Environmental Monitoring Performance Qualification (EMPQ) in New Facilities: Application of an Industry Harmonized Approach

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Introduction

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This presentation follows:

- The publication of the BioPhorum paper ***Environmental Monitoring Performance Qualification in new facilities: an industry-harmonized approach***, which provides a comprehensive overview of an EMPQ for new facilities based on industry-led guidance.

In this session you will:

- Gain a good understanding of the industry-harmonized approach to EMPQ for new facilities proposed by the BioPhorum Environmental Monitoring group.
- Learn more details about the key elements of an EMPQ:
  - prerequisites,
  - alert levels,
  - sampling requirements,
  - acceptance criteria,
  - post-qualification activities.
- Explore a case study to illustrate the application of the guidance and highlight lessons learned and best practices.

Structure of the presentation:

- Regulatory requirements and industry guidance
- EMPQ overview
- Pre-requisites to EMPQ
- Key elements of EMPQ
- Final report, area release, and post-qualification
- Case Study: Application of guidance in Cell Therapy Manufacturing Facility
- Q&As

Regulatory Requirements and Industry Guidance

Regulatory requirements and standards:

FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice (2004)

- Evaluating the quality of air and surfaces in the cleanroom environment should start with a well-defined written program and scientifically sound methods.

USP <1116> Microbiological Control And Monitoring Of Aseptic Processing Environments (2013)

- Environmental monitoring can only assure those responsible for a process that a production system is in a consistent, validated state of control.

EU Annex 1 Manufacture of Sterile Medicinal Products (2022)

- Controls and monitoring should be scientifically justified and should effectively evaluate the state of environmental conditions of cleanrooms, airlocks and pass-through hatches.

ISO 14644-2:2015

- A monitoring plan shall take into account the level of air cleanliness required, critical locations and performance attributes of the cleanroom or clean zone that affect the performance of the installation.

Industry-harmonized guidance:

PDA TR13 Fundamentals of an Environmental Monitoring Program

- A comprehensive EM program should demonstrate the effectiveness of a solid Contamination Control Strategy.
- Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state to minimize the risks of particulate or microbial contamination of the product or materials being handled.

Environmental Monitoring: A harmonized risk-based approach to selecting monitoring points and defining monitoring plans (BioPhorum, 2020)

- Typical RA tools are difficult to apply or insufficient when establishing a risk-based EM program.
- Absence of agreed guidance template can lead to wasted efforts in the industry and among regulatory agencies.
- An easy-to-use, standardized tool is required, based on objective criteria, that facilitates an EM program.

Environmental Monitoring Performance Qualification of New Facilities: an industry-harmonized approach (BioPhorum, 2024)

- Performing an EMPQ is an essential part of the Contamination Control Strategy (CCS) of each production facility.
- It is a GMP requirement to qualify cleanrooms over the lifecycle of the facility, and any planned changes that may impact product quality must be assessed including impact on the validation and qualification status.

EMPQ Overview

EMPQ:

WHAT

- Verifies performance of cleanrooms based on predefined parameters for microbial and particle limits
- Confirms effective cleaning and disinfection regime
- Confirms effective personnel gowning process
- Confirms effective material transfer process
- Evaluates appropriate aseptic behaviors of personnel

WHEN

- Initial facility qualification
- Post major changes or events
  - Facility modifications
  - Adverse EM trends
  - Extended shutdowns
  - Breach of Integrity to Facility

