Management of Facility and Critical Utility Systems (Contamination Control Strategies)

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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.

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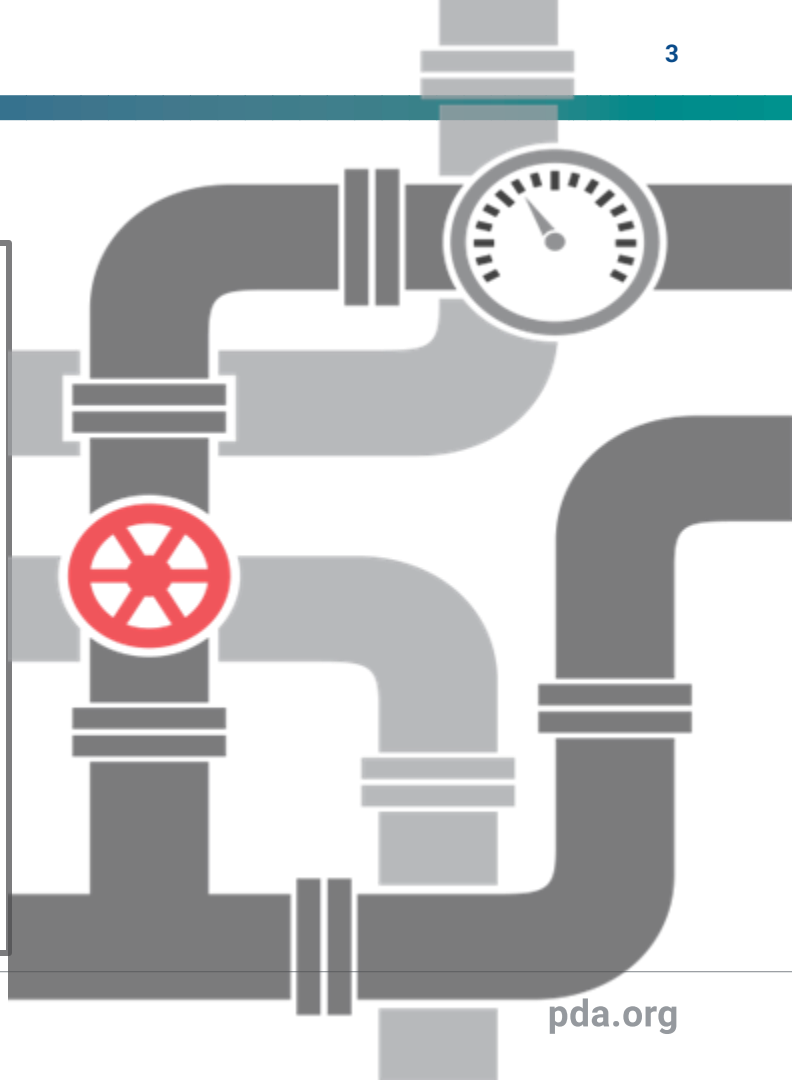
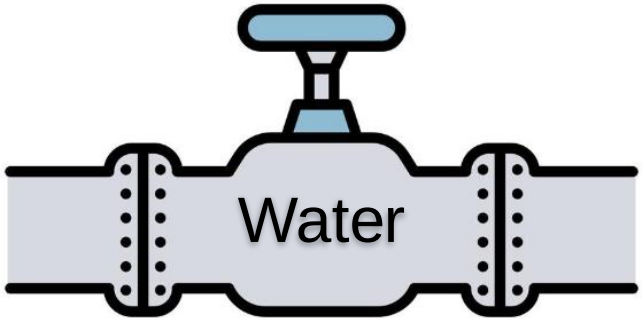
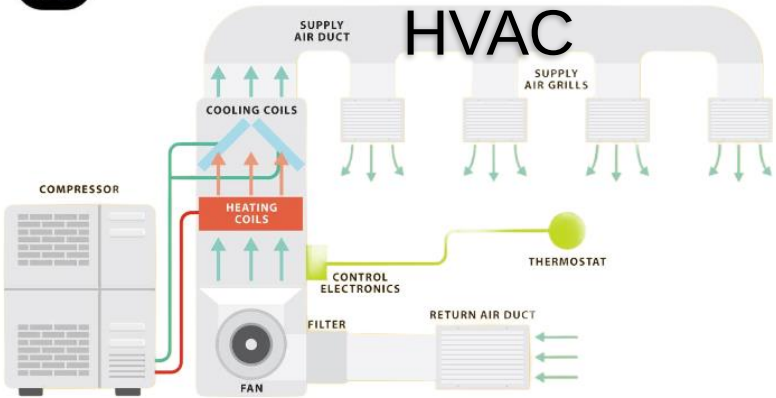
Topics

