Boulder Sterilization

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QUICK TURNAROUND ETHYLENE OXIDE STERILIZATION

Sterilization options during and after product development

Abstract

Ethylene Oxide (EO) sterilization is a largely used sterilization method for medical devices. This type of sterilization is needed in many stages of product development from engineering testing to clinical trials to production. This white paper explains the different sterilization options, advantages of each, and the benefits of quick turnaround EO sterilization.

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September 18, 2020

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Executive Summary

Ethylene Oxide (EO) sterilization is routinely performed in large chambers capable of holding multiple forklift pallets of product. Development of sterilization cycles for such chambers is a lengthy, involved, expensive process as is the operation of such chambers. Smaller batch commercially available EO sterilizers enable service organizations to offer quick turnaround (days versus weeks) sterilization services for production lots of product, for prototypes, for animal trial samples, for biocompatibility testing, for sterile packaging testing and for clinical trial purposes. The emergence of such quick turnaround EO services benefits medical device companies needing to test their prototypes, for early production runs and for ongoing production of modest volume, and high value devices.

Sterilization Overview

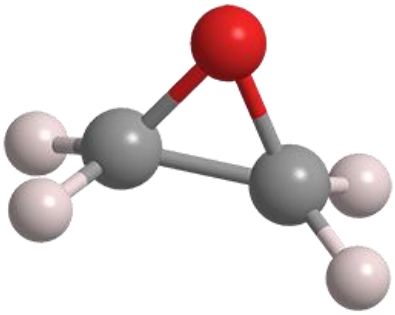
Sterilization inactivates all microorganisms on the surface of a product to prevent their infecting a patient or person who might come in contact with the product either directly (e.g., by touch) or indirectly (e.g., carried into the patient by IV fluid). The medical device industry uses a sterility assurance level (SAL), or a probability of sterility, to define what "sterile" means for a product. This SAL is defined as the reduction of viable microorganisms on a product after sterilization and is expressed in orders of magnitude (e.g., 10-6, or less than 1 viable microorganism remaining after sterilization for every 1 million viable microorganisms prior to sterilization).

It's important to note that running product through an appropriate sterilization process renders it "EO processed," but it cannot be labeled "Sterile" until proper tests have been completed, including microbiology testing, to confirm achievement of the SAL.

Product sterilization needs are dependent on the product's intended use. If the product comes in contact with wounds, tissues underneath the epidermis or certain bodily fluids then it most likely will need to be sterilized.

Ethylene Oxide Sterilization Overview

Ethylene Oxide (C_2H_4O) is a colorless, odorless gas. Its lethality comes from a chemical reaction (alkylation) with the DNA of bacteria, viruses, molds, and yeasts.



Ethylene Oxide (EO) sterilization has been known for many decades to be an efficient and cost-effective method for sterilization for materials not capable of withstanding the high temperatures of steam autoclaving or the rigors of radiation. Its relatively low-temperature cycles are gentle on plastics and other such materials widely used in sterile, single-use medical devices.

Four parameters, EO gas concentration, humidity, temperature, and exposure time, effect the lethality of the EO gas. Products to be sterilized are placed in a pressure/vacuum chamber. A vacuum is drawn to remove ambient air, which is then replaced with combinations of EO gas, humidity and clean air in specific combinations and sequences (the sterilization "cycle"). Temperatures are varied during the processing and are typically between 35 and 55 °C. Parameters vary in a controlled manner during the cycle including use of EO under pressure to drive it into the previously evacuated nooks and crannies of the product. Finally, the products are rinsed using clean air to remove EO residuals.

To accommodate these cycles, products must be packaged in gas permeable systems which incorporate a sterile barrier to allow for penetration and removal of the EO gas and withstand pressure changes. Such materials include clear bags or vacuum-formed trays with Tyvek® or similar gas-permeable seals.

Many medical products need to be sterilized in quantities of hundreds of thousands or millions per year. Surgical gowns, masks, drapes, disposable surgical tools, syringes, and IV tubing sets are a few common examples. The EO sterilization chambers used for such products are large enough to drive a fork-lift into and place multiple pallets of packaged product. The pressures and volumes of EO gas needed to support such chambers are inherently dangerous with the potential to explode or leak. EO gas is toxic. It must be carefully contained and handled. When exhausted from the chambers, it must be prevented from entering the atmosphere. Such methods these days are commonplace and reliable but add significantly to the expense of the process.

