

Microbial Contamination and Control Conference

Contamination Control Strategies for Critical Utility Systems

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PDA[®]
Parenteral Drug Association
Midwest Chapter





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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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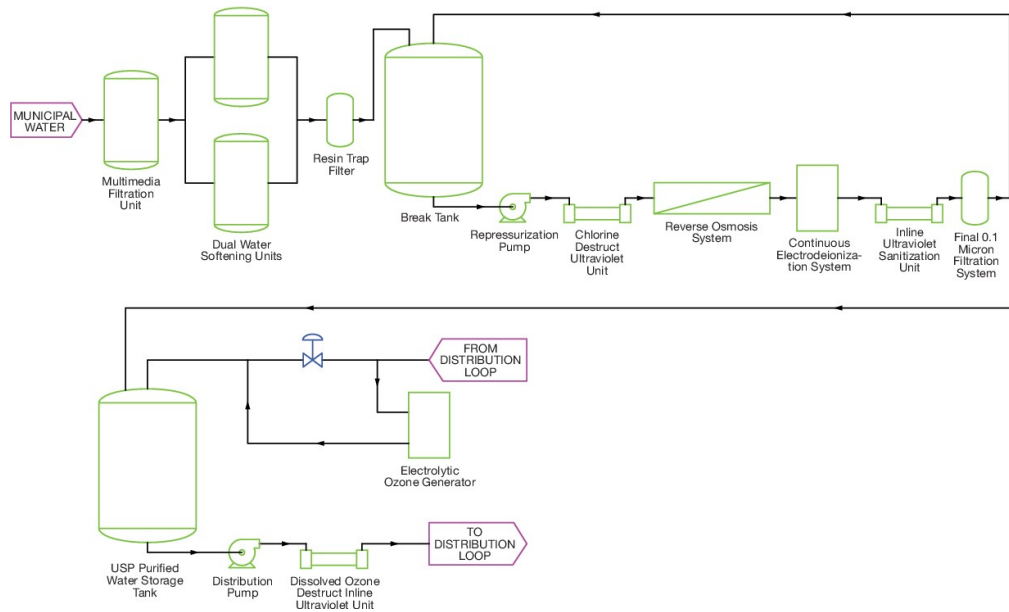


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Discussion Topics



- Contamination Control Strategy background
- Overview of Critical Utility Systems
- Understanding the role of critical utilities in contamination risk
- Regulatory expectations and observations
- Utility specific Contamination Control Strategies
- Integrating Utilities into a Contamination Control Strategy



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Critical Utilities

Directly impact the quality and safety of the final product





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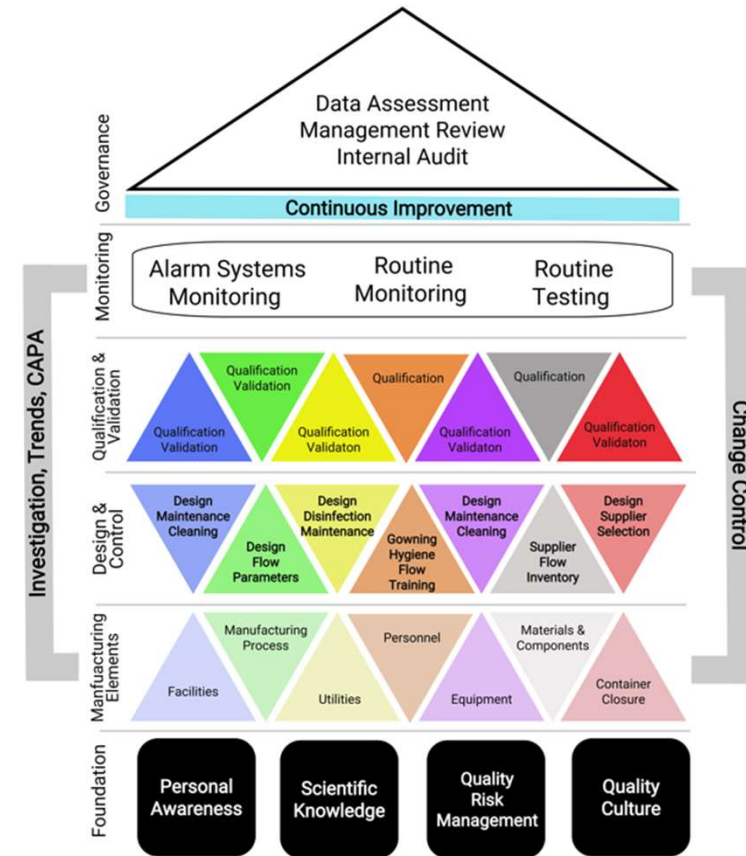
Contamination Control Strategy

