Technical Information Report

AAMI TIR56: 2013

Guidance for the development, validation and routine control of an ethylene oxide sterilization process utilizing flexible bag systems for the sterilization of medical devices

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Advancing Safety in Medical Technology

Guidance for the development, validation and routine control of an ethylene oxide sterilization process utilizing flexible bag systems for the sterilization of medical devices

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Association for the Advancement of Medical Instrumentation

Abstract: This AAMI Technical Information Report (TIR) provides information to be considered during the development, validation, and routine control of EO sterilization processes that are performed using gas diffusion within individually sealed flexible sterilization bags.

Keywords: sterilization, flexible bag systems, diffusion, EO, ethylene oxide

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Glossary of equivalent standards

International Standards adopted in the United States may include normative references to other International Standards. AAMI maintains a current list of each International Standard that has been adopted by AAMI (and ANSI). Available on the AAMI website at the address below, this list gives the corresponding U.S. designation and level of equivalency to the International Standard.

www.aami.org/standards/glossary.pdf

Committee representation

Association for the Advancement of Medical Instrumentation

Industrial EO Sterilization Working Group

This Technical Information Report (TIR) was developed by the AAMI Industrial EO Sterilization Working Group under the auspices of the AAMI Sterilization Standards Committee. Working Group approval of the TIR does not necessarily imply that all committee members voted for its approval.

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Foreword

The processes, methods, and equipment described in this TIR vary significantly from those described in ANSI/AAMI/ISO 11135-1:2007. These differences include but are not limited to the following:

- The body of information provided in ANSI/AAMI/ISO 11135-1:2007 is complemented by supporting documentation found in ANSI/AAMI/ISO 11135-2:2008, as well as a number of related AAMI TIR documents, significant parts of which may not apply to methods and materials that are the subject of this TIR.
- The 11135 series includes 100 % verification of chamber installation and the associated performance qualification (physical and microbiological) of fixed equipment; the methods described in this document rely upon the validation of an integrated, flexible bag/chamber design and a high degree of quality assurance during the manufacturing process of the flexible bag/chamber (and other accessories).
- Methods included in this document identify processes based solely on gas injection by weight, variable, or diminishing (i.e., decreasing by diffusion through the flexible bag) ethylene oxide (EO) concentrations in the atmosphere external to the package but internal to the “flexible bag sterilization systems” per the design of the method.
- Approaches to validation, routine monitoring, and control of cycles may differ significantly from those indicated in 11135.
- For some process designs, the lethality of the process relies completely on storage conditions and time (post introduction of EO) to effectively provide the requisite sterility assurance level. In addition, the lethality provided during the storage period within the sterilization/aeration cabinets may also act simultaneously in providing the aeration method. There are also a number of specialized and novel equipment designs necessary to remove EO from a flexible sterilization bag that vary considerably from the methods described in 11135. New considerations may arise regarding the identification of worst-case aeration processes, as well as subsequent validation.

Introduction

As a result of a revision to ANSI/AAMI/ISO 11135-1, the exclusion in the document stating “This part of ISO 11135 does not cover sterilization by injecting ethylene oxide or mixtures containing ethylene oxide directly into individual product packages,” was revised to state, “This International Standard does not cover sterilization by injecting EO or mixtures containing EO directly into packages **or a flexible chamber**.” The addition of the flexible chamber to the international standard clarified the intent that ANSI/AAMI/ISO 11135 should only be applied to traditional fixed sterilization chambers, and that ANSI/AAMI/ISO 14937:2009/(R)2013 should be used for the requirements and guidance related to these types of EO processes. Ethylene oxide sterilization is a long-standing sterilization process, and EO sterilization within flexible sterilization bags has been used commercially since the 1960s. However, little published information was available to provide guidance on adequately addressing development, validation, and routine control of these EO systems. Therefore, the Industrial EO Sterilization Working Group chose to develop a technical information report (TIR) that addresses these aspects as a prelude to the eventual development of an international standard.

During the development of the TIR, there was strong objection by some to the use of EO sterilization within a flexible sterilization bag; therefore, this document does *not* represent a committee or national consensus. Most of this objection centered around two specific areas of concern. The first objection was the lack of workplace safety information that is provided in this TIR. The decision not to include safety related details within this TIR is consistent with the position that has been taken in other industrial sterilization standards or guidance documents. Information related to the safe use of EO in the workplace is readily available (see https://www.osha.gov/SLTC/ethyleneoxide/) and its use falls under the regulatory auspices of OSHA (29 CFR 1910.1047) (2005). Additional information related to the carcinogenic properties of EO can be found in World Health Organization, 2008.

The second objection was related to the dearth of published information related to EO sterilization in flexible sterilization bags that documented its efficacy or repeatability. The biggest differences between traditional EO sterilization and this non-traditional method are the use of the flexible sterilization bag with a very low concentration of EO and the absence of significant air removal during the process. While there is not significant literature related to this process in particular, there is considerable literature on the efficacy and repeatability of EO sterilization in general, even under conditions that are somewhat similar to those used during EO sterilization in a flexible sterilization bag ([1] and [2]). During the development of this TIR, two articles were published ([5] [6]) that have particular relevance to this process. The expectation is that as the TIR is used, additional information will be made public to further substantiate its efficacy and repeatability, as well as to refine how the processes are developed, validated and routinely controlled.

Guidance for the development, validation, and routine control of an ethylene oxide sterilization process utilizing flexible bag systems for the sterilization of medical devices

1 Scope

This TIR includes information to be considered during the development, validation, and routine control of EO sterilization processes that are performed using gas diffusion within individually sealed flexible sterilization bags.

2 Terms and definitions

2.1
abatement system
device that is attached to the exhaust from the sterilization/aeration cabinet and connected to the outside atmosphere. It is designed to absorb and/or react with the EO gas exhausted from the cabinet and reduce the amount of EO exhausted to the external atmosphere

2.2
aeration cycle
part of the sterilization process, after the sterilization portion of the cycle, during which EO and/or its reaction products dissipate from the device(s)

2.3
chemical integrator
demonstrates that the sterilization parameters over a specified range of sterilization cycles have been met in a specified sterilization wrap, container, cassette, or pouch

2.4
dunnage
material that duplicates the weight, volume, thermal characteristics, EO absorption characteristics, surface geometry and tortuosity, and other critical properties of the devices being tested

2.5
effectively impermeable
term used to describe a bag material that does not allow for diffusion of EO during the sterilization cycle

2.6
EO cartridge
single use, hermetically sealed container that holds a predetermined weight of EO. The EO cartridge is designed to be manually activated through the flexible material of the flexible sterilization bag, releasing 100 % EO

2.7
exposure time
period for which the process parameters (temperature, relative humidity, and EO concentration) are maintained within specified tolerances

2.8
flexible sterilization bag
flexible membrane that acts as the sterilization chamber. The flexible sterilization bag may be manufactured from material that is either permeable or effectively impermeable to EO gas

2.9
humidity release device
accessory to the sterilization system that serves to maintain the relative humidity inside of the sealed flexible sterilization bag above 30 %

2.10
injection system
mechanical gas delivery system that operates by removing the air from a flexible sterilization bag containing the product to be sterilized, injecting a pre-determined quantity of gaseous EO into the bag, and then heat sealing the bag closed

2.11
load
contents of one flexible sterilization bag

2.12
manufacturing area
controlled area for the assembly and/or packaging of devices prior to sterilization

