PARAMETRIC RELEASE FOR ETHYLENE OXIDE STERILIZED DEVICES

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TECHNICAL TIP #16

Background

Traditionally, ethylene oxide sterilization processes are routinely monitored with biological indicators which are 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 adequate. The sterilizer load may then be considered for release to market, provided all other release criteria are met.

Using this traditional biological indicator approach of monitoring the EO sterilization process, expenses are incurred in two ways. First, there is the expense of the biological indicators and the associated laboratory testing; and 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.

In addition to the expense, the use of biological indicators increase risks due to the possibility of contamination of the indicator while being handled at the testing laboratory. In most cases, the failure of the 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

Section 7.2 of document ANSI/AAMI/ISO 11135[2], titled "Parametric Release," addresses an alternative method of monitoring the efficacy of an ethylene oxide process. The document defines parametric release as "Declaring product as sterile, based on physical and/or chemical process data rather than on the basis of sample testing or biological indicators."

In short, 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 associated with biological indicators and laboratory testing. Also, there may be an additional savings associated with a reduced unreleased inventory time providing that the EO residue hold time is shorter than the biological incubation times.

Overview – Microbiology Requirements

If parametric release is considered for routine product release, ANSI/AAMI/ISO 11135 provides specific requirements and guidance to assist in the validation process.

First, an understanding of the lethality of the sterilization process generated through fractional (sublethal) cycles is required. To achieve this, ANSI/AAMI/ISO 11135 has embraced two methods (only) to establish the minimum process parameters for parametric release of products. These methods establish the suitability and reliability of the process to completely destroy a biological indicator placed in the most-difficult-to-sterilize position, within the most difficult- to-sterilize device which will be sterilized in the Customer load. The first method (Method A) consists of an enumeration or physical count of the biological indicator survivors, and the second method (Method B) uses growth/no growth during sublethal cycles.

Method A is the process of determining the lethality of the sterilization process by construction of a survivor curve using direct enumeration (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.

As in Method A, Method B utilizes 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 in lieu of the physical count performed in Method A. Using the data generated and statistical equations provided in the standard, the death kinetics or D-value, may be calculated. Using the D-value data, an exposure time needed to achieve sterility can be determined.

Either method will yield information which will contribute to a better understanding of the sterilization process used to promote parametric release.

Equipment Requirements

As stated in ANSI/AAMI/ISO 11135, Annex D, paragraph D.2, "the use of a system of parametric release for ethylene oxide sterilization will require a greater knowledge and more control of the sterilization parameters." This method necessitates control and documentation of the sterilization parameters.

The following equipment capabilities are established.

- Preconditioning
  a. Adequate air circulation to assure uniformity of temperatures and humidity in the room.
  b. Airflow detection alarms on the circulation system to ensure it is operating within validated parameters.
  c. Separate monitoring and controlling sensors for temperature and humidity determination in the room.
  d. Product temperature probes to continuously monitor product.
  e. Humidity probes within the product.
  f. A method for recording time of product entry and removal from the preconditioning room.
- Sterilization Chamber
  a. Product temperature recording probes to continuously monitor the product.
  b. Independent systems for recording and controlling chamber pressure and chamber temperature.
  c. Instrumentation for analysis of humidity during conditioning and EO concentrations during exposure.
  d. A gas circulation system, equipped with monitoring systems to verify the system is operating within specification.
  e. Instrumentation for monitoring gas inlet temperature.
- Aeration
  a. Airflow detection alarms on the air handling system to ensure it is operating within specified parameters.
  b. Product temperature recording probe available to continuously monitor product temperatures.
  c. A method for recording time of product entry into and removal from the room.

Process Analysis

The continuous measurement and documentation of relative humidity during conditioning and gas concentrations during exposure require particular attention when parametric release is being utilized. In a conventional biological indicator monitored EO process, the concentration of moisture and ethylene oxide are calculated using partial pressure and temperatures. In addition, the amount of EO can be verified using gas consumed by weight.

ANSI/AAMI/ISO 11135 requires that for parametric release the addition of both moisture and EO be verified both during validation and routine cycles. Direct analysis for moisture can be accomplished by the use of electronic sensors or by use of analytical instrumentation such as gas chromatography or spectroscopic methods (infrared [IR] or near-infrared [NIR]). EO analysis can presently be accomplished using only chromatography or spectroscopic methods. The reproducibility and accuracy of the analysis equipment should be determined during validation. During routine processing, the analysis of moisture and gas concentration must fall within the predetermined range for the cycle to be acceptable.

Load Configuration

The loading configuration used for validation should be evaluated for the impact to the delivery of the process parameters. If the volume of the load will not be consistent for routine production, then the range should be evaluated for its effect on the delivered process parameters and lethality. Control of loading patterns and densities is required when practicing parametric release.

References

1. United States Pharmacopeia, 31st edition, 2008.
2. ANSI/AAMI/ISO 11135, Medical devices - Validation and routine control of ethylene oxide sterilization, 2007.

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