Equipment and Process Validation for an Industrial VH2O2 (VHP) Sterilization Application

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ABSTRACT

FDA announcement (Jan 8, 2024)

"Today, the U.S. Food and Drug Administration is announcing that it considers vaporized hydrogen peroxide (VHP) to be an established method of sterilization for medical devices, recognizing VHP's long history of safety and effectiveness. The FDA has revised the final guidance, Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile, to list VHP as an example of an Established Category A method of sterilization. This update will facilitate broader adoption of VHP as a sterilization method for the medical device industry, is part of the agency's multi-pronged approach to reducing the use of ethylene oxide (EtO) where possible and further supports the agency's efforts to advance medical device supply chain resiliency."

SOURCE: https://www.fda.gov/news-events/press-announcements/fda-facilitates-broader-adoption-vaporized-hydrogen-peroxide-medical-device-sterilization

FDA recognition announcement for ISO 22441 (May 29, 2023)

"Rationale for Recognition

This standard is relevant to medical devices and is recognized on its scientific and technical merit and/or because it supports existing regulatory policies.

NOTE: Defined critical parameters can vary depending on the technology and cycle design of various VH2O2 sterilizers. If you are considering releasing product loads using parametric release, please pay attention to process variables [see definition 3.32 and 3.33] to monitor when releasing product loads using parametric release [see definition 3.28]. We encourage you to contact the review division for your device regarding the appropriate parameters to monitor for parametric release of product loads sterilized with VH2O2."

SOURCE: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard__identification_no=44295

In the biopharmaceutical manufacturing context this will help the pre-filled syringe / combination device manufacturers improve patient safety by having the option of VH2O2 terminal surface sterilization of the pre-filled syringe device that includes temperature or radiation sensitive injectable drug products. Additional VH2O2 work items in review status include ISO 11138-6 (VH2O2 biological indicators standard) and EN 17180 (VH2O2 sterilizer equipment standard).

Objectives

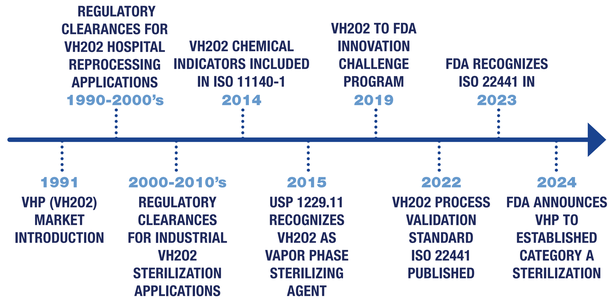
- VH2O2 regulatory developments
- Regulatory pathway options for VH2O2 sterilization
- Key elements of conforming to ISO 22441 requirements for sterilization process and equipment validation
- Differences between VH2O2 sterilization and biodecontamination requirements and applications

STERIS VHP LTS-V

Typical Medical Devices Sterilized

Orthopedic Implants | *Prefilled Syringes* | *Electronic Implants* | *Subcutaneous Patches*

VH2O2 Regulatory Developments



VH2O2 Regulatory Pathways

Validation of industrial VH2O2 sterilization equipment and process is required when implementing a VH2O2 sterilizer in a manufacturing facility. ISO 22441 is currently recognized by US FDA and several European countries.

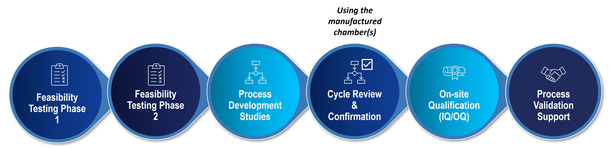
For countries that have recognized this standard, the regulatory requirements for process validation are set to follow the requirements of ISO 22441:2022.

Sterilization of health care products — Low temperature vaporized hydrogen peroxide — Requirements for the development, validation, and routine control of a sterilization process for medical devices.

For countries that currently have not recognized ISO 22441, the regulatory pathway for VH2O2 process validation may follow ISO 14937 requirements. However, it is advisable to adhere to the latest and modality-specific standard, such as ISO 22441.

