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Technical Information Report

AAMI TIR20:2001

Parametric release for ethylene oxide sterilization

AAMI Association for the Advancement of Medical Instrumentation

AAMI Technical Information Report AAMI TIR20:2001

Parametric release for ethylene oxide sterilization

Approved 24 September 2001 by
Association for the Advancement of Medical Instrumentation

Abstract: This AAMI technical information report (TIR) provides guidance to augment information and requirements for parametric release provided in ANSI/AAMI/ISO 11135:1994, *Medical devices—Validation and routine control of ethylene oxide (EO) sterilization*. This TIR is intended to assist those individuals using ANSI/AAMI/ISO 11135:1994 in understanding the steps necessary to develop and validate an ethylene oxide sterilization process that meets the standard's requirements for parametric release. This TIR also provides guidance for choosing the appropriate actions where alternatives are given. The guidance in this TIR is limited to the sections of the standard that specifically address parametric release.

Keywords: ethylene oxide, parametric release, sterilization, validation

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Note—Documents are sorted by international designation.

Other normatively referenced International Standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

International designation	U.S. designation	Equivalency
IEC 60601-1-2:2001	ANSI/AAMI/IEC 60601-1-2:2001	Identical
IEC 60601-2-21:1994 and Amendment 1:1996	ANSI/AAMI/IEC 60601-2-21 & Amendment 1:2000 (consolidated texts)	Identical
IEC 60601-2-24:1998	ANSI/AAMI ID26:1998	Major technical variations
ISO 5840:1996	ANSI/AAMI/ISO 5840:1996	Identical
ISO 7198:1998	ANSI/AAMI/ISO 7198:1998/2001	Identical
ISO 7199:1996	ANSI/AAMI/ISO 7199:1996	Identical
ISO 10993-1:1997	ANSI/AAMI/ISO 10993-1:1997	Identical
ISO 10993-2:1992	ANSI/AAMI/ISO 10993-2:1993/(R)2001	Identical
ISO 10993-3:1992	ANSI/AAMI/ISO 10993-3:1993	Identical
ISO 10993-4:1992	ANSI/AAMI/ISO 10993-4:1993	Identical
ISO 10993-5:1999	ANSI/AAMI/ISO 10993-5:1999	Identical
ISO 10993-6:1994	ANSI/AAMI/ISO 10993-6:1995/(R)2001	Identical
ISO 10993-7:1995	ANSI/AAMI/ISO 10993-7:1995/(R)2001	Identical
ISO 10993-8:2000	ANSI/AAMI/ISO 10993-8:2000	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999	Identical
ISO 10993-10:1995	ANSI/AAMI/ISO 10993-10:1995	Identical
ISO 10993-11:1993	ANSI/AAMI 10993-11:1993	Minor technical variations
ISO 10993-12:1996	ANSI/AAMI/ISO/CEN 10993-12:1996	Identical
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ISO 10993-16:1997	ANSI/AAMI/ISO 10993-16:1997	Identical
ISO 11134:1994	ANSI/AAMI/ISO 11134:1993	Identical
ISO 11135:1994	ANSI/AAMI/ISO 11135:1994	Identical
ISO 11137:1995	ANSI/AAMI/ISO 11137:1994	Identical
ISO 11138-1:1994	ANSI/AAMI ST59:1999	Major technical variations

