MOIST HEAT STERILIZATION VALIDATION AND REQUALIFICATION

Introduction

Moist heat (steam) sterilization processes in environments that follow current Good Manufacturing Practices (cGMPs) involve autoclaves that must be installed and validated prior to use, and requalified on a routine basis. This Technical Tip is not intended to provide detailed process descriptions of validation and requalification, nor to provide instruction on the types of moist heat applications and vessels (retorts, hot water spray autoclaves, steam/air mixture autoclaves, steam-in-place of equipment, etc.); rather, it is intended to answer common questions regarding the use of STERIS Sterility Assurance Products (SAP) during validation and requalification of equipment used for moist heat sterilization processes.

This document provides a short background on validation and requalification answers to frequently asked questions (FAQs), lists STERIS products typically used in initial validation or requalification, and references the standards and guidance documents that detail the validation and requalification processes.

Basic primers on moist heat sterilization procedures are available in the literature. Understanding moist heat sterilization cycle principles can help avoid common mistakes made when using steam autoclaves and similar equipment.

Why do we validate a process at all? In addition to the importance of validation, it is expected by both the Food and Drug Administration (FDA) and European Medicines Agency (EMA). The FDA cites the Code of Federal Regulations Title 21 Part 211 (21 CFR 211.113[b]) “Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.” The EMA Guideline on process validation for finished products views process validation not as a single event, but as “a lifecycle approach linking product and process development, validation of the commercial manufacturing process, and maintenance of the process in a state of control.”

Definitions

The terms validation, qualification and requalification are sometimes used interchangeably, but they in fact are different, and the definition of each term can vary slightly depending on the guidance document or standard. For example, in the Parenteral Drug Association’s (PDA) Technical Report No. 1, the definition of validation is “a documented program that provides a high level of scientific assurance that a manufacturing process reliably produces acceptable product. The proof of validation is obtained through rational experimental design and the evaluation of data, preferably beginning from the process development phase and continuing through the commercial production phase.”

ISO 17665-1 defines validation as a “documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specification.”

In contrast, qualification is typically not used to describe an overall process, but can be a component of an overall validation program, e.g., Installation Qualification (IQ) and Operational Qualification (OQ). ISO 17665-1 defines requalification as “repetition of part of validation for the purpose of confirming the continued acceptability of a specified process.” Successful requalification provides assurance that inadvertent process changes have not compromised the process.

Validation Overview – IQ, OQ, PQ

A typical validation exercise is comprised of three parts, all of which are required as part of overall validation scheme (Figure 1). Performance Qualification (PQ) always follows parameter development and is crucial for the life cycle approach to sterilization process validation. Prior to PQ, the following activities should be completed and documented according to company sterilization policy and current regulatory expectations:

- Utility qualification, e.g.; steam, compressed air, water, electric supply for proper functioning of the sterilizer
- Sterilizer Design Qualification (DQ), IQ, OQ or commissioning, and calibration of control systems, monitoring devices, and alarms
- Development of parameters for each phase of the cycle
- Defining loads, load patterns, and which loads are used in qualification studies
- Temperature mapping of the chamber and load items to identify appropriate locations for physical and biological monitoring

The IQ shall demonstrate that the sterilization equipment and ancillary items have been supplied and installed per specification. For a list of items typically checked during IQ, see Practical Guide to Autoclave Validation. The OQ shall demonstrate that the installed equipment is capable of delivering the specified process within defined tolerances, and that it is ready for load testing. For a list of items typically checked during OQ, including use of the Bowie-Dick test pack in an empty chamber. The PQ shall use product to demonstrate that equipment consistently operates in accordance with predetermined criteria, and results in a sterile product.