WHY

- To establish and qualify a robust process for Environmental Monitoring

EMPQ within the Cleanroom Lifecycle

Pre-EMPQ	Design	Change request / change control initiated User / design / functional requirements / specifications determined
	Classification	HVAC commissioning Cleanroom classification according to ISO 14644-1 - At-Rest and In-Operation (with max occupancy)
	Disinfection	Maximum occupancy defined GMP cleaning and disinfection program implemented
EMPQ	**EMPQ Plan**	Design of the EMPQ to assess environmental controls under At-Rest and In-Operation conditions
	EMRA	Perform risk-based EM assessment (EMRA) to determine sample locations for EMPQ
	EMPQ	EMPQ sampling 'At-Rest' and 'In-Operation' according to sample points from risk-based EM assessment Inclusion of maximum occupancy in process relevant rooms/areas during In-Operation monitoring sessions
Post-EMPQ	Routine EM	Determine and perform sampling on a routine basis for EM sampling locations, methods and frequencies based on risk-based EM assessment and EMPQ results
	Validation Maintenance	Periodic classification according to ISO 14644-2 EM requalification (EMRQ)
	Decommissioning	Cleanroom decommissioning

Prerequisites for EMPQ

Establishing Alert Levels and Action Limits

Sampling Requirements

Acceptance Criteria

Final Report and Area Release

Prerequisites to EMPQ

EMPQ: Prerequisites (1/3)

Cleanroom Qualification

- HVAC system calibration
- HEPA filter integrity testing
- HVAC OQ
- Alarm and interlock checks
- Airflow velocity, air exchange rate, air balancing
- Physical parameter qualification
- Airflow visualization studies/smoke studies

Cleanroom Qualification

Maximum occupancy defined

- Max defined number of personnel present performing representative activities during in-operation sampling
    - Minimally for critical processing rooms and associated airlocks e.g., Grade A & B processing rooms & Grade A/B airlocks

Cleanroom classification per ISO 14644-1

All equipment installed, qualified/calibrated

EMPQ: Prerequisites (2/3)

Contamination Control Strategy & Quality Risk Assessments

SOPs approved/in place

- Operational SOPs
- Equipment/material/waste transfer and flow
- Housekeeping and cleaning/disinfection
- Gowning and personnel flow
- EM sampling methods, media, growth promotion, and incubation strategy

Operators trained

- Procedures
- Aseptic behaviors/techniques
- Contamination control

Disinfectant efficacy studies

Final, approved facility maps

Training and Procedures

EMPQ: Prerequisites (3/3)

Harmonized industry Guidance for EM Risk Based Assessment (EMRA)[1]

- Map the layout of the room, overlay with grids, and combine them into functional sections
- Walk the process with a cross-functional risk assessment team, noting process activities grid-by-grid
- Assess each grid against six risk factors, scoring to determine relative probability of contamination for each grid
- Evaluate the results by functional sections to select sampling locations, methods, and frequency/timing of the samples

EM Risk Based Assessment

[1]Biophorum: A Harmonized Risk-Based Approach to Selecting Monitoring Points and Defining Monitoring Plans

Key Elements of EMPQ

Establishing Alert Levels

Alert Levels

- Early warning of potential drift from normal operating condition
- Can provide value in early detection of potential issues at sampling location or in room/area prior to releasing area for production

Setting alert levels

- If comparable qualified facility exist – alert levels from existing facility can be used initially, prior to having any data
- If no comparable qualified facility exists – set at approx. 50-60% of action limit

→ Following EMPQ, alert levels should be reassessed

Establishing Action Limits

Action Limits

Apply action limits following regulatory requirements with respect to classification in which EMPQ is performed:

- EU GMP Annex 1
- FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice

SOPs must be established to define how to set Alert and Action limits and frequencies for re-evaluation