Types of Critical Utility Systems
Critical Utilities as a part of the CCS
Water and Steam
HVAC
Gasses
Control, Validation, and Monitoring
EMPQ
Disruption and Recovery Plan
Sources of Contamination in Critical Utility Systems
Investigating Critical Utility System Deviations



Types of Utility Systems



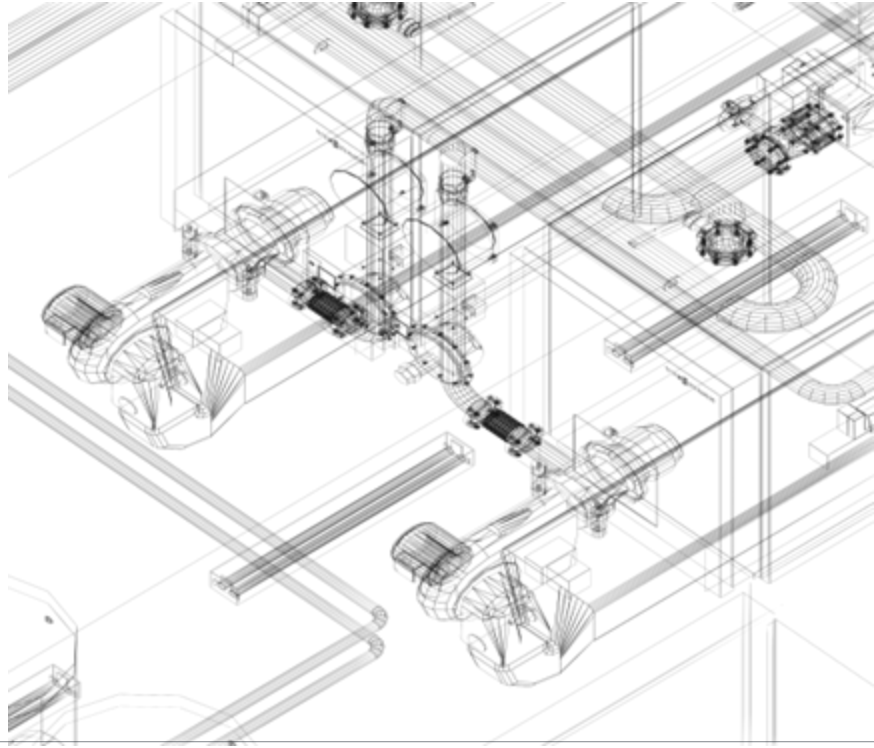


- Vacuum
- Cooling
- Feed water

Critical Utilities as a part of the CCS

Critical utility systems, including water, steam, HVAC, and gas systems, are important elements of the CCS because they come in direct contact with the product stream

When running well, critical utility systems appear to fade into the background, but if not designed, maintained, operated, and monitored properly, they can lead to a shutdown of production or even adulteration of products



