Status: Currently Official on 12-Feb-2025
Official Date: Official as of 01-Dec-2016
Document Type: General Chapter
DocId: GUID-3B9D0AC3-55B5-4709-B814-1BA70DF8CB45_1_en-US
DOI: https://doi.org/10.31003/USPNF_M10237_01_01
DOI Ref: 14rnu

⟨1229.13⟩ STERILIZATION-IN-PLACE

INTRODUCTION

Sterilization-in-place (SIP) can be defined as the sterilization of a system or piece of process equipment in situ. The purpose of SIP[1] is to eliminate, or greatly reduce, the need for post-sterilization handling, including that necessary to make aseptic connections. Mobile process equipment (e.g., portable tanks, storage vessels, and other equipment), once sterilized in this manner, may be relocated. The SIP process can be carried out by using any of the following physical methods: moist heat, dry heat, gas, liquid, or vapor (described below) according to the approaches described in *Sterilization of Compendial Articles* ⟨1229⟩, as adapted for use with the specific equipment or system.

COMMON ELEMENTS OF SIP PROCESSES

There are a number of considerations appropriate for the design and use of SIP procedures that apply to all of the sterilization methods:

- The use of an SIP method is normally associated with a “closed system.” Closed systems are almost always sterilized in situ, and the design elements of the typical closed system are consistent with many SIP process needs.
- For large systems, it may be necessary to sterilize in portions. The individual sterilization processes should overlap to ensure treatment of all internal surfaces.
- The focus of the SIP procedure is sterilization of the product contact surfaces (the interior of the system). Demonstration of process lethality relies upon physical measurements and biological indicators. This confirmation should extend to the “sterile boundary” of the system, including vessel headspace, connections to other vessels/equipment, and other parts of the system. The interior surfaces of the process equipment, irrespective of their materials of construction, should be exposed to lethal conditions sufficient to sterilize the system and confirmed as lethal with an appropriate biological challenge.
- SIP is accomplished almost exclusively using the overkill approach to sterilization. The components of the physical equipment should be chosen based upon their ability to withstand the sterilizing conditions to be used. Filters in the process system, whether membrane or high-efficiency particulate air (HEPA), are typically susceptible to damage during SIP, and care must be taken to preserve their integrity. Filter manufacturers can provide guidance on acceptable sterilization methods and parameters.
- The absence of specifically designed equipment in which the sterilization process is performed places the bulk of responsibility for design onto the user. SIP systems ordinarily cannot be purchased directly in the way one purchases a steam sterilizer or a dry heat oven. Instead, the system, which was designed for the operating process, may require modification to accommodate the SIP process to be used. The user must assume the role of designer for the process, equipment, and control system.
- The system design and operating procedures must provide for an efficient means of introducing and removing the sterilization agent. Sterilization agent removal must consider the potential effects of residual sterilant on the materials to be processed. Establishment of a reliable process sequence is a critical part of the cycle development exercise. The sterilizing agent is normally introduced through a filter on the system that may also serve as a process, purge gas, or vent filter.
- At the conclusion of the sterilization process sequence and until ready for use, the system should be pressurized with a purge gas (sterile air or nitrogen are the most common) to prevent the introduction of contaminants to the sterilized system.
- The critical process parameters for the SIP process should be recorded as the process is executed. The important parameters may include temperature, pressure, concentration, flow rate, humidity, and time, among others.

CLOSED SYSTEMS

In pharmaceutical manufacturing operations, closed systems are used for various applications including maintenance of large quantities of materials (liquids or powders) in a sterile state; manufacture of biological and synthetic organic active ingredients (especially where microbial absence is essential); and preparation of process equipment for use in sterile drug product manufacturing and filling. The use of closed systems provides superior separation of sterile materials from the surrounding environment. Typically, closed systems are maintained under positive pressure at all times. The characteristics of a closed system that establish its designation as “closed” include the following:[2]

- It maintains integrity during all operating periods and under all conditions.
- It is sterilized-in-place or sterilized while closed before use.
- It can be adapted for materials transfer in and/or out while maintaining its sterile state.
- It can be connected to other closed systems while maintaining the integrity of all systems.
- It is subject to scheduled preventive maintenance.
- It uses sterilizing-grade filters for sterilization of liquid and gas process streams.

SIP METHODS

Moist Heat

The use of saturated steam is the most prevalent method for SIP of large systems. The majority of installations use gravity displacement cycles adapted from those originally used in steam sterilizers (the size and complexity of many systems preclude the use of prevacuum cycles). Important considerations include the provision for air removal, condensate discharge, and steam removal post-dwell.[3,4] This method is commonly used for bioreactors, sterile bulk production, holding tank and delivery lines, and other large systems.

Superheated Water

Systems used for *Water for Injection* and *Purified Water* can be sterilized by using superheated water (water that is heated above its boiling point and pressurized to maintain it as a liquid) circulating through the system. This method has the ability to sterilize vessels, filters, and other wetted components at the same time.[5] Removal of residual water subsequent to the sterilization phase is recommended.

Dry Heat

Dry heat has been used for SIP of spray dryers and their associated material collection systems. The air supply for sterilization in these systems is provided through HEPA filters.

Gas

Gas-phase SIP has been used for non- and low-pressure-rated process equipment, such as freeze dryers, prefreezers, process vessels, and other equipment.

Liquid

Liquid chemical sterilization is best suited for liquid-handling systems and can be used only for fully wetted surfaces. This process is similar to those using superheated water except the lethal modality is chemical rather than thermal.

Vapor

Sterilizing vapors have been used for the in situ sterilization of the same types of process equipment as those treated with sterilizing gases. The precautions associated with vapor sterilization described in *Vapor Phase Sterilization* ⟨1229.11⟩ are required.

ROUTINE PROCESS CONTROL

SIP processes are subject to formal controls that maintain a validated state over time. The practices outlined in ⟨1229⟩ include the general requirements appropriate for all sterilization systems as well as those specific to an individual sterilization method. Sterilization is accomplished by a number of related practices that are essential for continued use of the process over an extended period of time. The essential practices to maintain validated status include calibration, physical measurements, physical integrators or indicators, ongoing process control, change control, preventive maintenance, periodic reassessment, and training.

1 AAMI/ISO 13408-5. Aseptic processing of health care products—part 5: sterilization in place; 2008.

2 Parenteral Drug Association, Technical Report No. 28, Revised. Supplement Volume 60, No. S-2, Process simulation testing for sterile bulk pharmaceutical chemicals. Bethesda, MD: PDA; 2005.

3 Agalloco J. Steam sterilization-in-place technology and validation. In: Agalloco J, Carleton FJ, editors. Validation of pharmaceutical processes. 3rd ed. New York: Informa USA; 2007.

4 Parenteral Drug Association, Technical Report No. 61, Steam in place. Bethesda, MD: PDA; 2013.

5 Haggstrom M. Sterilization-in-place using steam or superheated water. In: Proceedings of the PDA Basel conference. Bethesda, MD: PDA; 2002.

Loading Auxiliary Information...

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 41(5)

Current DocID: GUID-3B9D0AC3-55B5-4709-B814-1BA70DF8CB45_1_en-US
DOI: https://doi.org/10.31003/USPNF_M10237_01_01
DOI ref: 14rnu