A risk based approach to managing environmental excursions

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Introduction

Established Environmental Monitoring and Personnel Monitoring programs based on risk assessments and risk management system.

Environmental or personnel excursions exceeding alert or action limits should be based on trending data rather than isolated events.

Corrective actions and risk mitigation will be dependant on the level of risk. i.e. Sterile manufacturer vs non sterile.

Identification of environmental isolates will determine and assess the presence/absence of objectionable organisms.

Documented Risk Assessments

Risk = Likelihood of occurrence x consequence

Risk assessment definition: A systematic process of organizing information to support a risk decision to be made within a risk management process.

Three fundamentals:

Risk Identification – What might go wrong?

Risk Analysis – What is the likelihood it will go wrong?

Risk Evaluation – What are the consequences?

General Risk Matrix



		Likelihood of Occurrence		
		High value	Medium value	Low value
Consequence	High value	High risk		
	Medium value		Moderate risk	
	Low value			Low risk

Qualitative categories are defined and ranked from high to low risk.

Failure modes, effects and analysis

Item	Failure Mode	Effects on		Likelihood (L)	Consequence (C)	Criticality (LxC)	Control
		Other items	System				
				↕			

HACCP

Process Unit: _____

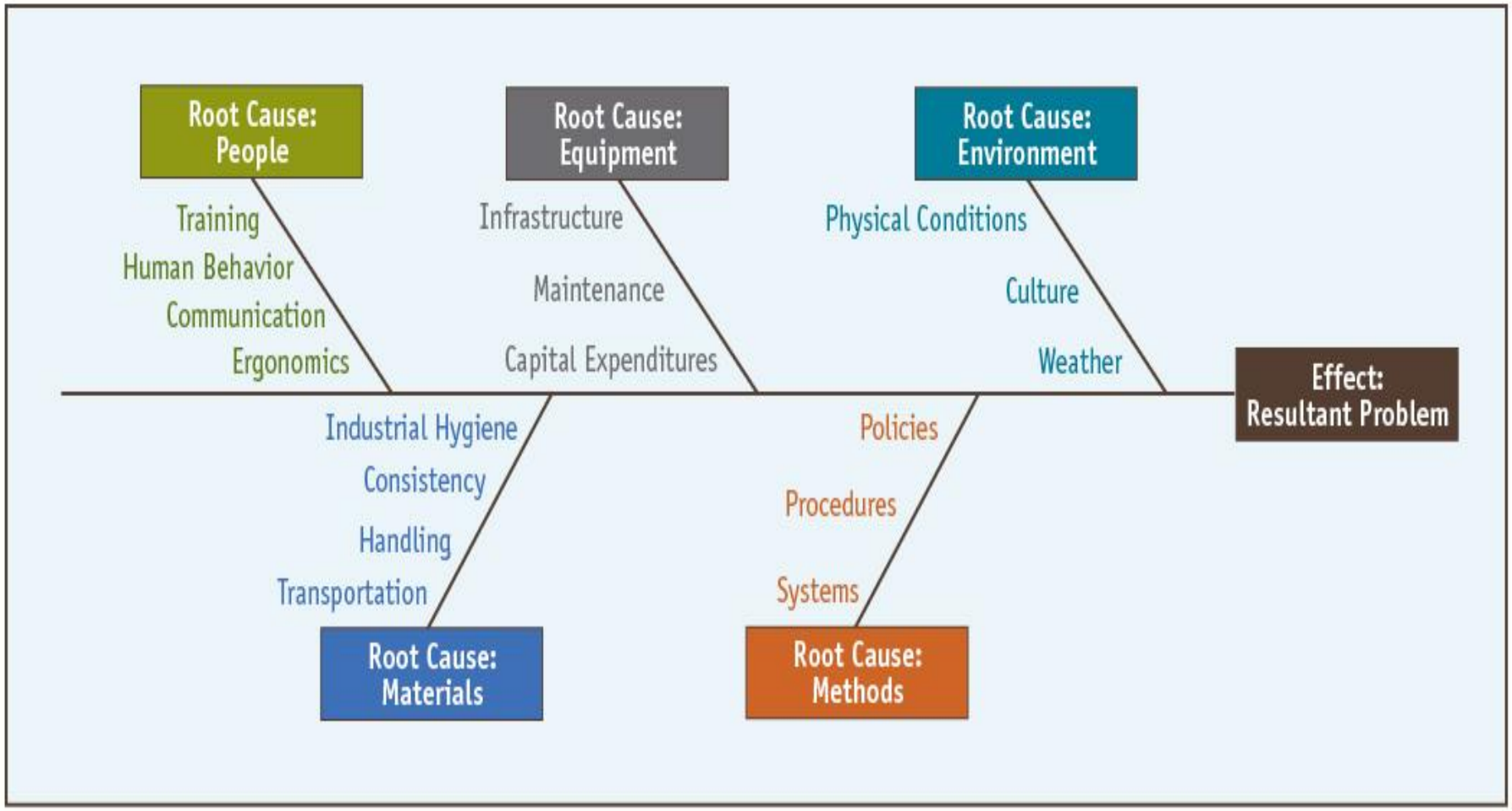
Node: _____ Process Parameter: _____

Guide	Deviation	Consequence	Causes	Suggested Action

Ishikawa Fishbone Diagram



Auditing Cause-and-Effect Diagram



Example of a fishbone diagram

Kepner-Tragoe Trouble Shooting



Key Trouble Shooting Process Steps

Determine responsibilities
Define the next steps
List Concerns
Determine priorities
Separate and clarify situation

Situation Analysis

Problem Analysis	Decision Analysis	Potential Problem Analysis
Define problem	State decision	Identify potential problems
Specify problem	Define and classify objectives	Identify causes
Identify differences and changes	Weigh objectives	Take preventive action