Critical Utilities as a part of the CCS

PDA TR90

Critical Utilities as a part of the CCS

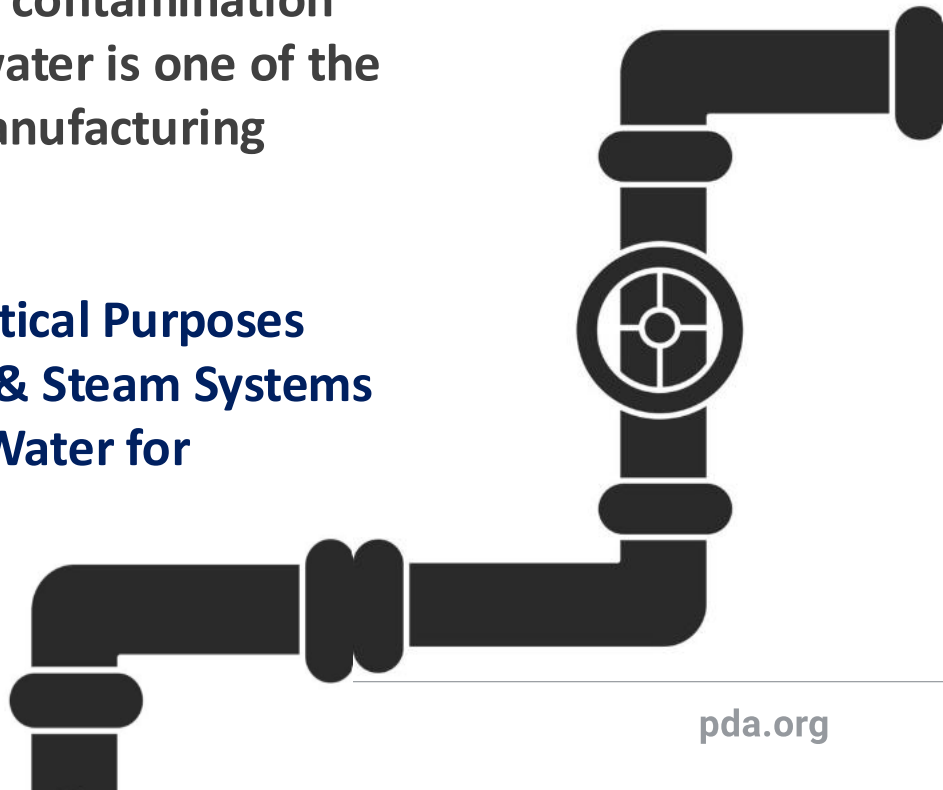
Non-Holistic Approach	Holistic Approach
A critical utility is a standalone piece of equipment	Critical utilities are a major part of the overall CCS; they can introduce contamination into the facility, equipment, and process stream that are very difficult to correct.
Microbial contamination cannot occur if the utility monitoring test results are passing	Microbiological testing has known limitations; the physical parameter data for HVAC, water, and gas offer early warning signs of performance issues that can lead to serious contamination. Physical parameters are monitored, and atypical trends are responded to in a timely manner.
Only action-level results require investigation and CAPA	Any atypical result or trend, including sub-alert level results, can be an early warning sign and may warrant investigation.

PDA TR90

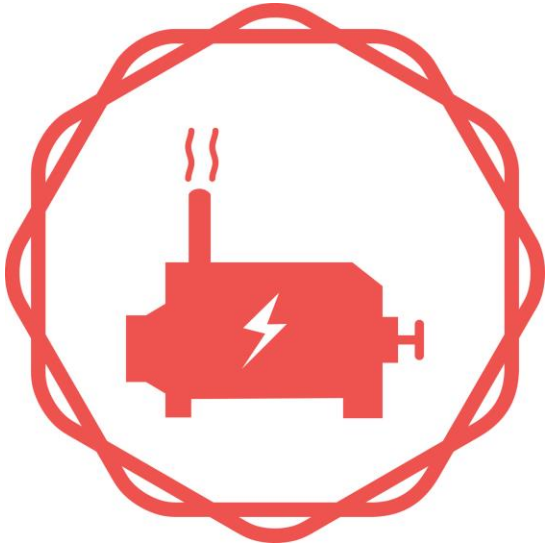
Water and Steam

Several detailed guidelines exist for contamination control of water systems because water is one of the main raw materials used in drug manufacturing