2.13
preconditioning
treatment of product, prior to sterilization, in a room or chamber to attain specified limits for temperature and relative humidity

2.14
preconditioning area
room or chamber for the treatment of product, prior to sterilization, to attain specified conditions for temperature and relative humidity

2.15
purge device
mechanical means of removing EO from a flexible sterilization bag at the end of a cycle. A purge device may also serve to flush the bag with fresh air as part of the aeration process

2.16
sterilization/aeration cabinet
enclosure into which a flexible sterilization bag (or bags) is placed for sterilization and/or aeration. The sterilization/aeration cabinet provides a continuous exhaust throughout the cycle, drawing off EO as it diffuses through the flexible sterilization bags. The sterilization/aeration cabinet should operate under sub-atmospheric pressure to ensure that EO does not escape into the workplace. Larger volume processes may include use of a sterilization/aeration room with the same performance characteristics. For this TIR, the term sterilization/aeration cabinet will cover all sizes of sterilization/aeration enclosures, as the sterilization/aeration cabinets and rooms are all subject to the same commissioning requirements

2.17
sterilization/aeration cabinet load
number and location of flexible sterilization bags within a sterilization/aeration cabinet or room

3 Process descriptions

EO flexible sterilization bag systems can be described or categorized by their method for delivering EO to the product. Table 1 compares three different types of systems based on the aspects that would make them a uniquely different type of EO flexible sterilization bag system.

NOTE 1 There may be other flexible bag system designs that represent variations of these generic types.

NOTE 2 Note guidance provided in Section 5 of this TIR for information regarding potential exposure to EO

Table 1: Flexible bag sterilization system types

Flexible bag sterilization system type	Type 1	Type 2	Type 3
Flexible sterilization bag material	Permeable to EO	Permeable to EO	Effectively impermeable to EO
Typical application	Large quantities of devices	Small quantities of devices	Small quantities of devices
Preconditioning (if used)	External to sterilization/aeration cabinet	External to sterilization/aeration cabinet	External to sterilization/aeration cabinet
Method of initial air removal	Evacuation external to sterilization/aeration cabinet	Evacuation external to sterilization/aeration cabinet	Evacuation inside sterilization/aeration cabinet
Method of EO gas delivery	Gas injection into flexible sterilization bag	Unit dose EO cartridge	Unit dose EO cartridge
Method of sealing flexible sterilization bag	Bar sealer external to sterilization/aeration cabinet	Bar sealer external to sterilization/aeration cabinet	Secured to evacuation port inside sterilization/aeration cabinet
Method of gas removal	Gas diffusion through bag material	Gas diffusion through bag material	Purge device

3.1 Type 1 - Gas injection systems

These general steps should be followed when using a Type 1 system:

a) Devices to be sterilized are packaged in appropriate sterile barrier packaging. The packaged devices may be preconditioned for a designated time.

b) Devices to be sterilized are placed into permeable flexible sterilization bags. Process challenge bags, containing either devices or dunnage, are seeded with process challenge devices (PCDs). The flexible bags are transferred to the sterilization/aeration cabinet within a defined time period.

c) During processing, the operator places individual flexible sterilization bags, one at a time, into the injection system. The flexible sterilization bag may contain a humidity release device to maintain the relative humidity above 30 %. The flexible sterilization bag may also contain an intrinsically safe wireless data logger to measure for temperature and relative humidity. The system draws a specified vacuum, determined during validation, on a loaded flexible sterilization bag. The vacuum parameters should be established and validated.

d) The system then injects a unit-dose weight of EO (measured in grams for each flexible sterilization bag) and hermetically heat-seals the open end of the flexible sterilization bag using a validated heat-sealing process.

e) During the process, a constant airflow is maintained to provide temperature uniformity within the sterilization/aeration cabinet. The typical temperature range in the sterilization/aeration cabinet is 20 °C to 55 °C.

f) During sterilization and aeration, the EO is absorbed into the product and also diffuses through the flexible sterilization bag into the sterilization/aeration cabinet. EO is continuously exhausted from the sterilization/aeration cabinet during the sterilization/aeration cycle.

g) At the end of the sterilization portion of the cycle, the flexible bags containing PCDs are removed from the sterilization/aeration cabinet.

h) At the end of the sterilization/aeration cycle, the operator confirms through visual inspection that the flexible sterilization bags were properly sealed and remained intact throughout the cycle.

3.2 Type 2 – EO cartridge based systems utilizing permeable flexible sterilization bags

These general steps should be followed when using a Type 2 system:

a) Devices to be sterilized are packaged in appropriate sterile barrier packaging. The packaged devices may be preconditioned for a designated time.

b) Devices to be sterilized are placed into permeable flexible sterilization bags. Process challenge bags, containing either devices or dunnage, are seeded with process challenge devices (PCDs).

c) A unit dose EO cartridge that has been validated for the load/flexible bag combination is placed in the flexible sterilization bag.

d) In addition to the EO cartridge, the flexible sterilization bag may also contain a humidity release device to maintain relative humidity ≥ 30 %.

e) An intrinsically safe wireless data-logger for temperature and relative humidity should be placed inside the flexible sterilization bag, as specified during validation and documented.

f) The flexible sterilization bag is hermetically vacuum-sealed using an external sealer and placed in a sterilization/aeration cabinet. The flexible sterilization bags are transferred to the

sterilization/aeration cabinet within a defined time period. The sterilization/aeration cabinet operates under sub-atmospheric pressure during the duration of the cycle and maintains a constant airflow.

g) The typical sterilization/aeration cabinet temperature range is 20 ^{o}C – 55 ^{o}C.

h) During sterilization and aeration, the EO is absorbed into the product and also diffuses through the flexible sterilization bag into the sterilization/aeration cabinet. EO is continuously exhausted from the sterilization/aeration cabinet during the sterilization/aeration cycle.

i) At the end of the sterilization/aeration cycle, the flexible sterilization bag is manually slit open while still in the sterilization/aeration cabinet. The flexible bags containing PCDs are removed from the sterilization/aeration cabinet. The opened flexible sterilization bag containing the packaged device(s) remains in the cabinet for the duration of the aeration cycle.

j) After completion of aeration, the packaged device(s) are removed from the flexible sterilization bag, and the used flexible sterilization bags and empty EO cartridge are discarded.

3.3 Type 3 - EO cartridge based systems utilizing effectively impermeable flexible sterilization bags

These general steps should be followed when using a Type 3 system:

a) Devices to be sterilized are packaged in appropriate sterile barrier packaging. The packaged devices may be preconditioned for a designated time.

b) Individually packaged devices in their sterile barrier system are placed in an effectively impermeable flexible sterilization bag.

c) A unit dose EO cartridge that has been validated for the load/bag combination is placed in the flexible sterilization bag.

d) In addition to the EO cartridge, the flexible sterilization bag may also contain a humidity release device to maintain relative humidity ≥ 30 %. Each flexible sterilization bag should contain a biological indicator in a PCD and a chemical integrator for EO.

e) The flexible sterilization bag is sealed around a purge device, and the flexible sterilization bag with purge device attached is placed in a sterilization/aeration cabinet. The sterilization/aeration cabinet operates under sub-atmospheric pressure during the duration of the cycle and maintains a constant airflow. This airflow will be appropriately monitored and measured to assure the validated airflow requirements are being met.

f) The typical sterilization/aeration cabinet temperature range is 20 ^{o}C – 55 ^{o}C

g) At the start of the cycle the purge device removes excess air and draws a specified vacuum on the flexible sterilization bag. The vacuum specification is determined in the validation process.

h) The EO cartridge is activated per manufacturer's instructions through the bag, releasing EO inside the flexible sterilization bag.

i) During sterilization, the EO from the EO cartridge fills the flexible sterilization bag. The EO remains in the bag for the duration of the sterilization cycle.

j) At the end of the sterilization cycle, the purge system removes the EO from the flexible sterilization bag. The purge system continues to flush the bag with fresh air, aerating the load.

