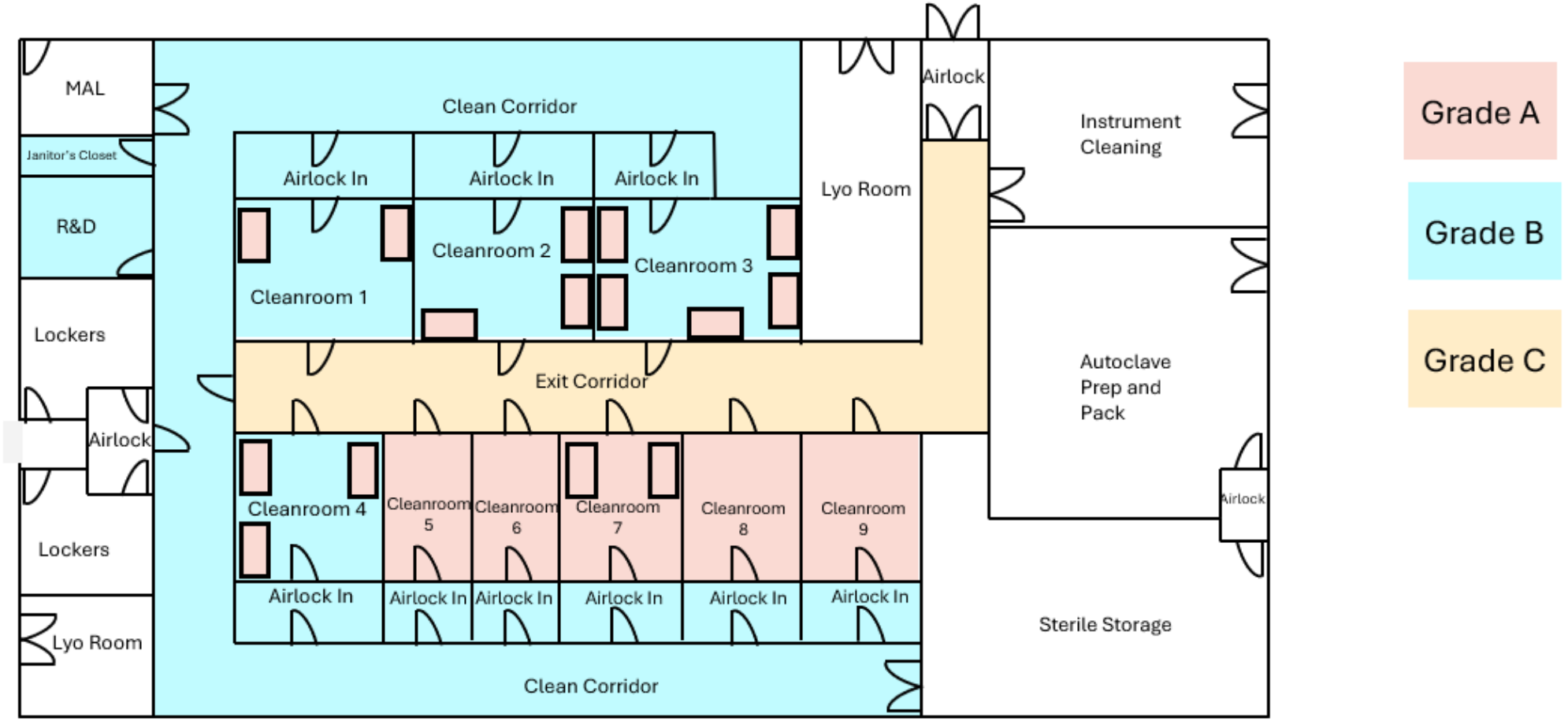
7	2
8	3
9	1
10	1
11	1
12	2
13	2
14	3
15	3
16	4
17	3
18	4
19	4
20	5

