Environmental Monitoring: Key Elements for Success

Kim Sobien, MBA

Senior Consultant – Microbiology

ValSource

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Introduction

Kim Sobien is a Microbiology Senior Consultant with ValSource, Inc. Her pharmaceutical industry career encompasses a breadth of quality, compliance, and technical experience with injectable pharmaceutical products. She has expertise in microbiology, sterility assurance, contamination control, investigations, capability building, and inspection readiness.

Kim has a BS in Microbiology from the University of Wisconsin–La Crosse and a Master of Business (MBA) degree with an emphasis in Global Management from the University of Phoenix. She is an active member of the Parenteral Drug Association (PDA) and the PDA Southeast Chapter, Co-Lead for the PDA EM/Microbiology Interest group, and a past co-chair and committee member for the PDA Pharmaceutical Microbiology Conference. She also participates on several ASTM E55.06 “Microbial and Sterility Assurance” subcommittees.

ksobien@valsource.com

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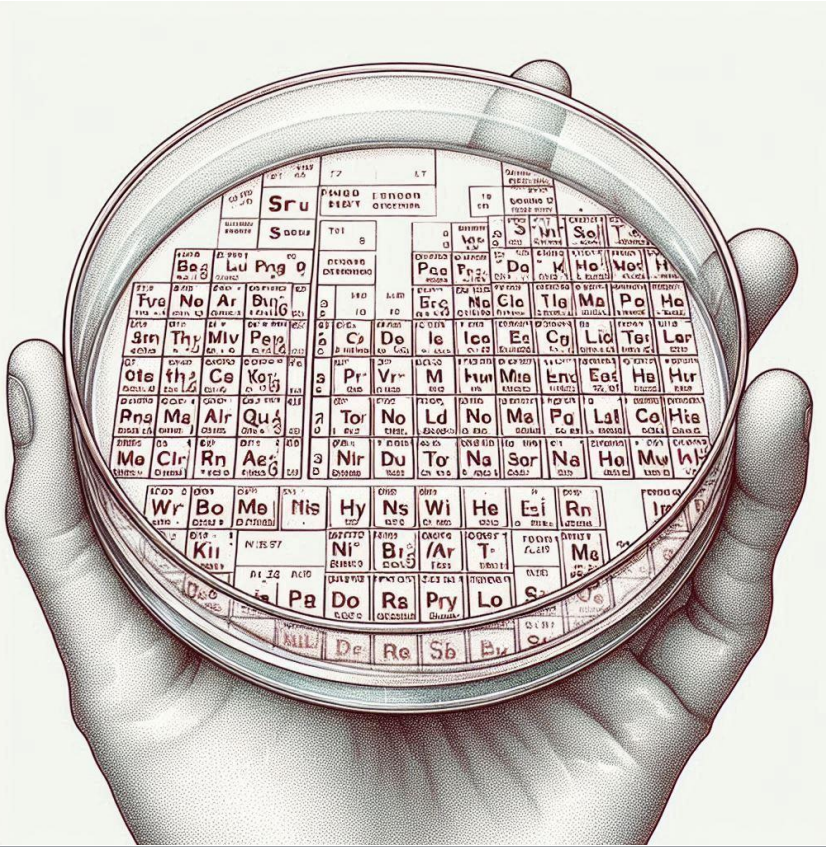
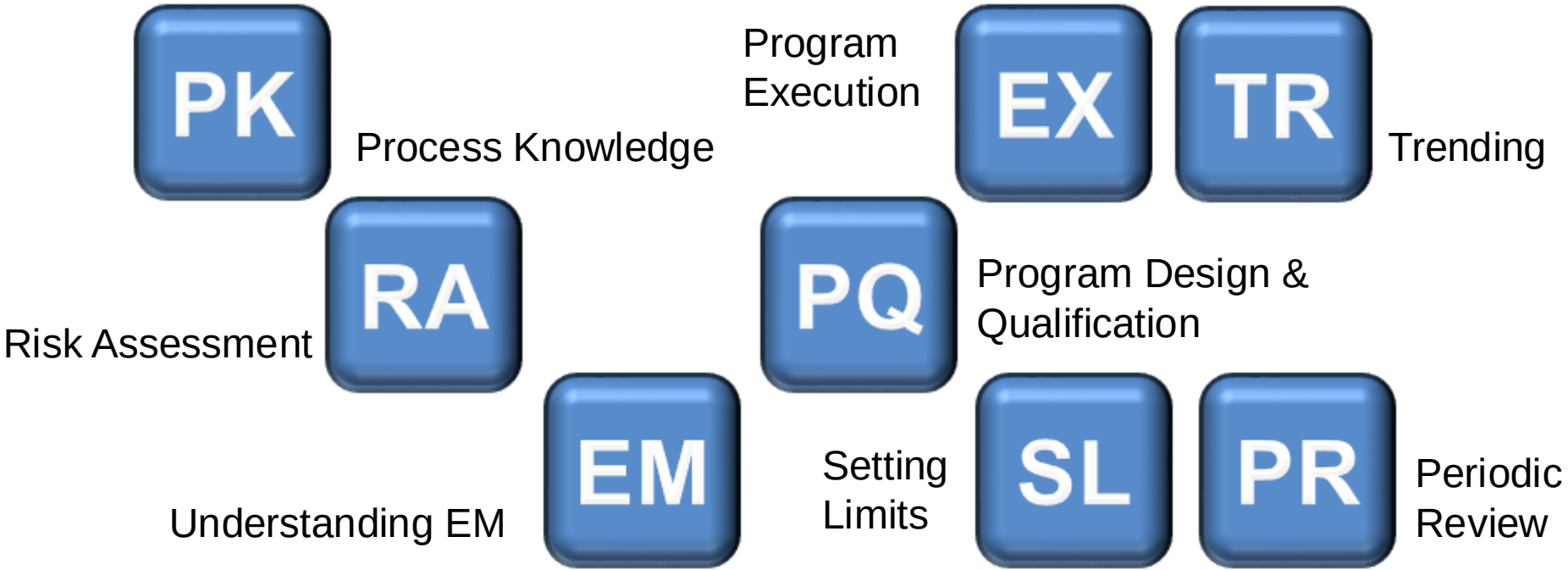
With thanks to Paula Peacos

