

HYDE HIGHLIGHTS

Just Published

Ruggedness of visible-residue limits for cleaning (part 2), by Richard Forsyth, Principal Consultant, in Pharmaceutical Technology

April 5

ISPE CASA Annual Tech Show—Hyde presents “New approaches for cleaning for biologics” in Raleigh, NC

April 11–14

PDA Annual Conference—San Antonio
Ronald Berk, VP Engineering presents “Producing vaccines for the global marketplace”

SIP/Autoclaves: Project Success Factors For Reducing COGS

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When it comes to COGS, nothing is more important than getting a new facility up and running as quickly as possible, whether for getting a new product to market or minimizing the duration of redundant manufacturing operations when transferring a product from one facility to another.

The validation of sterilization processes is among the most critical to product quality. Most sterilization processes use clean steam as the sterilizing agent. The project team must have expert knowledge of the following considerations:

- An understanding of the mechanism of action of clean steam in delivering sterilizing lethality to equipment surfaces
- Understanding the principles and standards of design
- Applying the most efficient and robust approach to the design and validation of effective steam sterilization cycles

A system lifecycle approach, as shown in the following figure, should be followed, with all stakeholders involved.

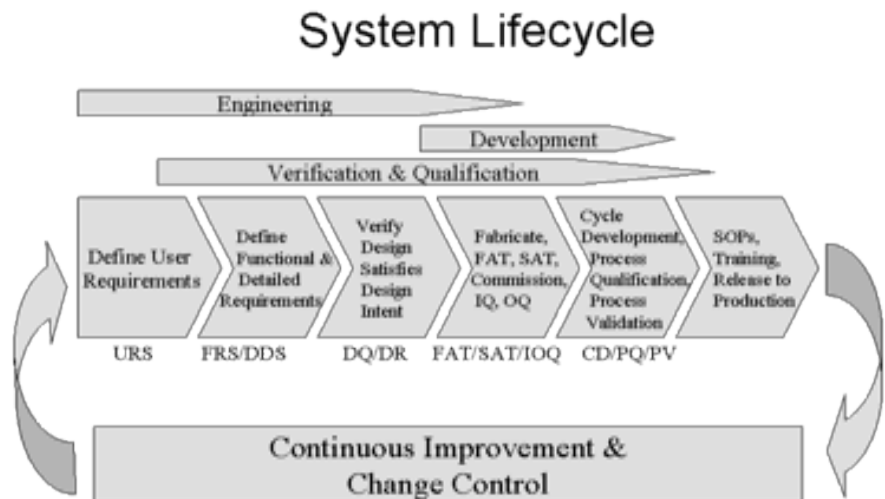
Mechanism of Delivering Lethality

Microorganisms are killed by the latent heat released from condensing steam. The effectiveness of this process is typically

described as the “lethality factor” or F-value, expressed in minutes. The F-value is calculated using algorithms that use time, temperature, and the heat resistance characteristics of the target microorganism. The minimum expectation is a sterilization cycle that delivers an accumulated F-value of at least 12 minutes at a minimum temperature of 121.1°C (250°F) under clean, dry

saturated steam conditions. Critical Process Parameters (CPPs), are Time, Temperature, and, by necessity to verify saturated steam conditions, Pressure. Such a cycle is generally understood to reduce a microbial population from about one million to less than one, yielding a minimum 6-log reduction in population, also known as a Spore Log Reduction (SLR) of 6.

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The sterilization project team expertise is applied first to establish user requirements, then at the conceptual and detailed design phases, and finally in the preparation of the qualification master plan, design qualification reviews, and execution of the various qualification activities.

System Design Considerations

To ensure that acceptable lethality is delivered to all necessary locations within a system, several key considerations and principles must be understood and addressed by the design and qualification team.

- A validated source of clean, dry saturated steam must be provided. If steam is wet or superheated, the heat transfer rate from condensing steam to surfaces will be adversely affected.
- The sterile boundary of the system must be defined, and steam sterilization across the boundary-forming elements, such

as valves and filters, must be ensured. System visualization techniques such as valve sequence tables, marked up P&IDs with steam paths and sterile boundaries highlighted. For autoclaves, the items to be sterilized must be understood as to their characteristics that might affect steam penetration (for example, porosity, mass, surface area, or steam path), and organized into technically sterilizable loads (such as with large items on the bottom of a load, and all items oriented to drain condensate).

- Steam must be able to penetrate all surfaces. If air or condensate is trapped in pockets in the system, steam will not penetrate to the targeted surfaces, and lethality will not be delivered. The system must therefore be designed for rapid and complete clearance of air and condensate. While not recommended for piping and vessel systems, the use of an air-removing vacuum phase in the cycle prior to the

exposure (or dwell) phase is typically a feature in an autoclave cycle.

- Filter and seal integrity must be maintained, system materials of construction must be compatible with steam under pressure, and pressure and temperature gradients must be managed to avoid damage to goods (such as wrapping materials, bottles, gaskets, polymers, etc.).
- CPPs must be controlled and monitored to certain accuracy and precision standards to ensure delivery of lethality.

A summary of a hypothetical FMEA assessment is shown in the chart below:

Efficient Qualification

Efficient qualification begins in the design review phase of the project.