- **PDA Technical Report 69**
- **USP <1231> Water for Pharmaceutical Purposes**
- **ISPE Baseline Guide vol. 4: Water & Steam Systems**
- **EMA Guideline on the Quality of Water for Pharmaceutical Use**



Water and Steam

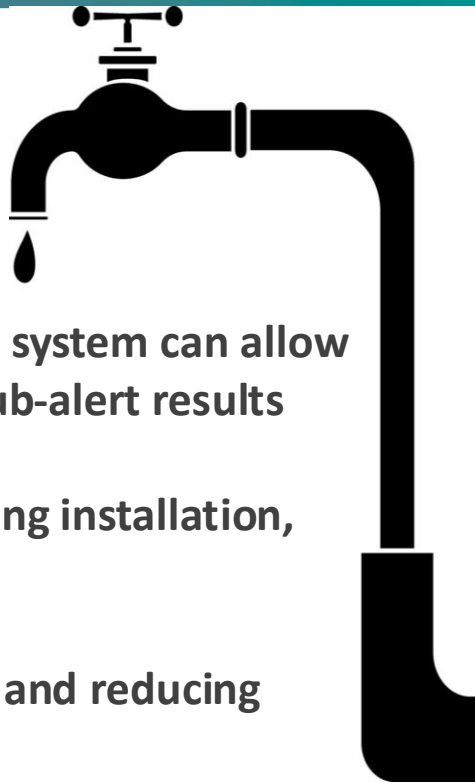


Steam is derived from process water and used for sterilization activities, which are critical to the CCS

Qualification and management strategies should be formed by an interdepartmental team that includes a microbiologist experienced in monitoring and contamination control

During the entire qualification period, all results, including sub-alert level results and species identification, should be reviewed for adverse trends by an appropriate SME

Water and Steam



Viewing new water systems as "inherently risky" is useful

Unknown flows in the design, assembly, or management of the system can allow microbial biofilm to develop, which may present as sporadic, sub-alert results

All recoveries in the water and steam system, especially following installation, should be identified to gather information and assess risk

PDA Technical Report 69 contains further details on preventing and reducing biofilm

Water and Steam

The routine water monitoring program should be based on QRM principles and the learnings from the qualification period

The critical points of use that deliver water to the process should be monitored more frequently than noncritical points of use that are used for facility cleaning or not used at all

Also, water ports that represent the worst-case location in the distribution loop should be monitored frequently

Water and Steam

On-line technologies, such as total organic carbon and conductivity, have increased the ability to detect water system problems in real time, potentially avoiding the use of compromised water for production

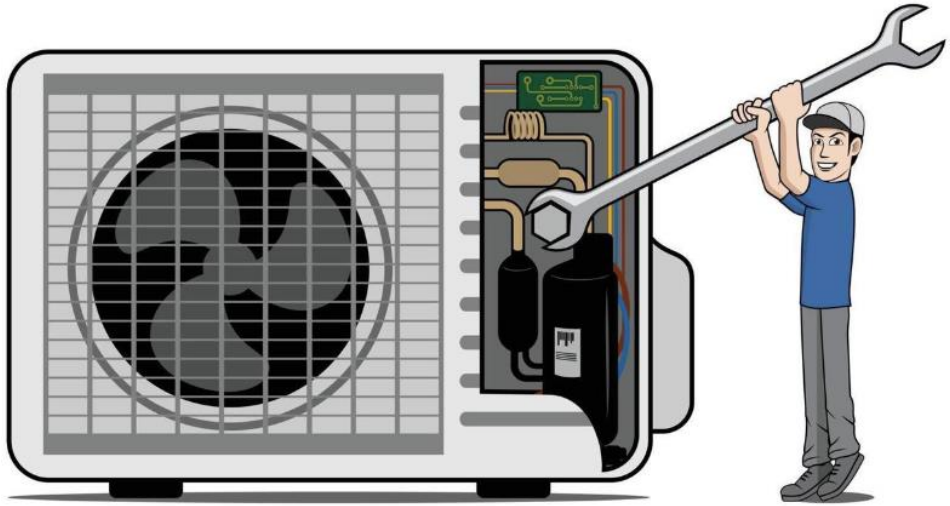
Similar on-line technologies for real-time bioburden and endotoxins are currently being investigated; they offer a huge advantage over lengthy lab-based assays in that atypical results are identified immediately and can be corrected, thus addressing contamination issue in a timelier manner.