Topics

- EM Process Knowledge
- EM Risk Assessment
- Understanding EM
- EM Program Design & Qualification
- EM Site Selection
- EM Program Execution
- Setting Appropriate Limits
- EM Trending
- Periodic Review



Elements of an Environmental Monitoring Program



Knowing your Process

- Microbiologists need to spend time on the manufacturing floor and observe
  - How procedures are executed
  - Look for opportunities for contaminants to enter the process stream.
  - Talk to line operators -what do they see?
- Critical to ensure the program is designed and implemented correctly

TR90; PDA

Risk Assessment

- An EM program should be based on an in-depth, end to end process risk assessment.
  - Required per new Annex 1
- Commonly used risk assessment tools include:
  - Failure Mode Evaluation and Analysis (FMEA)
  - Hazard Analysis and Critical Control Points (HACCP)
  - Preliminary Hazard Analysis (PHA), Fault Tree Analysis (FTA) etc. may be more applicable to early phase clinical processes
- The selected tool needs to be justified as suitable for intended use
  - ICH Q9R1 (2023) “Quality Risk Management”

Risk Assessment

The risk assessment should include, at minimum:

- An actual walkthrough of the process as it will be executed in the facility (e.g., Gemba (“the actual place”)
- A step-by-step assessment of the process and supporting procedures
- Identification of existing and potential risks
- Evaluation of risks for likelihood, severity, and detection

Risk Assessment

Method

- HACCP is a preferred method for EM program development.
  - Identifies critical control points in the process
- Assesses risk and control strategies around each critical control point
- Provide for elimination or mitigation of identified risks

