Microbial Contamination and Control Conference

Back to the Basics with EMPQs

A Critical Component to Contamination Control

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Agenda

01 Background on EMPQs

02 Regulatory Guidance

03 Expectations for EMPQs

04 Microbial Identifications

05 EMPQ Challenges

06 Summary/Ongoing EM Program

Cleanrooms 101

What is the goal of a Cleanroom?

- Basic function of a cleanroom – **protect the manufactured product from contamination.**
- Patient protection and economical survival of the manufacturer depends on the safety of the finished product.
- Cleanrooms are divided into different grades or classes.
- Manufacturing or processing occurs in Grades A-D or ISO Classes 5, 7, and 8.

Why Does a Cleanroom Need to be Qualified?

Regulatory Requirement

- EM systems must reflect the cleanroom's state of control.

Process Validation and Facility Qualification

- Demonstrate cleanroom environment consistently meets microbial cleanliness.

System Optimization

- Verify sampling methods are appropriate and effective.

Audit Readiness

- Well-documented Environmental Monitoring Performance Qualification (EMPQ) builds confidence during inspections and may reduce number of observations from regulatory bodies (i.e. FDA).

Patient Safety

- EMPQs help identify contamination risks, safeguarding the integrity of products and protecting patients.

EMPQs are **NOT** just a regulatory checkbox

They are a proactive investment in quality, compliance, and ultimately patient safety

EMPQs are the foundation of your future CCS!

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What is an EMPQ?

Environmental Monitoring Performing Qualification

Environmental Monitoring Performance Qualification (EMPQ) is a documented process to ensure the EM system accurately represents the cleanroom's microbial and particulate control.

EMPQs verify…

- Environmental monitoring systems accurately reflect the **cleanroom's state of control.**
- Microbial and particulate contamination are consistently within **acceptable limits.**
- Monitoring systems are **reliable during routine operations.**
- Provide a **documented record** of control for regulators.

What do Regulators Expect from Manufacturers?

EU GMP Annex 1

- Requires companies to have a risk-based EM program.
- Expectations: *Grades A and B should be requalified at least every 6 months, while Grades C and D should be requalified at least every 12 months to demonstrate that the cleanroom is still operating under a state of control.*

ISO 14644

- Covers design, construction, classification of cleanrooms, and controlled environments.
- Expectations: *Cleanrooms must undergo IQ using validated methods, calibrated instruments, and trained personnel under static and dynamic conditions.*

CFR 210 and 211

- Provides current Good Manufacturing Practices (cGMP) for pharmaceuticals, including requirements for facilitates, equipment and quality systems.
- Expectations: *Cleanrooms must be designed and maintained to prevent contamination. All cleanroom related systems and processes must be validated and documented to ensure they perform reliably.*

What does Annex 1 say about EMPQs?

Risk assessments and ongoing data trending

EU GMP Annex 1:

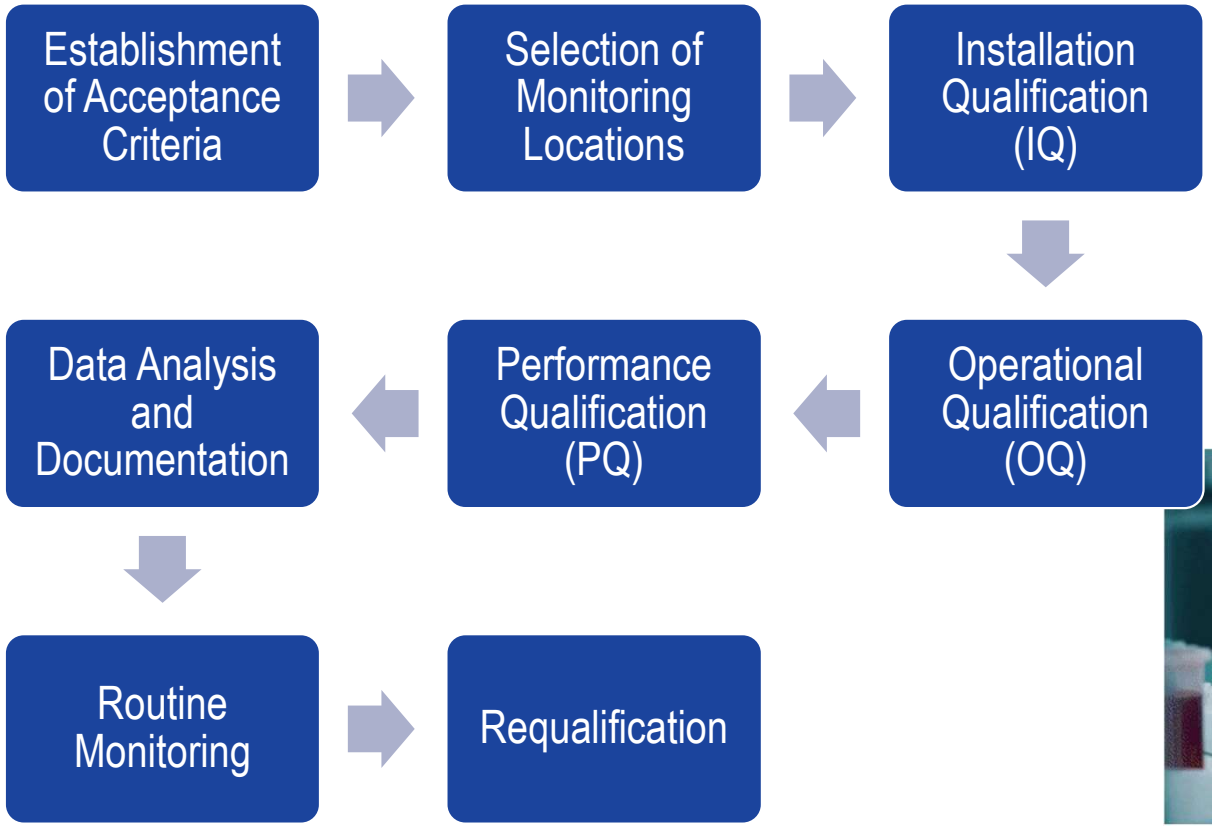
Risk assessments should be performed in order to establish this comprehensive environmental monitoring program, i.e. sampling locations, frequency of monitoring, monitoring methods and incubation conditions (e.g. time, temperature(s), aerobic and/or anaerobic conditions).

These risk assessments should be conducted based on detailed knowledge of; the process inputs and final product, the facility, equipment, the criticality of specific processes and steps, the operations involved, routine monitoring data**, monitoring data obtained during qualification and knowledge of typical microbial flora isolated from the environment.**

The monitoring of grade C and D cleanrooms in operation should be performed based on data collected during qualification and routine data to allow effective trend analysis.

Cleanroom Validation Workflow

Includes EMPQ



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Cleanroom Validation Workflow

Pre IQOQPQ

Establishment of Acceptance Criteria

- **Define criteria**
- What must the environmental monitoring system meet to be considered qualified?
  - Specs on microbial limits
  - Sampling methods
  - Equipment calibration
  - Data analysis

Selection of Monitoring Locations

- **Identify sampling points**
  - Risk-based approach is used when selecting
  - Sampling locations must represent areas with the highest risk of contamination
  - Focus on critical manufacturing areas, operator workspaces, etc.
- Refer to ISO 14644-1, -2, and -3 for standard on m^2 space; *note may need to be adjusted based on facility layout and equipment*

Cleanroom Validation Workflow

IQOQPQ

Installation Qualification (IQ)

- **Equipment is confirmed/verified to conform to user requirements and design requirements.**
- Is environmental control system installed correctly?
- Does the environmental control system operate reliably under normal operation conditions?
- Are the alarm settings working properly?
- Can the system record data accordingly?

Operational Qualification (OQ)

- **Demonstrate cleanroom operates in conformance with design requirements and user defined requirements.**
- Does the cleanroom perform as intended under controlled conditions?
- Are specified limits met (i.e. temperature, humidity, etc.)?
- Are particle counts within limits during non-operational testing?

Performance Qualification (PQ)

- **Demonstrate cleanroom consistently operates within defined parameters to product the defined, desired environmental outcome.**
- Can the cleanroom stay in control during simulated production?
- Does equipment work properly?
- Is the cleaning program maintaining environmental conditions over time?
- Are particle counts within limits during active operations?

Cleanroom Validation Workflow

Post IQOQPQ

Data Analysis and Documentation

- Thoroughly analyze results and compare results to acceptance criteria.
- Document deviations from acceptance criteria and what corrective actions were taken.
- Documents serve as proof of compliance with regulatory requirements.

