Quick-Turn Ethylene Oxide Sterilization: Sterilization Options During and After Product Development

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Abstract

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

Executive summary

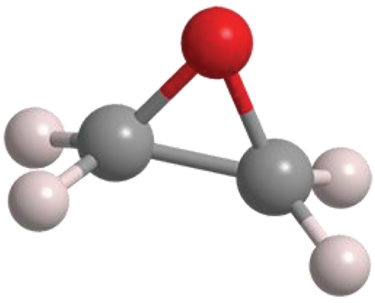
Ethylene oxide (EO) sterilization is routinely performed in large chambers capable of holding multiple forklift pallets of product. The operation of these chambers, and the development of sterilization cycles for them, are lengthy, involved, expensive processes. In contrast, smaller-batch, commercially available EO sterilizers allow quick-turn (days versus weeks) sterilization services for production lots of product, prototypes, animal trial samples, biocompatibility testing, sterile packaging testing and clinical trial purposes. The emergence of quick-turn EO services benefits medical device companies in prototype testing, early production runs and ongoing production of modest-volume, high-value devices.

Sterilization overview

Sterilization inactivates all microorganisms on the surface of a product to prevent infecting a patient or person who might come in contact with the product 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. SAL, the reduction of viable microorganisms on a product after sterilization, is expressed in orders of magnitude. For example, a SAL of 106 is 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 as “sterile” until the completion of proper testing, including microbiology testing, to confirm achievement of the SAL. Product sterilization needs depend on each product’s intended use. In general, if a product comes in contact with wounds, tissues underneath the epidermis or certain bodily fluids, it most likely will need to be sterilized.

Ethylene oxide sterilization process



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.

For decades, EO sterilization has served as an efficient and cost-effective method for sterilization of materials that are not capable of withstanding the high temperatures of steam autoclaving or the rigors of radiation methods. Its relatively low-temperature cycles are gentle on plastics and other materials widely used in sterile, single-use medical devices.

Four parameters – gas concentration, humidity, temperature and exposure time – affect the lethality of the EO gas. In EO sterilization, products 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. This process is the sterilization "cycle." Temperatures vary during the process, typically between 35° and 55°C. During the cycle, parameters vary in a controlled manner. This includes the 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 that incorporate a sterile barrier to allow for penetration and removal of the EO gas, and to withstand pressure changes. These systems include clear bags or vacuum-formed trays with Tyvek® or similar gas-permeable seals.

Typical large-chamber EO sterilization

For many medical products, sterilization must take place in quantities of hundreds of thousands – or millions – per year. Surgical gowns, masks, drapes, disposable surgical tools, syringes and IV tubing sets are common examples. With the need to sterilize such quantities, the EO sterilization chambers used are often large enough to drive a forklift into, and can contain 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. As EO gas is toxic, it must be carefully contained and handled. When exhausted from the chambers, it must be prevented from entering the atmosphere. While these systems are common and reliable, they do add significantly to the expense of the process.

Most commercial sterilization companies employ these types of large chambers, and focus on high-volume products to assure profitability. While commercial sterilization companies generally do have smaller-volume chambers for experimentation and cycle development, they use them primarily to feed new products into validation for the large chambers. Large-chamber sterilization cycle validation takes many weeks and is very expensive, as is running the massive chambers. The resulting sterilization cost per product, however, is low.

Quick-turn EO sterilization

The need for EO sterilization on smaller lots of product is growing, for uses including:

- 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

New-product development groups and start-up companies have particular need for quick-turn services, as do companies involved in the ongoing production of low- modest and/or high-value products.

Service providers offering quick-turn EO sterilization – such as Boulder Sterilization – can provide these businesses with turnaround times in days rather than weeks. Instead of large quantities of potentially dangerous-to-handle EO gas, small canisters provide simple, safe loading and unloading. Catalytic converters known as abators prevent EO from entering the atmosphere.

Providers of quick-turn EO sterilization also typically offer associated services medical device companies need (in-house or through external labs, seamless to the client):

- Clean-room final assembly of products to be sterilized
- Bioburden testing to establish 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
  - 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. Yet that by itself doesn’t mean that the product can be labeled “sterile.” Adequate testing of the process and documentation still must take place. Sterilization process cycles are performed in three basic categories, each for a different purpose:

- Non-validated run (EO-processed only)
- Single-lot release
- Full validation and lot releases

(Note that a product labeled “sterile” must include an expiration date. Sterility expiration dating, including the options and process, is not included in this paper.)