Formulate causes	Generate alternatives	Plan contingent action
Test causes against the facts	Evaluate alternatives	Set triggers
Prove true cause	Assess risks	
	Make decision	

Comparison of requirements – Class A & B



Table 1: Class 100 Monitoring Table (Max. values are given).

COUNTRY DOCUMENT	U.S. FS 209E	U.S. USP <1116>	EU (at rest, static)	EU (operational, dynamic)	EU (operational, dynamic)	ISO 14644-1
CLASSIFICATION	M 3.5 (100)	M 3.5	A and B	A	B	5
FREQUENCY	Not stated	Each Operating Shift	Not stated	Frequent, using a variety of methods	Frequent, using a variety of methods	Not stated
TOTAL PARTICULATE COUNT	3,500/m^3 (> 0.5 µm) 100/cu. ft.	100/cu. ft. (> 0.5 µm)	3,500/m^3 (equal to or above 0.5 µm) 0/m^3 (> 5 µm)	3,500/m^3 (equal to or above 0.5 µm) 0/m^3 (> 5 µm)	350,000/m^3 (equal to or above 0.5 µm) 2,000/m^3 (> 5 µm)	3,520/m^3 (equal to or above 0.5 µm) 29/m^3 (5.0 µm)
AIRBORNE VIABLES	Not stated	0.1 CFU per cu. ft.	Not stated	<1 CFU/m^3 Settle plate 90 mm <1 CFU/4 hours	<10 CFU/m^3 Settle plate 90 mm 5 CFU/4 hours	Not stated
SURFACE VIABLES (except floors)	Not stated	3 CFU per contact plate*	Not stated	<1 CFU per contact plate (no distinction for floors and walls)	5 CFU per contact plate (no distinction for floors and walls)	Not stated
SURFACE VIABLES (floors)	Not stated	3 CFU per contact plate	Not stated	<1 CFU per contact plate (no distinction for floors and walls)	5 CFU per contact plate (no distinction for floors and walls)	Not stated
PERSONNEL GOWN	Not stated	5 CFU per contact plate	Not stated	Not stated	Not stated	Not stated
PERSONNEL GLOVES	Not stated	3 CFU per contact plate	Not stated	Glove print 5 fingers <1 CFU per glove	Glove print 5 fingers 5 CFU per glove	Not stated
AIR VELOCITY UNIDIRECTIONAL	Not stated	Not stated	0.45 m/s ± 20%	0.45 m/s ± 20%	Not appropriate	Not stated
FREQUENCY OF ΔP MONITORING	Not stated	Each shift	Not stated	Continuous	Continuous	Not stated

ΔP= Differential pressure

*Contact plate areas vary from 24–30 cm^2

Comparison of requirements – Class C

Table 2: Class 10,000 Monitoring Table (Max. values are given).