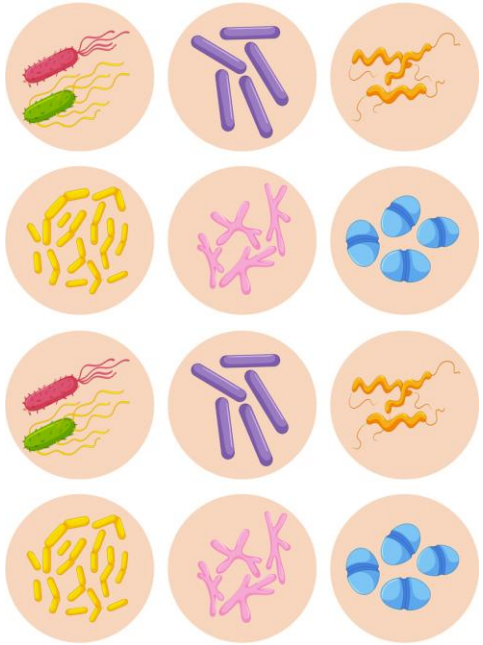
Team

- It is critical to have the correct multi-disciplinary subject matter experts (SMEs) on the team, and that they fully participate.
- Consider all stakeholders for EM
- Need a qualified facilitator

Risk Assessment

- The risk assessment must not :
  - Improperly justify or ignore risks
  - Avoid changes or necessary mitigations
  - Justify bad or improper practices
  - Have a pre-determined outcome
- Business concerns should never drive the assessment.
- Risk assessments should always reflect the current state of the process.

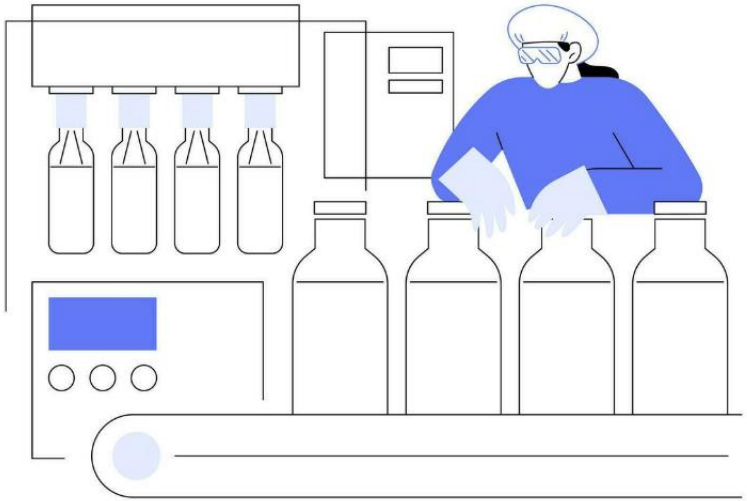
Understanding Environmental Monitoring



- EM is a tool.
- Used to collect data in-situ which allows us to assess the overall state of microbial control in the facility.
- The microbial population in any given area or facility is dynamic.
- Many samples collected over time can provide information on how much variability and fluctuation there are between samples.
- An EM program is a “living program”.

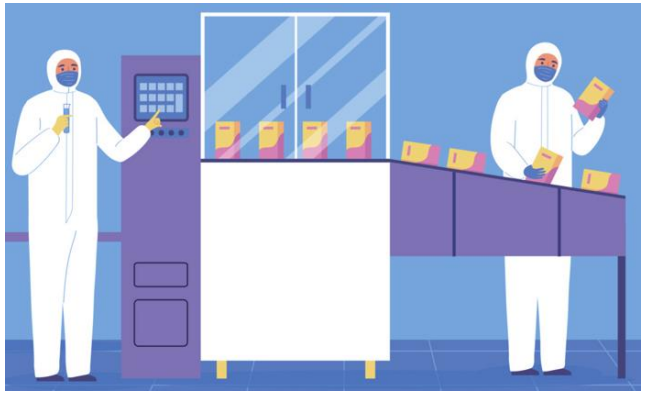
Understanding Environmental Monitoring

- Any classified area must be monitored at a regular frequency to ensure that it is still meeting the requirements of its dedicated classification.
- Processes must also be monitored during execution.
- Monitoring should be performed at the height of activity (worst-case) and after any significant interventions.