NOTE: The bag may be flushed with medical grade nitrogen as an alternative to fresh filtered air.

k) The flexible sterilization bag remains in the sterilization/aeration cabinet for the duration of the aeration cycle.

l) After completion of aeration, the sterile, packaged devices and any monitoring devices (e.g., temp/RH data loggers, biological indicators, chemical integrators) are removed from the flexible sterilization bag, and the used flexible sterilization bag and empty EO cartridge are discarded.

4 Quality management systems

4.1 Sterilization processes employing flexible bag sterilization systems should comply with all aspects of Quality Management Systems applied to sterile device manufacturers, including requirements for documentation, management responsibility, and product realization.

4.2 Procedures for identification and traceability of product shall be specified.

4.3 A system shall be specified for the calibration of all equipment including the instrumentation for test purposes.

5 Sterilizing agent characterization

5.1 General

The purpose of this activity is to define the sterilizing agent, demonstrate its microbicidal effectiveness, identify the factors that influence microbicidal effectiveness, assess the effects that exposure to the sterilizing agent has on materials, and identify requirements for safety of personnel and protection of the environment. This activity may be undertaken in a test or prototype system. Where this occurs, the final equipment specification should be comparable to the results of experimental studies undertaken in the test or prototype equipment. The sterilizing agent is EO.

5.2 Sterilizing agent

The composition, storage conditions, and shelf life for the sterilizing agent should be specified.

5.3 Microbicidal effectiveness

Microbicidal effectiveness data should be developed if using a sterilant other than 100 % EO (i.e., gas mixtures).

NOTE The inactivation of microorganisms by EO has been comprehensively documented in the literature, therefore, reference to these general studies on microbial inactivation would not be required.

5.4 Material effects

The effects of EO on a wide variety of materials used to manufacture medical devices have been comprehensively documented, and such documentation is of value to those designing and developing medical devices that are to be sterilized by EO. There is no requirement to perform specific studies on material effects. AAMI TIR17:2008 provides general information on the compatibility of common medical device materials with EO. The users of EO flexible bag systems are responsible for assuring that the devices sterilized in these systems are compatible with the sterilant and the sterilization process to meet all required regulations.

5.5 Safety and the environment

5.5.1 A material safety data sheet or analogous safety information should be specified for the EO.

5.5.2 The potential effect on the environment of the operation of the sterilization equipment should be assessed, and measures to protect the environment should be identified. This assessment, including potential impact and measures for control, should be documented.

5.5.3 Users of EO should comply with applicable local, national, and international requirements regarding the emission and disposal of EO and its diluents, as well as any by-products.

5.5.4 U.S. Department of Transportation regulations for the transport of EO (49 CFR 173.323) and the handling and storage requirements issued by the gas supplier and sterilizer manufacturer should be followed. The gas supplier and user should abide by the U.S. Environmental Protection Agency (EPA) label instructions on the supplier's shipping containers (Federal Insecticide, Fungicide and Rodenticide Act [FIFRA] 7 U.S.C. §136j) and U.S. Occupational Safety and Health Administration (OSHA) process safety management (if applicable). The gas supplier's facility and the sterilant must be registered with the EPA (FIFRA 7 U.S.C. §136a, §136a-1, and §136e). Manufacturers and gas suppliers outside of the United States should meet local regulations that are comparable to the above. Storage requirements at the facility should meet NFPA 30.

5.5.5 Controls should be in place to ensure that sterilant gas delivered to the facility meets specifications that include (but are not limited to) labeling and container integrity. The certificate of analysis of each lot or container (where applicable) should be reviewed against specified gas acceptance criteria prior to use.

5.5.6 Ensure that the sterilant EO cartridge is within current expiry. Inventories of sterilant EO cartridges should be rotated on a first in, first out basis.

NOTE Each gas supplier should be a qualified supplier, and a periodic on-site audit of the supplier should be conducted.

5.5.7 Exposure to EO: Consideration should be given to appropriate protection of personnel from potential exposure to liquid or gaseous EO, at all steps of the flexible bag sterilization process. Local and national regulations regarding occupational health and safety must be followed. OSHA 29 CFR 1910.1047 (OSHA, 2005) contains the U.S. requirements for protecting personnel from EO exposure.

5.5.8 Installation and ventilation: The current version of AAMI ST41:2008/(R)2012 may be referenced for recommendations on installation and ventilation requirements for the sterilization/aeration cabinet.

6 Process and Equipment Characterization

6.1 Process characterization

6.1.1 The range of process variables and the equipment necessary to deliver the sterilization process shall be defined and documented.

6.1.2 Process characterization should include the following:

a. preconditioning, if used;

b. the sterilization cycle; and

c. aeration.

6.1.3 The characterization of these EO gas diffusion sterilization processes should include the following:

a) Preconditioning (if used) of product to achieve specified temperature and humidity levels should be performed under controlled conditions. This includes setpoints and acceptable ranges for

temperature and humidity for the process. Conditioning of product can also be performed using a humidity release device placed within the flexible sterilization bag.

b) Air removal – when air is removed actively by connection to an external vacuum pump, the rate and depth of the vacuum should be defined.

c) Gas delivery – EO can be delivered to the product by either the use of an EO cartridge located within the sealed flexible sterilization bag that can be activated without compromising the integrity of the flexible sterilization bag, or by an external source. The amount of EO delivered should be determined. This may be done by weight. To confirm the weight of EO delivered, weigh the EO cartridge or flexible sterilization bag before and after the sterilization process.

d) Transfer time – a maximum transfer time from the completion of EO injection to transfer to the sterilization/aeration cabinet and closing the sterilization/aeration cabinet door shall be established and validated.

e) Exposure time – the period for which the process parameters are maintained within their specified tolerances.

f) EO removal (by diffusion or by use of a purge device).

g) Humidity release – if a humidity-releasing device is used during validation of a cycle, then the same device must be used for all routine processing.

6.1.4 The tolerances for the process variables, including but not limited to temperature, humidity, weight of delivered EO, and gas exposure time should be established and specified.

6.1.5 The means of monitoring and controlling the process variables should be determined and specified.

6.2 Equipment characterization

6.2.1 The specification for the equipment to be used should be developed and documented. This specification should include the preconditioning equipment or area (if used), the sterilization/aeration cabinet, and the flexible sterilization bag.

6.2.2 The area containing the injection system should be environmentally controlled in order to maintain a defined range of temperature and relative humidity (RH). If this area is not environmentally controlled, the maximum elapsed time between the completion of preconditioning (if used) and the commencement of the sterilization cycle shall be specified and validated.

6.2.3 The temperature and airflow will be appropriately monitored and measured to assure minimum airflow requirements are being met.