Action: 5 CFU

Versus

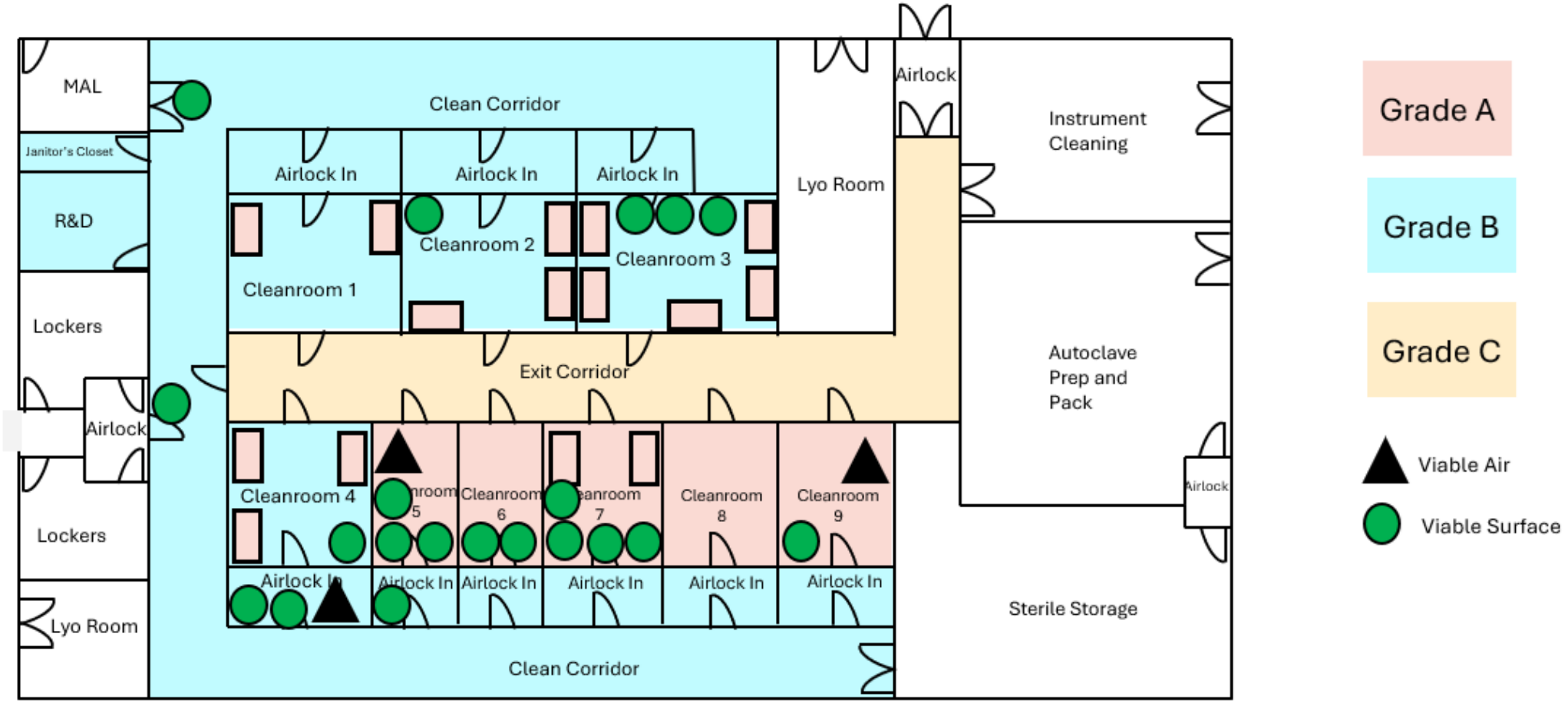


Case Study: Heat Maps



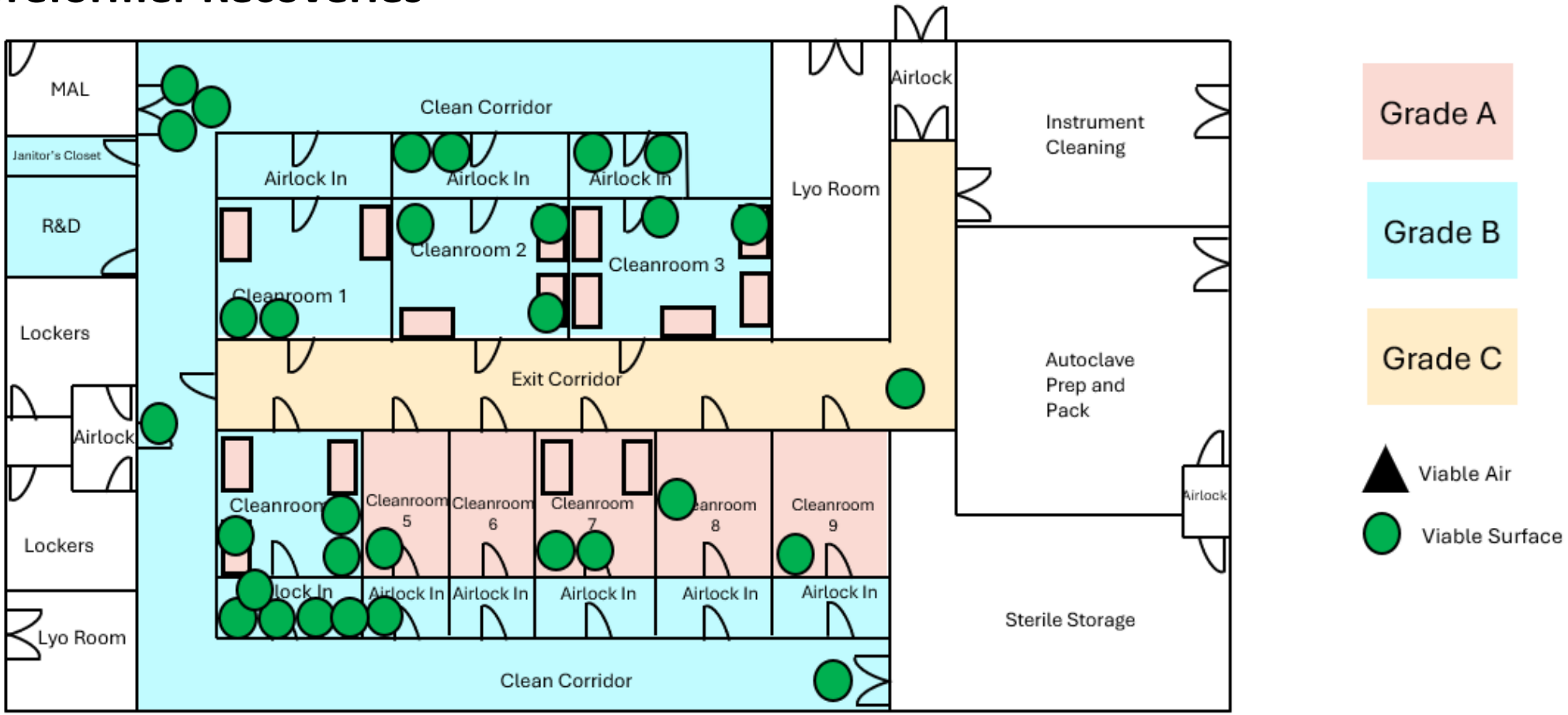
Case Study: Heat Maps