COUNTRY DOCUMENT	U.S. FS 209E	U.S. USP <1116>	EU (at rest, static)	EU (operational, dynamic)	ISO 14644-1
CLASSIFICATION	M 5.5 (10,000)	M 5.5	C	C	7
FREQUENCY	Not stated	Each Operating Shift	Not stated	Not stated	Not stated
TOTAL PARTICULATE COUNT	353,000/m^3 (≥ 0.5 µm) 10,000/cu. ft.	10,000/cu. ft. (≥ 0.5 µm)	350,000/m^3 (equal to or above 0.5 µm) 2,000/m^3 (>5 µm)	3,500,000/m^3 (equal to or above 0.5 µm) 20,000/m^3 (>5 µm)	352,000/m^3 (equal to or above 0.5 µm) 2930/m^3 (>5 µm)
AIRBORNE VIABLES	Not stated	0.5 CFU per cu. ft.	Not stated	100 CFU/m^3 Settle plate 90 mm 50 CFU/4 hours	Not stated
SURFACE VIABLES (except floors)	Not stated	5 CFU per contact plate*	Not stated	25 CFU per contact plate	Not stated
SURFACE VIABLES (floors)	Not stated	10 CFU per contact plate	Not stated	Not stated	Not stated
PERSONNEL GOWN	Not stated	20 CFU per contact plate	Not stated	Not stated	Not stated
PERSONNEL GLOVES	Not stated	10 CFU per contact plate	Not stated	Not stated	Not stated
FREQUENCY OF ΔP MONITORING	Not stated	Each shift[1] 2x/week[2]	Not stated	Not stated	Not stated

ΔP= Differential pressure

*Contact plate areas vary from 24–30 cm^2

Comparison of requirements – Class D



Table 3: Class 100,000 Monitoring Table (Max. values are given).

COUNTRY DOCUMENT	U.S. FS 209E	U.S. USP <1116>	EU (at rest, static)	EU (operational, dynamic)	ISO 14644-1
CLASSIFICATION	M 6.5 (100,000)	M 6.5	D	D	8
FREQUENCY	Not stated	Twice/week	Not stated	Not stated	Not stated
TOTAL PARTICULATE COUNT	3,530,000/m^3 (≥ 0.5 µm) 100,000/cu. ft.	100,000/cu. ft. (≥ 0.5 µm)	3,500,000/m^3 (equal to or above 0.5 µm) 20,000/m^3 (>5 µm)	Not defined	3,520,000/m^3 (equal to or above 0.5 µm) 29,300/m^3 (>5 µm)
AIRBORNE VIABLES	Not stated	2.5 CFU per cu. ft.	Not stated	200 CFU/m^3 Settle plate 90 mm 100 CFU/4 hours	Not stated
SURFACE VIABLES (except floors)	Not stated	Not stated	Not stated	50 CFU per contact plate	Not stated
SURFACE VIABLES (floors)	Not stated	Not stated	Not stated	Not stated	Not stated
FREQUENCY OF ΔP MONITORING	Not stated	Weekly	Not stated	Not stated	Not stated

ΔP= Differential pressure

*Contact plate areas vary from 24–30 cm^2

Identification of significant excursions

Identification of organisms recovered.

- **Identify isolates from critical areas at a minimum.**
- **Identify isolates from noncritical areas to gain a knowledge of the facility flora.**
- **Not all isolates will be required to be identified to species level.**
- **Characterization may include morphology, Gram stain, genus for moulds and speciation.**
- **Identification to species level assists in determining root cause or source of contamination.**
- **Why did I not obtain an identification match?**
- **Objectionable organisms: How is this determined?**

VITEK® MS

VITEK® MS is an automated mass spectrometry microbial identification system that uses Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) technology.

Proteins are detected with a sensor to create a spectrum that represents the protein makeup of each sample.

Provides a percentage match with low, medium or high confidence level.