6.2.4 The specification should include the following:

a) A description of the equipment, as well as any necessary ancillary items (vacuum pump, abatement system, bag sealer), including materials of construction (cabinet construction, bag material) and dimensional specifications. This should include information from the equipment manufacturer (e.g., sterilization/aeration cabinet, or flexible sterilization bag) on the proper use of these devices.

b) The composition of the sterilizing agent and safe operating procedures for the EO cartridges or EO injection system.

c) A description of instrumentation for monitoring, controlling, and recording the sterilization process, including cabinet sensors and any sensors sealed within the flexible sterilization bag.

d) All fault(s) recognized by the sterilizing equipment.

e) All safety features, including those for personnel and environmental protection.

f) All installation requirements, including requirements for the control of emissions.

g) Software used to control and/or monitor the process should be prepared and validated in accordance with the elements of a quality system that provides documented evidence that the software meets its design specification.

h) Risk analysis should be performed to ensure that failure in a control function does not lead to failure in recording of process parameters such that an ineffective process appears effective.

i) Each flexible sterilization bag should contain a biological indicator. Each flexible sterilization bag may contain a chemical integrator.

7 Product definition

7.1 General

7.1.1 Product definition involves documentation of essential information about the medical device to be sterilized (i.e., the new or modified product, product density, EO absorption characteristics, etc.). Product definition should be performed prior to the introduction of a new or altered product, package, or assembly configuration.

7.1.2 Product definition for a medical device includes the medical device itself, the sterile barrier system containing the device, and any accessories, instructions, or other items included in the sterile barrier system.

7.1.3 The product definition process should also consider whether this is a new design or part of an existing EO product family. (Reference AAMI TIR28:2009/(R)2013 for more information on product families.)

7.1.4 Product should be designed to allow the penetration of humidity and EO to the most difficult-to-sterilize locations.

7.1.5 Individual products in their sterile barrier packaging, if used, should be designed for penetration of heat, humidity, and EO during the sterilization process, and removal of EO at the end of the process.

7.1.6 For systems where the flexible sterilization bag is also the sterile barrier, the user will demonstrate the appropriateness and consistency of each product bag lot based on the gas diffusion characteristics of the bags.

7.1.7 It should be demonstrated that the specified sterilization process is effective at the most difficult-to sterilize location within the product. This may be achieved by a demonstration of equivalence to a previously validated product or process challenge device (PCD) used to qualify the sterilization process. Equivalence may also be demonstrated by performing process definition and validation of the new product.

7.1.8 The following should be considered as part of product definition:

a) the physical description of the medical device (composition and configuration);

b) the intended use of the medical device;

c) whether the medical device is intended for single use or for multiple use;

d) the design characteristics that affect the choice of sterilization process;

e) raw materials/manufacturing conditions that could affect microbiological quality (e.g., materials of natural origin);

f) the required sterility assurance level (SAL);

g) the sterile barrier system;

h) the assembly and loading pattern, requirements for a specific load or mixed assembly patterns, or range of acceptable assembly patterns within the flexible bag;

i) the compatibility with EO and EO processing conditions (preconditioning, sterilization, and the sterilization/aeration cabinet and aeration processes); and

j) components with variation in densities and construction that could impact the absorption and inactivation rate inside a custom procedural tray.

7.2 Demonstration of equivalence

7.2.1 A demonstration of equivalence (with reference to the challenge to the sterilization process) to a previously validated product, package, or loading pattern is considered to meet the requirements listed above. Any demonstration of equivalence should be documented. A documented technical review should be performed to compare the new or modified product to the validated product and/or process challenge device (PCD) that was used to validate the existing EO process.

7.2.2 The construction and configuration of the new or modified product should be carefully examined for any features that could present obstacles to the penetration of EO, heat, or humidity.

7.2.3 This comparison should also involve an examination of factors that could affect the initial bioburden on the product, including the location of the manufacturing facilities, the types of raw material used, the sources of these materials, and production methods.

7.2.4 If the resistance to the sterilization challenge of a new or modified product is demonstrated to be equivalent to or less than an existing medical device or PCD for which sterilization characteristics are already known, the new or modified product becomes part of the EO product family or a processing group.

NOTE AAMI TIR28 is a useful guide for minimizing the risk of introducing a new or modified product that presents a greater challenge to the sterilization cycle than was previously validated.

7.3 Product safety and performance

7.3.1 It should be confirmed that the product and its packaging meet specified requirements for safety, quality, and performance, following the application of the defined sterilization process at the most challenging process parameters for the product/package. The influence of the tolerances for the process

parameters should be taken into consideration. For example, the user should confirm device compatibility with EO sterilization, as well as the different sterilization process parameters (i.e., process temperature, vacuum depth, etc.).

7.3.2 If multiple sterilization cycles are permitted, the effects of such processing on the product should be evaluated. This includes residuals testing.

7.3.3 The biological safety of product following exposure to the sterilization process should be established in accordance with ANSI/AAMI/ISO 10993-1:2009/(R)2013 and any subsequent parts of ISO 10993 that apply.

7.3.4 Maximum allowable limits for EO residuals in EO sterilized medical devices are given in ANSI/AAMI/ISO 10993-7:2008/(R)2012. Means should be established to reduce EO residual levels such that the processed products comply with the requirements of 10993-7.

7.3.5 Medical devices containing a potential source of ignition (e.g., a battery) should not use this process unless the device is classified as intrinsically safe, or the atmosphere in the flexible sterilization bag is modified with an inert gas such as nitrogen to assure the atmosphere is in the non-flammable zone.

7.4 Microbiological quality

7.4.1 A system should be specified and maintained to ensure that the microbiological quality and cleanliness of the product presented for sterilization do not compromise the effectiveness of the sterilization process. Microbiological estimation of the bioburden should be conducted quarterly. This data should be trended to confirm process control of the manufacturing process.

7.4.2 The effectiveness of the system defined above should be demonstrated. This demonstration should include an estimation of bioburden at a defined interval in accordance with ANSI/AAMI/ISO 11737-1:2006/(R)2011.

7.5 Documentation

Upon completion of the product definition, the following should be documented.

7.5.1 The sterilization specification for the product. This specification should fully describe the product configuration and how it is to be presented to the EO process (packaging and load configuration).

7.5.2 The specification should also include or reference the required SAL, as well as evidence for or assessment of the compatibility of the product with the process.

7.5.3 The result of the comparison between the new or modified product and the existing validated product(s). This result should clearly demonstrate that product complexity, materials, packaging, EO absorption, and load configuration were assessed.

7.5.4 Evidence or assessment of the bioburden of the product and its resistance relative to the biological indicator (BI).

7.5.5 The documented conclusion that the new or modified product is suitable for adoption into the EO product family/processing group, specifically referenced in the current validation study to achieve the specified SAL. This conclusion should include or reference any results from additional tests performed to supplement the existing validation study and any further testing performed for confirmation/qualification for routine release of product from the existing validated cycle (i.e., residual testing, functional testing).

8 Process definition

8.1 The sterilization process to be validated and the flexible sterilization bag size should be specified prior to the introduction of a new or altered product, package, or change in the weight of contents placed in the bag.

8.2 Process definition activities should also be performed for additional equipment used during processing, e.g., preconditioning area (if used), the sterilization/aeration cabinet, the flexible bag sealer, and the aeration area (if used). Such equipment must undergo Installation Qualification (IQ) and Operational Qualification (OQ) procedures.

8.3 The flexible sterilization bag must be qualified such that the integrity of the bag is ensured and the characteristics of the bag are consistent with those that have been validated.