EU GMP Annex 1 (2022) requires holistic CCS, to include the following for utilities:

*“The nature and extent of controls applied to **utility systems** should be commensurate with the risk to product quality associated with the utility. The impact should be determined via a risk assessment documented as part of the CCS.”*

*“The development of the CCS requires **thorough technical and process knowledge**. Potential sources of contamination are attributable to microbial and cellular debris (e.g. pyrogen, endotoxins) as well as particulate matter (e.g. glass and other visible and sub-visible particulates). Elements to be considered within a documented CCS should include (but are not limited to):*

*... Preventative maintenance – maintaining equipment, **utilities** and premises (planned and unplanned maintenance) to a standard that will not add significant risk of contamination.”*



Derived from PDA TR90



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Regulations and Guidance for Utilities (not entire list)

- **EU GMP Annex 1 (2022), Utilities:** design, installation, operation, and maintenance. Trending, life cycle, cleaning and disinfection
- **FDA Sterile Drug Products Guidance:** System design, integrity, validation, deviations, change control, and monitoring of utilities
- **FDA Inspection Technical Guide:** Water for Pharmaceutical Use – sources of contamination, expectations for function
- **USP <1231>, Water for Pharmaceutical Purposes:** Water quality standards, maintenance to produce high quality water, qualification, monitoring of the water system
- **PIC/S GMP for Medicinal Products, Premises and Equipment:** design, impact, cleanliness, maintenance, controls
- **PDA Guidance:** Points to Consider No. 1: Aseptic Processing (2024), TR1 (Steam), TR40 (Gases), TR48 (Steam), TR61 (Steam/SIP), TR69 (Water/biofilm), multiple for QRM/risk assessment, ANSI PDA Standard 03-2025 QRM of Aseptic Processes, TR90 (CCS)
- **ISPE Good Practice Guide on Critical Utilities:** Practical recommendations and best practices for water, steam, compressed air, and medical gasses, maintenance, sampling techniques





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Risk Management Approach for CCS



- Apply ICH Q9 Risk Management Principles
- Perform Criticality Assessments
- Identify Contamination Types
- Develop Control and Monitoring Plans



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Critical Utility Systems Contamination Overview

- Pharmaceutical water (WFI, PW, Clean Steam)
- Compressed gases (Air, Nitrogen, others)
- HVAC systems – HEPA filtration
- Other utility systems (vacuum, CIP/SIP)



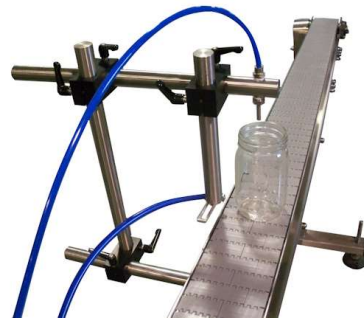
Cleaning



Formulation



Product Transfer



-Blanketing
-Purge
-Overlay



Particulate Control



CIP/SIP

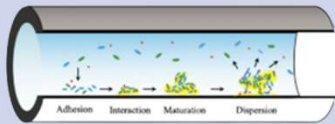

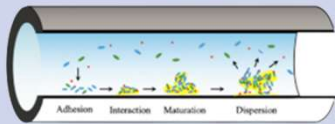


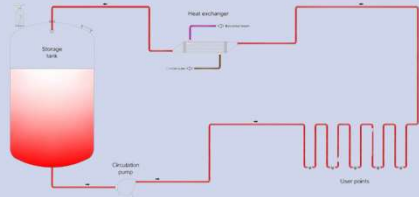



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Pharmaceutical Water/Steam Systems Contamination

