Technical Data Monograph

STERIS VHP LTS-V - Low Temperature Surfaces
Terminal Sterilization

STERIS
Life Sciences

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1. Abstract

STERIS is a global leader in infection and contamination prevention for healthcare, pharmaceutical, research, food and industrial customers.

STERIS manufactures several lines of products for sanitization and sterilization.
These include:

- Low temperature sterilization (Vaporized Hydrogen Peroxide (VHP®) and Ethylene Oxide)
- High temperature sterilization Finn-Aqua® GMP Steam Sterilizer and STERIS Finn-Aqua Bio-Pharma Series (BPS) Steam Sterilizer
- Water systems Multiple-Effect Water Still
- Washers GMP and research grade
- Pure steam generators
- A range of formulated chemistries for sanitization
- Various kinds of biological and chemical indicators

Heat and/or radiation sensitive biological drug products in pre-filled syringes, vials, mixing or other drug delivery devices can be challenging from terminal sterilization perspective. In many applications it may be necessary to assemble and individually package these devices in grade A or B cleanrooms. Understanding and applying VHP® technology in vacuum or partial vacuum applications can streamline critical manufacturing processes, enhance product package sterility, cut operating costs and simplify quality control.

The terminal sterilization of individually-packaged, aseptically filled devices, such as pre-filled syringes or other delivery devices, containing temperature and/or radiation sensitive drug products has been difficult or even impossible using conventional technologies such as ethylene oxide, steam or gamma irradiation.

The STERIS VHP® LTS-V Low Temperature Sterilizer (Fig. 1) is designed for VHP® sterilization. It is ideal for on-site surface sterilization of temperature sensitive biological drug packages and drug delivery devices. The VHP LTS-V sterilization system utilizes STERIS VAPROX® hydrogen peroxide sterilant. Other required utilities include 3-phase electricity, instrument air, and purified water.

VHP = Vaporized Hydrogen Peroxide. LTS-V = Low Temperature Sterilization - Vacuum

Figure 1: STERIS VHP LTS-V 91515 (2000-liter chamber)

2. VHP LTS-V applications and benefits

In the pharmaceutical industry, there is a growing need for low temperature terminal surface sterilization solutions for delivery devices with sensitive biological products or other products with sensitive drug components. These applications especially include ophthalmic injectable drug delivery devices, hyaluronic acid-based drug injections, or ready to mix protein products.

VHP® generally exhibits good to excellent material compatibility, as shown in Table 1, especially across a range of different types of plastic. Some gases used for terminal sterilization pose significant challenges in terms of material compatibility and residue formation. Various materials can negatively impact the VHP process. Cellulose-type materials (wood, paper, and cardboard) can absorb and degrade VHP, reduce concentrations, and result in prolonged aeration. In addition, some metals such as copper, brass, or platinum can catalyze hydrogen peroxide to water vapor and oxygen. However, platinum alloys, for example, are used to catalyze VHP exhaust safely and effectively. Such catalysts are often used in self aerating decontamination chambers or in room decontamination scenarios.

Although much is known about the effect of oxidizers, like hydrogen peroxide, on various materials, feasibility testing is always recommended in an early project phase. The design and selection of secondary packaging materials will also impact the VHP process. For example, harder surfaces work better than porous, softer ones. Softer materials, namely those that have a greater capacity to absorb water or potentially contain more plasticizers can lead to longer aeration times. Softer plastics can absorb peroxide more readily than harder surfaces and tend to “out-gas” slowly. One advantage of vaporized hydrogen peroxide is that it does not penetrate the material, but is generally limited to moderate surface adsorption only. The process removes adsorbed/absorbed peroxide during the standard post-exposure or aeration phase of the sterilization cycle.

MATERIAL COMPATIBILITY WITH HYDROGEN PEROXIDE GAS.