International designation	U.S. designation	Equivalency
ISO 11138-2:1994	ANSI/AAMI ST21:1999	Major technical variations
ISO 11138-3:1995	ANSI/AAMI ST19:1999	Major technical variations
ISO 11140-1:1995 and Technical Corrigendum 1:1998	ANSI/AAMI ST60:1996	Major technical variations
ISO 11607:200x [1)]	ANSI/AAMI/ISO 11607:2000	Identical
ISO 11737-1:1995	ANSI/AAMI/ISO 11737-1:1995	Identical
ISO 11737-2:1998	ANSI/AAMI/ISO 11737-2:1998	Identical
ISO TR 13409:1996	AAMI/ISO TIR 13409:1996	Identical
ISO 13485:1996	ANSI/AAMI/ISO 13485:1996	Identical
ISO 13488:1996	ANSI/AAMI/ISO 13488:1996	Identical
ISO 14155:1996	ANSI/AAMI/ISO 14155:1996	Identical
ISO 14160:1998	ANSI/AAMI/ISO 14160:1998	Identical
ISO 14161: 2000	ANSI/AAMI/ISO 14161:2000	Identical
ISO 14937:2000	ANSI/AAMI/ISO 14937:2000	Identical
ISO 14969:1999	ANSI/AAMI/ISO 14969:1999	Identical
ISO 14971:2000	ANSI/AAMI/ISO 14971:2000	Identical
ISO 15223:2000	ANSI/AAMI/ISO 15223:2000	Identical
ISO 15223/A1:2001	ANSI/AAMI/ISO 15223:2000/A1:2001	Identical
ISO 15225:2000	ANSI/AAMI/ISO 15225:2000	Identical
ISO 15674:2001	ANSI/AAMI/ISO 15674:2001	Identical
ISO 15675:2001	ANSI/AAMI/ISO 15675:2001	Identical
ISO TS 15843:2000	ANSI/AAMI/ISO TIR15843:2000	Identical
ISO TR 15844:1998	AAMI/ISO TIR15844:1998	Identical
ISO TR 16142:1999	ANSI/AAMI/ISO TIR16142:2000	Identical

[1)] FDIS approved; being prepared for publication.

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Association for the Advancement of Medical Instrumentation

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The AAMI Industrial Ethylene Oxide Sterilization Working Group (WG), under the auspices of the AAMI Sterilization Standards Committee, developed this technical information report based on drafting work of the WG's Task Group on Parametric Release.

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NOTE—Participation by federal agency representatives in the development of this technical information report does not constitute endorsement by the federal government or any of its agencies.

Introduction

This document is part of a series of reports intended to be used in conjunction with ANSI/AAMI/ISO 11135:1994, *Medical devices—Validation and routine control of ethylene oxide sterilization*. The other reports in the series are:

— AAMI TIR14:1997, *Contract sterilization for ethylene oxide*

— AAMI TIR15:1997, *Ethylene oxide sterilization equipment, process considerations and pertinent calculations*

— AAMI TIR16:2000, *Process development and performance qualification for ethylene oxide sterilization—Microbiological aspects*, and

— AAMI TIR 28:2001, *Product adoption and process equivalency for ethylene oxide sterilization*.

One of the activities encompassed within the 1994 standard is the mechanism used for product release. ANSI/AAMI/ISO 11135:1994 specifies that one of two approaches is to be used to release the product, either conventional product release or parametric release. Further guidance for application of parametric release is needed because this method of release has not been widely used in the industry.

The requirements for release of product following sterilization depend on the methods used for validation of the sterilization process. Ethylene oxide (EO) sterilization validation requires that both physical and microbiological testing be performed. Therefore, product release has traditionally required confirmation both that the process parameters were within the validated tolerance and that the biological indicators exposed to the sterilization process were inactivated. This traditional method of release is called “conventional product release.” Over the past few decades, the equipment available to monitor and control the sterilization process has been enhanced. In addition, the methods used to evaluate the impact of process parameters on microbial inactivation have vastly improved. These improvements eliminate the need for using biological indicators during routine processing. Product release that relies solely on the monitoring and evaluation of process parameters to determine the adequacy of the sterilization cycle is called “parametric release.”

Parametric release requires that manufacturers and contract sterilizers be willing to commit resources to meet the following:

— utilization of state-of-the-art controls and monitoring systems;

— determination of biological indicator inactivation using either the survivor-curve or fraction-negative method;

— maintenance of specified, validated, and consistent product load configuration(s); and

— maintenance of sufficient control over bioburden levels to ensure continued capability of the sterilization processes to achieve the specified sterility assurance level.