HVAC

The heating, ventilation, and air conditioning (HVAC) system is a critical element of the contamination control strategy as it is the primary system that attains the appropriate environmental quality

In addition, isolators or other barrier technology should be used to protect sterile products

HVAC



Correct operation of the HVAC system ensures appropriate air quality by:

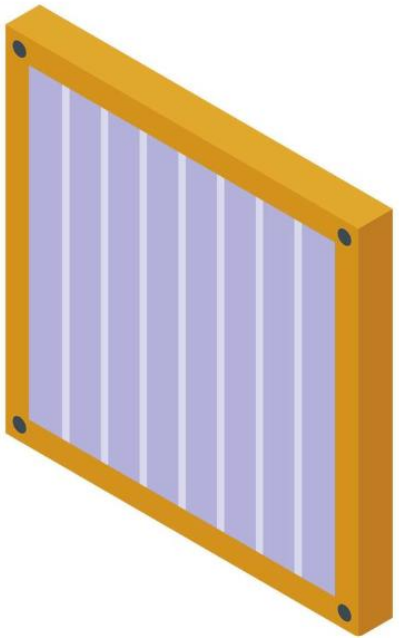
- **Introducing preconditioned air of the right quality**
- **Distributing dean air while removing contamination via strategically placed HEPA filters and air returns**
- **Establishing the air pressure cascade to prevent ingress of contaminants from less-controlled areas**
- **Maintaining the temperature and relative humidity to prevent microbial growth and provide optimal working conditions for operators (e.g., to avoid sweating, shivering, and distracting discomfort)**

HVAC

HVAC environmental controls should be optimized and qualified to maintain the appropriate level of environmental quality

To prevent process contamination, the other elements of the CCS, including the traffic of personnel and materials, cleaning and disinfection program, and specific hazards in each area, should be considered

An area with heavy personnel traffic will require more air changes than a lightly used area, and an area that is routinely exposed to steaming operations may require active temperature and humidity control and a robust exhaust system.



Gasses

Compressed gases are often introduced into the manufacturing process stream and into production equipment after point-of-use filtration

Noncritical support gases that are not product-contacting may also warrant strong control because they can impact other critical systems

Once qualified, a routine monitoring program should be put in place that includes physical and microbiological parameters

Moisture is a critical parameter because moisture can lead to microbial proliferation, especially for molds, which require less moisture than bacteria and yeasts

Gasses

Information about gases is provided in

- **ISO 12500-1 Filters for compressed air Test methods Part 1: Oil aerosols**
- **ISO 8573-1: 2010 Compressed Air- Part 1: Contaminants and Purity Classes**
- **ISPE's Good Practice Guide: Process Gases, and the major pharmacopeias**
- **PDA Technical Report No. 40: Sterilizing Filtration of Gases**

Control, Validation, and Monitoring

Environmental control is a fundamental part of the CCS because contaminants from the environment can enter the utilities, raw materials, equipment, and the process stream from the air and through surface transfer

A spike in environmental contaminants (e.g., seasonal variations) can challenge the other elements of the CCS