Quarter 1 Sporeformer Recoveries



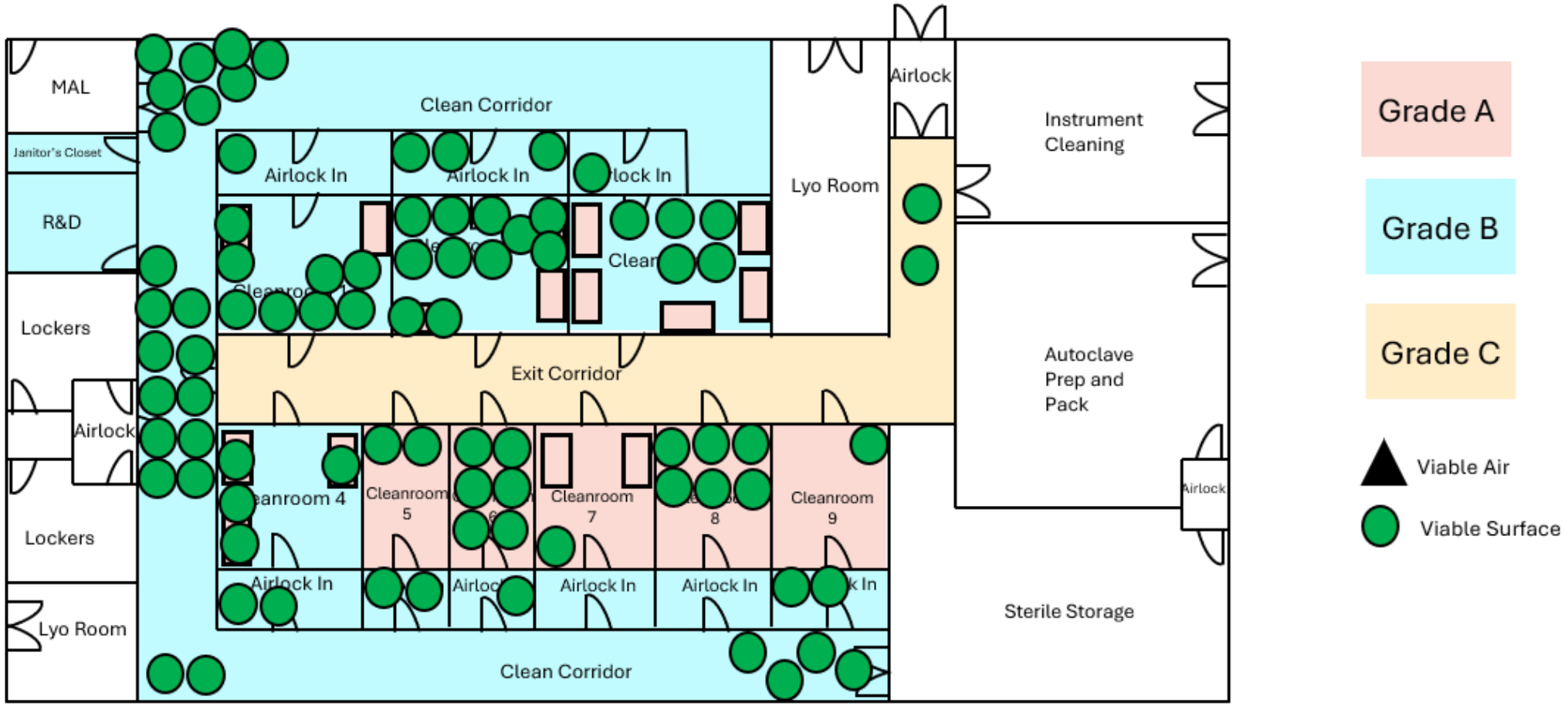
Case Study: Heat Maps

Quarter 2 Sporeformer Recoveries