8.4 The user should follow the manufacturer's requirements or demonstrate equivalent performance. In addition, the sourcing, manufacturing, and testing activity may be performed by the manufacturer of the flexible bag system, but the user will test, verify, and document the suitability of the bags prior to use.

8.5 The sterilization process applicable for the defined product should be established.

NOTE During cycle development, it is not always possible to obtain sufficient devices to test a fully loaded sterilization/aeration cabinet. In this case, dunnage material that duplicates the weight, volume, thermal characteristics, EO absorption characteristics, surface geometry and tortuosity, and other critical properties of the devices being tested may be used as a substitute for actual devices.

8.6 Documentation and records should support the validity of process parameters and their tolerances as defined in the process specification.

8.7 The rate of microbial inactivation of the process should be defined and determined. This must demonstrate the achievement of the required sterility assurance level (SAL). See Annexes for more information.

8.8 Biological indicators used as part of the establishment of the sterilization process should do the following:

a) comply with Clauses 5 and 9.5 of ANSI/AAMI/ISO 11138-2:2006/(R)2010 ;

b) be shown to be at least as resistant to EO as is the bioburden of product to be sterilized when the BI is placed in a validated PCD;

c) be placed within the product at location(s) where sterilizing conditions are most difficult to achieve lethality or placed in a PCD that has been demonstrated to reflect a BI placement that is more difficult to sterilize in the flexible bag process; and

d) if a PCD is used for process definition, validation, or routine monitoring and control, the appropriateness of the PCD should be determined. The PCD should provide an equivalent or greater challenge to the process than the most difficult-to-sterilize part of the product. The user can demonstrate that the resistance of the Process Challenge Device is appropriate by using fractional cycles for the purpose of demonstrating that the product bioburden is not more resistant than the biological indicator in the PCD. This relative resistance can be demonstrated by having all product tests of sterility and some positive PCDs.

NOTE: For information on the selection, use, and interpretation of biological indicators, see ANSI/AAMI/ ISO 14161:2009.

8.9 If chemical integrators are used as part of the definition of the sterilization process, these should comply with ANSI/AAMI/ISO 11140-1:2005/(R)2010. Chemical integrators should not be used as the sole means of establishing the sterilization process.

8.10 If tests of sterility are performed during the definition of the sterilization process, they should comply with ANSI/AAMI/ISO 11737-2:2009.

9 Validation

9.1 Installation qualification

9.1.1 Installation qualification (IQ) should demonstrate that the sterilization equipment and any ancillary items (e.g., heat sealers, external blowers) have been supplied and installed in accordance with their specification.

9.1.2 All equipment used to deliver the EO, including any ancillary items, should be supplied and/or installed in accordance with their specification.

9.1.3 The operating procedures for the equipment (see 5.2) should be specified. These operating procedures should include but are not limited to the following:

a) step-by-step operating instructions;

b) fault conditions, the manner in which they are indicated, and actions to be taken;

c) instructions for maintenance and calibration; and

d) details of contacts for technical support.

9.1.4 The location in which the equipment is to be installed, including any services required, should be specified. Any special precautions and provisions, including electrical classifications for storage of EO or protection of operating personnel, should be identified.

EXAMPLE: Verify that storage conditions for EO meet the requirements given by the supplier as well as any pertinent national, regional, or local requirements.

9.1.5 Instructions for installation should be documented and should include instructions pertinent to the health and safety of personnel.

9.1.6 Drawings of the equipment installed, plumbing, and other ancillary equipment should be finalized during IQ.

9.2 Operational qualification

9.2.1 Prior to operational qualification (OQ), the calibration of all instrumentation (including any test instruments) used for monitoring, controlling, indicating, or recording should be confirmed.

9.2.2 Operational qualification (OQ) should demonstrate that the installed electromechanical equipment as defined in the IQ is capable of delivering the specified process within defined tolerances.

9.2.3 Temperature distribution studies conducted in the sterilization/aeration cabinet environment should consist of three empty sterilization/aeration cabinet runs, three runs with a minimum number of flexible sterilization bags in the sterilization/aeration cabinet, and three runs with a maximum number of flexible sterilization bags in the sterilization/aeration cabinet. These configurations of flexible sterilization bags within the sterilization/aeration cabinet would be those deemed to provide the minimum and maximum

challenge to the sterilization/aeration cabinet's heating and circulation systems. If the sterilization/aeration cabinets are used to process flexible sterilization bags having different heat capacity/penetration characteristics, the effects of the different flexible sterilization bag configurations should be evaluated during the temperature distribution studies.

NOTE Doors remain closed for the duration of the process.

9.2.4 When preconditioning is performed in a preconditioning area, the OQ for the preconditioning area should include the following:

a) The pattern of air circulation throughout the area to be occupied by the sterilization load(s) should be determined. This can be performed by smoke tests in combination with calculation of air change rates and anemometric determinations.

b) Temperature and humidity should be monitored throughout the preconditioning area over a period long enough to demonstrate that values are within the desired ranges. The temperature and humidity in a number of locations distributed throughout the preconditioning area should be determined. Refer to Annex C of ANSI/AAMI/ISO 11135-1:2007 for suggestions on the number of sensors to be used.

When the product is preconditioned by using a thermostatically and humidity controlled manufacturing environment, the area minimum temperature and humidity required based on the subsequent PQ should be qualified.

9.2.5 When performing aeration, the temperature profile of the aeration area should be determined in the same manner as recommended for preconditioning areas. The airflow rates and airflow patterns through the area should also be determined.

9.2.6 The range of allowable loading patterns supported by the operational qualification should be specified in the operational procedure.

9.2.7 Three typical methods can be used to provide the EO necessary for the sterilization process:

a) Placement of an EO cartridge that contains a measured amount of EO either directly inside the flexible sterilization bag or sealed within a gas release bag that is then placed in the flexible sterilization bag. The EO cartridge is activated to release EO into the sealed flexible sterilization bag prior to placing the flexible sterilization bag into the sterilization/aeration cabinet.

b) An external system that removes air from the flexible sterilization bag injects a measured amount of EO into the flexible sterilization bag and then seals the flexible sterilization bag.

c) Sterilization/aeration cabinets in which the individual flexible sterilization bag(s) is attached to a system that evacuates the air from the bag and then injects EO into the bag. These systems also remove EO from the flexible sterilization bag at the completion of exposure.

9.2.8 All equipment used to evacuate air, inject EO, or remove EO should be tested and calibrated for proper operation.

9.2.9 Temperature measuring devices should be placed throughout the sterilization/aeration cabinet and should include suspected hot and cold regions.

9.3 Performance qualification

9.3.1 General

9.3.1.1 Performance qualification (PQ) should be performed on the introduction of new or altered products, sterile barrier systems, loading patterns, equipment, or process parameters, unless equivalence to a previously validated flexible sterilization bag size can be demonstrated for an alternative product, sterile barrier system, or loading pattern combination. The demonstration of equivalence should be documented.

PQ should be performed in the sterilization/aeration cabinet that will be used to sterilize the product.

9.3.1.2 PQ should demonstrate that equipment consistently operates in accordance with predetermined criteria and that the process produces product that is sterile.

9.3.1.3 The load should be representative of items that are to be routinely sterilized and should represent the most challenging load. The load should consist of product or materials that have characteristics similar to those of the load to be sterilized routinely, including EO absorption, moisture absorption, geometry, and heat capacity.

9.3.1.4 For sterilization/aeration cabinets that can contain multiple flexible sterilization bags, each bag should be loaded with material of similar volume, density, geometry, and heat capacity characteristics.