LOWER		BETTER		BEST
Cellulosics	Some Polyamides (Nylon 6/6, 11)	Some Polyamides (Polyaramid, Kevlar)	Polycarbonates (Mild outgassing)	Polyethylenes (LLPE, LD HD, UHMW)
Copper (Decomposes Peroxide)	Some Polyurethanes (Ester based)	Some Polyurethanes (Ether based)	PVC, CPVC, Polyvinylidene Fluoride (PVDF)	Polypropylene (LD, HD)
	Some Silicones	Carbonate Filled Epoxy	ABS	Polyphenylene Oxide (NORYL)
	Soft Anodized Aluminium (Dye bleaching)	Polysulfones, Polystyrene (Outgassing)	Acrylates (Outgassing)	Teflon (PTFE, PFA, FEP) Viton
	Natural Rubber, Polyacetal (Delrin)	Brass (Decomposes Peroxide)	Polytherimide (ULTEM)	Glass, Quartz
	Silver (Decomposes Peroxide)		Most Medical Grade Silicones	Aluminium 300 Series SS

Table 1: General hydrogen peroxide material compatibility VHP is compatible with most materials. The fastest cycles can be achieved on hard non porous materials.

Typical VHP loads include:

- individually-packaged delivery devices with parenteral drugs (Fig. 2)
- biologicals, biosimilars, or other sensitive products, e.g. containing specific proteins that are sensitive to heat and radiation.
- Complex devices that combine two components immediately before use
- Packaged implant products or custom made devices produced in small to moderate quantities

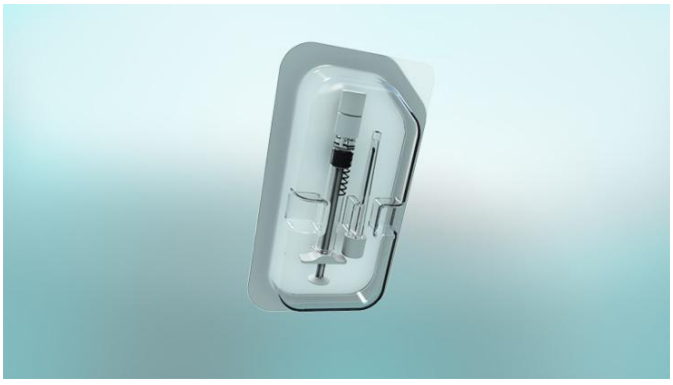


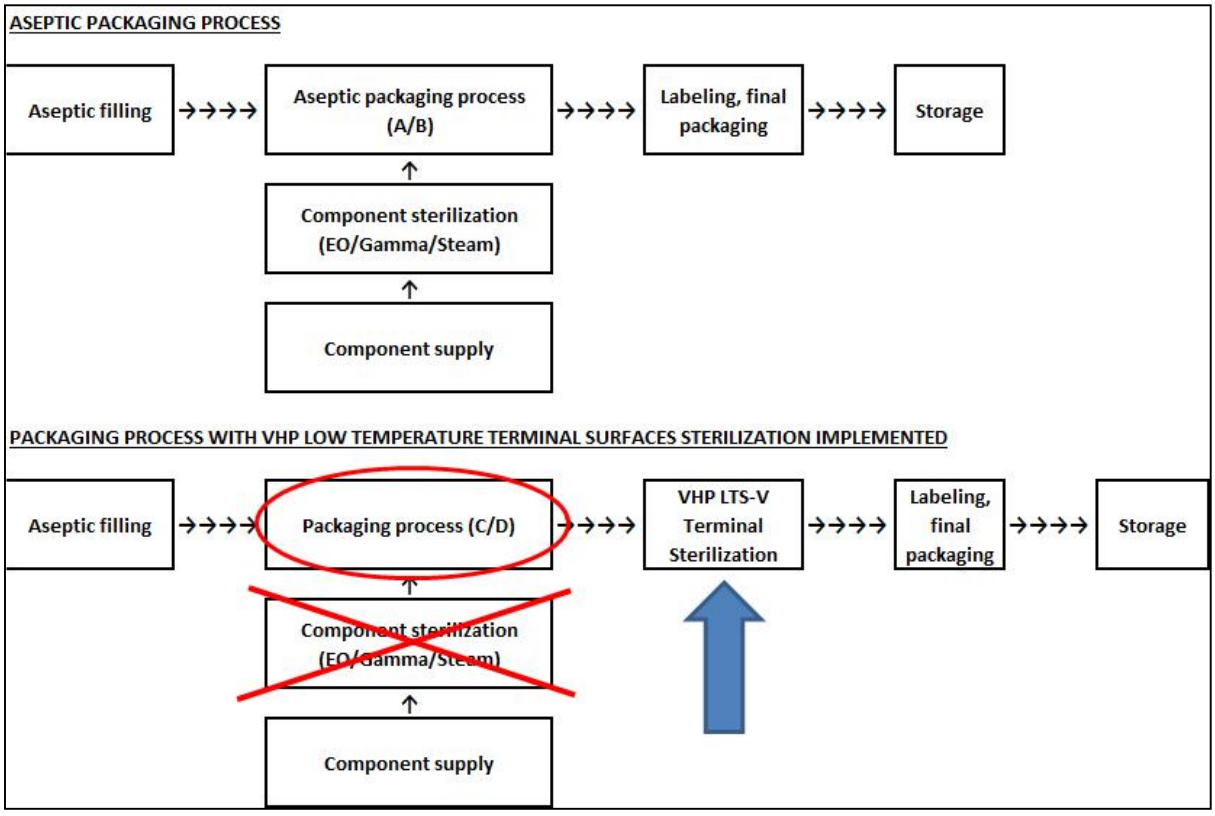
Figure 2: Typical configuration and packaging of a single-packaged device