The main objective in pursuing parametric release is the reduction in time between sterilization and product release. The sterility testing of biological indicators typically requires an incubation period of up to 7 days. Under parametric release, the manufacturer can release product immediately upon completion of the sterilization process. The only additional requirements for release would be those stipulated for product quality and the achievement of acceptable residue levels. If product materials are such that the residuals cannot be reduced to allow release within a short period of time following sterilization, the manufacturer should re-evaluate the need to implement parametric release.

Parametric release for ethylene oxide sterilization

1 Scope

Parametric release is the declaration of adequacy of routine processing for a validated sterilization process based solely on measurement and documentation of physical process parameters rather than results of biological indicator or product sterility evaluation.

This technical information report (TIR) presents the rationale and approach necessary for the implementation of parametric release for product sterilized by ethylene oxide (EO). Additionally, this report highlights the importance and inter-relationship of other process factors (i.e., load configuration and equipment performance) that ultimately influence EO sterilization reproducibility.

Product adoption and process equivalency are not addressed in this document but will be addressed in a separate Association for the Advancement of Medical Instrumentation (AAMI) TIR.

2 Cited references

ANSI/AAMI/ISO 11135:1994, *Medical devices—Validation and routine control of ethylene oxide sterilization.*

EN 550:1994, *Sterilization of medical devices—Validation and routine control of ethylene oxide sterilization.*

AAMI TIR15:1997, *Ethylene oxide sterilization equipment, process considerations, and pertinent calculations.*

AAMI TIR16:2000, *Process development and performance qualification for ethylene oxide sterilization—Microbiological aspects.*

AAMI TIR19:1998, *Guidance for ANSI/AAMI/ISO 10993-7:1995, Biological evaluation of medical devices—Part 7: Ethylene oxide sterilization residuals.*

ANSI/AAMI/ISO 10993-7:1995, *Biological evaluation of medical devices—Part 7: Ethylene oxide sterilization residuals.*

ISO 11138-1:1994, *Sterilization of health care products—Biological indicators—Part 1: General requirements.*

ISO 11138-2:1994, *Sterilization of health care products—Biological indicators—Part 2: Biological indicators for ethylene oxide sterilization.*

ANSI/AAMI/ISO 11737-1:1995, *Sterilization of medical devices—Microbiological methods—Part 1: Estimation of bioburden on product.*

Block, SS (ed.). 2000. *Disinfection, Sterilization, and Preservation*, 5th ed., Lippincott, Williams & Wilkins, Philadelphia.

3 Definitions

For the purposes of this TIR, the following definitions apply.

3.1 aeration: Part of the sterilization process during which ethylene oxide and/or its reaction products desorb from the medical device until predetermined levels are reached.

NOTE—Aeration may be performed within the sterilizer and/or in a separate chamber or room.

3.2 aeration area: Either a chamber or a room in which aeration occurs.

3.3 bioburden: Population of viable microorganisms on a raw material, component, finished product, and/or package.

3.4 biological indicator (BI): Inoculated carrier contained within its primary pack providing a known resistance to the relevant process.

3.5 calibration: Comparison of a measurement system or device of unknown accuracy to a measurement system or device of known accuracy (traceable to national standards) to detect, correlate, report, or eliminate by adjustment any variation from the required performance limits of the unverified measurement system or device.

3.6 chamber: Enclosed area that accommodates only sufficient product to fill the sterilizer.

3.7 commissioning; installation qualification: Obtaining and documenting evidence that equipment has been provided and installed in accordance with its specifications and that it functions within predetermined limits when operated in accordance with operational instructions. (See also *validation*.)

3.8 conditioning: Treatment of product within the sterilization cycle, but prior to sterilant admission, to attain a predetermined temperature and relative humidity. This part of the sterilization cycle may be carried out either at atmospheric pressure or under vacuum. (See also *preconditioning*.)

3.9 D-value, D_{10} value: Time required to achieve inactivation of 90 % of a population of the test microorganism under stated conditions.