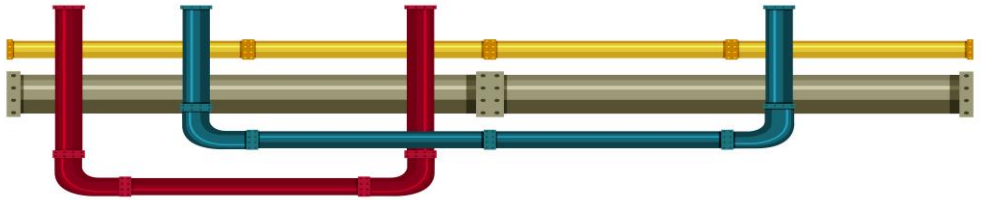
Understanding Environmental Monitoring EM During Set-Up Activities: New Annex 1

- Continuous EM during set-up is expected for both viable air and total particulate in Grade A.
  - Personnel EM is also expected where applicable.
  - Contamination introduced during set-up has potential to be transferred downstream during processing.



- Consider doing this even if Annex 1 does not apply

Understanding Environmental Monitoring EM of Utilities



- Compressed Air & Gases
  - Need to be monitored to the requirements of the area they will be used in
  - Viable and nonviable particulates, oils & hydrocarbons, dewpoint
  - Monitor points of use and the end of the line in particular
  - Frequency should be based on risk (quarterly is common).
- Pharmaceutical Waters
  - Frequency of monitoring should be sufficient to catch any system contamination in the early stages
    - Consider the potential for biofilm

EM Program Design and Qualification

- It is critical to understand the specific regulatory agency requirements and expectations for your process.
- Classify and qualify the area to the standard the process will be conducted under.
- Related informative documents
  - Parenteral Drug Association Technical Report No. 13. (2021) “Fundamentals of an Environmental Monitoring Program (Revised Edition)”
  - USP <1115> “Bioburden Control of Nonsterile Drug Substances and Products”
  - USP <1116> “Microbiological Evaluation of Clean Rooms and Other Controlled Environments

EM Performance Qualification (EMPQ)

Be ready to start EMPQ

- Avoid common mistakes:
  - Rush for business pressure
  - Oversampling out of fear/lack of understanding
  - Lack of trained staff to perform sampling
  - Lack of process knowledge

During EMPQ:

- Collect EM Samples during static and dynamic conditions
- Number of runs: suggested is 3 static and 3 dynamic
- Ensure the plan for sample collection is based on risk

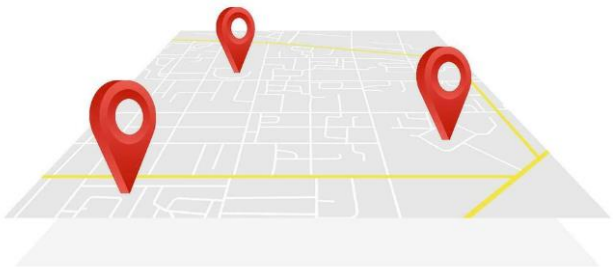
EM Performance Qualification (EMPQ)

After sampling is completed:

- Complete EMPQ reports
- Begin routine sampling with same sample locations
    - Add clause to EMPQ that sampling plan will continue as EM Start Up
- Make EM Program SOPs official
- Gain knowledge from data
- Cut back for routine EM once confident in results

Selecting EM Sampling Locations

- ISO 14644-1 stipulates dividing the cleanroom or clean zone into a grid pattern with sections of equal area.
- Select within each grid section a sampling location that is representative of that section based on risk.