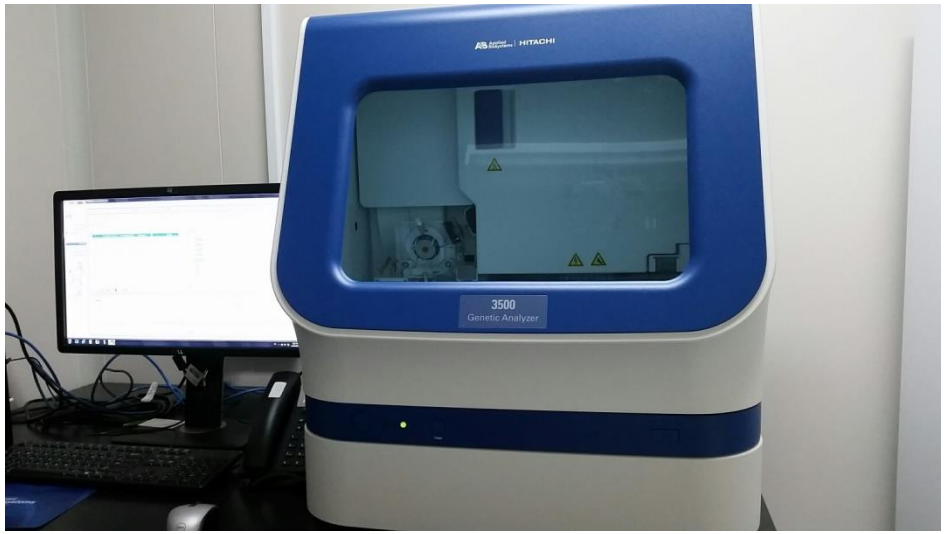
Suitable for bacterial and yeast identification to species level.

RiboPrinter®

The DuPont™ RiboPrinter® System automates restriction fragment length polymorphism (RFLP) analysis and targets the rRNA-coding region of the bacterial genome.
Only suitable for bacterial ID's.

Highly similar patterns are assigned to specific Ribogroups. Contaminants can be compared to environmental isolates, or those from other samples, both current and historical. Additionally changes in the predominant strain over time can be observed allowing for changes in cleaning and disinfection protocols.

MicroSEQ®



After sequencing the rRNA gene, the MicroSEQ® system automatically compares the results to validated sequences in the MicroSEQ® microbial libraries. The results are ranked according to genetic distance of the reference sequences to the sample and displayed on the system monitor along with a phylogenetic tree.

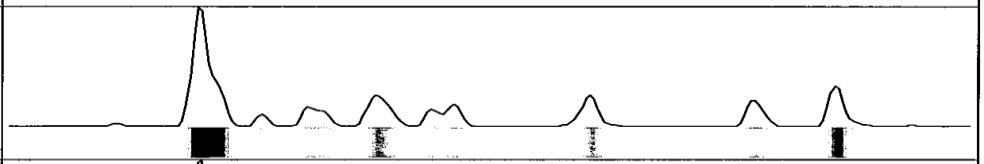
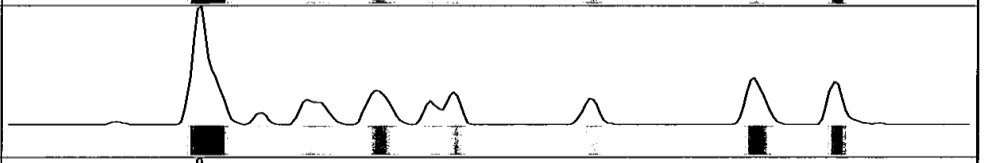
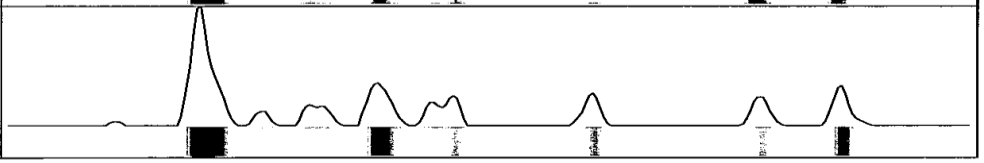
The system includes the largest fully validated bacterial and fungal libraries. The bacterial library includes over 2000 species and for fungal species includes over 1100 entries.

MicroSEQ®

MicroSEQ® vs MALDI-TOF system

- More accurate
- Able to identify bacteria, yeast and moulds.
- A single, standardize procedure for both bacterial and fungal isolate
- Routine bacterial identification is performed using the first 500 bp of the rDNA.