The VHP® vapor phase sterilization method is designed to achieve product and package surface sterility (validated to SAL 10^{-6}) in-house (SAL = sterility assurance level). This terminal sterilization step eliminates the need for setting up grade A or B assembly operations with extensive monitoring methods in upstream manufacturing steps.

Thus efficiencies can be achieved by implementing VHP LTS-V after the final packaging but before final storage, as shown in Schematic 1.

It may also be possible to eliminate specific component sterilization efforts prior to device assembly, assuming all surfaces are exposed to LTS-V terminal surfaces sterilization after device assembly is completed. See below a generic example of the aseptic packaging process - before and after implementing VHP® surfaces terminal sterilization phase.

The major time and cost saving factor in this process is being able to minimize manual grade A or B class area work around the device that would otherwise take place inside an isolator, clean room, or RABS environment and may include several assembly steps. Thus it may be possible to work in a lower grade environment (grade C). Additionally, less costly methods such as the use of automated assembly or robotics may be readily employed in a lower grade environment.



Schematic 1: Generic aseptic packaging process before and after implementing LTS-V terminal sterilization phase

Figure 3 & 4: Loading a VHP LTS-V sterilizer.

Terminal sterilization of package interior and device exterior surfaces

Terminal sterilization of product and package surfaces is a different application compared to conventional terminal sterilization by heat (steam). The main difference is that the deep penetrating heat component is absent in surface terminal sterilization process. The drug or drug components in the primary container(s) are aseptically filled and the container is closed. VHP® low temperature surface sterilization affects only the exposed surfaces of the device and any ancillary components. Both the external and internal surfaces of the secondary packaging of the device are also sterilized, with the internal surfaces remaining sterile until product use (Fig. 5).

SAL 10^{-6} requirement is verified on the device surfaces and package by using biological indicators (*Geobacillus stearothermophilus*) placed in the most challenging locations in the package/load, or by using a PCD (process challenging device).