EMPQ Occupancy States

AT REST: Intrinsic State of Control

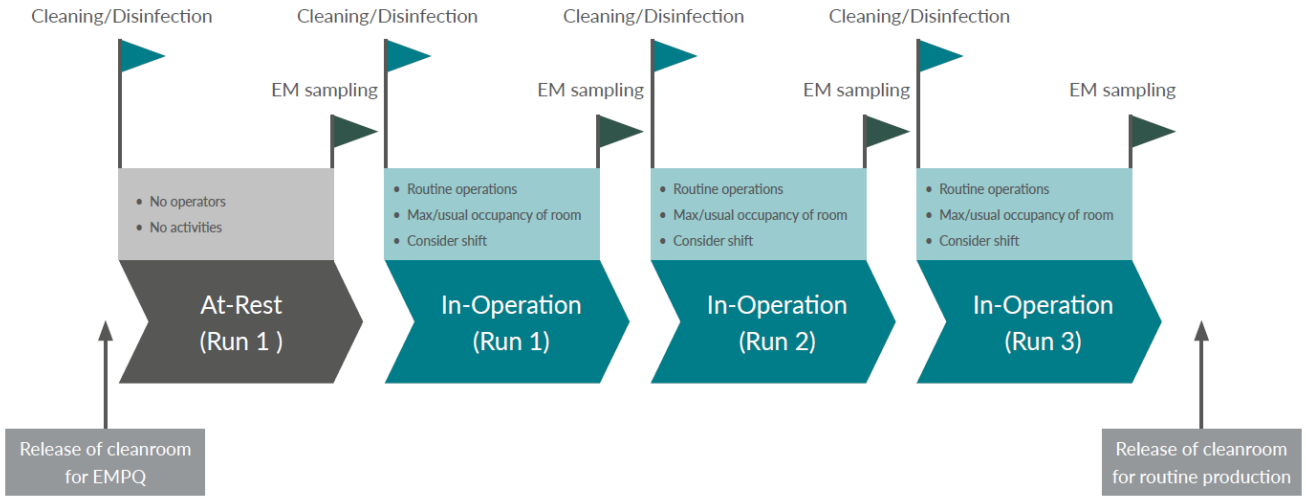
- Evaluates the efficacy of technical and procedural measures to operate the cleanroom (e.g., HVAC, cleaning/disinfection program)
- No personnel present or processing activities in progress
- Minimum one sampling set

IN OPERATION: State of Control with Activity and Personnel

- Enables the evaluation of the potential impact that people and processes have on the status of a cleanroom
- Minimum of three sampling sets across different shifts/days with maximum occupancy:
  - Ensures results are consistent and meaningful
  - Demonstrates reproducibility
  - Allows for EM sampling of representative activities across operations/shifts
  - Accounts for variability in production operations – activities are representative of those expected during routine operation (e.g., set-up, interventions, different processes occurring in one room)
  - Aligned with process validation and aseptic process simulation (common in industry)

EMPQ Sampling Requirements

- Sample location selection per EMRA
- Occupancy states
- Sampling type and number of sets of sampling



EMPQ Sampling types and number of sets

Sampling Condition	Total particle air	Microbial surface	Active microbial air	Passive microbial air
At-Rest	1 set	1 set	1 set	1 set
In-Operation*	3 sets	3 sets	3 sets	3 sets

*Sampling to be performed across different shifts and/or days of the week with maximum occupancy