ISO 14937:2009 - 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 devices

Recommended pathway of VH2O2 process implementation



Key Elements of Conforming to ISO 22441 Requirements for Sterilization Process Validation

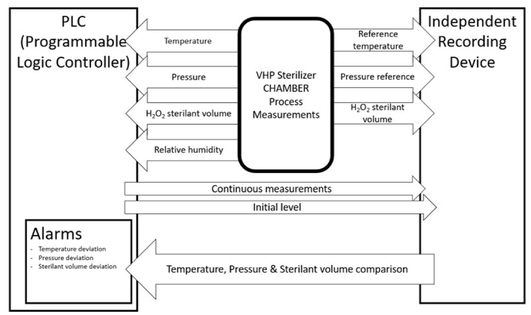
Key Subclauses of ISO 22441

4.0 Quality Management system requirements
5.0 Sterilizing Agent Characterization
6.0 Process and Equipment Characterization
7.0 Product Definition
8.0 Process Definition
9.0 Validation
10.0 Routine Monitoring and Control
11.0 Product Release from Sterilization
12.0 Maintaining Process Effectiveness

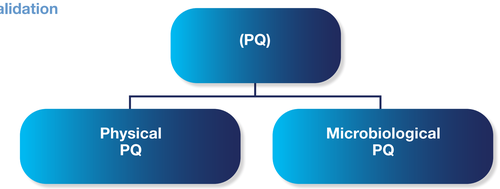
5.0 Sterilizing Agent Characterization

Finding and Outcomes	
1. Identification of most resistant organism (MRO)	Probabilistic sterility assurance level (SAL) may be determined with half-cycle and cycle calculation methods. *G. stearothermophilus* preferred as most resistant organism (MRO per ISO 22441). Work with B. Atrophaeus provides methodology for application of ISO 22441:2022 Annex A. Also demonstrates that the make-up and the effect of the PCD (process challenge device) on the inactivation kinetics may need to be considered when using MROs from Annex A.
2. Relationship to sterilant concentration	Micro-organism inactivation demonstrating a direct relationship to calculated concentration from grams of hydrogen peroxide injected to a known chamber volume; may be used for parametric release.
3. Use of chemical indicators	BIs are used to challenge VH2O2 vapor penetration (same for EO gas penetration). CIs are used for chamber and load distribution studies to show relative exposure to VH2O2.
4. Fulfilment of requirements of ISO 22441:2022 section 5.3	Example: STERIS has completed this work using the VHP LTS-V sterilization process on behalf of Customer specific applications.

6.0 Process and Equipment Characterization – Control and Monitoring



9.0 Validation



10.0 Routine Monitoring and Control

- Defined loads, batch release by Process Challenge Devices (PCD)
- Develop the worst-case applicable cycle
- Development BI for actual device most challenging location
- Comparative resistance study for ePCD

Differences Between VH2O2 Industrial Sterilization and Biodecontamination Requirements and Applications

Item	Sterilization	Biodecontamination
Application	Surfaces, lumen, and other pathways of single-use or reprocessing medical devices (PFS and other combination devices with drug product, implants, electronics, instruments)	Surfaces of rooms, enclosures, isolators, facility spaces, labs, material airlocks, transfer hatches, empty vessels
Process type	Vacuum in a sterilizer chamber	Atmospheric, in-situ, via facility HVAC (integrated) or pass-through chamber / hatch
Packaging	Sterile barrier + blister / pouch	Protective plastic wrapping (pre-sterilized components) or none (surfaces exposed to biodecontamination, e.g. isolator interiors)
Conditions	Clean and dry virgin product surfaces.	Clean and dry room / equipment / wrapping surfaces.
Performance requirement	Sterility Assurance Level achieved for a medical device - SAL 10-6 (12-log reduction) inside packaging. Sterility maintained by sterile barrier until taken in use.	Biodecontamination of surfaces to minimize bioburden risk in manufacturing spaces, equipment, and material transfer - to 6-log bioburden reduction.
Regulatory requirements	Conformance to cGMP and cGAMP, EU Annex 1, 21 CFR Part 11 / EU Annex 11	Conformance to cGMP and cGAMP, EU Annex 1, 21 CFR Part 11 / EU Annex 11
Process standard	ISO 22441	Per US EPA and EHCA BPR registrations and applicable validations
Equipment standard	EN 17180 (draft) / ISO/TS 22421	Follows applicable guidelines from cGMP, cGAMP, EU Annex 1, 21 CFR Part 11 / EU Annex 11
Biological indicator	*Geobacillus Stearothermophilus*, 6-log population, ISO 11138-1	*Geobacillus Stearothermophilus*, 6-log population, ISO 11138-1
Chemical indicator	ISO 11140-1	ISO 11140-1