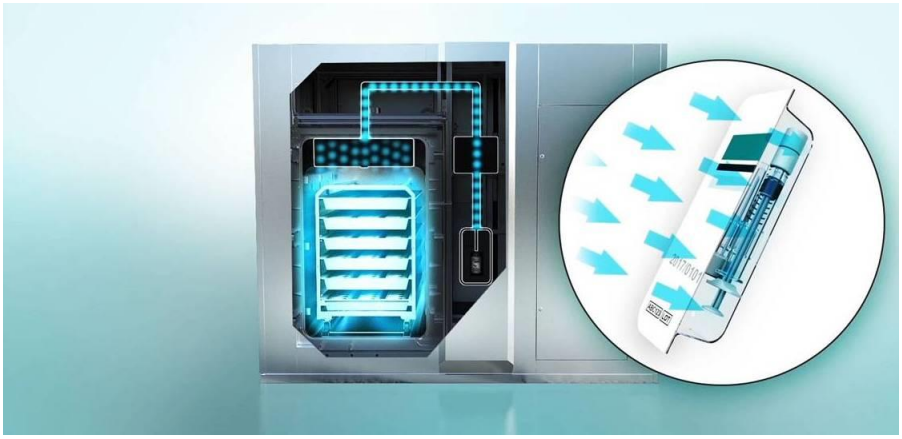
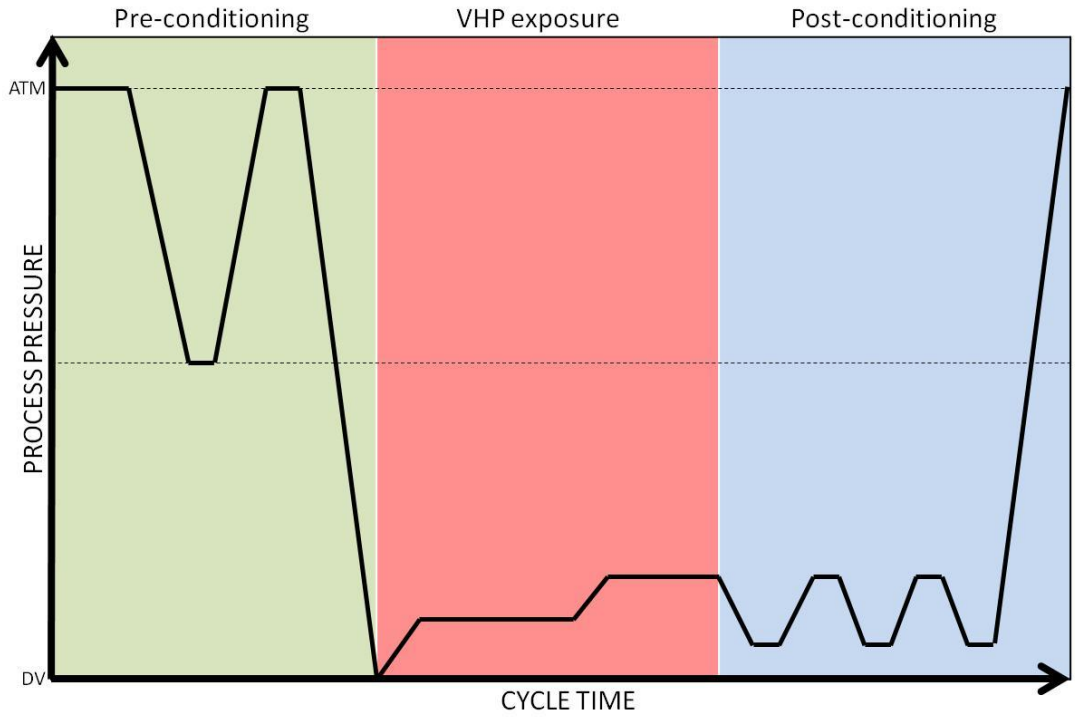


Figure 5: VHP LTS-V terminal sterilization chamber cycle

Surfaces sterilization of other packaged products such as implants and products with sensitive components

Sterilization under deep vacuum conditions can also be used on implant type products or devices, where a high level of sterility is critical. Products for these applications are individually packaged in a blister with Tyvek or in a Tyvek bag or other enclosure with a Tyvek window. It is essential that the packaging design minimize occluded surfaces allowing VHP exposure of all surfaces. The obvious benefit is a sterility claim of the product for implant use that can be presented to the surgeon in the sterile field. Thus a ready-to-use sterile component or implant device can simplify the surgical operation and add to patient safety. The packaging and sterilization of custom or small batch high value products can be kept “in-house” for streamlined manufacturing and order fulfillment.

3. VHP LTS-V Process description



Graph 1: STERIS VHP LTS-V Surfaces Terminal Sterilization (vacuum) process steps

VHP LTS-V Sterilization Process

Sterilization is carried out under deep vacuum conditions. A vacuum level of typically 1 to10 mbar, or as low as 1000th of atmospheric pressure at sea level, the VHP® LTS-V sterilization process temperature range is typically +28 to 40 °C.

Total cycle time is counted from door closed to door open. This includes post-conditioning (also referred to as "aeration"). Typical cycle times for VHP® LTS-V sterilization process is between 2to 4 hours. Cycle time may vary depending on product composition, packaging materials, temperature, and load size and configuration.