3.10 exposure time: Time for which the sterilizer chamber is maintained within the specified range for temperature, sterilant concentration, pressure, and humidity.

3.11 flushing: Procedure by which the sterilant is removed from the load and chamber by either

a) multiple alternate admissions of filtered air or inert gas and evacuations of the chamber, or

b) continuous passage of filtered air or inert gas through the load and chamber.

3.12 inoculated carrier: Carrier on which a defined number of test organisms has been deposited.

3.13 medical device: Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purposes of:

a) diagnosis, prevention, monitoring, treatment, or alleviation of disease;

b) diagnosis, monitoring, treatment, alleviation of, or compensation for an injury or handicap;

c) investigation, replacement, or modification of the anatomy or of a physiological process; or

d) control of conception;

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means.

3.14 parametric release: Declaring product as sterile, on the basis of physical and/or chemical process data, rather than on the basis of sample testing or biological indicator results.

3.15 performance qualification: Obtaining and documenting evidence that the equipment as commissioned will produce acceptable product when operated in accordance with the process specification. (See also *validation*.)

3.16 preconditioning: Treatment of product prior to the sterilization cycle in a room or chamber to attain specified limits for temperature and relative humidity. (See also *conditioning*.)

NOTE—This part of the sterilization cycle may be carried out either at atmospheric pressure or under vacuum.

3.17 preconditioning area: Either a chamber or a room in which preconditioning occurs.

3.18 process challenge device (PCD): Object that simulates the worst case of conditions as they are given for the sterilizing agent(s) in the items or the goods to be sterilized.

a) The device is so constituted that a biological indicator can be arranged in the place most difficult for the sterilant to reach. The design of the process challenge device depends on the kind of goods to be sterilized and the sterilization procedure. The biological indicator should not interfere with the function of the process challenge device.

b) In some process challenge devices, an inoculated carrier may be used in place of a biological indicator.

3.19 process development: Documented program of studies that is performed in order to define the sterilization process based on the product/packaging/loading pattern and/or equipment limitations.

3.20 quantal region: Area of the survivor curve where a dichotomous response is expected because of a low number of survivors that is less than 10 but greater than 0.01 organisms per BI.

3.21 reference load: Specified sterilization load made up to represent the most difficult combination of products to be sterilized.

3.22 revalidation: Set of documented procedures to confirm an established validation.

3.23 room: Enclosed area capable of holding more product than can be accommodated in the sterilizer(s) at any one time.

3.24 sterile: Free from viable microorganisms. (See *sterilization* and NOTE in 3.25.)

3.25 sterility: State of being free from viable microorganisms. (See *sterilization*.)

NOTE—In practice, no such absolute statement regarding the absence of microorganisms can be proven.

3.26 sterility assurance level (SAL): Probability of a viable microorganism being present on a product unit after sterilization.

3.27 sterilization: Validated process used to render a product free of all forms of viable microorganisms.

NOTE 1—In a sterilization process, the nature of microbial death is described by an exponential function. Therefore, the presence of viable microorganisms on any individual item can be expressed in terms of probability. Although this probability may be reduced to a very low number, it can never be reduced to zero. The probability can be expressed as a sterility assurance level.

NOTE 2—SAL is normally expressed as 10^{-n}.

3.28 sterilization cycle: Treatment in a sealed chamber comprising air removal, conditioning (if used), injection of sterilant, exposure to ethylene oxide, removal of ethylene oxide, and flushing (if used).

3.29 sterilization load: Goods that are to be or have been sterilized simultaneously in the same sterilization chamber.

NOTE—The sterilization load may include more than one manufacturing batch or lot.

3.30 sterilization process: All treatments that are required to accomplish sterilization, including preconditioning (if used), the sterilization cycle, and aeration.

3.31 usable sterilizer chamber volume: Space inside the sterilizer chamber that is not restricted by fixed or mobile parts (loading units, pallets, etc.) and that is consequently available to accept the sterilization load.

NOTE—The usable sterilizer chamber volume is calculated using available height, width, and depth, and expressed as a measure of volume.