The PQ is comprised of both physical qualification and microbiological qualification, as seen in Figure 2. Consistency between physical and microbiological results is central to sterilization validation. The initial sterilizer validation typically includes three consecutive acceptable runs for each load configuration evaluated. It is important that biological challenge results should be in general agreement with physical data, and vice versa.
Use of Thermocouples, Steam Integrators and Biological Indicators

As part of PQ, loaded chamber steam penetration runs are conducted on every load. This is a time consuming process as it requires determining which load items are the most difficult to sterilize and which locations, within the items, present the worst-case conditions. To find the worst-case items/locations, both Thermocouples (TC) and steam integrators are used. The TC provides a direct physical measurement of temperature at the location of the probe tip, while the chemical indicator/integrator (CI) provides an indication of the exposure to steam to a defined set of values. Many experts recommend use of steam integrators in addition to TCs, as TCs can give misleading data, for example, measuring a temperature without regard to whether steam (without air) was present around the probe tip. Typical worst-case locations are within long sections of tubing (the center), and in items that can trap air such as upright bottles, flasks, vials and graduated cylinders. These items should be placed on their sides or upside down, if possible, to minimize the presence of trapped air. Use of a steam integrator, such as the VERIFY® Integrating Indicator for Steam Sterilization (product PCC039), can help minimize the number of runs needed to challenge a load, as one can use as many as one wants, whereas the number of TC probes is usually limited.

Once the worst-case items and locations (in the chamber) have been determined using both temperature distribution mapping and heat penetration studies, load configurations (which can be fixed or variable) should be determined. This exercise is also known as “cycle development” or “trial runs.” It determines what maximum load can physically fit into a chamber, and allows for determination of heat penetration and minimum accumulated heat lethality across the load. This information provides a basis for repeatable acceptance criteria for the PQ protocol. This avoids problems with documentation (amendments and deviations) of the PQ execution that one encounters if proceeding without knowing pre-defined acceptance criteria. This practice is analogous to commissioning/start up activity prior to execution of the IQ/OQ protocol to eliminate deviations and keep a GMP protocol as clean as possible.

At this point, the items are challenged with biological indicators (BIs). It is recommended that a TC be placed along with each BI, as temperature data is needed to extrapolate the cycle to achieve the desired Sterility Assurance Level (SAL) which should be at least 10^{-6}. Placing the BI adjacent to the temperature sensor allows for correlation between microbial lethality (F_{Bio}) and predicted lethality (F_{Phy}) based on thermal input. Runs are conducted with various cycle times until three consecutive runs show no BI growth post-processing. Best practice includes rotating TCs from run to run, and each TC probe should be labeled with autoclave tape. TC calibration should be verified frequently, especially if the PQ encompasses multiple days or weeks. Extensive documentation should be kept, including diagrams showing the location of all load items, and which items contain integrators as well as the locations of TCs and BIs.

Requalification

Ongoing process control – when to requalify?

The FDA guidance on aseptic processing states that “Requalification studies should also be performed on a periodic basis. The specific load configurations, as well as biological indicator and temperature sensor locations, should be documented in validation records. Batch production records should subsequently document adherence to the validated load patterns.”

Subsequent to the initial validation, ongoing event-based requalification (change control) and time-based requalification should be conducted. The sterilizer ongoing process control should incorporate periodic system suitability tests which may include chamber leak tests, air removal tests for saturated steam prevacuum cycles, air detector devices (if applicable) and CI/integrator and biological challenge results (if not used in routine loads). The sterilizer ongoing process control should continue to focus on the load areas/configurations identified as most difficult to penetrate or heat. Change control procedures should adequately address issues such as a load configuration change or a modification of a sterilizer.

Requalification should be performed whenever there is a major modification to the sterilizer system or a product change that has the potential to affect process efficacy. Verification of acceptable steam quality should also be performed during
requalification. Steam quality testing (saturation or dryness test) should be in the firm’s validation master plan or quality plan. The end user should define criteria (or a rationale for requalification) in the validation master plan or quality plan. Regarding time-based requalification, see next section.