NOTE If saleable product has been used during validation, the product should be held and sterilized in a validated cycle prior to release for sale.

When possible, flexible sterilization bags containing the process challenge devices should contain product that has not been previously exposed to a sterilization cycle. If products or dunnage are reused for the MPQ, they should be aerated between exposures to ensure that EO residues in the load do not affect the biological indicator. Process challenge devices should be prepared from materials that have not previously been exposed to EO. Flexible sterilization bags are not to be reused unless the manufacturer has designed and validated them for reuse; follow the manufacturer's recommendations when reusing the flexible sterilization bags. Each flexible sterilization bag should contain a PCD.

9.3.1.5 The manner of presenting product for sterilization, including the loading pattern of the product within each bag, should be documented. The loads should be re-evaluated at a predetermined frequency for appropriateness.

9.3.1.6 If chemical indicators are used as part of PQ, these should comply with ISO 11140-1:2005/(R)2010.

9.3.2 Performance qualification — Microbiological

9.3.2.1 The microbiological PQ should demonstrate that the process produces sterile product. Studies should be performed in the production flexible sterilization bag and the sterilization /aeration cabinet using defined process parameters selected to deliver less lethality than the specified sterilization process. During microbiological PQ, it is common practice to reduce the set point of one or more process variables (e.g., EO concentration, temperature, humidity) compared to the set points used in routine sterilization. The defined parameters may be at or below the minimum levels specified for routine control.

9.3.2.2 Microbiological PQ should confirm the effectiveness of the defined process for the product/load combination in the flexible sterilization bag and sterilization/aeration cabinet to be used in production.

The flexible sterilization bag systems currently in use can be categorized based on the properties of the flexible sterilization bag.

a) Systems that use effectively impermeable flexible sterilization bags

Systems of this type can undergo microbiological PQ using the same approaches currently used for conventional sterilizers. See ISO 11135-1, Annexes A and B.

b) Systems that use permeable flexible sterilization bags

These systems require a modified approach, because EO diffuses out of the bag over time. These systems require a modified approach to microbiological process qualification. One method would be to demonstrate a 6-spore log reduction (SLR) to a biological indicator in the first half of exposure. Then in a second run to expose a second set of PCDs and demonstrate a 6-SLR in the last half of exposure. A second method would be to run a complete cycle with the EO concentration reduced to 50 % of the production value; thereby, reducing the lethality by 50 %. Literature supports that lethality is proportional to EO concentration at 22-1200 mg/liter for both gas diffusion and vacuum systems and non-vacuum systems. See Annex A and B, of this TIR.

9.3.2.3 The same method for stabilizing product humidity before and/or during sterilization used during the microbial performance qualification should be used for routine production.

9.3.2.4 Sterilization equipment (sterilization/aeration cabinets and EO delivery systems) that delivers the same process parameters, having undergone installation IQ and OQ, should be qualified in one of the following ways:

a) in the same manner as the original flexible sterilization bag and sterilization/aeration cabinet;

b) by using a reduced PQ that demonstrates the delivery of the required level of microbiological lethality (the rationale for this reduced qualification should be recorded and documented); or

c) by determining the influence of different geographical locations on the load properties.

9.3.3 Performance qualification — Physical

9.3.3.1 Physical PQ should demonstrate the following:

a) The reproducibility of the process; this should include a minimum of three consecutive, planned qualification runs, for each sterilization/aeration cabinet load that is to be sterilized, in which all the specified acceptance criteria are met.

b) That the specified acceptance criteria are met throughout the load for the duration of the proposed routine process specification. Elements of the physical PQ may be conducted during the microbiological PQ. If the physical PQ is performed in parallel with the microbiological PQ, then at least one additional physical PQ qualification run should be performed at nominal conditions to demonstrate compliance with the process specification.

If a failure can be attributed to factors not relevant to the effectiveness of the process being validated, this may be documented as unrelated to the performance of the process without requiring three further consecutive successful runs. Examples of this type of failure may include, but are not limited to, power failures, other loss of services, or failure of external monitoring equipment.

c) The specified acceptance criteria are met for each flexible sterilization bag (equivalent to sterilizer load) and the sterilization/aeration cabinet (similar to a sterilizer jacket used to maintain temperature in the flexible sterilization bag).

d) A minimum of one temperature and humidity sensor should be used per cubic meter, with a minimum of 3 per bag.

9.3.3.2 Physical PQ requires confirmation that:

a) at the end of the defined preconditioning time (if used), the product that will be placed in the flexible sterilization bag is within the defined temperature and humidity ranges;

Note Typically this is controlled by manufacturing and holding the product under controlled temperature and humidity prior to placing it in the flexible sterilization bag.

b) the maximum elapsed time between the completion of preconditioning (if used) and the introduction of EO into the flexible sterilization bag and then into the sterilization aeration cabinet is identified and documented;

c) the quantity of EO released by EO cartridge or by injection is appropriate to the size of the flexible sterilization bag and the load being sterilized;

d) during the sterilization cycle, the temperature and humidity of the flexible sterilization bag meet specified acceptance criteria;

e) the temperature of the product load during exposure meets specified acceptance criteria; and

f) the variability of the flexible sterilization bag thickness used is within the range of flexible sterilization bag thicknesses documented during the validation.

9.4 Varying load configurations

For establishments that have widely varying sterilization/aeration cabinet load configurations, the extent to which product volume to bag volume affects the sterilization process should be evaluated. It should be demonstrated that all product sterilized with a given sterilization process achieves the required sterility assurance level.

This includes evaluation of the effects of various numbers of bags in a cabinet on the heat-up of individual bags within the range of bags that will be processed at any given time.

The impact of product volume or maximum and minimum loading of the Sterilizer/Aeration cabinet on the residual levels and on the overall out-gassing of EO for worker exposure level protection must be ascertained as part of the validation process.

9.5 Review and approval of validation

9.5.1 The purpose of this activity is to undertake and document a review of the validation data to confirm its acceptability against the approved sterilization process protocol and to approve the process specification.

9.5.2 Information gathered or produced during product definition, process definition, IQ, OQ and PQ, including results from incubation of biological indicators, should be recorded and reviewed for acceptability (see also 5.1). The results of this review should be recorded.

9.5.3 A validation report should be prepared. The report should be reviewed and approved by the designated responsible person(s).