3.32 validation: Documented procedure for obtaining, recording, and interpreting the results needed to show that a process will consistently yield a product complying with predetermined specifications.

NOTE—Validation is considered as a total process that consists of commissioning and performance qualification.

3.33 zero EO exposure cycle: A sterilization cycle in which the load is exposed to all aspects of the sterilization process except ethylene oxide (EO).

3.34 zero EO exposure time: A sterilization cycle in which the load is exposed to all aspects of the sterilization process including EO injection.

NOTE—The EO is evacuated immediately on obtaining the desired concentration.

4 Equipment requirements

As stated in ANSI/AAMI/ISO 11135:1994, annex D, paragraph D.2, “the use of a system of parametric release for ethylene oxide sterilization will require a greater knowledge and more control of the sterilization parameters.” This release method is an option and necessitates the ability to consistently control and document the sterilization process parameters.

In the presence of flammable gas, use appropriate explosion protection in accordance with local government requirements.

4.1 Preconditioning

Preconditioning or conditioning may be performed in the sterilization chamber or in a separate preconditioning area (chamber, cell, or room). The preconditioning area (sterilization chamber if conditioning is used) shall have the following performance and measurement capabilities:

a) Adequate air circulation to ensure the uniformity of temperature and humidity in the space.

b) Airflow detection alarms or indicators on the circulation system to ensure that it is operating within validated parameters.

c) Separate monitoring and controlling sensors for temperature and humidity determination in the room, if temperature and humidity are controlled by sensor readings.

d) Load temperature recording probes available to continuously monitor the load. Annex B may be referenced for the recommended number of probes used during validation. The number of probes used in routine production should be sufficient to demonstrate that the prescribed load temperature range was maintained for the entire load. Typically, the number and location of probes used during routine production should be determined on the basis of validation data.

e) Humidity probes within the room or chamber (load humidity probes are required only during validation). Annex B may be referenced for the necessary number of probes used during validation. The number of probes used in routine production should be sufficient to demonstrate that the prescribed room humidity limits were maintained.

f) A method, such as a time clock or other means, for recording time of load entry into, and removal from, the preconditioning area.

4.2 Sterilization chamber

The sterilization chamber should have the following performance and monitoring capabilities to control and document parametric release:

a) Load temperature recording probes available to continuously monitor the load. Annex B may be referenced for the necessary number of probes used during validation. The number of probes used in routine production should be sufficient to demonstrate that the prescribed load temperature limits were maintained for the entire load. Typically, the number and placement of probes used during routine production should be determined on the basis of validation data.

b) Independent systems for recording and controlling chamber pressure, chamber temperature, and chamber humidity (if humidity additions are controlled by sensor readings).

c) Instrumentation for analysis of humidity during conditioning and the EO concentration during sterilant dwell time. Calibration of gas analysis equipment is discussed in annex A, section A.5.

d) Adequate circulation to ensure the uniformity of temperature, humidity, and gas concentration within the chamber. Chamber uniformity may be demonstrated by temperature, humidity profiles, and lethality mapping studies. Circulation systems may be used to achieve homogeneous conditions within the chamber. These systems, when used, should be monitored to ensure proper operation during the sterilization cycle.

e) Instrumentation to monitor gas inlet temperature.

4.3 Aeration/degassing

Load aeration for the removal of ethylene oxide residuals may be performed in the aeration area (chamber, cell, or room). Temperature uniformity and air recirculation throughout the area are important. These parameters should be specified to ensure consistent and reproducible results. Forced air circulation is commonly used. Methods other than mechanical ones may be used, provided that the process is validated and monitored. The aeration area shall have the following capabilities:

a) airflow detection alarms or indicators on the air handling system to ensure that it is operating within specified parameters;

b) load temperature recording probes available to continuously monitor the load during validation; and

c) a method, such as a time clock or other means, for recording time of the load entry into, and removal from, the room area.