Microbial	Particulate	Chemical
Biofilm 	Corrosion 	Leachables Chemical sanitization
Dead legs 	Filtration Failure Lack of Maintenance	Feedwater quality
Slope 	Materials of construction (surfaces) 	
Flow rate Valves Sanitization method/frequency 		






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Pharmaceutical Gasses Contamination

Microbial	Particulate	Chemical
<p>Moisture</p> <p>Poor drainage</p> 	<p>Filtration inadequate/failure</p> <p>Rust/debris – corroded piping or compressor wear</p> 	<p>Oil (filtration failure)</p> 

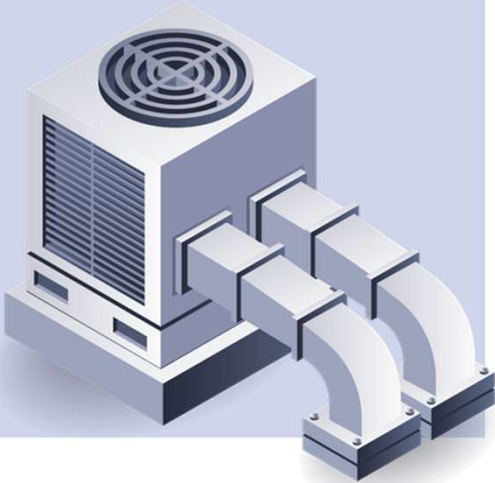


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Pharmaceutical HVAC System Contamination

Microbial	Particulate	Chemical
Filtration failure/degradation	Leaks in HEPAs	N/A
Ducting	Unsealed ductwork	
Condensation	Lack of Maintenance/Cleaning	
	Stagnant air/flow	
	Backflow (pressure differential)	





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Examples of Utility Contamination and Observations

US Pharmaceuticals Inc. (FDA Warning Letter 573233, June 6, 2019)

- The purified water system exhibited recurring excessive microbial levels dating back to 2016.
- Design issues, including biofilm formation, were identified in 2016 but remained unaddressed.
- Sampling procedures were inadequate, with samples collected immediately after system sanitization, not reflecting actual water quality during manufacturing.

Impact on Contamination Control Strategy:

- The FDA mandated a comprehensive, independent assessment of the water system's design, control, and maintenance.
- A detailed corrective and preventive action (CAPA) plan was required to remediate and validate a suitable water system.
- Revised procedures for daily microbiological sampling and microbial identification.



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Examples of Utility Contamination and Observations

Pure Source LLC (FDA Warning Letter 555240, February 20, 2019)

- The firm used deionized water without adequate validation or chemical and microbial testing.
- Acceptance limits for water quality were inadequate, and microbial monitoring was infrequent.

Impact on Contamination Control Strategy:

- The FDA required a comprehensive evaluation of the water system design, including a CAPA plan to install and validate a suitable system.
- An effective program for ongoing control, maintenance, and monitoring was mandated
- The firm was instructed to increase the frequency of microbial testing and assess the impact of water system deficiencies on the quality of products within expiry.



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Examples of Utility Contamination and Observations

In 2016, the FDA and CDC traced a multistate outbreak of *Burkholderia cepacia* infections to the water system at PharmaTech's Florida facility. The company had produced 10 contaminated lots of the constipation drug docusate sodium, which were distributed to six U.S. states.

Sixty patients, including those with cystic fibrosis, were affected. The outbreak led to a nationwide recall of the affected product and highlighted the risks of waterborne pathogens in pharmaceutical manufacturing.

Tom's of Maine Toothpaste Contamination (2021–2022)

The FDA identified the presence of *Pseudomonas aeruginosa* and *Ralstonia insidiosa* in the water used at Colgate-Palmolive's Sanford, Maine plant.