Rationale for number of sampling sets collected

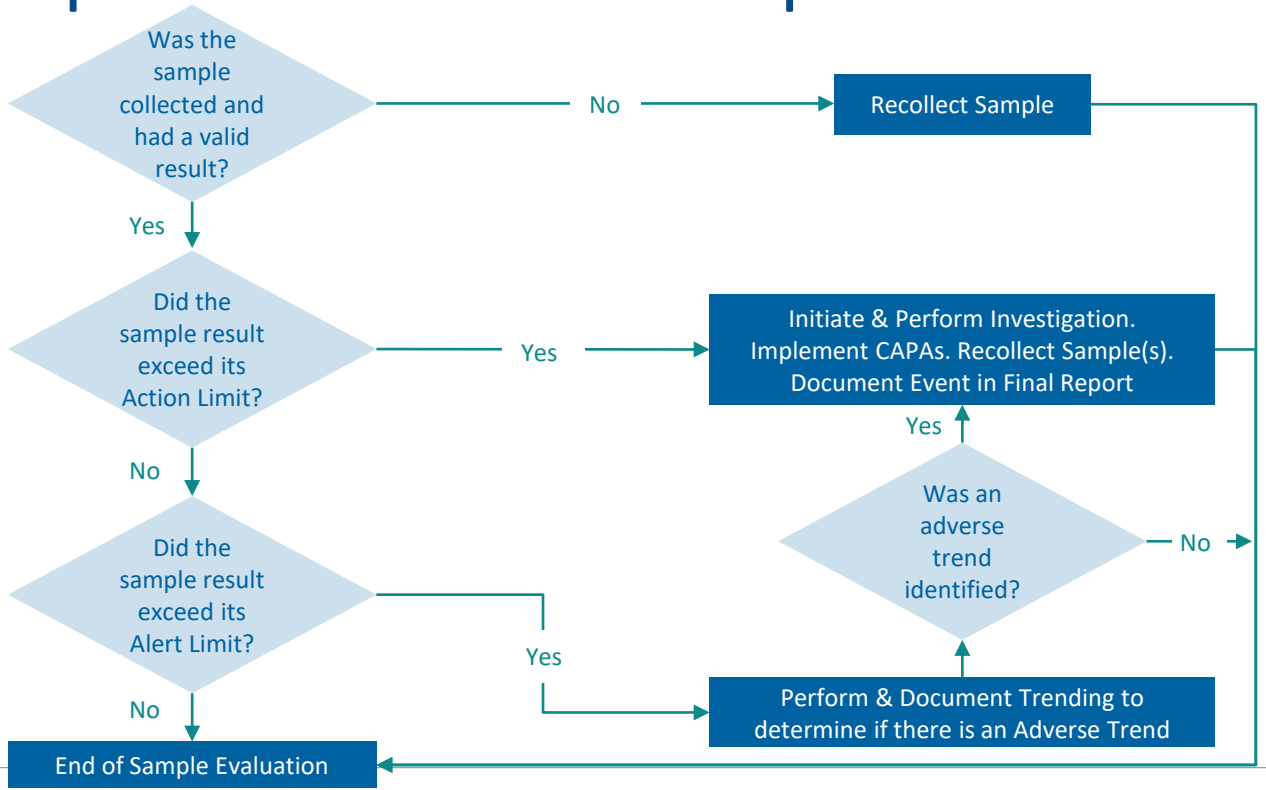
1 sampling set under At-Rest conditions

- No personnel present and no processing activities occurring, hence low risk of ingress of microorganisms following cleaning and disinfection.
- Sample points from Cleanroom classification (pre-requisite to EMPQ which requires passing total air particle results) may be used to inform the overall levels of particles in the room.
- Low risk of potential impact to the state of control of the cleanroom and consistent across additional sampling sets (due to low variability).

3 sampling sets under In-Operation conditions

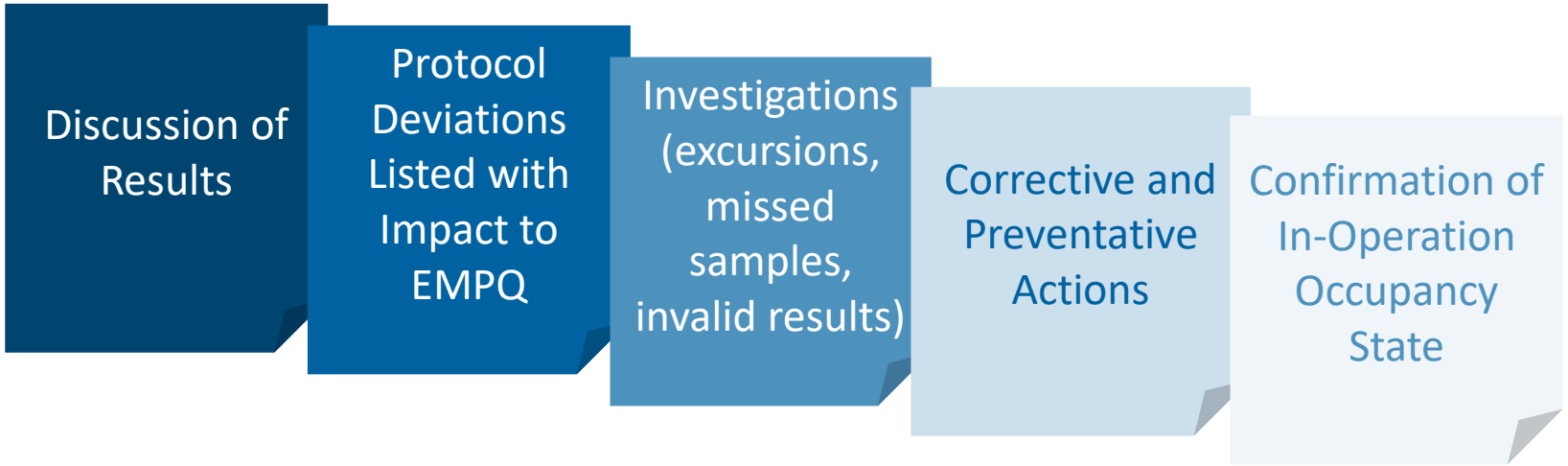
- Used throughout industry to validate or qualify processes, typically a regulatory requirement.
- Allow for EM sampling during operational activities or the simulation of operations.
- Help ensure that results are consistent and meaningful, demonstrate reproducibility and account for variability.

