⟨1229.11⟩ VAPOR PHASE STERILIZATION

INTRODUCTION

Sterilization can be accomplished using sporicidal agents suspended in air (i.e., vapor). Sterilizing agents that operate in this fashion include hydrogen peroxide (H_2O_2), peracetic acid (CH_3CO_3CH), formaldehyde (CH_2O), and glutaraldehyde [$CH_2(CH_2CHO)_2$] in aqueous solution. At room temperature these are liquids or solids that can be vaporized for introduction into a vessel or chamber. They differ from sterilizing gases and liquids in that there are multiple phases within the vessel during sterilization. Vapor sterilization systems are well suited for heat-sensitive materials and surface sterilization. Items exposed to the process should have their surfaces exposed to the greatest extent possible. Vapor sterilization processes require appropriate sterilant concentration, temperature, and relative humidity, all of which may be variable during the exposure period. Because the agent is ordinarily supplied as an aqueous solution, moisture is introduced with the agent. The consequences of variation in these parameters may be localized differences in relative humidity, agent concentration, and condensation rates on the surfaces to be treated, resulting in variations in process lethality. The parameters to be established include sterilant amount (usually derived from injection quantities), relative humidity, and temperature. There is no demonstrated correlation between gas phase conditions, surface conditions, and microbial kill. For this reason, online monitoring of vapor phase concentration is not widely utilized as a control parameter. Efforts to develop a standardized biological indicator for vapor systems have been hampered by the multiphasic nature of these sterilants. Selection of the appropriate biological indicator (BI) and resistance should be based on experimentation within the user's system. Only under well-defined, specific conditions (e.g., agent concentration, humidity level, temperature, substrate, and phase) can a reliable D-value be established (for a definition of D-value, see *Sterilization of Compendial Articles* ⟨1229⟩).

This chapter will briefly review hydrogen peroxide and peracetic acid sterilization systems, because they are more widely used than other vapor phase sterilizing agents in the pharmaceutical and medical device industries.

HYDROGEN PEROXIDE

The efficacy of hydrogen peroxide as a liquid sterilant has been long established.[1] There are several effective approaches to hydrogen peroxide (H_2O_2) injection, including continuous, intermittent, or all at once. Some of the systems utilize an evacuation or drying step prior to introduction of the hydrogen peroxide (H_2O_2) to allow for increased concentration without excess condensation. Alternatively, hydrogen peroxide (H_2O_2) can be introduced as a liquid, followed by target heating. Following the exposure period, the chamber or target is aerated to an acceptable level for further processing of materials and/or personnel exposure (whichever is lowest) prior to opening and removing the sterilized article.

PERACETIC ACID

Peracetic acid (CH_3CO_3CH), alone or mixed with hydrogen peroxide, is a sporicidal agent that has been proven effective.[1] Peracetic acid is introduced as a liquid through an atomizer, resulting in the presence of liquid and vapor phases within the chamber. After the process dwell period, it is removed by evaporation.

VALIDATION OF VAPOR STERILIZATION

Standard sterilizing conditions have not been defined due to the varying phase and multiphase nature of the sterilant during sterilization processes. Therefore, no standardized BIs with D-values that may be used for conventional predictive analysis of kill rates exist. In the absence of BI D-values, and due to the variation in vapor sterilization cycle parameters, an empirical approach must be used. The kill rates in the gas and liquid phases that constitute the vapor may be substantially different (liquid kill rates are considered greater than gaseous kill rates). Destruction of BIs distributed across the system or load demonstrates lethality regardless of which phase effects the kill. Sterilization process parameters (usually time) that do not kill the BIs may be adjusted until a complete kill is achieved. This establishes the minimum conditions necessary for a complete kill. Vapor sterilization may be validated using a half-cycle, bracketing, or other suitable approach as defined in ⟨1229⟩ and *Gaseous Sterilization* ⟨1229.7⟩.

The half-cycle validation method requires the destruction of a suitable concentration of a resistant microorganism under defined, minimum conditions for a complete kill. Then, in routine operation, the minimum lethal time period is arbitrarily doubled, which supports a doubling of the spore log reduction of the BI, and is more than sufficient to inactivate the bioburden.

A bracketing approach, which better supports process operating ranges for the critical parameters than does the half-cycle method, also can be employed. In the bracketing method, one evaluates conditions that bracket the defined process condition in order to establish parameters for the minimum and maximum effects on the materials and bioburden. The minimum lethal process dwell time establishes the worst case for microbial kill. Incremental increases in process dwell time beyond the minimum lethal time period are used to establish the maximum exposure periods, which impart the greatest effect on materials. In addition, adjustments to the quantity of agent introduced, operating temperature, and relative humidity are utilized to further enhance the bracketing approach. By this method, the routine process conditions may be established between the minimum and maximum process conditions to ensure complete microbial kill while maintaining the integrity of the materials.

[1] Block SS, editor. *Disinfection, Sterilization, and Preservation.* 5th ed. Philadelphia: Lippincott Williams & Wilkins; c2001. Chapter 9, Peroxygen compounds; pp. 185–204.

The following activities are defined for a batch process, and therefore appropriate adaptation is necessary when they are applied to intermittent or continuous sterilization processes.

- *Equipment qualification*—The equipment qualification for vapor sterilization mimics that of other sterilization processes in order to confirm that the equipment has been properly installed and operates as intended.
- *Empty chamber parameter distribution*—Although multipoint measurement is possible, it lacks correlation to surface microbial kill. Humidity and temperature measurements, along with chemical indicators, can provide a limited indication of sterilant distribution. BIs are not required in the evaluation of the empty chamber.
- *Component mapping*—For surface sterilization, internal mapping of load items is not required. Although vapors are primarily used as surface sterilants, when they are used for packaged articles with internal surfaces and volumes that need to be sterilized, internal mapping should be performed, with BIs placed in difficult-to-penetrate locations to confirm process lethality.
- *Load mapping*—Humidity and temperature measurements, along with chemical indicators, can provide a limited indication of sterilant distribution on component surfaces. BIs are not required. Effects of load size and patterns should be assessed.
- *Biological indicators*—The use of multiple BIs at each test location is recommended to more adequately support the process lethality.
- *Process confirmation and microbiological challenge*—The core of the validation activity is the confirmation of acceptable process parameters and inactivation of the microbial challenge. Proof of cycle efficacy is provided in replicate studies in which the BIs are killed and chemical or physical measurements are utilized.

ROUTINE PROCESS CONTROL

Vapor sterilization is subject to controls that maintain a validated state over time. The practices outlined in ⟨1229⟩ describe the general requirements appropriate for all sterilization systems. The essential practices required to maintain validated status include calibration, physical measurements, use of BIs, physical or chemical integrators and indicators, ongoing process control, change control, preventive maintenance, periodic reassessment, and training.