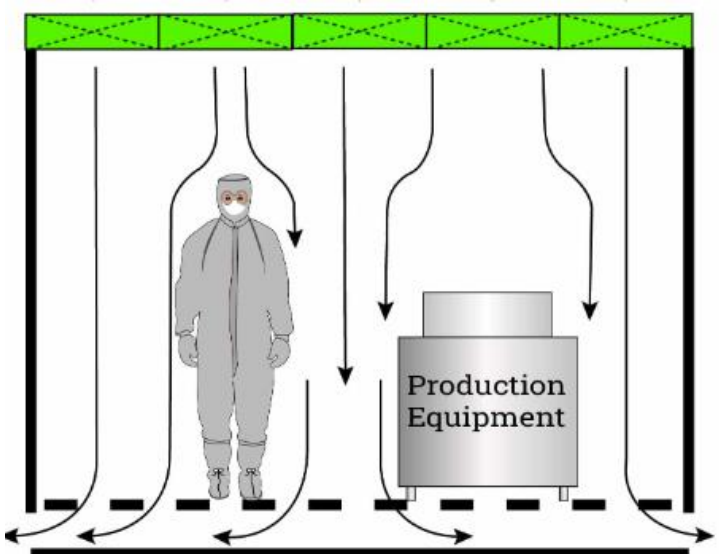


- Additional sampling locations may be added for locations considered to be critical.
- Leverage the process risk assessment.

Selecting EM Sampling Locations

- Human presence is the main source of contamination.
- Contamination is spread most easily by airborne means and direct contact.
- The EM program should be tailored to:
  - Facility design/floorplan
  - Area classification
  - Personnel and material flow patterns and traffic levels
  - Processes being conducted (e.g., open or closed)
  - Product being manufacturing
  - Identified risks from your process risk assessment

Selecting EM Sampling Locations



- Site selection should also consider the following:
  - Proximity to operator activity (e.g., touchscreens, glove ports, computer stations)
  - Proximity to areas of potential air turbulence (e.g., doors, return vents, moving machine parts, vibration, personnel flows etc.)
  - Consider also the physical ease/safety of sampling.
  - Sampling height (for both viable and nonviable air sampling)
  - Areas that are difficult to access or clean or that could gather particulates
- Sampling must not unduly increase risk to the process or product or impede operator's ability to correctly execute tasks.
- Visual Air Studies (smoke studies) should be leveraged to identify areas of turbulence.

EM Program Execution - Procedures

Procedural issues are often overlooked.

- Are they too long?
- Are the instructions clear and executable as written?
- Are they specific enough, or are decisions or interpretations left up to the operator?
- Does an operator need multiple procedures to execute a single task?
- Could there be a language barrier potentially impacting correct understanding?
- Who performs periodic review? Author or user?

EM – Setting Appropriate Limits

- Alert levels and action limits must be appropriate for the specific process being conducted and/or the intended usage of a classified area.
- These should be set using appropriate statistical methods.
  - Parenteral Drug Association Technical Report No. 13. (2021) “Fundamentals of an Environmental Monitoring Program (Revised Edition)”

EM – Setting Appropriate Limits

- Appropriateness of action limits must be scientifically justified.
  - Action limits, and alert levels, when set appropriately, should be exceeded occasionally as they are intended to provide an early warning to a potentially catastrophic failure.
  - In some instances, the actual operating levels are much lower than the recommended industry action level.
  - Therefore, action limits more stringent than the maximum limits listed in the guidance may need to be implemented. Applies to Grades A-D.