Molds and spore-forming bacteria are in high concentrations outdoors, and a spike in these organisms in the cleanroom can challenge the facility cleaning/disinfection and equipment sanitization/sterilization programs

Increased skin bacteria from the operators in the environment can challenge the aseptic processing controls; skin bacteria are still the most common contaminants found in products intended to be sterile

Control, Validation, and Monitoring

Environmental monitoring (EM) programs do not prevent or control contamination, but they provide an indicator of environmental quality through multiple discrete snapshots in time

The main purpose of the EM program is to measure the performance of the contamination controls related to the environment and to highlight the potential loss of control due to a variety of causes, such as personnel behavior, disinfection practices, HVAC equipment malfunction, and facility age

An ongoing generation of EM trends can be used for remediation to ensure that the facility continues to operate in a state of control and to prevent extrinsic contamination of the product

Control, Validation, and Monitoring

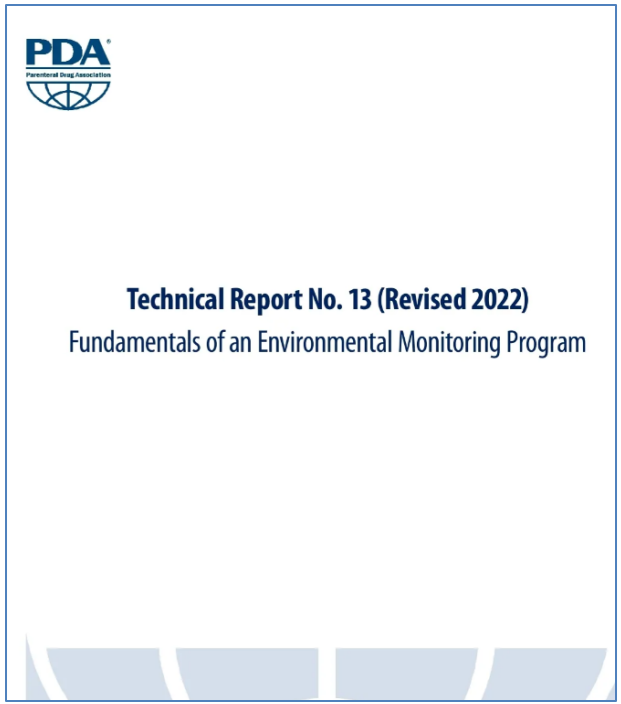
The effectiveness of an EM program is dependent on the proper identification of critical control points (CCPs) as part of a risk assessment (e.g., HACCP)

An EM program with acceptable trends should not be used to support poor aseptic or disinfection practices, for example, to defend a decrease in disinfection frequencies or the elimination of sporicidal agents

Control, Validation, and Monitoring

Setting Levels	Alert levels and action limits for impurities and contaminants serve to reinforce that purification steps are effective control measures in removing untoward substances at each step of the manufacturing process
	Alert levels and action limits for EM allow signals to be monitored and appropriate corrective action to be taken
Trending	Process trending below the action level is a highly sensitive measure for the consistency and effectiveness of cleaning and disinfection practices
Benefit to Preventing Contamination	
• Testing controls allow an understanding of the materials introduced and the environment in which the process is occurring. • Timely trending provides valuable information for decisions on EM programs and contamination risks. • Caveat: Laboratories should not be relied upon to detect contamination as a control of the process. Process and engineering controls should be put in place to control bioburden; laboratory testing only verifies the continued performance of those controls.	