These bacteria can cause severe infections, especially in immunocompromised individuals.

The FDA issued a warning letter criticizing the company's inadequate response and lack of comprehensive assessment of their manufacturing operations.

Tom's of Maine engaged water specialists and invested in upgrading the water system to address the issues.

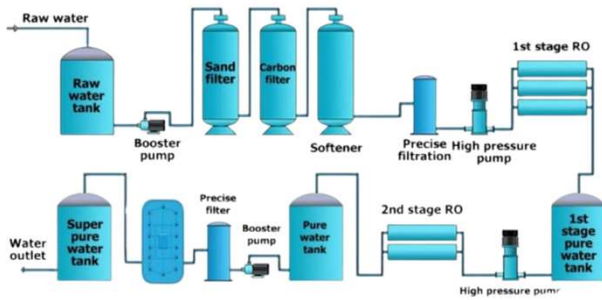


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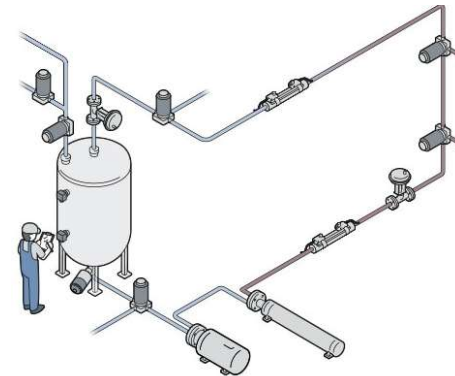
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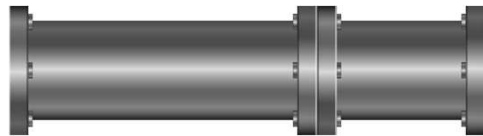
Utility Contamination Controls (+Prevention)



Design & Qualification



Maintenance



Materials



Filtration



Sanitization



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Why do Utility Systems get Missed in CCS?

- Assumed Coverage Under Other Systems
 - Utilities are controlled under independent qualification and monitoring systems
- Lack of Cross-Functional Coordination
 - Failure to get input from all relevant teams when developing the CCS, leading to gaps
- Misunderstanding of CCS Scope
 - Scope of CCS is too narrow and fails to identify utility systems as potential contamination sources
- Legacy Systems and Documentation Gaps
 - Aging and older facilities may have been installed when documentation was not as controlled, or documentation was not updated over time
- Assumption of Low Risk
 - Critical utilities are running in the background, automated, and/or closed systems that do not get captured as a risk in the CCS



Just to save time you understand, it's best if we assume I'm never wrong.



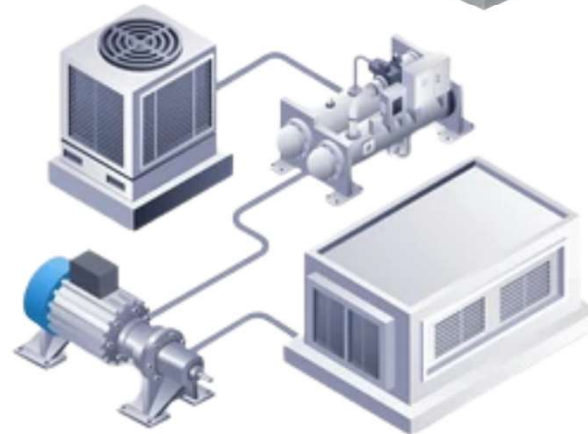
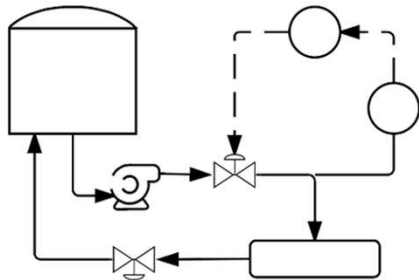
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Including Critical Utility Systems in your CCS