Frequently Asked Questions (FAQs)

1. **Are end users required to requalify steam sterilizers annually or within a certain time frame?**

   No, there is no set time frame required from any standard; only recommendations to perform at specified intervals. In cases where parametric release is utilized, annual requalification is required. The industry norm is to requalify every 1–2 years. The best practice and World Health Organization (WHO) recommendation is to requalify annually. In general, a risk-based analysis and approach should be used, as minor changes to the equipment, product or load configuration may affect the effectiveness of the sterilization process.

   Industry standard ISO 17665, part 1 Sterilization of health care products – Moist heat Requirements for the development, validation and routine control of a sterilization process for medical devices states: “...requalification carried out at specified intervals” and “Requalification of a sterilization process shall be carried out... at defined intervals.” Similarly, ISO TIR 17665, part 2 Sterilization of health care products - Moist heat Guidance on the application of ISO 17665-1 states: “typically, requalification is performed annually” and “…routine operational requalification and performance requalification should, typically, be performed annually.” Also, “if biological indicators are used during requalification, their performance should present a similar challenge to those used during validation.”

   PDA Technical Report 1 Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control section 6.4 states “a requalification of your sterilizer should be performed on a regular basis (typically every 12 months).” Lastly, the Association for the Advancement of Medical Instrumentation (AAMI) recommends revalidating the sterilization process at least every two years.

2. **When are end users required to requalify their process?**

   If changes or repairs are made to the autoclave or supporting/ancillary equipment, load configuration, or cycle parameters, or if unexplained cycle failures are seen, the process should be requalified. In addition, any change to the product or packaging, bioburden level, or component change could be reason for requalification.

3. **Must end users use the same brand of BIs for requalification as was used in the initial validation?**

   No, there is no requirement to use the same brand of BIs stated in the associated literature or standards. It is recommended to use “like for like” products for requalification and routine use; the BIs must be of similar population and resistance (D-value) to those used during validation. ISO TIR 17665, part 2 states “if biological indicators are used during requalification, their performance should present a similar challenge to those used during validation.”

   BIs should be compliant to ISO 11138 Sterilization of health care products – Biological indicators, and CIs should be compliant to ISO 11140 Sterilization of health care products – Chemical indicators. STERIS products are compliant to both of these ISO standards.

**Typical STERIS products used for validation and requalification**

**Biological Indicators**
- Spordex® Strips
  - NA037: D_{121} 1.5-2.5, 500 per box
  - NA039: D_{121} 1.5-2.5, 100 per box
  - NA139: D_{121} 2.0-2.5, 100 per box
  - NA141: D_{121} 2.0-2.5, 500 per box
  - NA142: D_{121} 1.5-1.9, 500 per box
  - NA143: D_{121} 1.5-1.9, 100 per box
- Spordex® Discs
  - NA111: D_{121} 1.5-2.5, 1000 per box
- VERIFY® Self Contained Biological Indicators
  - S3111: d-value 1.5-3.0, 100 per box
  - S3060: dual species, D_{121} greater than or equal to 1.5, 100 per box
  - S3061: dual species, D_{121} greater than or equal to 1.5, 50 per box
- Spordex Culture Media
  - NA114: Used on all Spordex and Spordi brand products to generate product data, 100 per box

**Chemical Indicators**
- VERIFY® Integrating Indicator for Steam Sterilization, class 5 (per ISO 11140-1:2005)
  - PCC039: Stated values at 121°C, 18 min; 132°C, 3 min; and 134°C, 2.5 min

**Air removal tests are recommended during validation, requalification and on a daily basis (ISO TIR 17665 – 2)**
- Steraffirm® Bowie-Dick Test Pack
  - EQC003: Used for cycle temperatures at 121°C-124°C, 20 per box
- DART® Daily Air Removal Test
  - NB113: Used for cycle temperatures at 132°C-134°C, 50 per box
  - NB215: Used for cycle temperatures at 132°C-134°C, 10 per box
- VERIFY® Bowie Dick Test Pack
  - EQC010: Used for cycle temperatures at 132°C-135°C, 40 per box
  - EQC009: Used for cycle temperatures at 132°C-135°C, 20 per box

**Relevant Guidelines and Standards**
For further information, please contact:

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References


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