Routine Monitoring

- Post initial validation…
- Routine monitoring demonstrates ongoing compliance
- Monitor the following:
  - Operator Performance (i.e. personnel monitoring).
  - Aseptic process integrity.
  - Effectiveness of cleaning and sanitization programs.

Cleanroom Validation Workflow

Ongoing Monitoring Post Initial Qualification

Requalification

- Necessary to ensure continued compliance.
- EMPQs should be included in requalification activities.
  - Changes or updates to the EM program.
  - Verify effectiveness of contamination control measures.

- EMPQs are triggered by:
  - Defined intervals (i.e. every 6 or 12 months).
  - Significant changes to facility, equipment, or process changes.
  - Large or unexplained environmental excursions.

Phases of EMPQ Process

3 Main Phases for Environmental Monitoring Performance Qualification (EMPQ)

Baseline (Phase I)

- Viable sampling establishes microbiota and action limits
- Microorganisms recovered are identified to characterize the cleanroom's microbiota

Initial (Phase II)

- Static and Dynamic testing confirm compliance with ISO/Grade Classifications and validate microbiological control under routine use
- Results validate suitability of cleaning protocols, and aseptic workflow design

Extended (Phase III)

- Long-term evaluation to ensure environmental stability across all seasons
- Supports assessment of cleanroom state of control and effectiveness of the CCS

EMPQ Process Misconceptions

Uncertainty from Manufacturers

Baseline (Phase I)

- Is a baseline required or needed?
- What are the steps from EMPQ to routine EM?

Initial (Phase II)

- What is the recommendation for static and dynamic testing (i.e. how many days for each)?
- How many samples per location is acceptable?

Extended (Phase III)

- How long should my phase III be?
- Should all recoveries be identified?
- How often should sampling occur?

EMPQ Process Misconceptions

Uncertainty from Manufacturers

Baseline (Phase I)

- Baseline sampling (post clean) evaluates microbiota present before introducing controlled processes and disinfection protocols.
- EMPQ forms the basis for your EM program in support of the site's contamination control strategy, and understanding your environment, processes, personnel and material flows.

Initial (Phase II)

- Test under both Static and Dynamic conditions to ensure the ISO/Grade classification is maintained.
- No strict requirement, at least one day of each with multiple days for dynamic monitoring based on your risk assessment.
- Sampling plan is based on the processes being done in the room/area and any risks identified in the risk assessment (i.e. critical areas like benchtops or inside hoods, and high traffic areas like door handles, carts where materials are found, etc.)

Extended (Phase III)

- 6 – 12 months; goal is to show the room classification is maintained for both particle and viable limits set during phase II.
- Microorganisms recovered over time should be identified as the trending data can help detect issues, prevent reoccurrences, and help support updates to your contamination control strategy.
- Frequency is based on what you can justify and what activity is being done in room.

What is in my Cleanroom?

Microbial Identifications

Annex 1: *Microorganisms detected in the grade A and grade B areas should be identified to species level and the potential impact of such microorganisms on product quality.*

Accurate species level ID provide

- Trending for future contamination events.
- Proper risk assessments are made (i.e. does the cleaning program need to be adjusted?).

Understanding the organisms' origin and risk level helps

- Improve contamination control strategies.
- Support root cause analysis during deviations.

Why are Risk Assessments Important?

Impact of Risk Assessments

EU GMP Annex 1 –

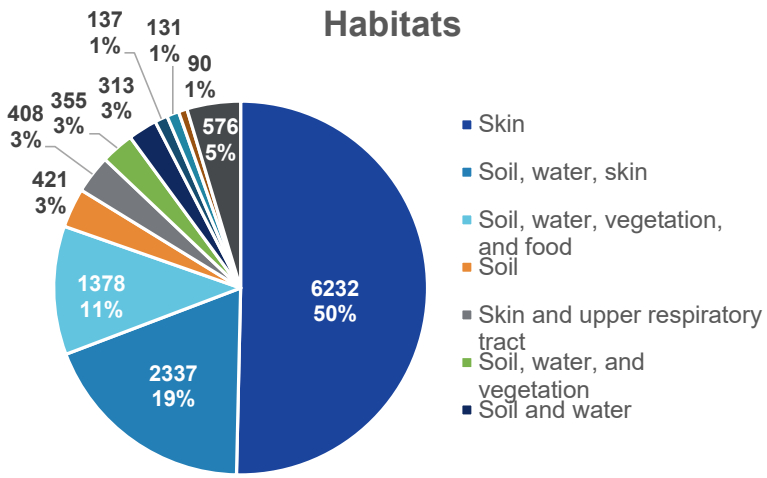
- "**Risk Assessment**" is mentioned **25 times**.
- *"Appropriate risk assessment and mitigation measures should be applied and recorded as per the manufacturer's CCS and should include a specific disinfection and monitoring program approved by quality assurance."*
- When there is a **risk of product or process contamination** from particular types of organisms, these are considered **objectionable organisms**.
- It's critical to **identify microorganisms** and **assess** their possibility of survival or likelihood of producing toxins.
- The potential for **causing contamination of the product** or **harm to the patient** should always be assessed.