Steps to ensure a holistic consideration of Utility Systems in your CC Strategy





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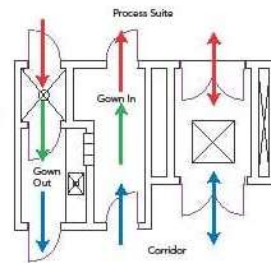
Including Critical Utility Systems in your CCS

1. Identify the applicable Utility Systems

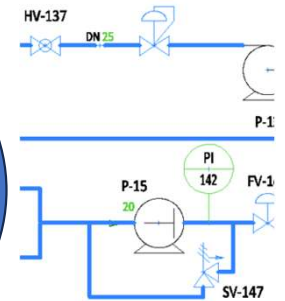
Subject Matter Experts



Facility Maps & Drawings



Utility Drawings



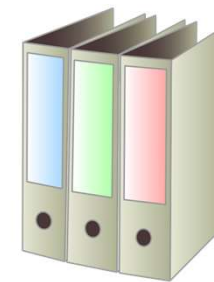
System Owners



GEMBA observation



Commissioning and Qualification Documents





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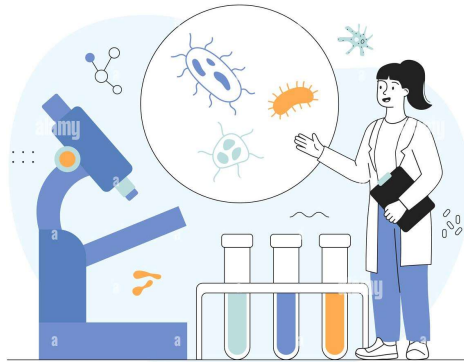
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Including Critical Utility Systems in your CCS

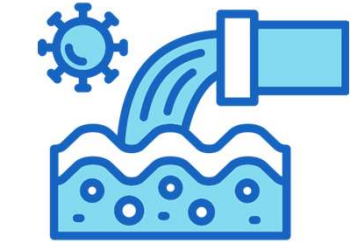
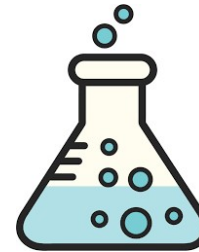
2. Assess Contamination Risks

Microbiological / Endotoxin

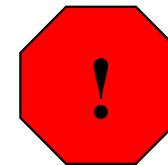


Particulate

Chemical



Extraneous / Cross Contamination



Don't forget your Risk Assessment tools!



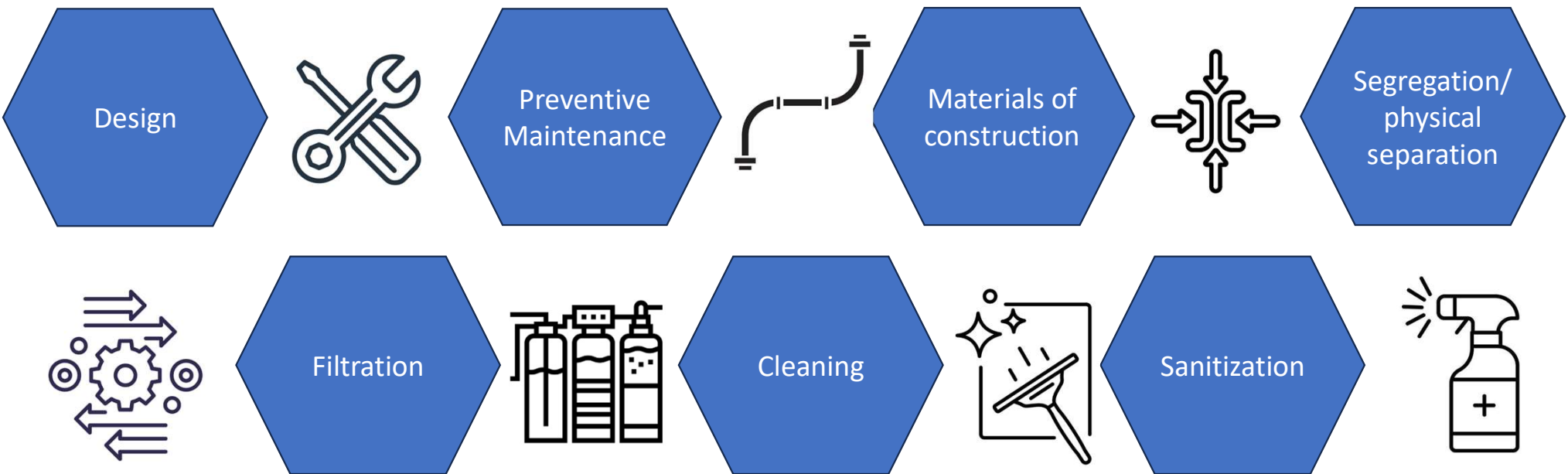
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Including Critical Utility Systems in your CCS