Acceptance Criteria Example Decision Tree



Final Report, Area Release, and Post-Qualification

EMPQ Final Report Criteria



Overall EMPQ conclusion:
Was EMPQ completed and in compliance with acceptance criteria?

Complete EMPQ: all samples collected or addressed via deviation (e.g., sampling in non-required location)

In compliance with criteria: samples collected in valid manner, have valid results, and no deviations or investigations that impact EMPQ

Area Release for Production

Area Release for Production

- All associated sampling/testing must be complete
- Impact of deviations/exceptions assessed
- Quality and area owner (minimum) approval of final EMPQ report

If report cannot be completed prior to manufacturing

- Utilize risk-based approach
- Interim sampling strategy (e.g., all EMPQ sample points)
- Interim report:
    - Validity/status of data/lots/batches/material produced during interim period
    - Conclusion statement on whether acceptance criteria were met for EMPQ
- Batch release contingent on approval of final report

Post Qualification

Routine EM Program

- Establishment of routine EM program based on:
  - Review of EMRA
  - EMPQ data

EM Requalification

- EM Requalification for periodic evaluation to demonstrate compliance
- EM Requalification (risk-based):
  - Facility/Equipment/Process modification (change control)
  - Adverse EM trends
  - Extended shutdowns
  - Breach of integrity to facility
  - Planned/unplanned events

Case Study

Case Study: EMPQ in Cell Therapy Manufacturing Facility

Manufacturing Facility for clinical phase allogeneic cell therapy products

Open aseptic process conducted in a Grade A Biosafety Cabinet with a Grade B background

EMPQ for new facility performed in alignment with the industry harmonized approach to EMPQ

Case Study: Prerequisites

- HVAC commissioned
- Cleanroom OQ completed, including classification
- Maximum occupancy defined
- Routine cleaning and disinfection program implemented
- Environmental Monitoring Risk Assessment (EMRA) completed

