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# **2020 Revision of TR #13 – Fundamentals of an Environmental Monitoring Program**

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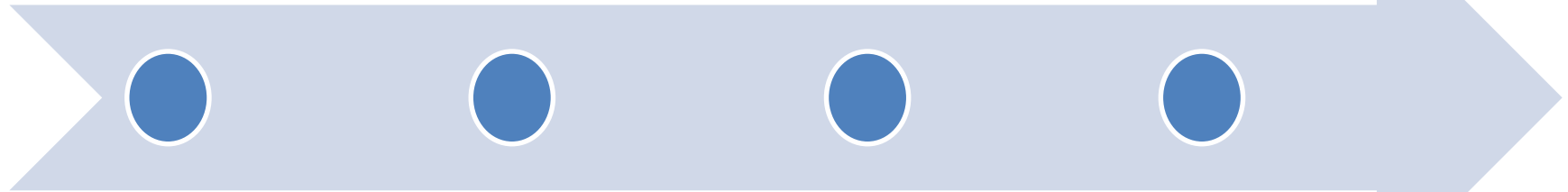
# TR #13 – Revision History



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**Publication of TR  
#13 – PDA  
Journal 1990 (1<sup>st</sup>  
Supplement)**

**Second Revision of  
TR #13 – 2014**



**First Revision of TR #13  
– PDA Journal 2001  
(5<sup>th</sup> Supplement)**

**Third/Current  
Revision of TR #13 –  
2020**

# Notable Expansion/Inclusion in 2020 Revision

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- ✓ EM in support of a Contamination Control Strategy (CCS)
- ✓ Use of QRM principles to establish a robust EM program.
- ✓ Data collection, management and integrity in relation to EM.
- ✓ Prerequisites to an effective EM program.
- ✓ Qualifying controlled environments and maintaining them in a qualified state.
- ✓ RMM selection, implementation and validation in relation to the EM program.

# TR #13 Responding to EU Annex 1 Draft:

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- General Housekeeping (cleaning up & elbow grease)
- Contamination Control Concept
  - Cleaning cleans
  - Disinfection disinfects
- QRM Principle
  - Bringing Annex 1 in line with principles in ICH Q9 & Q10
- Introduced New Technologies
  - Manufacturers need to keep up with current technology
  - Single-Use, closed, systems
  - Disposable systems
  - Innovation!
- **Get the Microbiologist out of the Lab!**

# Contamination Control Strategy



# CCS in Support of EM Program

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- Sound facility design, including barrier systems (i.e., isolators and RABS), operation and maintenance
- Established documentation systems
- Qualified sanitization, disinfection, and decontamination procedures
- Reliable process controls
- Good housekeeping practices
- Effective area access controls
- Consistent sample collection and analysis
- Effective training, certification or qualification, and evaluation programs
- Quality assurance of materials, facilities, and equipment



## EM - Risk Assessment

# Initiation of QRM for EM

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- Define scope & objective including risk question or problem statement
- Select Risk Assessment tool and risk-ranking criteria
- Assign facilitator and select multidisciplinary team
- Process mapping should be conducted on the shop floor using room layouts
  - Indicate equipment locations, people flow, material flow, and waste flow in the facility
  - During this process mock-up, the team will identify potential hazards within the areas under assessment.
- Based on the risk scoring, sampling locations are determined for performing the EMPQ and, afterwards, for conducting the routine monitoring.



# PtC for Identification of Risk in your EM Program



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## Sampling locations should be chosen based on:

- The criticality of the process being performed in the room or area
- Product exposure to the environment and susceptibility to microbial contamination
- Locations of potential ingress from supporting areas or adjacent non-classified areas
- Sites shown to be appropriately placed to detect a problem in the area.