The VHP low temperature surface terminal sterilization cycle is based on the principle of creating a controlled environment and treating all exposed surfaces. This translates into control over pressure, temperature, relative humidity, hydrogen peroxide concentration, and cycle time. The sterilization cycle is performed in deep vacuum, in order to achieve a controlled environment and to ensure that complex device surfaces receive exposure to VHP®. A typical plastic blister package using a Tyvek® or equivalent layer, allows penetration of VHP into and removal from the package.

During VHP® exposure, condensation is completely avoided. Dry vapor means that the entire decontamination process is carried out in a gaseous phase without exceeding the saturation point. Typically surface sterilization of the primary package has no adverse effect on pre-filled drug product inside, as vaporized hydrogen vapor does not readily penetrate nonporous materials.

The three phases of VHP® sterilization cycle (as shown in Graph 1):

1. **Pre-conditioning of chamber and load (temperature, pressure, humidity)**

   During the pre-conditioning phase, the load and chamber are conditioned to an even processing temperature and humidity is removed by pulsing dry filtered air. Following the preconditioning pulses, a deep vacuum is achieved prior to hydrogen peroxide vapour injection and load exposure.

2. **VHP injection and exposure**

   The VHP® injection and exposure phase initiates the controlled injection of vaporized hydrogen peroxide into the chamber and load. Hydrogen peroxide vapour exposure level is controlled and maintained via humidity and temperature measurements. A cycle time is determined based on the load's sterilization exposure requirement; generally, a SAL of 10^6 or greater is attained. For validation, a number of BIs with a population of 10^6 of *Geobacillus stearothermophilus* are placed in a specific array throughout the load. Additional indicators may be placed in the hardest to reach locations. Cycles are developed according to an overkill method.

3. **Post-conditioning to remove peroxide and equalization to atmosphere**

   The post-conditioning phase concludes the sterilization cycle. The most important thing during this phase is removal of any peroxide residue from the chamber, packaging, and most importantly from the device or component surfaces. Peroxide vapour does not penetrate through plastic materials, but it will be absorbed to some extent especially into softer plastics. Peroxide residue levels can be measured after the cycle from several locations in the load, inside the package and from where the operator would stand on the unloading side of the chamber. The VHP® LTS-V post-conditioning process utilizes vacuum humidification pulses to speed removal of residual peroxide from the load. Thus no subsequent out-gassing, aeration or ventilation of the load is required.

   An area room monitor is often used to detect even very low concentrations of peroxide outgassing from the load.

4. Feasibility Testing for products and packaging

Feasibility testing is recommended for determining material compatibility and efficacy of the LTS-V process for potential products. It is an excellent means of quickly gaining insight into the feasibility of the VHP process for terminal sterilization. Essentially, feasibility testing mitigates the risk of unknown factors that might otherwise become issues later in the project. It moves them forward in the project plan so that they can be dealt with in a timely manner. Feasibility testing will provide timely insight with regard to material compatibility, vacuum level, temperature, package type or material, etc. A customized test plan is proposed and executed at the STERIS factory by qualified STERIS representatives. Potential clients are often asked to participate in the assessments. Typical procedures include package/product exposure, efficacy, product ingress and product integrity assessment (study of any possibility of peroxide ingress into product container).

Although non-product containing samples are preferred, licensing is in place for the factory to accept product samples for feasibility and load cycle development tests. The test sponsor however is responsible for any verification of product or material integrity and compatibility associated with the process.

TYPICAL VHP LTS-V FEASIBILITY TESTING PROGRAM:

1. **Testing objectives:**

   a. Product tolerance with vacuum

      - Allowable vacuum level
      - Plunger movement (graphite test)
      - Physical failure(s) seen by naked eye (i.e. fracturing etc.)
      - Package failure(s) seen by naked eye (i.e. seam failure etc.)

   b. Vaporized hydrogen peroxide sterilization
      Testing with biological indicators
      - Penetration into the blister package for sterilizing outer surfaces of the product
      - Penetration into product cavities

   c. Hydrogen peroxide residuals

      - Ingress into the product
      - Operator safety - residuals in the end of the cycle

        (PEL 1 ppm 8 hours, STEK2 ppm 15 min)