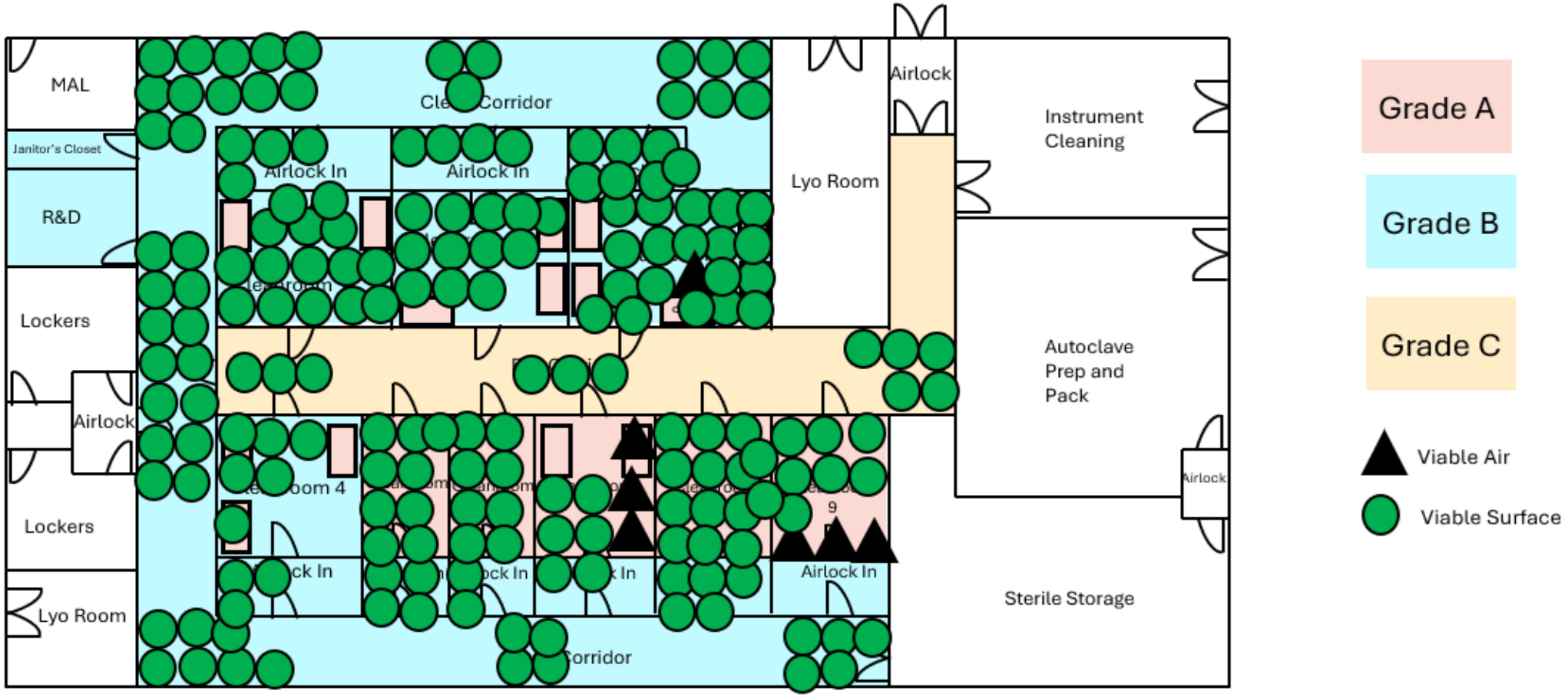
Case Study: Heat Maps

Quarter 3 Sporeformer Recoveries

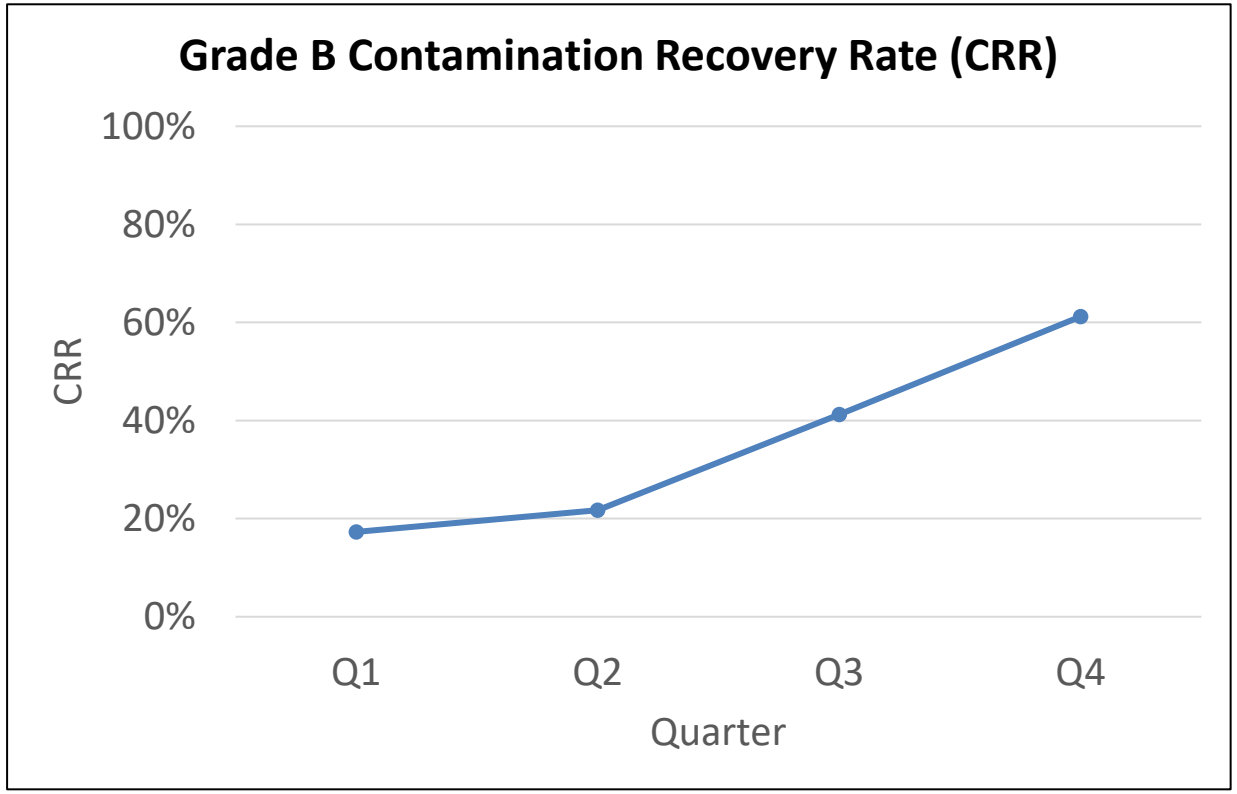