EM - Trending

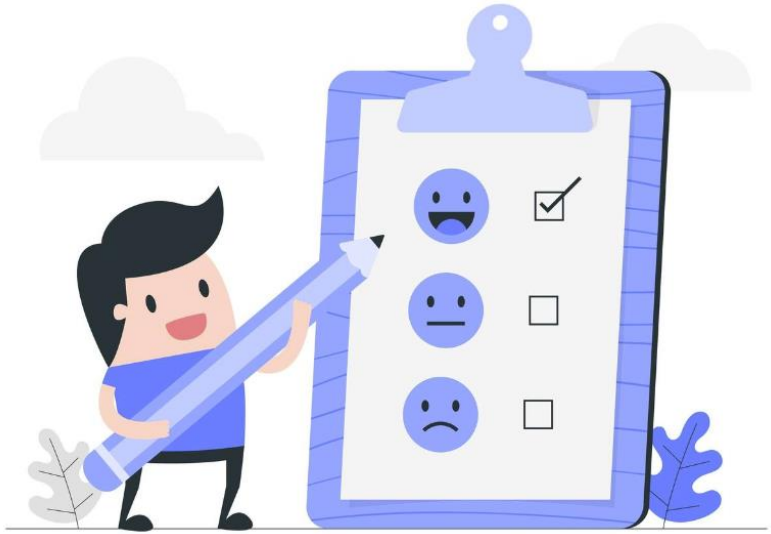
Good trending involves the thoughtful organization and critical analysis of the collected EM data.

- What do your results *mean?*
- *Why* are you seeing a trend?
- Amount and depth of organism identification is a critical component.
  - New Annex 1 speaks to this, particularly for Grade C & D areas.

EM Program Execution - Training

- All EM samplers should have training in basic, practical microbiology.
- Training must ensure proper and consistent execution of EM sampling procedures and use of sampling equipment.
  - Training should include a demonstration of proficiency.
- Conduct “awareness trainings” for specific events, such as excessive gowning recoveries, etc.
- Simple retraining is not always the answer to an EM deviation

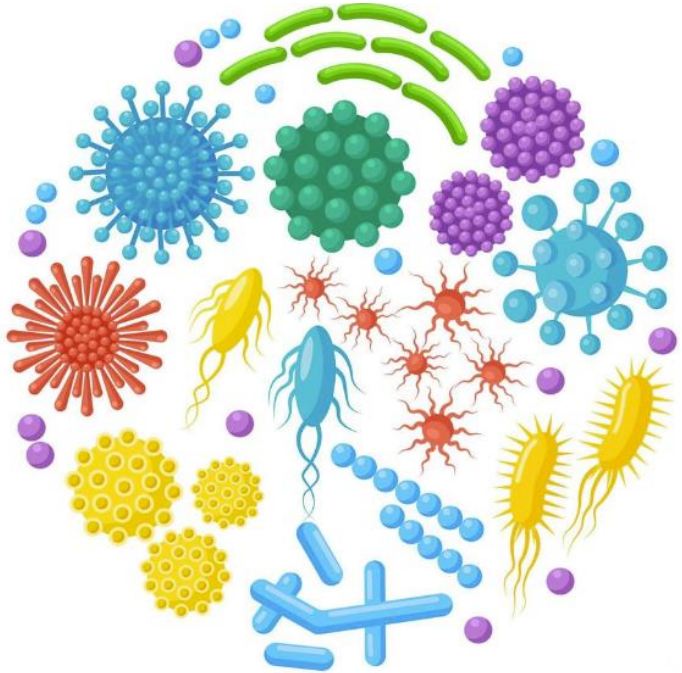
EM – Periodic Review



- The EM program, like the trending program, procedures, risk assessments and CCS, should be subject to periodic review.
  - Have your needs changed?
  - Is the program delivering the information you require?
  - Have there been significant changes to your processes, procedures or facility in general?
  - Have there been changes to your process or EM risk assessment?
  - Have you seen a shift in microbial flora composition?
- Annual review is common, but the program should be updated as needed.

Summary

- Designing and implementing a sound and robust EM program is not a simple or straightforward exercise.
- Understanding your process and facility will help to create a robust EM program.
- A well-designed EM and trending program is a major pillar of the facility contamination control strategy.
- Stronger contamination control results in increased process integrity, better product quality and increased patient safety.



ksobien@valsource.com

https://www.linkedin.com/in/kimsobien/