2. Efficacy / Ingress Testing Methods:

a. Chemical and Biological Indicators, Peroxide ingress test strips

- CI – Steraffirm® [VH202], Class 1 Process indicator; PCC060
- BI – Spordex® [VH202], Biological Indicator Disc; *Geobacillus Stearothermophilus* 12980; NA333 (Fig. 10)
- Direct inoculation if requested, placement e.g. as shown in Figures 6, 7 and 8

b. Peroxide residual ppm readings of load, product and packages

- Hand-held Draeger PAC III and/or X-AM 5100 (Fig. 12)
- Peroxide quick test strips for ingress (MERCKOQUANT), as shown in Fig. 11
- Xylenol Orange Spectrophotometric Assay
- Vapor monitoring two locations – at door, package x 3

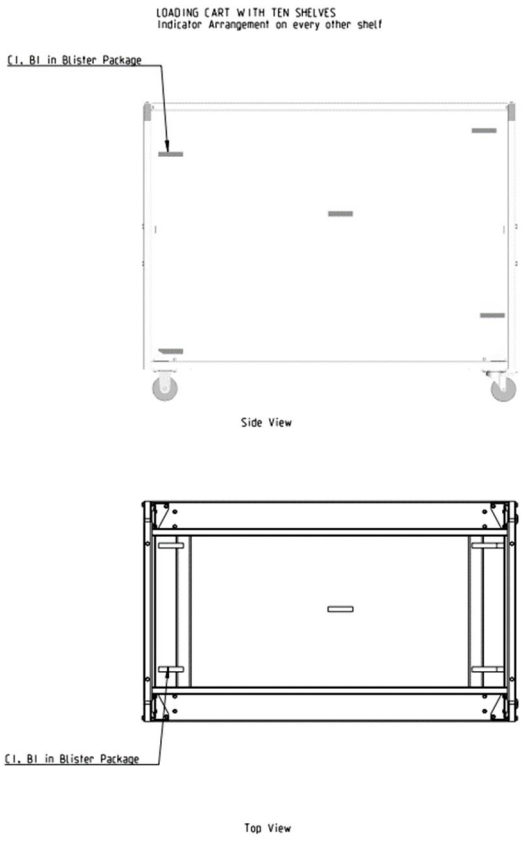


Figure 6: Typical biological indicator test map for entire load

3. Testing results:

- Indicator results
- PPM readings
- On-site peroxide ingress quick test for product (optional)
- Feasibility study results by test sponsor

Figure 7: Full chamber load for load cycle development testing

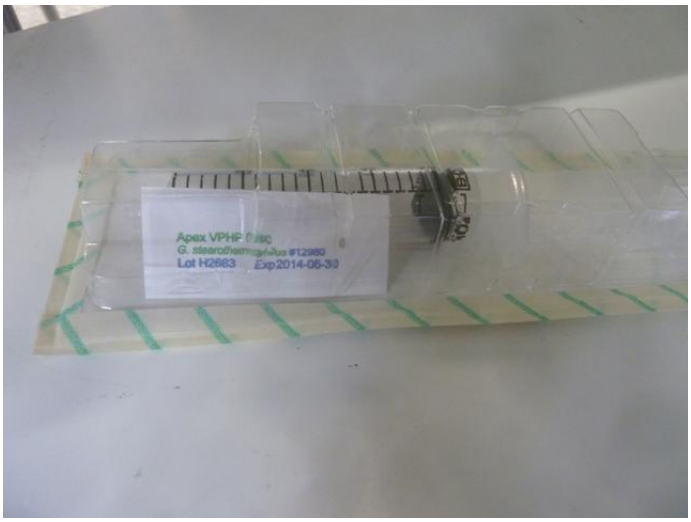


Figure 8: Tyvek-enveloped biological indicator placement inside packaged device

Figure 9: Tyvek layer of blister package for entering and exit of VHP vapor

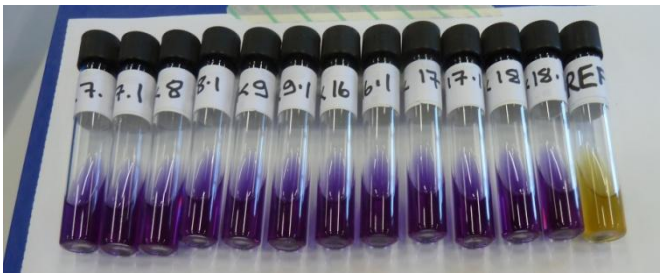


Figure 10: Biological indicators in test tubes. Control positive on the right.