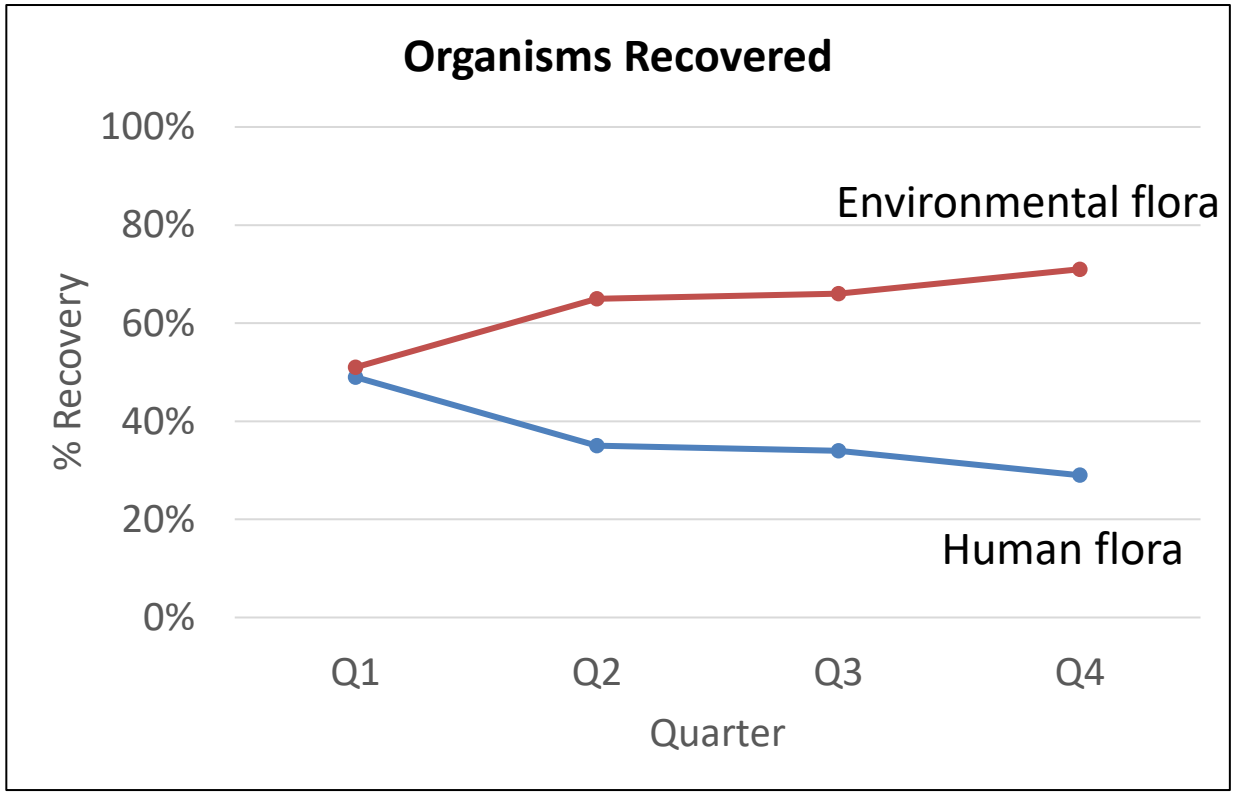
Case Study: Heat Maps

Quarter 4 Sporeformer Recoveries



Case Study: Charts and Graphs





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