9.5.4 The validation report should describe or reference specific validated product, the defined loading patterns, and the documented specification for the EO sterilization process. The validation report should also include the value and tolerances for the following:

a) preconditioning (if used):

   i. time in flexible sterilization bag/aeration cabinet/area, temperature and humidity of the product assembly area (to maintain humidity within the product and/or flexible sterilization bag);

   ii. minimum temperature of product permitted to enter preconditioning (if product has not been maintained under controlled temperature conditions);

   iii. temperature and humidity of the sterilization load prior to being sealed in the flexible sterilization bag;

   iv. maximum elapsed time between removal of the load from preconditioning and commencement of the sterilization cycle;

   v. ambient temperature of the area in which exposure is initiated, based on the requirements of validation

b) The method of bag sealing and the critical parameters, etc., used to control the sealing equipment, if used. Critical parameters for sealing should be validated;

c) EO injection and exposure;

   i. EO concentration will be determined by the size of the flexible sterilization bag used, its residual atmospheric volume, the amount of EO released into the bag, EO diffusion characteristics, and the type of devices in the bag. The weight of the EO released during the cycle will be determined (e.g., the EO cartridge will be weighed at the beginning of the sterilization cycle and again at the end). If an EO cartridge is used for the delivery of EO, ensure that all parts of the EO cartridge are recovered for the post-process weighing. A secondary measure for independently verifying that EO gas has been delivered to the bag (e.g., PCD or chemical integrator) must be validated and implemented.

   ii. temperature inside the sterilizer/aeration cabinet;

   iii. temperature inside the flexible sterilization bag;

   iv. exposure time;

   v. record of the pre- and post-weight of the humidity release device, if used; and

   vi. record of the sterilization/aeration cabinet circulation

d) aeration method;

   i. active aeration where the bag is evacuated and other gases are pulsed or swept through it to remove the EO; this is primarily done with non-permeable bags

   ii. passive aeration where the EO diffuses through the flexible sterilization bag into the sterilization/aeration cabinet and is removed by constant recirculation

iii. time and temperature of cabinet and load during aeration

iv. maximum elapsed time between removal of the load from the external sealer (if used) to placement in the Sterilizer/Aeration cabinet

v. the method for opening the bag, including slit length and location

NOTE If the EO exposure phase is initiated outside of the sterilizer/aeration cabinet, the following information should be documented.

i. recording of ambient temperature of the area in which exposure is initiated based on the requirements of validation

ii. time to transfer bags into the cabinet

e) a process specification, including the process parameters and their tolerances, should be confirmed. The process specification, including process parameters and their tolerances, should be established for routine processing based upon the data generated during the validation. This process specification should also include the criteria for designating an individual sterilization process used for a particular sterilization load as conforming.

10 Routine Monitoring and Control

10.1 The purpose of routine monitoring and control is to demonstrate that the validated and specified sterilization process has been delivered to the product. Data should be recorded and retained for each sterilization cycle to demonstrate that the sterilization process specifications have been met. These data should include the following, at a minimum:

a) the minimum temperature of packaged product to enter the sterilization process or the defined conditions used to acclimate the load;

b) temperature and humidity within the preconditioning area (if used), monitored and recorded from a specified position; if time is a parameter of the preconditioning process it will be recorded;

c) elapsed time between removal of the packaged product from preconditioning (if used) and the commencement of the sterilization cycle;

d) temperature of the sterilizer/aeration cabinet throughout the sterilization process;

e) evidence that the EO has been admitted to each flexible sterilization bag (e.g., PCD or chemical integrator) and the weight of EO used in each bag;

f) EO exposure time;

g) time, temperature, pressure changes (if any) and/or the operation of the air supply (if used) during aeration; and

h) evidence that validated humidification parameters have been achieved—demonstrated in several ways, e.g., preconditioning parameters, weight of the humidity release device, or through monitoring of environmental conditions prior to sterilization.

10.2 Biological indicators shall be used for routine monitoring of the sterilization process. The number and location shall be documented. At least one biological indicator/PCD should be used in each flexible sterilization bag.

10.3 If chemical indicators are used in routine monitoring, they should comply with ANSI/AAMI/ISO 11140-1 requirements for the relevant classification of EO chemical integrator.

11 Product Release from Sterilization

11.1 The criteria for designating conformance of the sterilization process used for a particular sterilization load should be documented. These criteria should include the following:

a) confirmation that the parameters specified and the corresponding data recorded during routine processing meet the sterilization process specification;

b) confirmation of no growth of the test organism from any processed biological indicator (i.e., all processed biological indicators must test negative). While the results of each bag can be viewed independently, consideration must be given to process parameters that can affect all bags, e.g., temperature. Therefore, any positive results in any bag necessitates that the entire cabinet load be quarantined until root cause can be determined. Where there is a positive growth (confirmed as the indicator organism) and the flexible sterilization bags contain different product, all product shall be quarantined;

c) positive controls show growth of the indicator organism; and

d) all chemical indicators, if used, should display a Pass result. Chemical indicators should not be used as the sole means of release.

11.2 Product should be considered as non-conforming and handled in accordance with the applicable clauses of ANSI/AAMI/ISO 13485:2003/(R)2009 if one or more of the conformance criteria of 10.1 are not fulfilled.

11.3 If saleable product has been used during validation, the product should be held and sterilized in a validated cycle prior to release for sale.

12 Maintaining Process Effectiveness

12.1 General

The continued effectiveness of the sterilization cycle is maintained through controlled changes of the product and equipment, control instrument calibration, equipment maintenance, and requalification of the sterilization process.

12.2 Calibration

The accuracy and the reliability of the instrumentation used to control and monitor the sterilization process should be verified periodically in accordance with the applicable clauses of ISO 13485 or ISO 10012:2003.

12.3 Maintenance of equipment

12.3.1 Preventative maintenance should be planned and performed in accordance with documented procedures. The procedures should follow the manufacturer's recommendations, as well as any pertinent national, regional, or local requirements.

12.3.2 Equipment should only be used to process product after all specified maintenance has been satisfactorily completed and documented.

12.3.3 Maintenance records should be retained in accordance with the applicable clauses of ISO 13485.

12.3.4 Use of non-like for like parts and/or equipment for maintenance requires a documented assessment of the impact of the change on the validated sterilization process.

In some cases, even when like for like equipment is replaced, it may also be necessary to assess the impact of the change on the validated sterilization process.

12.3.5 The maintenance plan, procedures, and records should be reviewed at specified intervals (at least annually) by a designated person, and the results of the review should be documented.

12.3.6 Receipts of flexible sterilization bags from the supplier will require an incoming inspection and analysis to determine the bag thickness variability in order to assure conformance with the variability found during the validation process.

12.4 Requalification

12.4.1 Requalification of a sterilization process carried out with specified equipment shall be performed at defined intervals against specified acceptance criteria and in accordance with documented procedures. These intervals shall be justified.

NOTE Requalification may include verification that allowable product EO residuals as delineated in ISO 10993-7 are being met.

12.4.2 The load and loading pattern shall be re-evaluated at a predetermined frequency for its appropriateness, and the results of this re-evaluation shall be documented.

12.4.3 Requalification should consist of at least one half lethality cycle for each sterilization cycle used.

12.4.4 If more than one sterilization/aeration cabinet is used and equivalence has been demonstrated, the results of the requalification will be applicable to all cabinets or chambers deemed equivalent. All non-conformances since the previous requalification run should be reviewed to determine if additional requalification runs are to be performed.

12.4.5 The appropriateness of the PCD in relationship to the product bioburden should be reviewed at defined periodic intervals.

12.4.6 If requalification indicates that the sterilization process might no longer be capable of achieving the required SAL, the cause should be determined and corrected before further product is processed using that cycle. If this determination shows the process to no longer be adequate, the sterilization process should be modified to provide for the required SAL and a complete validation should be performed.

12.4.7 Records of the requalification reviews, reports, and any corrective actions should be retained as part of the quality system.

12.5 Assessment of change

12.5.1 Changes to product and equipment should be controlled and documented through a change control system.

12.5.2 The changes should be assessed to determine their impact on the effectiveness of the sterilization process. The magnitude of the change should be considered in determining the extent to which process definition, IQ, OQ, and/or PQ is undertaken.