3. Define Controls





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Including Critical Utility Systems in your CCS

4. Include Qualification and Validation

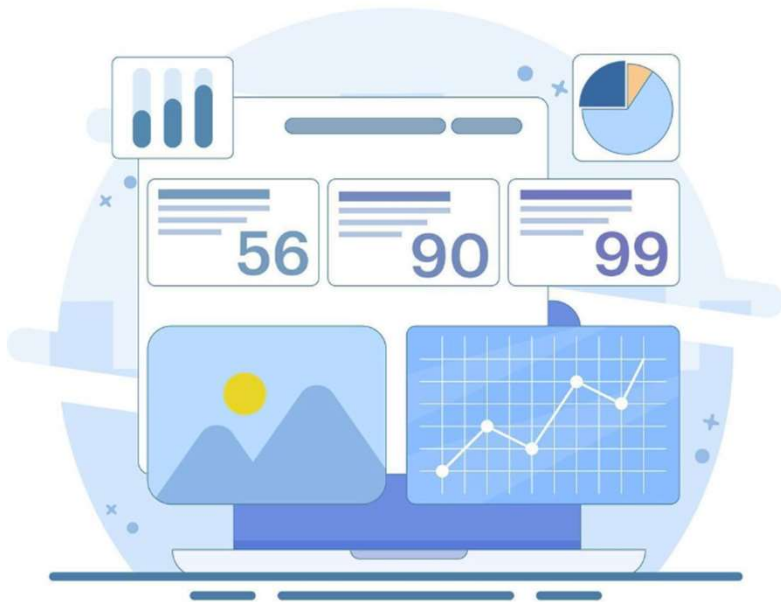
- Reference and Summarize URS, DQ, IQ, OQ, and PQ
- Discuss Initial and Periodic Requalification Plans
- State how these align with Contamination Control Objectives





Including Critical Utility Systems in your CCS

5. Describe Monitoring and Trending



- Define what is monitored
- Trending program for data from utilities
- How deviations and OOS are addressed
- How CAPAs and changes are integrated back into the 'living document' CCS



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Including Critical Utility Systems in your CCS

6. Indicate Interfaces with other Systems

- Integration locations
 - Water to CIP
 - Gas to filling line
 - HEPA's to cleanroom
- Contamination Controls at each interface point (filters, valves, pressure)





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Including Critical Utility Systems in your CCS

7. Roles and Responsibilities

- Clarify Ownership
- Show handoffs in responsibility





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Including Critical Utility Systems in your CCS

8. Continuous Improvement

- State that Utilities are included in periodic reviews of the CCS
- CAPAs involving utilities are tracked
- CCS is updated for changes made to the utility systems