Figure 11: Quick on-site strip test for ingress testing (container integrity).

5. Cycle Development and Validation

Sterilization applications are subject to cGMP and cGAMP requirements. Process control requirements often demand electronic data security, requiring 21 CFR part 11 compliance. Process validation must be performed for each application. Product feasibility testing (to verify VHP® compatibility with materials) and load cycle development are typically conducted and serve as basis for cycle validation. Chemical and biological indicators are used for validated cycle verification, qualification and production cycle quality control. Load configuration in a specific pattern is important from cycle repeatability perspective.

Standardizing the steps and environments immediately before and following treatment also need to be considered.

Load cycle development and testing is encouraged to be part of the factory acceptance test (FAT) for new applications. This development test is to ensure that an effective cycle can be run with a full load in the chamber. It is a starting point for post installation cycle development and Performance Qualification (PQ) activities. This testing is typically expected to be conducted over a 7-21-day period and is performed after the FAT testing is executed.

LOAD CYCLE DEVELOPMENT

Part 1

During the initial week of Factory Acceptance Testing the unit will be tested using the standard Factory Test Procedure. This testing will follow the Operation Qualification protocol and be used to verify the overall operation of the unit and that the drawings and the unit components align. This testing will be performed by STERIS (Fig. 14). Often customers participate in this activity.

Part 2

The chamber will be tested with peroxide (STERIS VAPROX®) and with chemical indicators. There will be a number of indicators placed in the empty chamber to verify complete exposure in the chamber. The purpose of this test is to show overall VHP® concentration and distribution in the empty chamber and to further verify the correct operation of the injection system and the sensors.

Part 3

A full load will be tested with a defined cycle using Chemical Indicators (CI), as shown in Figures 7 and 13. This will be used to determine relative exposure of a full load to peroxide. The test is intended as an initial VHP® distribution test. Exposure times and concentrations can be adjusted until all the chemical indicators indicate exposure sufficient to accomplish decontamination. This test does not guarantee but is an excellent indicator of potential biological indicator inactivation.

Part 4

The full load will be run with biological and chemical indicators (BI) and CIs. The BIs are cultured by STERIS personnel immediately following each run. The cycle developed with BIs will determine a complete kill cycle. The cycle is typically run 1-3 times. The load cycle development will be complete when the requested number of successful cycles has been completed. Two product loads are preferred if possible to expedite testing. If more than one chamber is to be tested, then one load with full size cart per chamber is required (minimum).

Factory load cycle development testing is not intended to replace PQ or further post installation cycle optimization activities.

VALIDATION

VHP® low temperature terminal sterilization is defined under Vapor Phase Sterilization, as per USP 1229.11 (August 1, 2015). ISO 14937 standard is recommended to be used as a basis in developing validation procedures.

Validated cycles typically include cycle studies and setup with an empty chamber, a half-loaded chamber and a fully loaded chamber. As minimum, three consecutive, successful runs are typically required for each of these cycle types, for proving process consistency. Three consecutive, successful runs are required for each of these cycle types. Typically, during validation, the chamber and load may need to be challenged using more biological indicators for verification when compared to required number of control BIs during manufacturing cycles. Reference devices may also be used for process charting, but only for validation purposes. In manufacturing process cycles the control relies on process measurement devices of the unit - humidity sensor(s), temperature sensor(s), and pressure sensor(s).

The following standards typically need to be considered when constructing the validation procedures, validated cycle, equipment, process control and documentation:

ISO 11138-1	Sterilization of health care products - Biological indicators
ISO 11140-1	Sterilization of health care products - Chemical indicators
ISO 11737-2	Sterilization of medical devices - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process
ISO 14937	Sterilization of health care products – General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical device
21 CFR Part 11	21 Code of Federal Regulations Part 11: Electronic Records; Electronic Signatures

Figure 12: Peroxide residue testing at chamber door-open, using hand-held device

Figure 13: A 10,000-liter volume chamber: Cycle development load

Figure 14: The Finn-Aqua 13-bay FAT testing area.

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