OVERVIEW OF A PARAMETRIC RELEASE VALIDATION FOR EO STERILIZATION

STERIS
Applied Sterilization Technologies

TECHNICAL TIP #31

Background: Traditional EO Monitoring

Traditionally, ethylene oxide (EO) sterilization processes are routinely monitored with biological indicators composed of the microorganism Bacillus atrophaeus, usually inoculated onto a 1.5 x 0.25 inch paper carrier. A good example of a biological indicator is the Spordex® (STERIS) bacterial test strip.

For routine monitoring purposes, the biological indicators are placed throughout the sterilizer load and subjected to the sterilization process. After the process, the biological indicators are removed from the load and forwarded to the testing laboratory, where they are placed into a special growth medium and subjected to ideal growth conditions for 7 days (as addressed in USP[1]). After the 7-day incubation period, negative growth of the biological indicators demonstrates that the sterilization process was effective. The sterilizer load may then be considered for release to market, provided all other release criteria are met.

When using this traditional biological indicator monitoring of the EO sterilization process, expenses are incurred in two ways. First, there is the expense of the biological indicators and the associated laboratory testing. Secondly, there is a large amount of capital tied up in the inventory which must be held "on status" until after the laboratory testing is complete (7 days).

In addition to the expense, the use of biological indicators will increase risks due to the possibility of contamination of the indicator while being handled at the testing laboratory. In most cases, a failure of a biological indicator, even though laboratory induced, would be considered a sterility failure and result in the requirement for reprocessing of all of the materials which were contained in the sterilizer load. This increases costs both of the monitoring system and held inventory.

An Alternative Monitoring Method

ANSI/AAMI/ISO 11135-1:2007, titled "Sterilization of health care products - Ethylene oxide - Part1: Requirements for development, validation, and routine control of a sterilization process for medical devices" defines Parametric Release as "declaration that product is sterile, ***based on records*** demonstrating that the process parameters were delivered within specified tolerances."

Simply, parametric release allows product to be released to the market based only on process records instead of the traditional biological indicator sterility test. This is advantageous in that it eliminates the routine costs and risks associated with biological indicators and laboratory testing. In addition, most companies realize additional savings associated with a reduced unreleased inventory time (providing that the EO residue hold time is shorter than the biological incubation times).

Process Performance Qualification (Microbiological)

ANSI/AAMI/ISO 11135-1 provides options for the process performance qualification of the EO sterilization process as reference Annex A and Annex B of the standard (note: Additional guidance may be found in ISO 14161).

Annex A, titled "Determination of lethal rate of the sterilization process – Biological indicator/bioburden approach" outlines a method where resistance determinations are demonstrated for the biological indicator and compared to the natural product bioburden.

This is accomplished by running a predefined process at graded exposure times and determining the lethal rate (rate of inactivation) delivered. The knowledge of this rate and the population and relative resistance of the bioburden allows one to establish an exposure time so that a Sterility Assurance Level (SAL) can be predicted.

Annex A outlines two options for data analysis.

1. **Direct enumeration:**

   Direct enumeration is the process of determining the lethality of the sterilization process by construction of a survivor curve using direct enumeration (physical counts through serial dilutions) of surviving organisms. At least five points employing graded exposure times, with all other parameters (except time) remaining constant, are utilized. The data generated will enable the calculation of the time of exposure needed to achieve sterility of the biological indicator.

2. **Fraction negative:**

   The fraction negative method also requires graded exposure times to assure survivors, but the post-processing testing methods are different. For this method, a minimum of five exposure times are required. After exposure to the process, the samples are assayed by direct immersion into the appropriate culture medium (pass/fail) in lieu of the physical count performed in Method A. Using the data generated and statistical models provided in the standard (Holcomb-Spearman Karber or Stumbo Murphy Cochran), the death kinetics or D-value, may be calculated. Using the D-value data, an exposure time needed to achieve the desired sterility assurance level can be determined.

TechTeam Discussion

Historically, the use of "process development" by direct enumeration or fraction negative methods (D-value determination) were requirements (ANSI/AAMI/ISO 11135:1994) for validation of a parametric release process. It was the opinion of industry experts (ISO) that these validation methods provided a better understanding of the lethality delivered by the chosen process thus should be a requirement for parametric release.

Unfortunately, the requirements for graded exposure times which promote partial survivors of the biological indicators are extremely difficult to achieve and, in many cases, lead to an extensive and expensive process development/validation effort. The complexity of the program and financial burden associated with the expensive laboratory testing prevented many clients from pursuing the parametric release options.

After many discussions within the ISO group, the 2007 issue of the standard was revised to allow validation of a parametric release process using the overkill method. The overkill method has been in use for many years and continues to be the predominant method of EO Process Performance Qualification within the industry today. Annex B identifies the methods utilized to validate with the overkill method.

Annex B: "Conservative determination of lethal rate of the sterilization process – Overkill approach".

The overkill method requires a total of three consecutive (1/2 EO exposure time) cycles be performed which result in total inactivation of the biological indicators (of which the initial population was not less than 10^6). By demonstrating the inactivation of the 10^6 BI using one half of the exposure time, a Sterility Assurance Level (SAL) 10^6 is assured when the exposure time is doubled for the routine full cycle.

In addition to the three successful half cycles, the standard requires a cycle of short duration (fractional) from which survivors can be recovered be performed to demonstrate (validate) the adequacy of the recovery technique. Also, it is during this fractional cycle that the resistance of the bioburden is proven to be equal to or less than the resistance of the biological indicator.