Control, Validation, and Monitoring



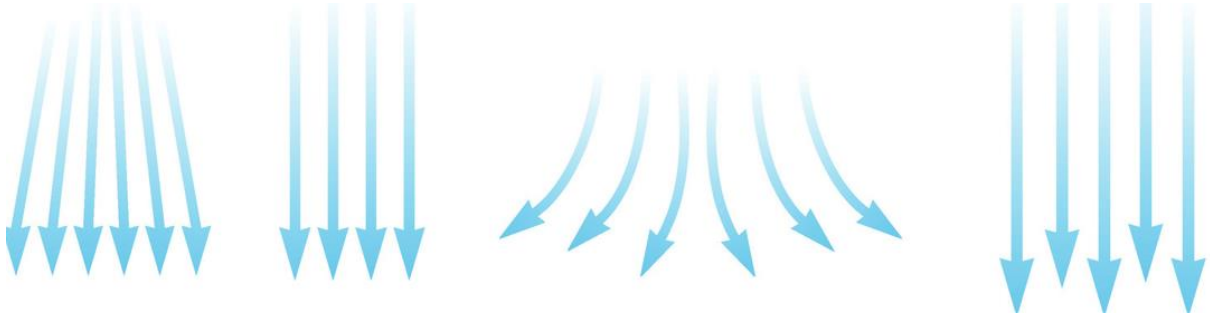
PDA Technical Report No. 13 (Revised 2022): Fundamentals of an Environmental Monitoring Program also provides extensive guidance on establishing an effective EM program for facilities, critical utilities, and personnel

EMPQ – Environmental Monitoring Performance Qualification

The EMPQ sample locations (including CCPs) should be selected based on a risk assessment using guidance from ISO 14644-1:2015 Cleanrooms and Associated Controlled Environments - Part 1: Classification of Air Cleanliness by Particle Concentration

Prior to the EMPQ, the new area should be fully functional with equipment installed and all relevant CCS programs established and underway

EMPQ



The cleanroom installation and operation qualification are outlined in ISO 14644 and include airflow visualization (smoke) studies, which should be performed under static and dynamic (worst-case or process-relevant) conditions

The data generated from the execution of the EMPQ supports the establishment of the ongoing EM program, which includes the selection of routine sampling locations

EM Requalification

Periodic requalification studies may be performed based on risk assessments, site validation procedures, or changes in the ongoing trend data or as required by local regulations

Annex I recommends Re-qualification of Grade A & B every 6 months and Grade C &D every 12 months

The study protocol should include the scope and requirements of the requalification, sampling plan, and acceptance criteria.

Utility Disruption and Recovery Plan

When a disruption occurs in a critical utility, the risk of contamination is inherently higher than during daily operations

For this reason, a containment strategy for disruptions and a recovery plan should be established with the aim of reducing the contamination risk

A disruption to the controlled , classified environment or critical utility may be planned or unplanned

Utility Disruption and Recovery Plan

Planned disruptions are deliberate, scheduled events, for example, construction projects, annual shutdown, preventive maintenance, equipment installation

Unplanned disruptions are unexpected events, such as leaks in critical utilities, loss of power, or equipment repair, and should be addressed immediately

The level of containment and recovery should be commensurate with the risk

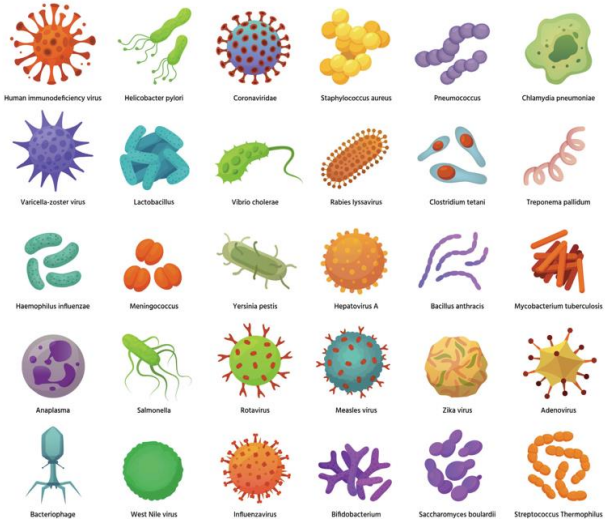
It is useful to define tiers of risk and outline the appropriate containment strategy and response plan for each tier