12.5.3 The outcome of the assessment, including its rationale, should be documented as part of the quality system.

12.6 Assessment of equivalence

12.6.1 Sterilization/aeration cabinets that have undergone complete IQ, OQ, and PQ and been shown to deliver the same process parameters may be deemed to be equivalent. Microbiological requalification on the sterilization/aeration cabinets shall be performed on a periodic basis. When sterilization/aeration cabinets have been deemed equivalent, the frequency of requalification and rationale of the frequency shall be documented. Validation of new sterilization processes in equivalent sterilization/aeration cabinets should be performed as follows:

a) complete microbiological qualification in one of the sterilizers; and
b) a single maximum load microbiological qualification run in each of the equivalent sterilization/aeration cabinets.

NOTE Assessment of equivalence for the sterilization/aeration cabinet cannot begin unless the flexible sterilization bag material, size, and volume are the same for the candidate devices and the originally validated devices.

12.6.2 A product may be added to a validated process if deemed to be equivalent to an existing validated product. A technical review should be performed comparing the candidate product with the currently validated process challenge device used to validate the sterilization process. The outcome of the technical review, including the rationale for the determination of equivalency should be documented as part of the quality system.

Annex A
(informative)

Microbial Validation Using an Augmented Overkill Approach

Validation method background: This method can be used with cycles where the EO concentration remains essentially constant or significantly changes during exposure. The use of flexible sterilization bag systems provides the ability to open the sterilization/aeration cabinet while a cycle is in progress and manipulate the EO cartridge at any time during the sterilization cycle. This validation method augments the "Overkill" approach described in Annex "B" of ANSI/AAMI/ISO 11135 and demonstrates a 12 SLR for the full exposure cycle.

This method involves the use of a PCD that is capable of exposing a fresh BI after the conclusion of the first half of the exposure time (see Figure 1 – PCD Style B) in order to demonstrate physical kill of a 10^6 BI in the second portion of the exposure time.

Figure 1 – Sample PCD styles (A & B)

Validation method

1. Develop a Process Challenge Device (PCD) that is more difficult to sterilize than the device inoculated or seeded with a BI containing ≥ 10^6 spores at the location where it is most difficult to achieve sterilizing conditions.
    a. Establish a D-value range for the inoculated device and the PCD (PCD Style A) device with the goal that the PCD D-value is greater than the inoculated product D-value.
    b. Perform a fractional or sub-lethal cycle to demonstrate the appropriateness of the PCD. In this cycle, the PCD (PCD Style A) is compared to the natural product bioburden to show that the challenge that the PCD presents to the sterilization process is equivalent or greater than equal to that of the product bioburden, i.e., a greater number of PCDs remain positive when compared to the product tests of sterility results.
    c. Confirm that Lot-to-Lot variation of PCD component materials yields consistent EO resistance values.
2. Calculate a half cycle time using the D-value.
3. Run three consecutive half cycles and demonstrate complete PCD kill (ten per half cycle using PCD Style A) – thereby demonstrating the first six (6) log kill. Perform three consecutive overkill

cycles (using PCD Style B) in which ten BIs are sealed in glass EO cartridges. These PCD BIs are broken at the end of half cycle and left until the end of the full cycle. The BIs from PCD Style B are then cultured to demonstrate that they are inactivated/sterile – thereby demonstrating the second six (6) log kill.

The biological kill obtained in the half cycles and overkill cycles together physically demonstrate a twelve (12) log reduction (minimum 10^{-6} SAL).

Figure 2 – How the overkill or SAL of 10^{-6} is achieved using the internal PCD (BI in EO cartridge)

NOTE When performing each validation cycle, it is imperative that immediate access to the flexible sterilization bag/load is designed into the validation procedure. To allow for this, the sterilizer door lock (if used) will be disabled. The validation technician must wear appropriate personal protection equipment (PPE) when opening a sterilization/aeration cabinet that contains flexible sterilization bags that have not fully aerated - this includes but is not limited to fractional, half cycles, and overkill cycles.

Annex B
(informative)

Microbial Validation Using Reduced EO Concentration

Sterilization process validation is accomplished by demonstrating a known log-reduction of a resistant organism under conditions of reduced lethality, and extrapolation of those results to a process that will provide a minimum sterility assurance level of 10^{-6}. EO process lethality is affected by humidity, temperature, time, and gas concentration. Of these process parameters, both time and EO concentration have a linear affect on process lethality. The current method of microbial process qualification is based on reducing exposure time to reduce process lethality; however, reducing EO concentration is also a valid approach for use during microbial process qualification.

The effects of EO concentration on the kinetics of microbial destruction have been well documented. [1,2,3,4] These studies have shown that microbial destruction is proportional to EO concentration within the range of 22-1,200 mg/liter; therefore, an overkill process can be validated by obtaining complete inactivation of a 10^6 challenge of *Bacillus atrophaeus* using a full exposure time and an EO concentration equal to half the production cycle concentration.

When validating systems where the EO is injected and evacuated from the bag the same injection and evacuation times (1/2 rate) would result in ½ of the lethality occurring during those portions of the cycle; use of the same injection and evacuation rates would result in a lesser (more conservative) lethality (refer to Figure 3).

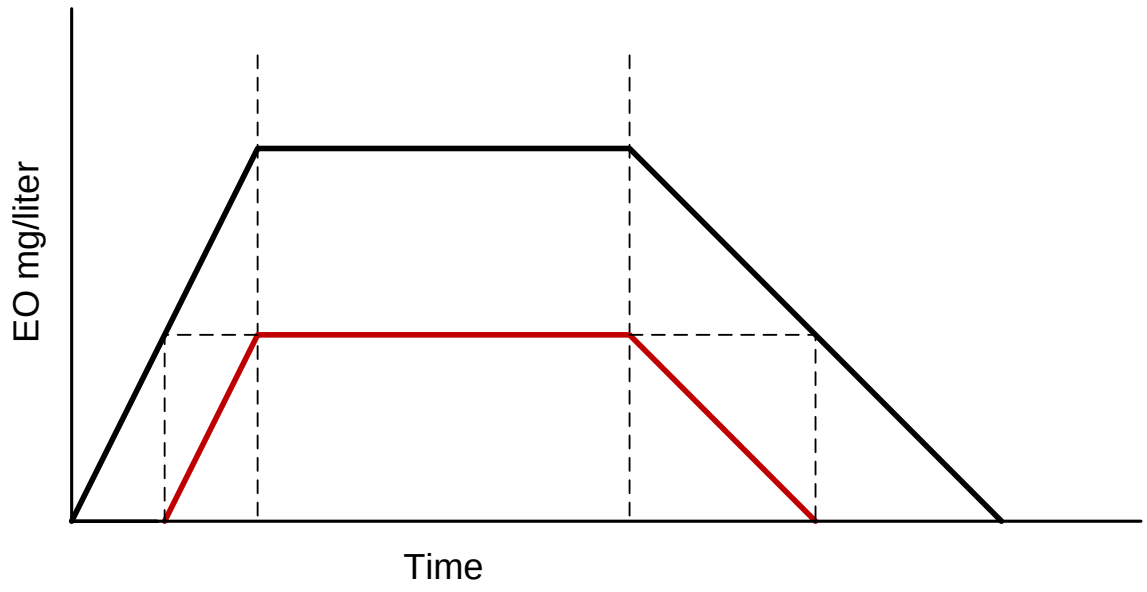

Figure 3 – Comparison of theoretical EO concentration (lethality) profiles for full production cycle and validation cycle using half the production EO concentration. Validation lethality is equal to ½ the exposure and ¼ the lethality obtained during EO injection and removal, based on using the same injection and evacuation rates

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