Case Study: Establishing Alert Level and Action Limit

Alert Level

50% of the action limit

Action Limit

Aligned with EU Annex 1

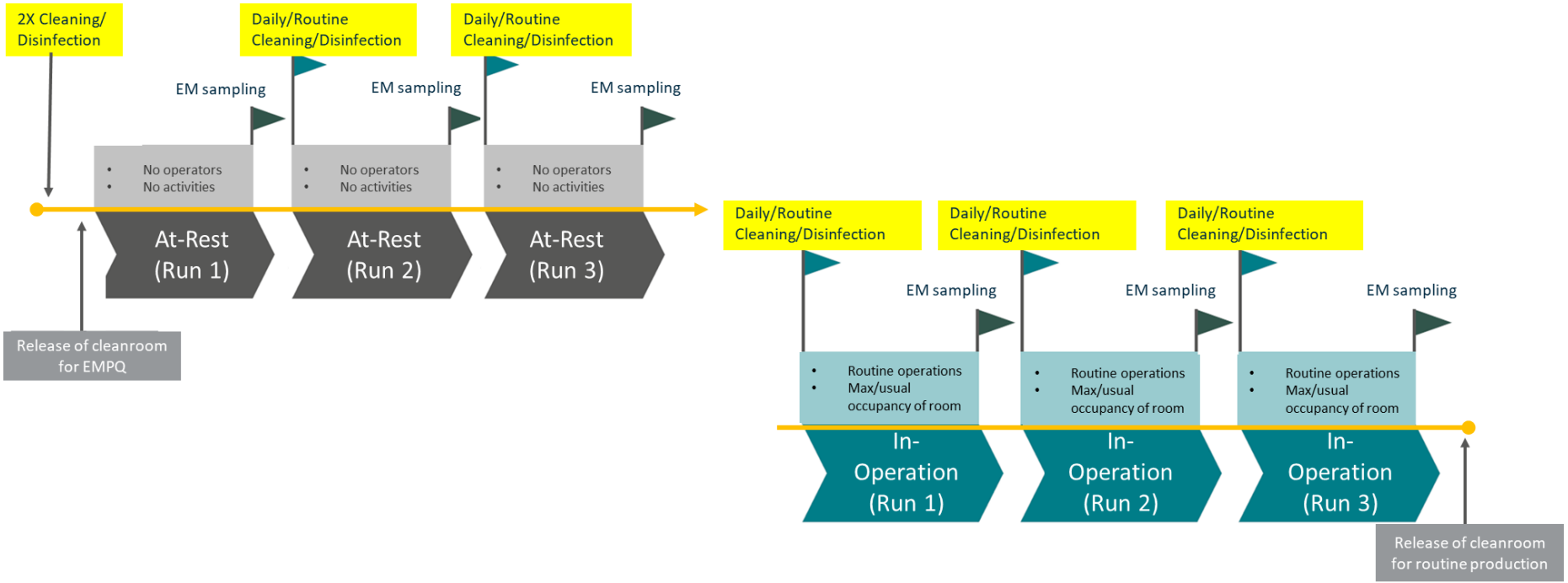
Grade D in-operation internally established based on risk

Case Study: EMPQ Plan

Sampling Condition	Total airborne particle (TAP)	Microbial surface	Active microbial air	Passive microbial air
At-Rest	3 sets	3 sets	3 sets	3 sets
In-Operation	3 sets	3 sets	3 sets	3 sets

Process streamlining opportunity: perform 1 set of At-Rest monitoring to align with the harmonized approach.

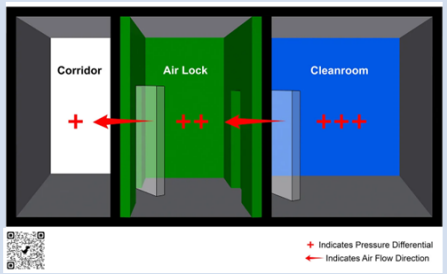
Case Study: Execution



Case Study: Protocol Discrepancy 1

Description

Two differential pressure alarms activated during Run 1 At-Rest monitoring.



Root Cause

Incorrect instructions regarding door operations were given to the samplers.

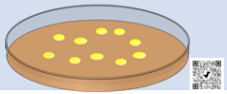
Actions

- Correct instructions were provided to the samplers.
- All total airborne particle, viable air and surface samples met the acceptance criteria, no resampling was required.
- No impact to EMPQ outcome

Case Study: Protocol Discrepancy 2

Description

A Grade D material airlock floor surface sample exceeded the alert level for all 3 consecutive days of In-Operation monitoring



Root Cause

Trend of alert excursions due to increased personnel presence and material transfer in the material airlock for EMPQ setup (beyond routine worst-case operation)

Actions

- Resampling occurred under routine operational conditions
- Resampling passed

Case Study: EMPQ in Cell Therapy Manufacturing Facility

Takeaway

Consider the impact of EMPQ setup activities on the environmental conditions of cleanrooms as they may not be reflective of normal operations.