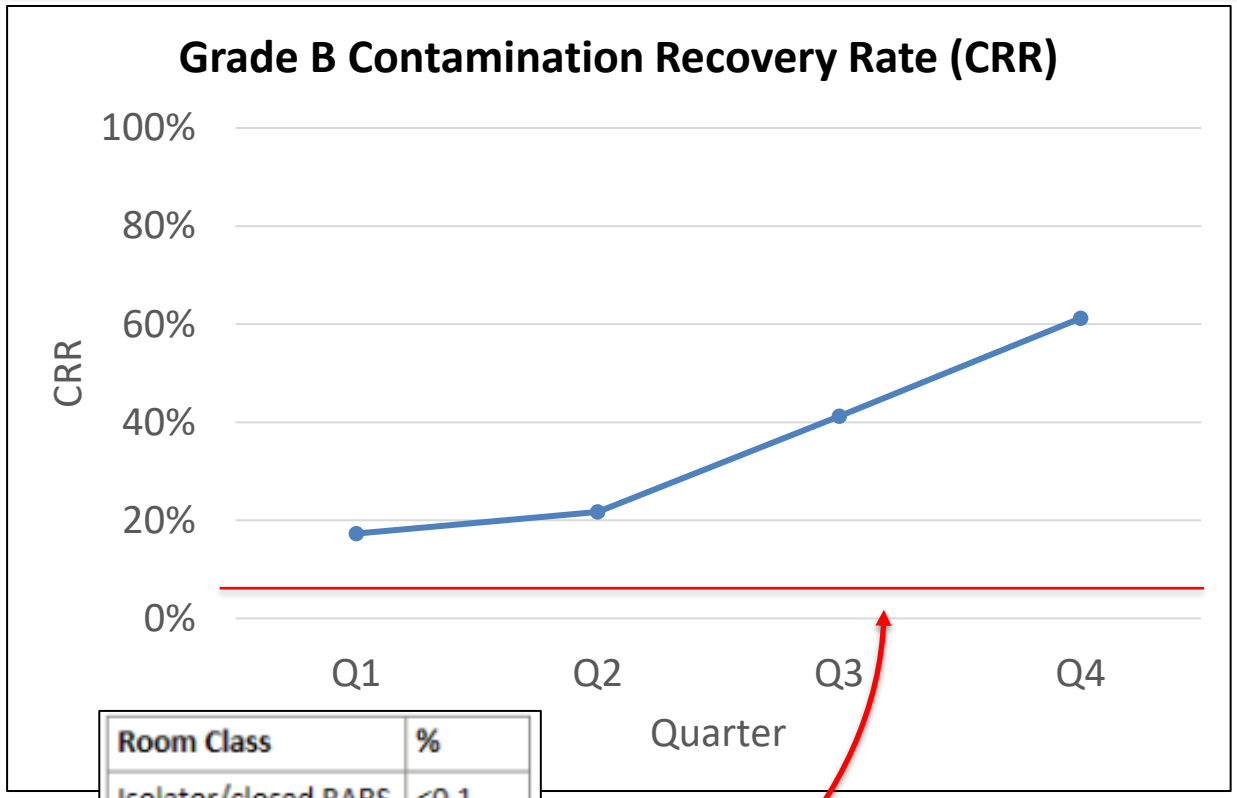
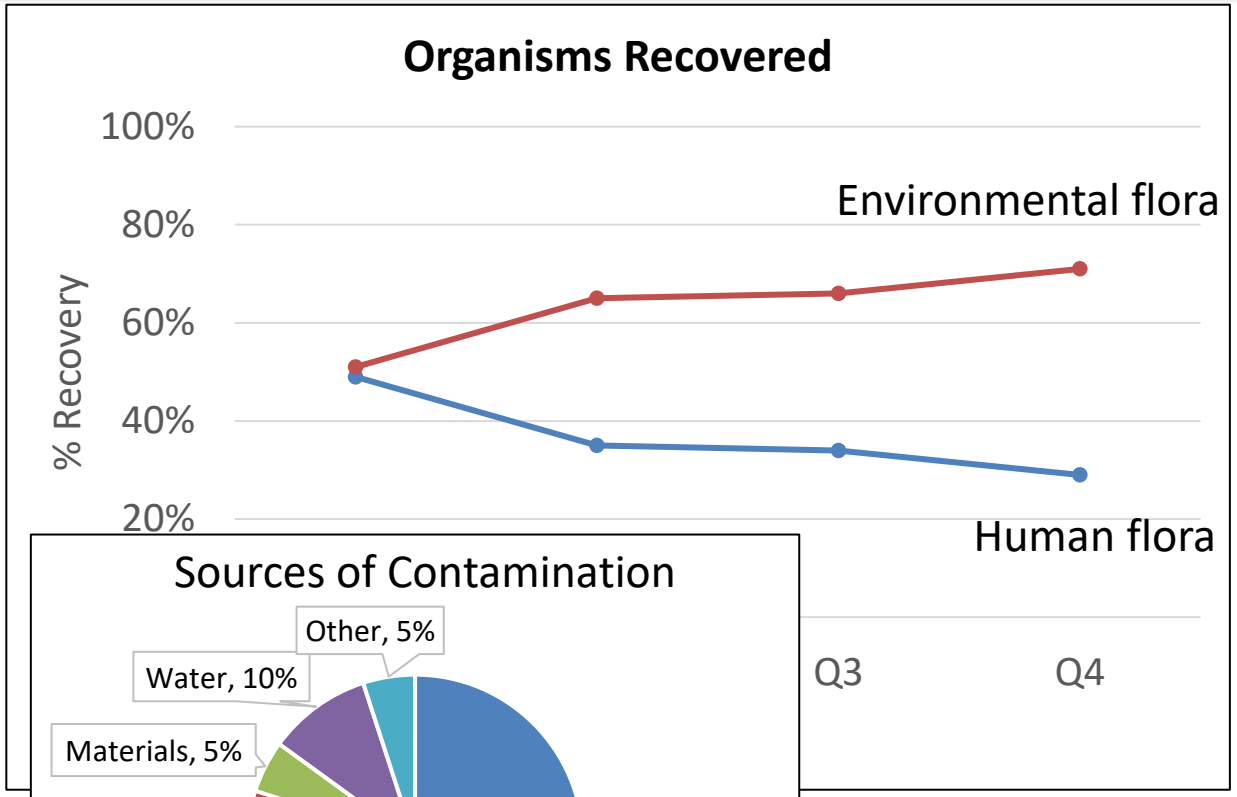
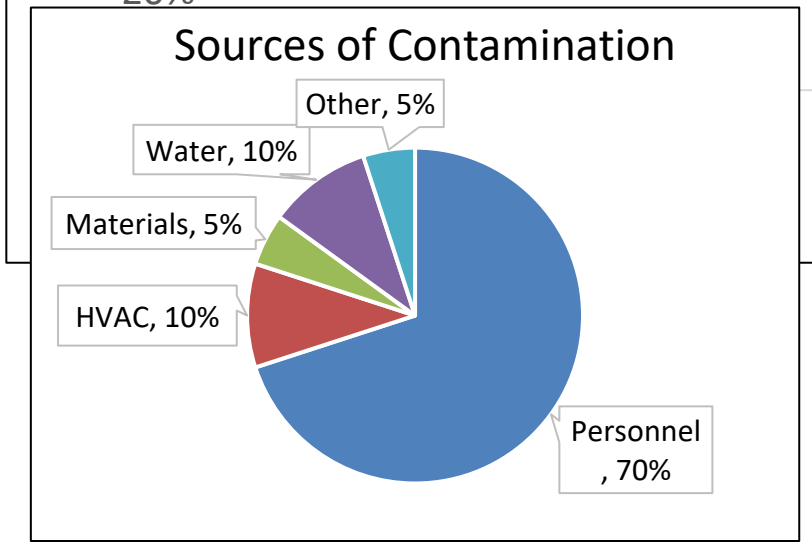