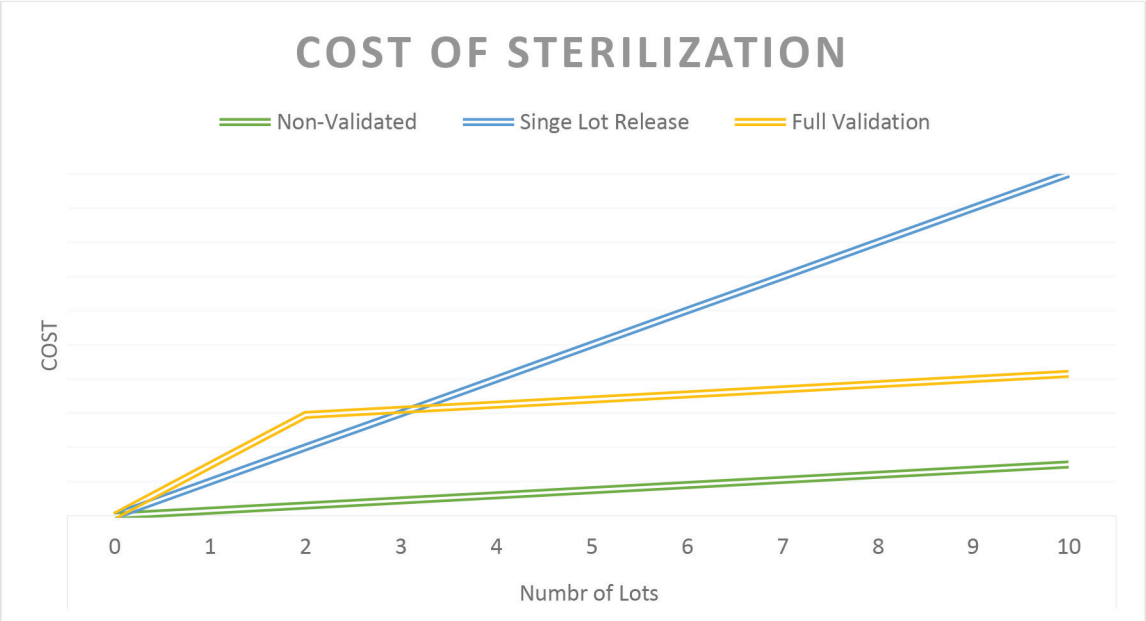


Figure 1 Chart showing cost comparison between non-validated sterilization runs, single lot release and a full validation. Full validation costs more up front, but becomes cost-effective after multiple lots.

Non-validated run (EO-processed only)

A non-validated run is typically used for non-human testing required during product development. This can include mechanical testing, sterile barrier package testing, biocompatibility testing and animal trials.

The product is run through a sterilization cycle, but is not tested for sterility. Therefore, it cannot legally be labeled as “sterile.”

Single-lot release

Single-lot release works particularly well for clinical trial products, initial product quantities for sale while full validation is underway, and very low-volume products.

- The product can be labeled “sterile” through testing of each lot; cost of the testing represents a financial burden on each lot.
- To assure sterility and product safety, a number of products are taken from each lot and tested to confirm sterility (BIs, bioburden, etc.). A quantity of 15-30 items is typical, but if the products are being built for limited testing, the number of samples required 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 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 – which is an auditable document – is required for each lot.

Full validation and lot releases

Full validation is appropriate for volumes of product that require many lots to be processed per year. Once full validation is completed, the lot can be released as “sterile” based on confirmation and recording of the cycle parameters that were validated.

The product can be released as “sterile” using process challenge devices and proof that biological indicators are negative for growth, or through a parametric release with 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 a year, when the cycle undergoes an annual review.

The result is a “sterile”-labeled product released with minimal testing. It is a much faster than a single-lot release, completed without taking out product for testing, and without the time and cost of full testing on each lot.

From a cost perspective, 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 lower.

A full validation follows ISO 11135. Three main steps each require several process and testing activities.

- Sublethal cycle (process challenge device selection): This very short cycle shows the effectiveness of the EO gas in killing the natural bioburden on the product, and aids in the selection of the process challenge device for the performance qualification and routine processing.
- Microbiological performance qualification (MPQ): Further demonstrates that specific requirements for sterility are met, using a series of partial cycles comparing BIs and process challenge devices.
- Process performance qualification (PPQ): Shows that all acceptance criteria are 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 EO sterilization. National, regional and local governments may have additional requirements.

- ISO 11135:2014: For all medical devices sterilized with EO
- ISO 109937:2008/AMD 1:2019: To test all sterilized products for EO residuals prior to release

Conclusion

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

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