



Guidelines for Validation

Ethylene Oxide

A sterile product is defined as “one that is free of viable micro-organisms.” The purpose of the sterilization process is to inactivate any microorganisms present and thereby transform the products from non-sterile to sterile.

Because the inactivation of microorganisms by physical or chemical agents equates to an exponential relationship, there is always a finite probability that a microorganism may survive regardless of the extent of the treatment applied.

Therefore, the sterility of one item in a population of items can only be expressed in terms of the probability of the existence of a non-sterile item in that population. This is frequently referred to as the Sterility Assurance Level (SAL). For an item to be labeled sterile it is usual for the SAL to be 10^{-6} .

The EN29000 Series of standards identifies sterilization as a “special process,” i.e., one that cannot be fully verified by subsequent inspection and testing. For this reason the sterilization process must be validated.

The steps that follow identify how this validation is achieved when the sterilization modality is Ethylene Oxide Sterilization.

1.0 Installation Qualification

Installation qualification, or “commissioning,” verifies that the equipment has been installed and operates in accordance with its specification. The qualification is conducted in the absence of product.

2.0 Cycle Selection

The development and selection of a sterilization process for a particular medical device must establish that the procedure is both effective and compatible with the device. Therefore, investigations into product compatibility, along with verification to identify and/or optimize the sterilization process, should be undertaken.

During an Ethylene Oxide (EO) sterilization process, products can be subjected to environmental stresses, elevated temperatures and changes in humidity. Thus, product design should ensure that functionality and safety are not compromised by exposure to the anticipated range of sterilization conditions.

The product may also react with or retain EO. Accordingly, it is imperative to determine that the proposed process does not result in unacceptable levels of Ethylene Oxide (Epoxy Ethane), Ethylene Chlorhydrin (2-Chloroethanol) and/or Ethylene Glycol (Ethanediol) in the product.

The effect of re-sterilization and maximum process parameters should also be investigated during this cycle selection study. Sterigenics can assist with both the production of a cycle selection protocol and post-sterilization residual analysis.

PERFORMANCE QUALIFICATION

2.1 Protocol Preparation

Before initiating Performance Qualification, a protocol must be approved by both Sterigenics and the customer. Sterigenics can assist in the development of a protocol covering the key areas of Physical and Microbiological Performance Qualification. It is recommended that customers complete the protocol qualification process with Sterigenics technical specialists before commencing any validation work.

Customers who prefer to do so are welcome to prepare their own protocols. In this case, Sterigenics must review and sign all related documents in advance of initiating validation.

Sterigenics operates chambers capable of holding up to 30 pallets/ 15 europallets of product. We recommend that customers routinely sterilize a “dedicated load” and validate accordingly.

When a customer cannot supply a dedicated load for routine sterilization and requests a “mixed load,” Sterigenics will, with the customer’s consent, mix the customer’s product with other products that are not considered to be incompatible.

Note: As no provision for this is included in any current standard, the implications of this approach should be thoroughly discussed with Sterigenics prior to beginning validation and desired special considerations should be addressed in the protocol.

2.2 Validation Load Selection

Single Product Load

When a single product is to be sterilized, the loading pattern should be defined for routine sterilization and the load used for validation should be assembled in an identical manner.

Dedicated Load

When a range of products from a single manufacturer are to be sterilized together, the load used for validation should reflect the most difficult combination of products. Validation for the composite load should document the rationale for its selection (based on complexity and configuration), and the composition should be recorded in the protocol.

Factors, which may be considered in such a load, are those likely to effect penetration of heat, humidity and gas. For example: density (kg/m³), insulation characteristics of materials and packaging, as well as factors such as the compatibility of the products and minimum and maximum routine volumes of any one product in the load.

Mixed Load

In the event of a mixed load, the considerations for a dedicated load apply. However, the pallets of product should not exceed 250kg and bulk density should not exceed 125kg/m³. Validation should be undertaken in combination with Sterigenics reference material.

2.3 Physical Performance Qualification

The purpose of Physical Performance Qualification is to ensure that the sterilization load reaches acceptable levels of temperature and Relative Humidity (RH) by the end of the minimum preconditioning time, and further, that these levels are maintained within acceptable limits throughout exposure to EO. Analysis of the data gathered will identify any areas in the load that are difficult to heat or humidify.

Where a “mixed load” is under consideration, the acceptance criteria must be carefully defined in both customer product and the Sterigenics Sterilization and Ionization reference material.

2.4 Microbiological Performance Qualification

The rate of microbiological inactivation for a given process is usually assessed using Biological Indicators of *B. subtilis var niger* which contain a known population possessing resistance to EO sterilization. The appropriateness of these indicators should be established and documented.