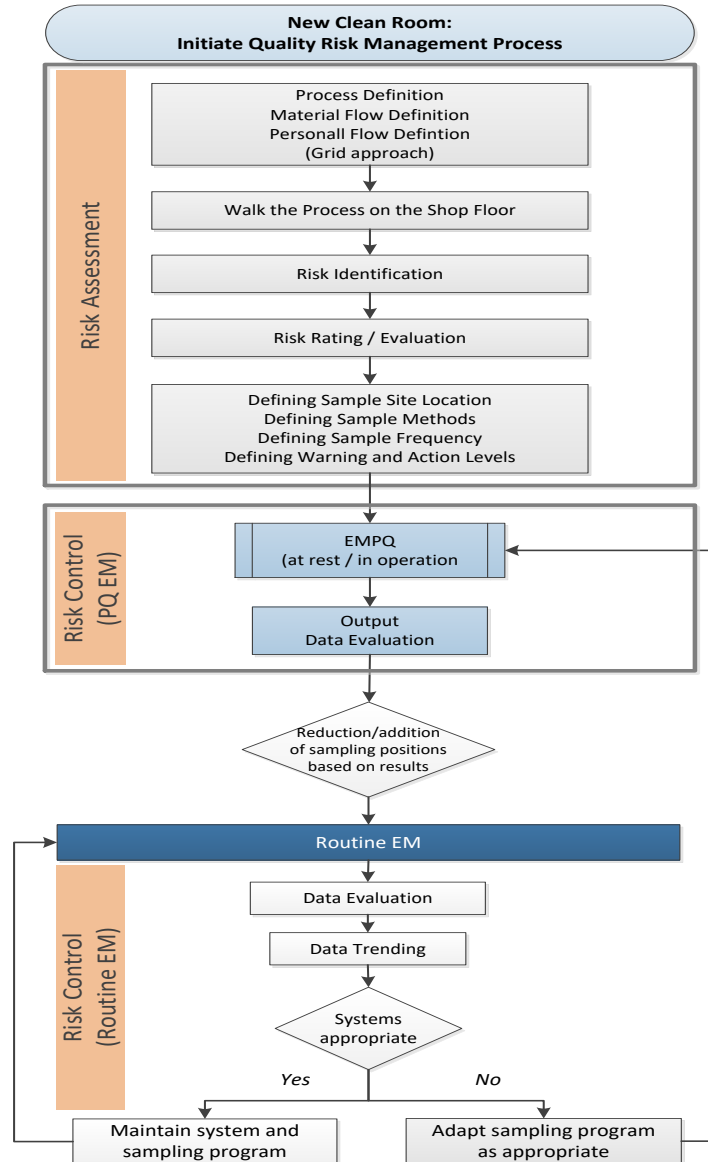
## Example factors to consider during initial walkthrough:

- Adherence to industry and regulatory guidelines
- Sites and locations where microbial contamination would most likely have an adverse effect on product quality and, therefore, have the highest risk
- Historical data, from similar facilities, if applicable
- Airflow visualization studies, that is, smoke studies; areas of concern, such as turbulences and eddies, should be addressed through increased airflow or facility redesign.

# EM Risk Assessment – Lifecycle Approach



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# Data



# Data Management Approach

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- Routine review and analysis of EM data for trends at an appropriate frequency
  - Interpretation of process stability and assess overall environmental control performance.
- Management must be kept abreast of trends and the subsequent state of operations within facilities
  - Review of quarterly and annual monitoring reports.
- Based on the large number of samples tested by a given facility, a computer-based data-tracking system may be essential.
  - Before implementation, all database applications used should be validated or qualified for specific software applications.

# Data Integrity Considerations for EM

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- Integrity of the sampling site data with full reconciliation of sampling locations
- EM data must be documented on controlled worksheets or in a validated computer system.
- Employees must adhere to the established site documentation requirement and will not discard or destroy raw data or original records
- Have in place a robust plate reading process, such as appropriate lighting and/or magnification (Quebec Colony Counter) and a thorough training of the technicians.
- Verification by a second person should be considered to confirm the integrity of the data set being reviewed in some instances, such as EM excursions in Grade A areas.
  - QRM principles can aid in the determination of whether a secondary verification is required for a specific assay.
  - Automated systems for plate readouts and data storage can eliminate bias and the need to perform a second verification.



- Routine data are aligned into a source in a consistent record format.
- Records must be signed and verified by the appropriate person, depending on the type of system used.
- Some alternative microbiological methods can use measurements other than CFUs
  - E.g. ATP relative light units (RLU), and fluorescent cells
- Manual data entry or image scanner system can be used to populate tables.
- Regardless of the type of system used, data integrity must be verified prior to data collection and analysis.



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*BALDWIN*



“The patient in the next bed is highly infectious. Thank God for these curtains.”