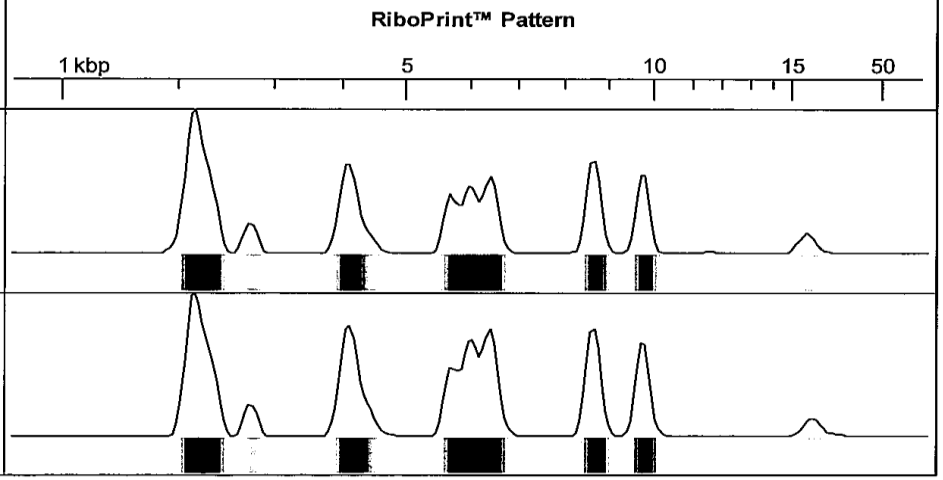
Environmental Excursion Investigation 1

	RiboGroup	Number	Label	DuPont ID Label	RiboPrint™ Pattern (1 kbp, 5, 10, 15, 50)
1	ECORI 216-672-S-3	216-676-S-4	[redacted]		
2	ECORI 216-672-S-3	216-676-S-7	[redacted]	Bacillus cohnii	
3	ECORI 216-672-S-3	216-672-S-3	[redacted]	Bacillus cohnii	

Sterile manufacturer investigated product contamination.
Identification by Vitek MS found product contaminant, settle plate and personnel plate to be *Bacillus cohnii*.
Riboprinter confirmed all three isolates were a genetic strain match and likely from the same source.

Environmental Excursion Investigation 2

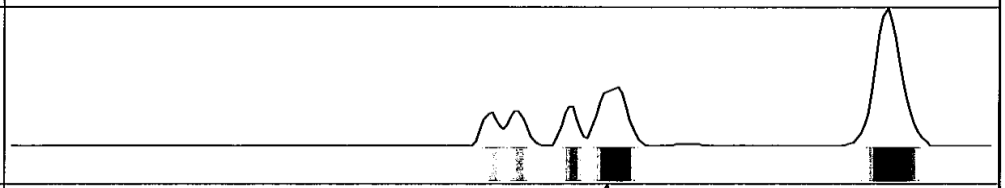
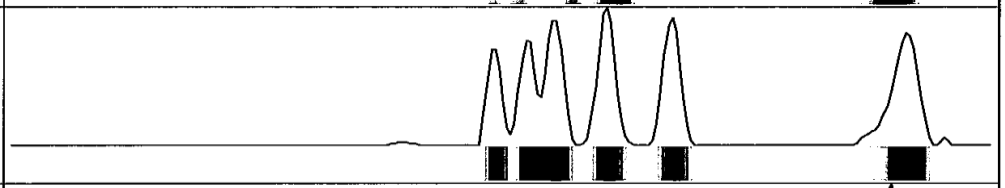
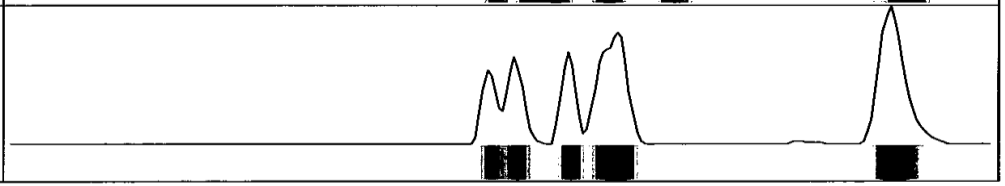
	RiboGroup	Number	Label	DuPont ID Label	RiboPrint™ Pattern
1	ECORI 216-127-S-2	216-127-S-8	[redacted]	Bacillus pumilus	
2	ECORI 216-127-S-2	216-127-S-2	Settle Plate	Bacillus pumilus	



Contract manufacturer environmental settle plate exceeding alert limits.