For a given load and process conditions, the rate of inactivation of these organisms will depend upon:

- The nature of the Biological Indicator (BI)
- The location of the BI in the product
- The location of such products in the load.

During validation, BIs should be located in the parts of the products which present the worst-case scenario for gas and humidity penetration as identified in the Physical Performance Qualification. The remainder of the BIs should be distributed throughout the load at specified intervals.

Three methods of Microbiological Performance Qualification Are Recognized:

□ Method A: Survivor curve construction

The lethality of the sterilization cycle shall be determined by construction of a survivor curve using direct enumeration of survivors.

At least five points employing graded exposure times to EO, with all other process parameters except time remaining constant, should be included on the survivor curve. The initial count (i.e., the time zero on the survivor curve) should be determined on BIs exposed to all stages prior to EO injection.

The resulting data enables the calculation of the time of exposure to EO required to achieve a particular probability of survival of the test organism.

□ Method B: Fraction-negative method.

Indicators for EO sterilization shall be exposed to graded exposures for EO with all parameters except time remaining constant. After exposure, the test samples are assayed by direct immersion into an appropriate culture medium. A minimum of seven days exposure should be maintained, including:

- At least one set of samples in which all tested samples show growth
- At least four sets in which a fraction of the samples show growth (quantal region)
- At least two sets of samples in which no growth is observed.

- The D-value can be calculated from the results obtained. The exposure time required to achieve a specified probability of the survival of the test organism shall be calculated from this D-value.

□ Method C: Half-cycle method

This method involves determination of the minimum time of exposure to EO, with all other process parameters except time remaining constant, at which there are no survivors. Two further experiments should be performed to confirm the minimum time. Both should show no growth from the BIs. The specified exposure time should be at least double this minimum time. A cycle of short duration from which survivors can be recovered should also be run to demonstrate the adequacy of the recovery technique.

2.4.1 Selecting Test Units

When more than one product is to be validated at the same time, the selection of Test Units must be justified and documented. The following procedure is suggested:

1. Group products into families
2. Calculate the density of each product based on a standard stacking pattern
3. Assess the complexity of each product with regard to gas and humidity penetration, taking into account packaging, length of the gas pathway, flow restrictions etc.
4. From the above, select the most challenging product from each family
5. Compare these products using the sub-lethal cycle to determine the relative rates of inactivation in each product. It may then be possible to select a worst case Test Unit or Process Challenge Device.

2.4.2 Bioburden

It is important to be aware that exposure to a properly validated and accurately controlled sterilization process is not the only factor associated with the provision of a reliable SAL. The microbiological contamination of product prior to sterilization should be minimized and controlled. For that reason, it is essential that this population is determined during validation and routinely monitored thereafter. Sterigenics provides a comprehensive bioburden evaluation service including initial validation and subsequent routine testing.

2.5 Product Evaluation

Although Sterigenics may be able to recommend a suitable process, it is the manufacturer's responsibility to evaluate product and packaging performance after exposure to the process.

To ensure product safety, the levels of EO and its by-products should be determined after sterilization and de-gassing. Sterigenics can provide both a residual determination protocol and test facilities.

3.0 Review Reporting and Approval

Sterigenics recommends that each validation run be reviewed with our technical specialists before proceeding to production.

A final report will be issued for customer approval. It will summarize the validation and detail the cycle specification. This report should be read in conjunction with the protocol and should be signed by the same individuals who approved the protocol.

4.0 Contract

Sterigenics will issue a technical contract containing the cycle specification and a customer card outlining customer details and any special handling, documentation and/or testing requirements.

5.0 Revalidation

Revalidation should be performed in cases where:

- new products or changes in existing product, packaging or loading pattern which cannot be shown to be equivalent to those previously validated, are introduced. Such demonstrations of equivalence must be documented and approved by the customer's microbiologist
- significant process or equipment changes have been made
- it is necessary to confirm that inadvertent changes have not been made and that the original validation remains valid

Revalidation may include all or some aspects of the original validation. In the absence of other factors, Sterigenics recommends that the validation be reviewed at least annually. This may be performed in conjunction with contract review. A decision on whether revalidation is required must be documented and approved by the customer's microbiologist.

References

- EN556 Sterilization of medical devices; Requirements for medical devices to be labeled "sterile"
- BS EN550 Sterilization of medical devices; Validation and routine use of Ethylene Oxide sterilization
- ISO 10993-7 Biological evaluation of medical devices, part 7 – Ethylene Oxide sterilization residuals