**EM Prerequisites**

# EM Prerequisite Examples

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1. Good facility and equipment design
2. Selection of culture media, vendor audit and qualification and media release (including shelf life)
3. Selection and culture maintenance of microorganisms for growth promotion
4. EM sample hold time and incubation strategy/validation
5. EM monitoring equipment qualification
6. Analyst training and qualification
7. IQ/OQ of HVAC/Building automation system and certification of HEPA filters
8. Airflow pattern measurements (at-rest and in-operation)
9. PQ of all critical room parameters (e.g., temperature, air velocity, differential pressure, humidity)
10. Disinfection of the area and baseline sampling



# Qualification of Cleanrooms



# Qualification of Cleanrooms

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- Initial particle counting performed at-rest should be supplemented by an at-rest qualification using viable tests.
  - These viable sample locations might focus on more specific aspects related to the actual design of the cleanroom and can be documented/justified as part of the EM risk assessment.
- Initial qualification is normally performed by simulating activities, ensuring that at a certain stage the maximum number of personnel and the worst-case level of activities are covered.
  - Need to be covered during one or more PQ runs.
  - Can be performed during media fill (**can be a business risk**) or activities can be simulated
  - PQ typically consists of three consecutive runs during routine (in-operation) conditions.

# Qualification of Cleanrooms (*continued*)

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- The action limits for qualification should correspond to the action limits for routine monitoring.
- Following the PQ, the routine sampling program should be risk-based, and some sampling locations used from the PQ may be eliminated.
- For new areas, the IQ should be performed in a prospective mode.
- For existing facilities that require a repeat of the initial qualification, the requalification can be performed in concurrence with routine production activities if historical data of existing rooms are shown to be in a good state of control.
  - Release of product should await final release of the cleanroom qualification exercise.
- Qualification is performed with the room and and UDAF in final operating parameters.
- Changes with a possible impact on EM (e.g., gowning procedures, cleaning set-up, layout, material or personnel flow, or other areas) should include a new assessment on the qualified status of the cleanroom and may require requalification as part of the change.



Early microbiologists



## Rapid Microbiology

# Potential Benefits of RMM in EM

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- Confirmation (in real-time or close to real-time) of microbial control during manufacturing activities, including compounding, filling, and packaging
- Determination of the impact of operator interventions during aseptic filling with the opportunity to segregate and reject impacted containers.
- Confirmation of microbial control in controlled areas prior to use (e.g., manufacturing suites, gowning rooms)
- Rapid assessment of controlled areas during facility qualification activities (e.g., EM PQ)
- Evaluation of contamination remediation efforts and root cause analysis (e.g., using rapid methods to find a source of contamination and/or determine the effectiveness of cleaning and disinfection procedures)

# Benefits of RMM from a QRM Perspective

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- Aid in the design robust processes that prevent contamination
- Ensure that a state of microbial control is maintained
- Evaluate the impact of human interventions during aseptic filling
- Establish recovery time after power shortages
- Develop more effective strategies to correct a contamination problem
- Continually improve processes and products
- Quickly and efficiently assess the potential impact of failing results on the patient.



- Sample type and size
- Frequency of sample collection and processing
- Sample compatibility with the rapid method
- Desired time to result
- Level of sensitivity required
- Potential for false positives or false negatives from test samples and/or cleaning or disinfectant residuals
- Automated and high-throughput methods using conventional media are also available that may afford faster results with better efficiency in terms of automation and data management and data integrity.
- **Return on Investment (ROI)**

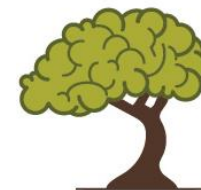


- Potential for reduced in-process microbiology testing and finished product release cycle times
- Reduction in risks associated with forward processing
- Elimination or reduction of off-line microbiology assays
- Increases in laboratory automation and reductions in manual testing, sample handling, and/or data management
  - Reduced repeat testing, lot rejection, reprocessing, and rework
  - Reduced overhead and/or headcount for sampling and/or testing
- Ability to make immediate quality decisions on the state of microbial control
  - Faster response to contamination events and initiation of investigations
  - Faster confirmation of contamination remediation efforts
- Reduction in room or facility downtime and investigations

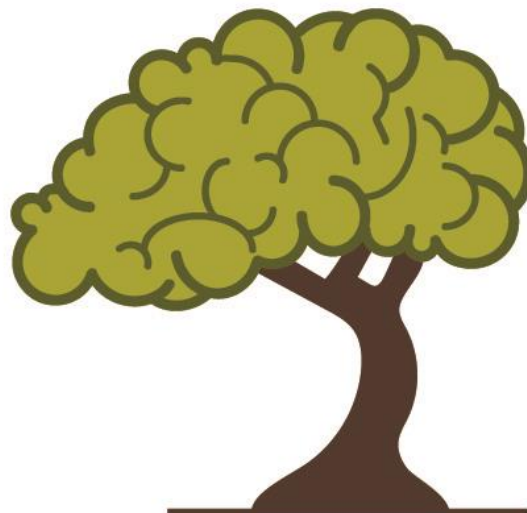


# Questions?

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