This resulted in one product batch failure. Comparison of the isolate from the settle plate and product found a genetic strain match.

Environmental Excursion Investigation 3

	RiboGroup	Number	Label	DuPont ID Label	RiboPrint™ Pattern
1	ECORI 216-307-S-2	216-307-S-2	[redacted]	Pseudomonas fluorescens	
2	ECORI 216-95-S-4	216-281-S-7	[redacted]	Pseudomonas fluorescens	
3	ECORI 216-307-S-2	216-307-S-3	[redacted]	Pseudomonas fluorescens	

Manufacturer identified source of product contamination from water system contaminated with *Pseudomonas fluorescens*.
Isolates were from product, swabs and purified water system.

Use of MicroSEQ® in an investigation

Identification of isolate by Vitek MS was unable to be identified.

Identification of isolate by Riboprinter found identification to species level was unable to be determined. Options for *Bacillus thuringiensis* and *Bacillus cereus*.

Identification of isolate by MicroSEQ® found the isolate to be *Bacillus thuringiensis*.

***Bacillus cereus* listed as an objectionable organism resulting in batch rejection. *Bacillus thuringiensis* considered low risk for pre-sterilisation batches.**

Corrective Actions of significant excursions



Additional environmental monitoring.

- **Sampled during normal operations.**
- **Critical zone monitoring may be increased for ISO 5 areas.**
- **Increased surface monitoring such as contact plates and swabs should be performed at the end of production operations.**
- **Gloves and gowns should be tested at the end of production operations.**
- **Testing effectiveness of sanitization programs may include infrequent sampling of walls, floors, airlocks and around doors.**
- **Recommended sampling of active air, settle plates, contact or swabs and glove/garment.**
- **Increase frequency of water monitoring; especially if pseudomonads have been previously found in the system.**

Corrective Actions of significant excursions

Retraining of personnel.

- **Collection of samples by personnel should be undertaken in a consistent manner.**
- **Interview and observe personnel during production for potential causes.**
- **Requalify personnel.**
- **Review gowning procedures and evaluate initial training of personnel.**
- **Evaluate operator impact upon product. Review sterility test data.**
- **Review preparation of disinfectants and expiry dates.**

Corrective Actions of significant excursions



Sampling methods and sites evaluation

- **Active air: near open containers, and work area.**
- **Compressed air: furthest from compressor.**
- **Water: point of use, consistent with manufacturing practices.**
- **Surface: filling line, control panels, door handles, walls, floors.**
- **Operator on filling line: fingerprints and gowns.**
- **LAF or BSC: high activity areas.**

Is your environmental monitoring program suitable?

Routine monitoring frequency may differ to batch related in-process monitoring.

Alert and action limits where not defined by guidelines may be based on historical data and periodically reviewed.

Methods may include cut off value, normal distribution approach and non-parametric tolerance limits approach.

Risk Mitigation

- Environmental controls during production
- Rotation of disinfectants
- Disinfectant qualification studies - these should be reviewed in line with EM trending data to determine ongoing suitability
- Gowning procedures in sterile manufacturing
- Personnel training and hygiene training

Summary

Identification of isolates obtained by environmental monitoring is a useful tool in the investigation of the source of contamination and assessment of risk to a product.

Identification tools used will be determined by the severity of risk.

Root causes of environmental excursions may never be determined, however, corrective actions and risk mitigation will reduce the occurrence of product batch rejections.

Risk mitigation may include disinfectant rotation, increased environmental monitoring and increased personnel monitoring.

References

1. Environmental monitoring: A comprehensive handbook vol 7, Jeanne Moldenhauer 2015.

2. USP General Chapter 1116 Microbiological control and monitoring of aseptic processing environments.

3. PDA Technical report no. 13 revised Fundamentals of an environmental monitoring program.

4. ICH 2006 Guidance for industry: Q9 Quality Risk Management.

5. ISO 14644 Cleanrooms and Associated Controlled Environments.



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Thank you

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