Process Performance Qualification (Physical)

As outlined in the standard, the physical performance qualification shall demonstrate:

1. Reproducibility of the process, and shall include a minimum of three consecutive, planned qualification runs in which all the specified criteria are met;
2. That the specified acceptance criteria are met throughout the load for the duration of the proposed routine specification.

Elements of the physical PQ may be conducted during the microbiological PQ. If a) is performed in parallel with the microbiological PQ, then at least one additional qualification run shall be performed in compliance with this requirement.

The physical PQ shall confirm the process such that:

1. At the end of the defined preconditioning time (if used), the sterilization load is within the defined temperature and humidity ranges;
2. The specified maximum elapse time between the completion of preconditioning (if used) and the commencement of the sterilization cycle is appropriate;
3. Gaseous ethylene oxide has been admitted to the sterilizer chamber;
4. Pressure rise and the quantity of ethylene oxide used or the concentration of ethylene oxide in the sterilizer chamber are within the ranges specified;
5. During the sterilization cycle, the temperature and humidity of the chamber and, where applicable, other process parameters are within the ranges documented in the sterilization process specification;
6. The temperature of the product load during exposure is within the defined range;
7. During aeration, the sterilization load is within the specified temperature range.

For establishments that have varying load configurations, the extent to which the variation affects the sterilization process shall be evaluated. It shall be demonstrated that product sterilized with the process achieves the required level of sterility assurance.

Review and Approval of the Validation

Upon completion of the validation effort, a report shall be prepared which describes or references specific validated product, the defined loading patterns, and the documented specification for the process. The report will include the value and tolerances for:

1. Preconditioning (if used):
    - Time in chamber/area, temperature and humidity of chamber/area;
    - Minimum temperature of product permitted to enter preconditioning;
    - Temperature and humidity of the sterilization load;
    - Maximum elapse time for transfer.
2. Conditioning (if used):
    - The initial vacuum level (rate and time);
    - Holding time under vacuum (leak test);
    - Time in chamber and chamber conditions;
    - Temperature and humidity of the sterilization load.
3. Ethylene oxide injection and exposure:
    - EO pressure rise, time and final pressure;
    - EO concentration determined independently from the increase in pressure using at least one of the following:
        – Mass of EO used;
        – Volume of EO used;
        – Direct measurement of EO concentration.
    - Sterilizer chamber temperature;
    - Exposure time;
    - Temperature of the sterilization load;
    - An indication of recirculation system (if used) activity during exposure.
4. Aeration (if used):
    - Time and temperature;
    - Pressure changes (if any) in the chamber/or room;
    - Rate of change of the room atmosphere;
    - Temperature of the sterilizer load.

If parametric release is to be used, the validation shall establish:

1. The value and tolerances for chamber humidity by direct measurement during conditioning;
2. The value and tolerance for the ethylene oxide concentration, determined from direct analysis of the chamber atmosphere as defined intervals sufficient to verify the required conditions throughout the exposure time.

Requalification Requirements

If parametric release is used, the following additional requirements (as compared to a biological release validation) shall apply:

1. Requalification shall be performed at least annually;
2. Requalification shall include confirmation of the specified SAL through microbiological studies.

Special Considerations for Parametric Release

When designing a parametric release program, special adjustments are made to the validation parameters to assure that the “routine process” falls within “acceptable limits” each time a load is routinely processed. This is accomplished by validating at “worst case” conditions designed to provide a wide “processing window” for routine processing.

1. Half cycles:
    - Simulating winter conditions for all half cycles:
      To assure that preconditioning (if used) is effective regardless of climatic conditions or facility location, each half cycle validation load is exposed to simulated winter conditions prior to half cycle processing. Successful biological results when challenged with this worst case load conditioning assures that the process is effective for all conditions regardless of the time of the year or the location of the facility.
    - Relative humidity during conditioning:
      During each half cycle, the set point for conditioning is set below the nominal (routine) value to demonstrate adequate process lethality in the lower region of the relative humidity processing range. The relative humidity value reported for the successful half cycle is used as the routine minimum for the end of conditioning which is a requirement for parametric release.
    - Establishing a minimum EO concentration during exposure:
      During each half cycle, the set point for gas injection is set for the nominal (routine) value less 50 mg/L. The minimum concentration reported for the successful half cycle is the routine minimum value for exposure which is a requirement for parametric release.
2. Full cycles:
    - During each full cycle (full loads), the set point for gas injection is set for the nominal (routine) value plus 50 mg/L. The maximum concentration reported for the

successful full cycle is the routine maximum value for exposure which is a requirement for parametric release.

3. Mixed loads:

   - For those Customers that present mixed loads to the sterilizing facility, a fourth half cycle is recommended using the minimum loading configuration at minimum density. This load is processed in a biological challenged half cycle using minimum cycle conditions. Successful biological results using this minimum loading condition when supported by the successful maximum loading half cycles, serves to validate the process for any load mix from the minimum loading qualified to the maximum loading qualified.

References

1. United States Pharmacopeia, 31st edition, 2008.
2. ANSI/AAMI/ISO 11135-1:2007, Sterilization of health care products – Ethylene oxide – Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices
3. ANSI/AAMI/ISO 11135-2:2008, Sterilization of health care products – Ethylene oxide – part 2: Guidance on the application of ANSI/AAMI/ISO 11135-1.

For more information, please contact:

STERIS Applied Sterilization Technologies
5960 Heisley Road
Mentor, OH 44077
877.783.7479
www.steris-ast.com

STERIS
Applied Sterilization Technologies