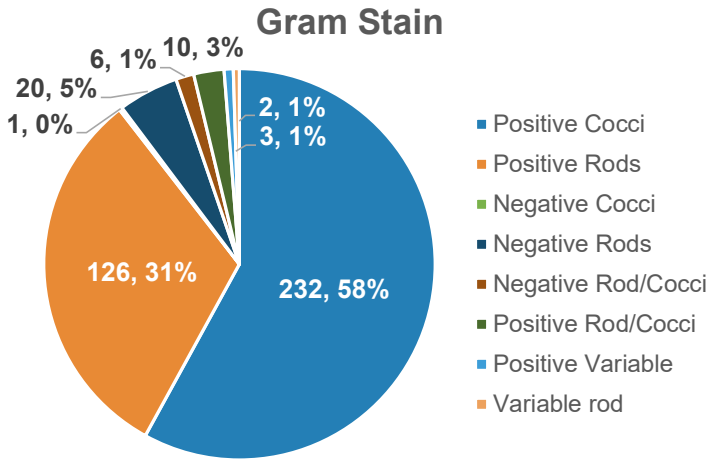
If a risk is not properly addressed during the EMPQ process, it can pose contamination challenges for your manufacturing processes down the road

Cleanroom Trends

Diversity in Cleanrooms

- Leverage external resources to support your data analysis.
- Understand the diversity of the microbiota in your cleanroom and what it means for your manufacturing environment.
- Summarizing your results provides a baseline to better understand the potential risks associated with the organisms found in the qualified environment.
- Example – Gram stain known to be unreliable; however, this information can be utilized to characterize the ID results and provide further insights to see the whole picture.





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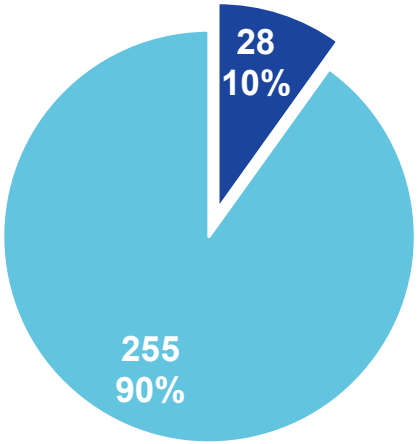
Cleanroom Trends

Diversity in Cleanrooms

- Leverage external resources to support your data analysis.
- Example – known organisms to cause biofilms, can be an indicator for biofilm presence in your water system as long as this data is accurately trended.
- *Note the list of genera can serve as an indicator for biofilm formation/ presence but is not representative for all genera that are linked to biofilms.*



10% (28) of all identified samples (n = 283) are members of frequently isolated genera associated with biofilms

Genus	# ID'd	# FIG
Staphylococcus	86	1
Micrococcus	35	2
Corynebacterium	30	3
Moraxella	**11**	**4**
Kytococcus	10	5
Kocuria	9	6
Dietzia	8	7
Dermacoccus	7	8
Micrococcales	7	9
Pseudomonas	**6**	**10**
Bacillus	**5**	**11**
Brevundimonas	5	12
Micrococcaceae	5	13
Roseomonas	5	14
Acinetobacter	**4**	**15**
Brevibacterium	4	16
Janibacter	3	17
Streptococcus	3	18
Agrobacterium	2	19
Brachybacterium	2	20
Candida	2	21
Curtobacterium	2	22
Metabacillus	2	23
Niallia	2	24
Priestia	2	25
Rothia	2	26
Aspergillus	2	27
Ralstonia	**1**	**28**
Sphingomonas	**1**	**29**
Aerococcaceae	1	30