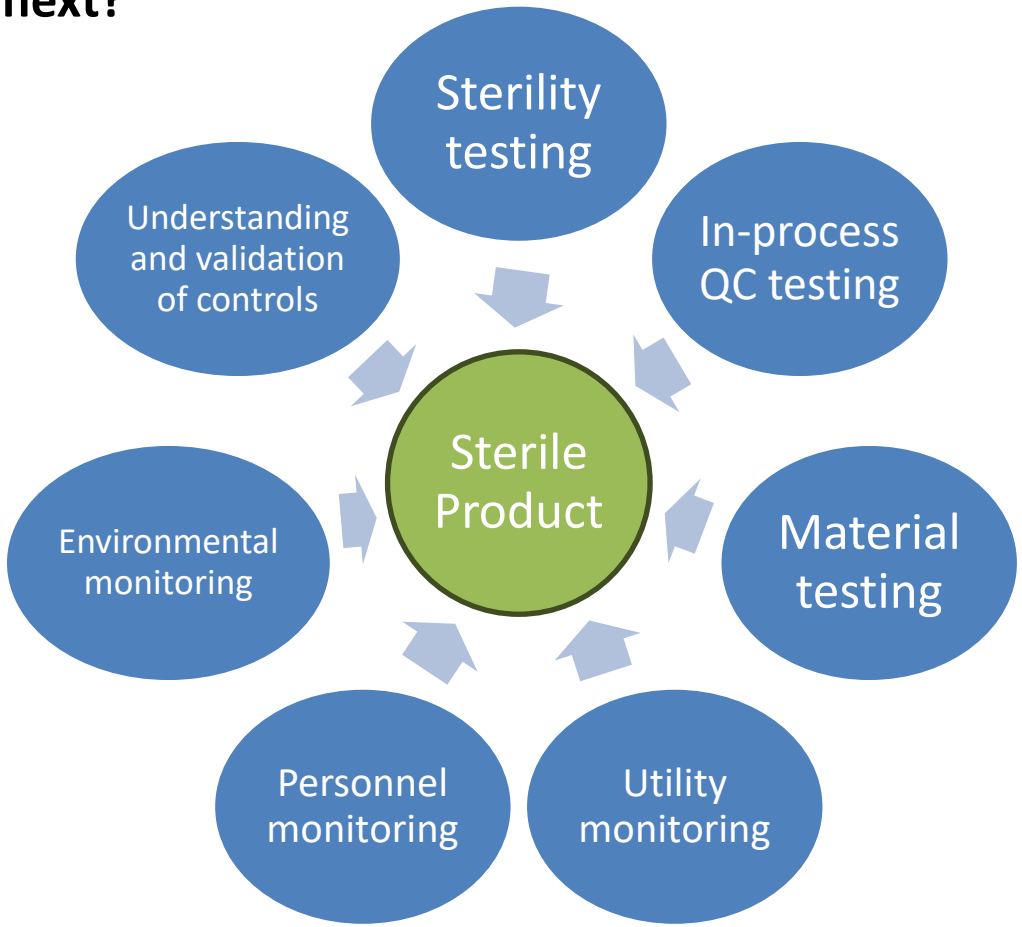
Room Class	%
Isolator/closed RABS	<0.1
ISO 5 / Grade A	<1
ISO 6	<3
ISO 7 / Grade B	<5
ISO 8 / Grade C	<10





Case Study: Conclusion

Question: What is the impact of the EM adverse trend(s) on product batches? What should the company do next?



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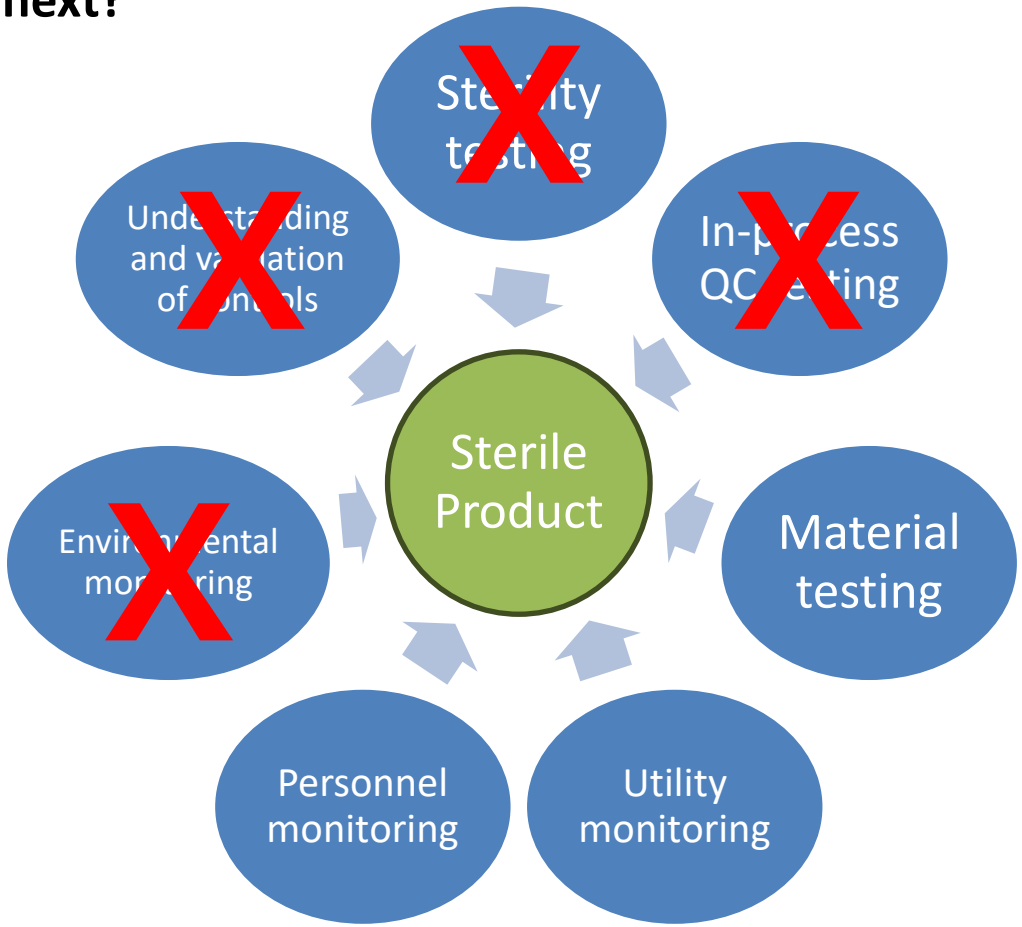