5 Process analysis

5.1 Overview

The measurement and documentation of humidity in conditioning and of gas concentration during exposure require particular attention when parametric release has been selected. In conventional EO sterilization processes, the concentration of humidity and EO in the chamber are typically calculated by measuring pressure change. In addition, the amount of EO can also be verified by measuring weight change in the storage container as EO is added to the chamber. ANSI/AAMI/ISO 11135:1994 requires that for parametric release, the humidity and EO concentration be measured both during validation and during routine cycles. Direct analysis for humidity can be accomplished by the use of electronic sensors or by use of analytical instruments such as gas chromatography (GC) or spectroscopy methods such as infrared (IR). The use of GC or IR technology to measure humidity is less common and may be more difficult to use than electronic sensors. EO analysis presently can be performed using methods such as GC or spectroscopic methods. The reproducibility and accuracy of the results from direct analysis should be determined during validation. Routine cycle analysis should fall within the determined range for the cycle to be acceptable.

Gas and humidity specifications for routine processing should be established using data obtained during the validation. The specification should cover the normal range observed during the entire gas exposure dwell time. This should be verified and correlated to the actual monitoring, as well as to the calculated values.

5.2 Frequency of EO analysis

In routine cycles, the frequency of analysis required to demonstrate that the minimum gas concentration is maintained throughout EO exposure should be established during the validation studies. These studies require analysis throughout the exposure dwell period to determine the effect of the sterilization load interaction with the gas. Monitoring throughout the gas exposure dwell period during the validation studies also will demonstrate how the gas concentration changes over time. The results of this analysis are specific to the product and load configuration being analyzed. The analysis performed during the validation study will result in documented specifications for: 1) how often direct analysis should be performed during routine processing; and 2) the appropriate times for making the analysis to ensure that monitoring can demonstrate how well gas concentration specifications are met throughout exposure. It is recommended that, at a minimum, direct analysis of gas concentration be performed routinely during the first and last portions of gas exposure.

5.3 EO analysis sampling location(s)

Validation studies that demonstrate a consistent uniformity of lethality, temperature, and humidity may support the use of one sampling point in any location. Alternatively, data from the validation studies may support the use of one sampling point in a location shown to represent minimum concentrations to which the load will be exposed. The number of sampling points and the location for sampling must be adequate to ensure that monitoring will be able to demonstrate that specifications for gas concentration are met throughout the chamber.

5.4 EO analysis accuracy

Measurement of water vapor and EO concentration can be influenced by a number of factors, including equipment capability, process parameter uniformity, and complexity of the gas mixture in the chamber. The accurate measurement of gas and uniformity of concentrations within the chamber depend on:

a) accurate determination of the composition and weight of the gas being added;

b) uniform mixing of the gases in the chamber;

c) accurate determination of the chamber temperature;

d) uniformity of pressure and temperature in the chamber; and

e) selective absorption of gases by the sterilization load.

These factors, which are covered in annex C, should be considered when determining the frequency of analysis and number of sampling locations.

6 Process development

6.1 Overview

The ANSI/AAMI/ISO 11135:1994 standard provides specific requirements and guidance to assist the manufacturer in implementing a parametric release program for release of EO sterilized product. Figure 1, below, identifies some of the key elements to be considered in developing and validating a cycle for parametric release. Section numbers refer the reader to the applicable section of this TIR. The guidance provided in AAMI TIR16*, Process development*

and performance qualification for ethylene oxide sterilization—Microbiological aspects, may also be referenced for guidance on the process development and validation program.