The system locations assessed during the FMEA, design review, or commissioning testing as the most likely to challenge the efficacy of the sterilization

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Failure Modes	Failure Effects	Potential Root Causes	Preventive Actions
CPPs Time, Temperature or Pressure out of range	Reduced lethality if Low, Component damage if High (especially filters), Cycle aborts	Steam supply pressure fluctuation; poor design of steam regulation and time control; mechanical failure (trap, valve)	Design steam supply regulation and time control to reduce variation; Specify appropriate and robust components.
Air/Gas Entrainment	Temperature looks good, but lethality is reduced. Validation fails.	Poor System Design, Poor Steam Quality, Poor Cycle Design	Design system and cycle for air removal; provide proper steam quality; test and monitor steam quality
Steam either superheated or wet (entrained water)	Temperature looks good, but lethality is reduced. Validation fails.	Temperature/Pressure ratio not controlled to maintain saturated steam; Poor Steam Quality; Overheating of system jacket.	Design instruments and controls to manage T/P ratio adequately; provide proper steam quality, monitor and test. Control jacket to avoid overheating.
Condensate pooling	Temperature lower than rest of system; lethality reduced. Validation fails, or cycle aborts.	Poor System Design, Mechanical Failure of Traps or Valves, Autoclave Load not designed properly	Design system and load for condensate draining and removal; Specify robust components.
CQAs of system or load are not met	System components or load items are damaged and not functionally fit for use. Sterility could be compromised	Poor System Design, Poor Cycle Design	Design system to withstand proposed cycle. Design cycle to avoid damage to system or load items.
Sterile Boundary	Loss of sterility or containment	Poor boundary definition and design	Design manages integrity of boundary
Target Lethality Not Attained	Lack of assurance of efficacy	Organism D and Z-values not known	Characterized the organism(s), design cycle accordingly

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cycle will have been identified, and the system design will have incorporated access ports and physical configurations that allow easy placement of thermocouples (TCs) and biological indicators (BIs). Instruments and controls will have been installed to facilitate data gathering, process control, and use of those data for qualification.

For autoclaves, understanding the items and loads early in the system lifecycle eases the application of item- and load-validation bracketing approaches, which can minimize testing requirements during validation. Sound and well-documented bracketing approaches will minimize the effort required to introduce new items after initial qualification work has been completed.

Conclusion

With adequate understanding and application of steam sterilization science, system design principles, and efficient qualification techniques, and by applying a system lifecycle approach with all stakeholders represented, project teams should be able to reliably deliver rigorous, efficiently qualified, and well controlled sterilization processes—all of which contribute to rapid readiness of a commercial production facility.

FDA Process Validation Guidance Revision Issued. What's Changed?

Two years ago the FDA issued a well-thought-out draft revision of the 1987 Process Validation guidance. The draft elaborated on modern Quality by Design (QbD) techniques for developing a process, analyzing risks, and monitoring control. In January, the FDA finalized Process Validation: General Principles and Practices, Revision 1. The initial draft remained largely intact, with adjustments focused on clarifying the FDA's intent, substantiating recommendations with more references to the CFRs, and the addition of a glossary. However, there were two notable changes.

The first change is the elimination of required process testing at extreme conditions that pose a high risk of process failure. This implies that the FDA is more interested in a firm proving acceptable operating ranges within that firm's commercial manufacturing conditions than in testing a process beyond actual conditions to the point of certain failure.

For products already on the market, the guidance clarifies that legacy products with an established history of operating in a

stage of control should leverage their existing process development and qualification data and focus on Stage 3 (ongoing process monitoring). This should alleviate industry concern that the guidance would create an expectation for substantial new characterization studies for existing processes.

Another significant change in the latest revision is the removal of the expectation that viral inactivation and impurity clearance studies be "performed under GMP conditions." Here the FDA correctly clarified that the intent is that the studies should have "quality unit oversight." The guidance still stops short of explaining specifically when to reduce the intensive testing of Stage 2. However, it does add that firms should consider process complexity, production volume, process knowledge, and experience. In effect, use the principles of QbD: the more experience and knowledge you have with your process, the lower the risk of a problem.

For a more detailed analysis of what has changed with this latest revision, read our white paper at www.hyde-ec.com/resources/publications.

Experts Ask Experts

Q: We are developing a cleaning cycle and seeing final rinse water conductivity values of 2.5 $\mu\text{S}/\text{cm}$. Is there a precedent for setting acceptance criteria above the USP WFI Stage 1 value of 1.3 $\mu\text{S}/\text{cm}$ at 25°C?

A: Justification or acceptance criteria is a must regardless of what levels you are setting—even if you rely on the USP levels. An ICH Q9 risk assessment will help build your justification as discussed in the FDA inspection guide Validation of Cleaning Processes (7/93) by considering the following questions:

- What is the process stream? Upstream or final product step?
- What are the potential contaminants that would contribute to conductivity (for example, detergents, product residue)?
- Are those contaminants detrimental to product quality and

safety at the level chosen?

- What are the clearance steps? Will they reduce the carry-over contaminant levels?
- Given the batch size, what would be the concentration of the contaminant in the product?
- How do rinse water values correlate to surface residue levels? Perform carryover calculations and studies as necessary.

Most cleaning cycles are capable of meeting USP WFI limits, since WFI is produced well below these limits. Difficulty in achieving them may indicate problems with piping design, cycle design, or conductivity probe placement. Be sure to document your justification, for as the FDA guidance states, "The objective of the inspection is to ensure that the basis for any limits is scientifically justifiable."