Most commercial sterilization companies employ such large chambers and focus on high-volume products to gain the profitability therewith associated. While they do have smaller-volume chambers for experimentation and cycle development, these are primarily used to feed new products into validation for the large chambers. Such large chamber sterilization cycle validation takes many weeks and is very expensive, as is running these massive chambers. The resulting sterilization cost per product, however, is low.

Quick Turnaround EO Sterilization

There is a continual and growing need for EO sterilization on smaller lots of product. Such needs include quick turnaround sterilization of:

- Prototypes
- Animal test samples
- Biocompatibility test samples
- Sterile barrier packaging test samples
- Clinical trial lots
- Production lots for low-modest volume and/or high value products

Companies such as Boulder Sterilization offer quick turn-around EO sterilization for just such purposes. Instead of large quantities of potentially dangerous-to-handle EO gas, small canisters provide simple, safe loading and unloading. Catalytic converters known as abators are available and used to prevent EO from entering the atmosphere. Such systems create the opportunity for much-needed quick turnaround sterilization services for new product development groups, start-up companies and for ongoing production of suitable products (e.g., modest volume and/or high value).

Such companies can react quickly, with turnaround times in days rather than weeks, and typically offer associated services such as the following, either within their own organizations or using external labs, seamless to the client:

- Clean room final assembly of products to be sterilized

- Bioburden testing to establish the required baselines for the sterilization cycle
- EO sterilization cycle development and validation
- Gas permeable packaging and sealing of products in a clean room
- Placement of Biological Indicators (BIs) into each batch as appropriate
- Sterilization in an EO sterilizer
- Incubation of the sterilized and control BIs to confirm bacterial sterilization
- Coordination of additional testing including:
  - Product sterilization validation (e.g., by sterile rinse and incubation)
  - Product biocompatibility testing per ISO 10993
  - Product non-pyrogenicity testing (e.g., LAL testing)
  - Post-sterilization sterile barrier testing (e.g., package integrity testing)

Confirming Sterility

Product that has been "EO processed" has undergone a sterilization process. That by itself doesn't mean that the product can be labeled "sterile" until adequate testing of the process has been performed and documented. Sterilization process cycles are performed in three basic categories for different purposes. The three basic categories are:

- Non-Validated Run (EO processed only)
- Single Lot Release
- Full Validation and lot Releases

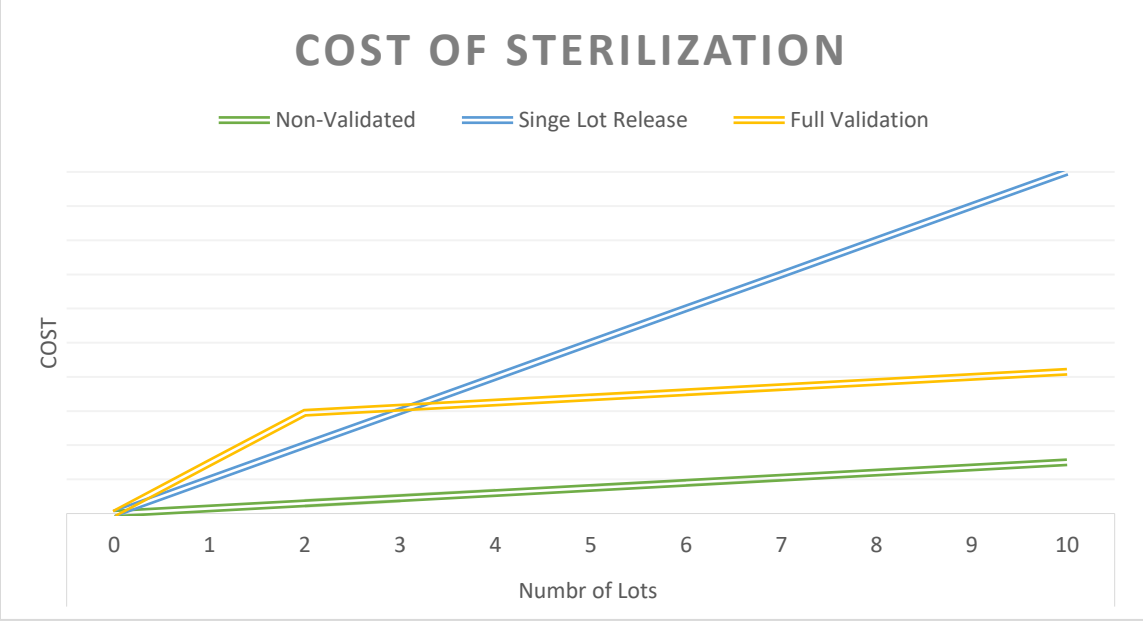


Figure 1 Chart showing cost comparison between non-validated sterilization runs, single lot release and a full validation. Full validation costs more up front, but becomes cost effective after multiple lots.