Utility Disruption and Recovery Plan

Level	Description
1	Noninvasive Disruption An activity that does not breach the integrity of a controlled classified area or critical utilities systems and is performed when no activity is occurring in the room/area. • Classified Areas, e.g., caulking repair, light switch or outlet repair (no cutting), spot painting (no sanding), calibration activities • Critical Utilities, e.g., preventive maintenance, valve maintenance, calibration
2	Invasive Disruption An activity that breaches the integrity of the controlled classified area or critical utilities systems and is performed when processing is occurring in the room/area. Classified Areas, e.g., opening an electrical panel, equipment repair or maintenance, light bulb change, sprinkler cover replacement Critical Utilities, e.g., cutting, welding, piping replacement, derouging, chemical cleaning

Sources of Contamination in Utility Systems

- Personnel – direct contact with points of use
- Inadequate or missing filtration
- Lack of maintenance
- Aging equipment
- Improper sloping
- Dead legs
- Rough surfaces and rouging (biofilm)
- Inadequate cleaning and sanitization processes
- Gasket management
- Valve management and maintenance
- Poor training or SOP instructions, causing operator error

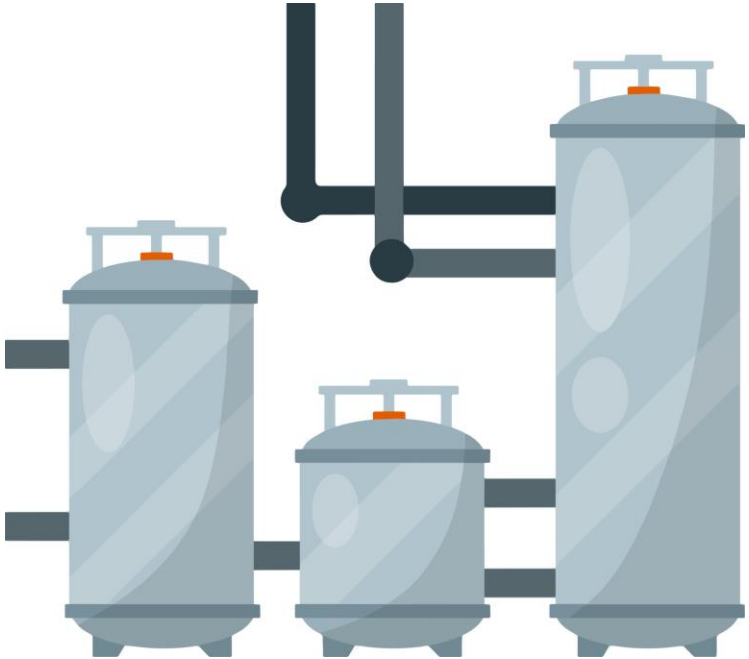


Investigating Critical Utility System Deviations

- Assemble a cross-functional team to investigate
- Assess both the laboratory practices (Phase I) and physical location and points of use (Phase II) for the utility
- Perform GEMBA to visualize the area of concern – look up and downstream of the issue
- Observe sampling and use of the point in question, if possible
- Compare practices vs SOP instructions
- Review change controls, recent maintenance, and historical EM data
- Document what was inspected, and what was ruled in/out as potential root causes
- Assess if there are other systems that have the same potential for contamination/deviation and apply preventive measures if possible
- Perform documented remediation and any necessary requalification

Summary

- Utilities are a key part of the Contamination Control Strategy and have great impact on the quality of products
- Thoughtful design and installation of critical utilities is necessary to ensure proper performance
- Risk assessment should be performed to identify critical control points and sampling locations
- There are many ways to contaminate utility systems
- Environmental Monitoring of utilities provides a way to visualize the level of control in the system
- Having a plan for disruption and outages will help to stay on track when systems go down



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