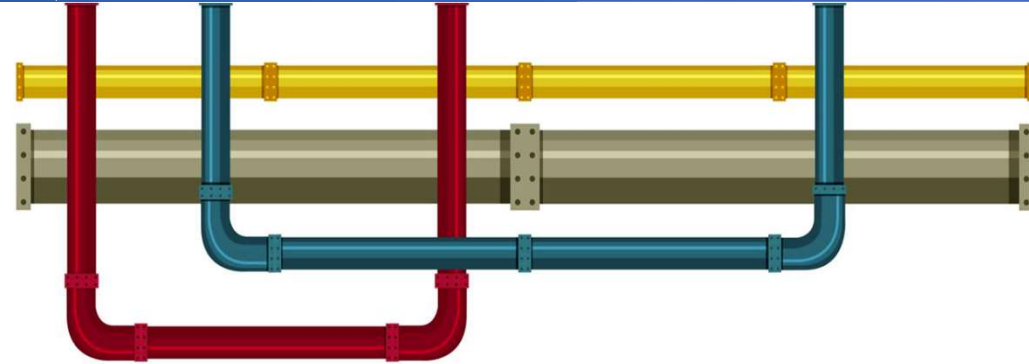


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Summary



Pharmaceutical Critical Utility Systems:

- Are the backbone of a well-functioning facility
- Require risk-based understanding to define contamination potential
- Have significant impact on contamination control for products
- Often run in the background unnoticed, until there is an issue
- Require thoughtful and thorough inclusion in your CCS!

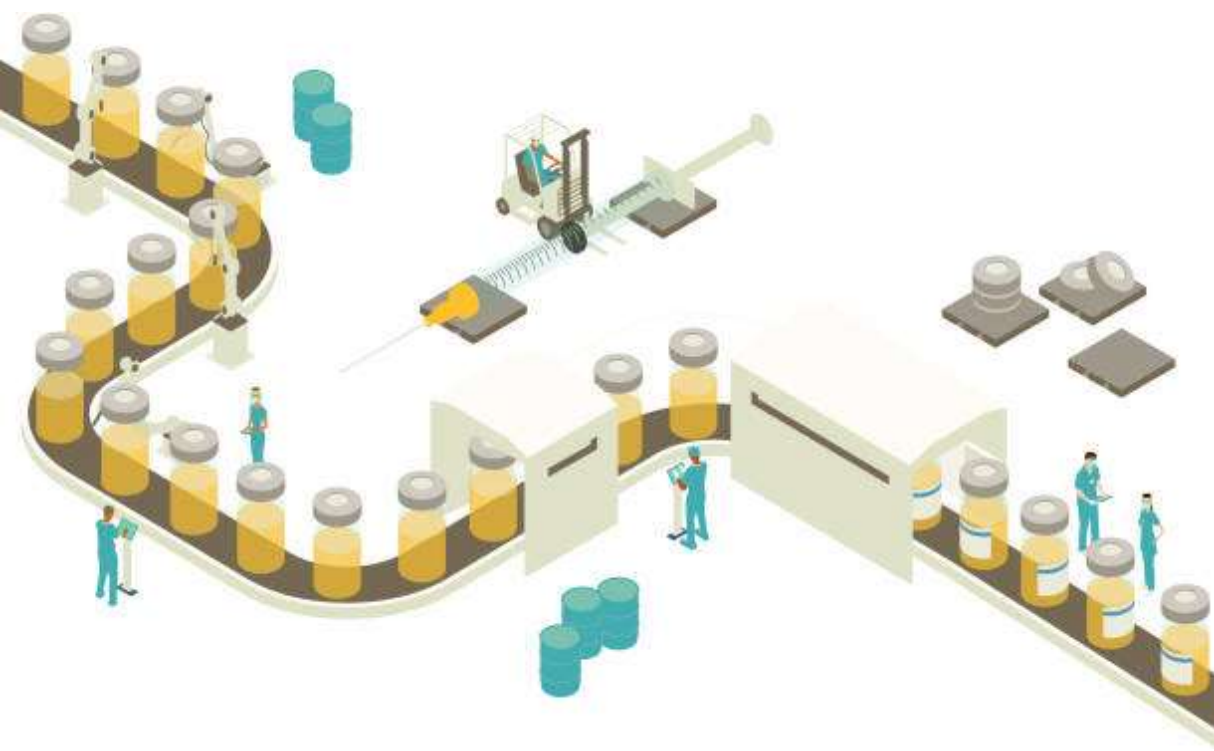


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Thank You!



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