The 6 genera occur within the top 30 Frequently Identified Genera

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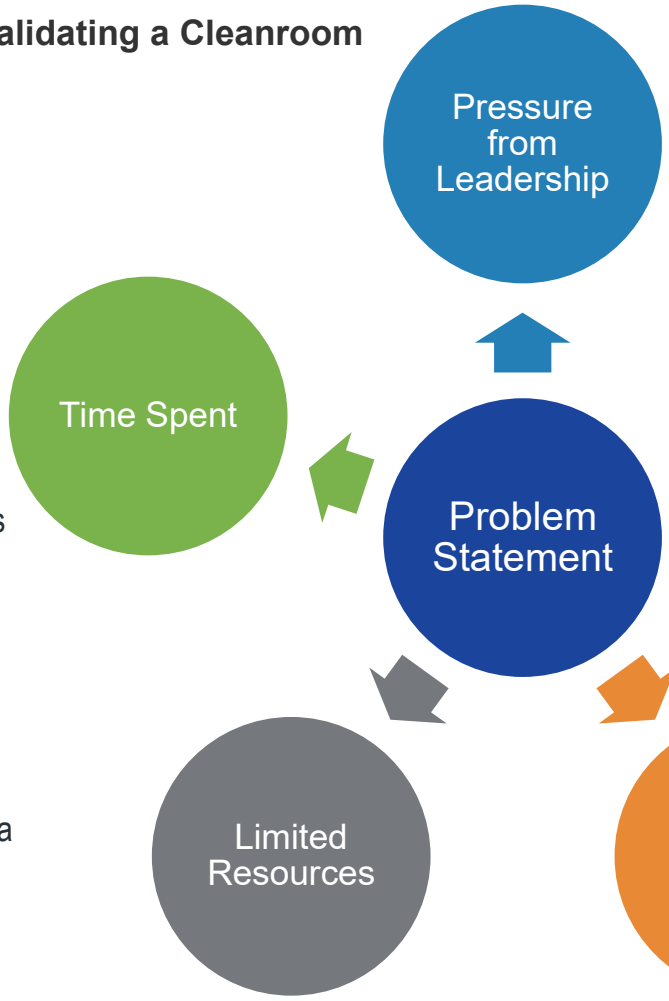
EMPQ Challenges

Considerations When Validating a Cleanroom



- Management pressure
- Manufacturing is at a halt in that cleanroom
- Cost of overall project

- Day-to-day tasks become harder to manage

- Long hours
- Stress and frustration to employees
- Disruption of other activities

- Management of results/data
- Trending results

- Risk to overall EMPQ
- Costs of Retest

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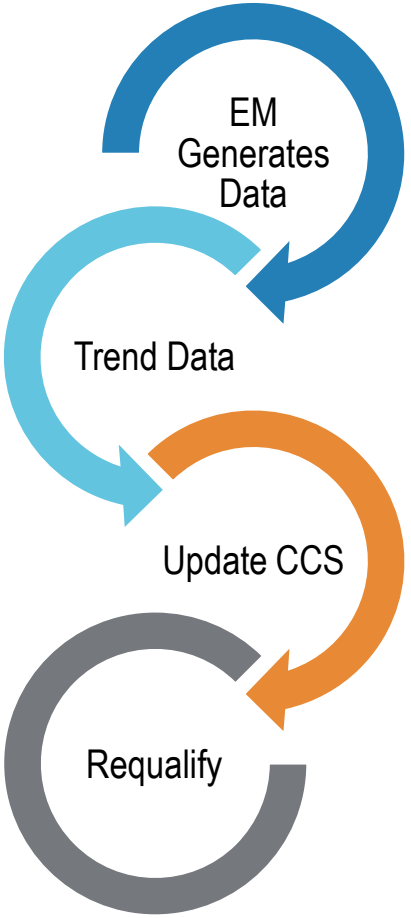
Summary

We have gone over...

- EMPQs are critical to proving your cleanrooms are **effectively controlled**.
- Proper EM **safeguards patient safety** and **ensures compliance** with global regulations.
- **Requalify your cleanrooms** as needed or when there is a **significant change** to your facility
- Stay up to date with regulations!
- Continuously **challenge** your contamination control strategy.
- If you need help find a **partner to support** your Validation!



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Thank You!

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