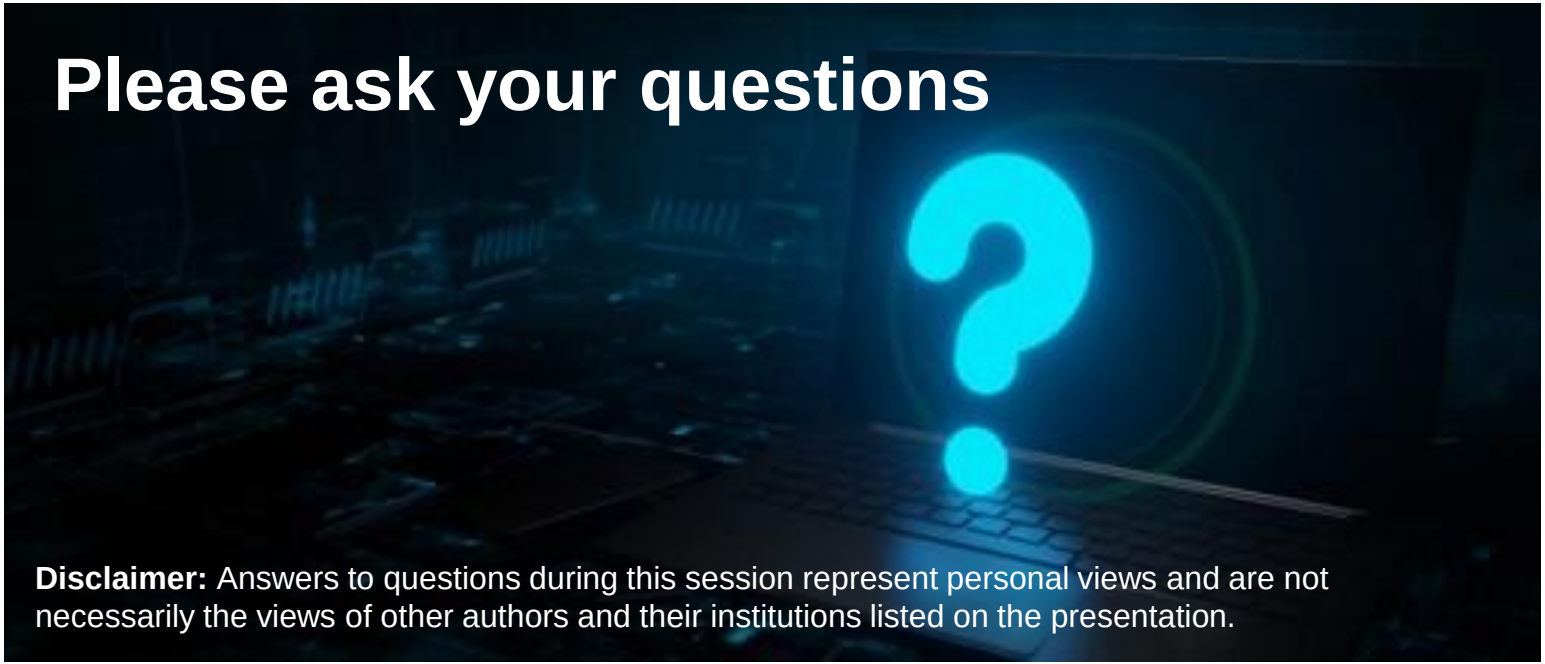
Additional Consideration

Ensure robust training on appropriate procedures (e.g., gowning and material transfer) and appropriate Quality oversight if contractors are used

Post EMPQ Execution

- Cleanrooms were released following completion of review of data with passing results.
- Batch disposition was conditional on the completion and approval of the EMPQ final report.
- Routine environmental monitoring of EMPQ sampling sites occurred in the interim of completion of EMPQ and approval of EMPQ report

Q&As



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