Considerations:

- Continuing to see sterility failures positive for sporeformers and other environmental flora, including post-terminal sterilization
- Actively working on multiple major gaps identified with equipment cleaning and sterilization cycles
- Obvious loss of control in the facility based on their EM data
- Identified multiple major issues with their EM and cleaning and disinfection program

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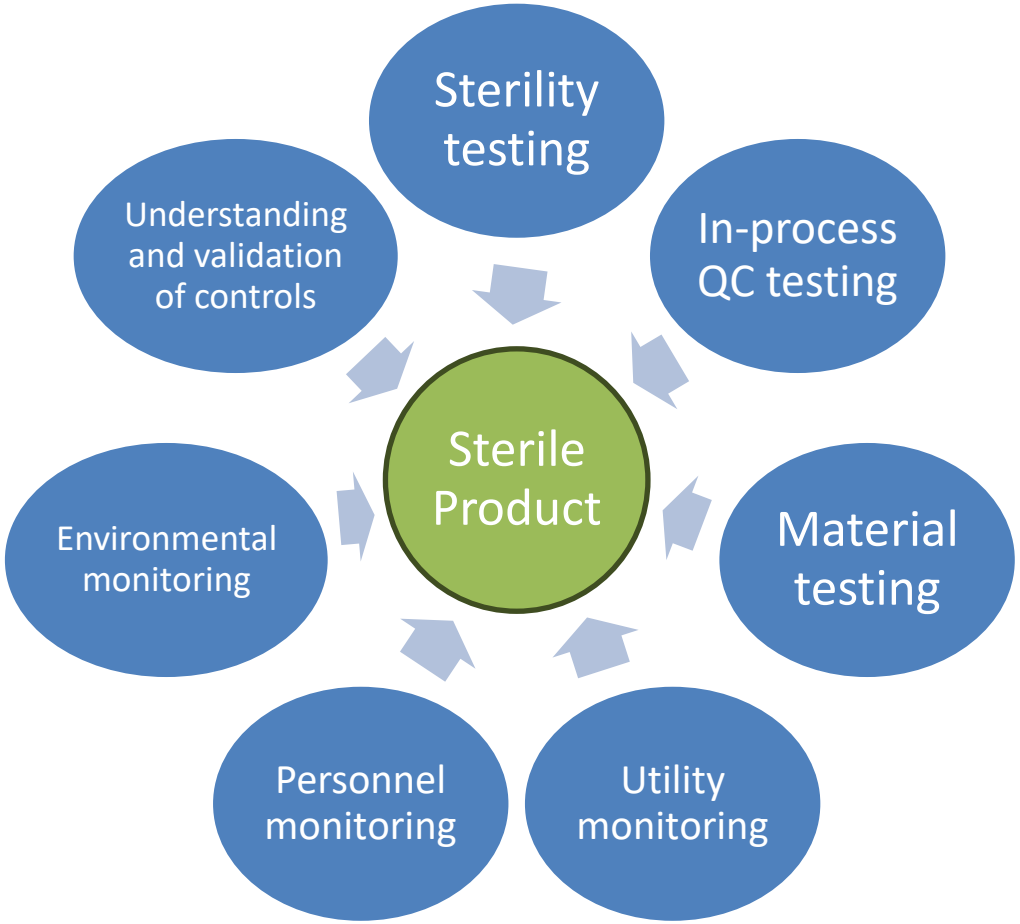
Recommendation: Pause production, perform intensive product impact assessment on released batches, inform the FDA, and focus on investigation and remediation efforts.

Conclusion: Key Takeaways

- Microbiological data is valuable but has its limitations.
- Microbiological testing represents a point in time. EM data demonstrates its full value when trended over time.
- Numerical data is most effectively communicated using meaningful visuals that consider the audience.
- All contamination controls work together to ensure a sterile product. The various methods used to monitor their effectiveness must all be considered when evaluating product impact.



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Thank you! Any questions?


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