Non-Validated Run (EO processed only)

- The product is run through a sterilization cycle but not tested for sterility
- Such product cannot be legally labeled as “sterile”
- This is typically used for non-human testing required during product development. This can include mechanical testing, sterile barrier package testing, biocompatibility testing, animal trials, etc.

Single Lot Release

- The product can be labeled “sterile” through testing of each lot
- Single Lot Release is great for:
  - Clinical trial product
  - Initial product quantities for sale while full validation is underway
  - Very low volume products
- To assure sterility and product safety, a number of products are taken from each lot and tested to confirm sterility (BIs, bioburden, etc.)
- The number of products taken from the lot for testing can be significant
  - 15 to 30 items is typical
  - If the products are being built for limited testing, the number of samples needed may be a significant percentage of the total build
  - This can be very “expensive” from a product standpoint, though some leeway is possible using “representative” product for sterility testing
- The cost of the testing represents a financial burden on each lot
- The time it takes to perform the tests to release each lot is a consideration and is significantly longer (weeks rather than days) compared to a routine processing run after full validation.
- A sterility report is required for each lot, which is an auditable document

Full Validation and lot Releases

- Once full validation is completed, the lot can be released as “sterile” based on confirmation and recording of the cycle parameters which were validated
- Product can be released as “sterile” using process challenge devices, biological indicators must be negative for growth, or a parametric release, a thorough documented review of the processing records.
- This can be done lot after lot without repeating the sterilization validation testing for a period of time, typically one year, when the cycle undergoes an annual review
- The result is “sterile” labeled product released with minimal testing, much faster than a single lot release, without taking out product for testing and without the time and cost of full testing on each lot
- Full validation is great for volumes of product that require many lots to be processed per year
- Full validation is a lengthier and more expensive endeavor than single lot release, but when amortized over multiple lots, the per-product cost to claim “sterile” is dramatically reduced.
- A full validation follows ISO 11135
- There are three main steps, each requiring several process and testing activities
  - Sublethal Cycle (Process Challenge Device Selection)

    - Microbiological Performance Qualification (MPQ)
    - Process Performance Qualification (PPQ)
- Sublethal Cycle
    - A sublethal cycle is a very short cycle which is used to show the effectiveness of the EO gas in killing the natural bioburden on the product and to select the process challenge device that will be used for the performance qualification and routine processing.
- MPQ
    - The MPQ further demonstrates that specific requirements for sterility are met using a series of partial cycles comparing BIs and process challenge devices
- PPQ
    - The PPQ is used to show that all acceptance criteria is met during routine processing using the established cycle parameters

	Non-Validated Run	**Single Lot Release**	**Full Validation**
Sterility Assured	No	Yes	Yes
Used For	Non-human testing	Clinical trials and very low volumes of product	Production
Timing	Days before product processed	Each lot is weeks before release	Initial setup longer than single lot, but quick product releases once validation is complete
Cost	Low Cost	Lower cost than full validation for first couple lots, then gets more costly	Most expensive option initially, put pays off when doing more than 3 sterilization runs
Test Samples	No Samples for testing required	15-30 samples required for each lot	30-60 samples required for validation; no samples needed for routine processing
Design Changes	Design can change between lots	Design can change between lots	Design changes need to be reviewed

Regulatory Requirements for EO Sterilization

The following international standards apply to Ethylene Oxide Sterilization. Additional national, regional and local governments may have their own requirements as well.

- Medical Devices sterilized using Ethylene Oxide must follow ISO 11135:2014
- Prior to release, sterilized product must be tested for EO residuals following ISO 10993-7:2008/AMD 1:2019.

Conclusion

Quick turnaround EO sterilization services can greatly enhance and accelerate product development processes and provide low to modest volume products a timely and cost-effective sterilization solution.

Note: A product labeled “sterile” must include an expiration date. Sterility expiration dating – the options and how to get it done – is the topic of a separate white paper.

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