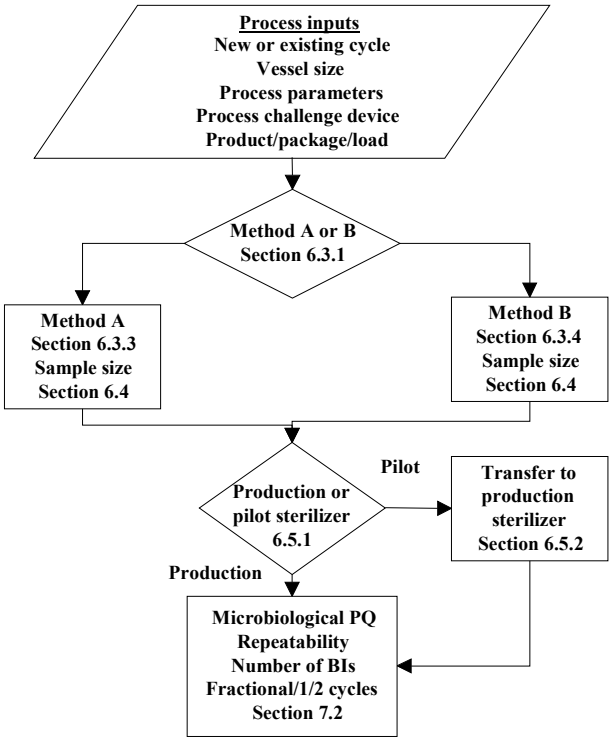

Figure 1—Microbiological cycle development

One of the first steps in a process development and validation program is to determine the lethality of the sterilization process. The standard requires that this determination be made by running fractional cycles before implementation of parametric release. This cycle operation requires an understanding of the resistance relationship of the product bioburden and inoculated carriers when placed in the most-difficult-to-sterilize position in the product. Attributes to be considered include:

a) product material composition;

b) product design;

c) product packaging; and

d) manufacturing environment.

The process lethality, generally expressed as the D-value or spore log reduction, may be calculated by using the results from one of the two methods identified in section 6.3, in accordance with the equations described in ANSI/AAMI/ISO 11135:1994 or a graphical method.

There are three methods commonly used to develop a sterilization cycle:

1) Overkill—This method involves developing a standard ≥ 12 D-value sterilization cycle using biological indicators.

2) Bioburden/biological indicator—This method involves monitoring the developmental cycle with a biological indicator, which reflects the bioburden and the SAL desired for the product.

3) Bioburden—This method involves evaluating product bioburden inactivation in fractional studies to establish the process needed to ensure the SAL desired for the product.

Because the development of the ethylene oxide sterilization process is so complex, it is common practice to use the overkill or bioburden/biological indicator-based methods to establish parametric release programs.

6.2 Use of biological indicators to develop the sterilization process

Biological indicators are used to develop and validate sterilization processes for overkill and bioburden/biological indicator processes. The appropriateness of the biological indicator (inoculated product model or process challenge device (PCD)) relative to the natural product bioburden resistance may be demonstrated either before or during process development. Guidance for determining the appropriateness of the biological indicator, preparation of inoculated product or PCD, and alternate inoculation methods can be found in section B.4 of ANSI/AAMI/ISO 11135:1994.

6.3 Methods of determining lethality

6.3.1 Methods overview

The ANSI/AAMI/ISO 11135:1994 standard for EO sterilization has embraced two methods for establishing the parameters for parametric release of products. These methods determine the suitability and reliability of the PCD used to validate the sterilization cycle. The first (Method A) consists of an enumeration or physical count of the survivors, and the second (Method B) uses growth/no growth during fractional cycles. Either of these methods may be used as a part of the initial validation for a new process that is being developed, or may be used as a mechanism for the data development needed to support the process during a revalidation program. Whether the cycle has been used historically with traditional release methods or is a new cycle, the standard requires a determination of process lethality using either Method A or Method B as described in section 7.2 of the standard.

Method A requires the enumeration of the biological indicator survivors following exposure to fractional cycles with graded time increments. The advantage of using Method A is that, in providing point-to-point values, the enumeration data can better predict the slope of the curve using fewer studies to establish the curve shape. The major deficiency of this recovery method is the difficulty in recovering survivors at lower counts. As a result, the counts at low levels are usually estimated as less than 10 colony forming units (CFU)/carrier.

NOTE—A fraction/negative cycle in the quantal region may assist in identifying the low survivors for understanding the “tailing effect.”

Method B is easier to perform because it consists of sterility testing the BIs for pass/fail results instead of enumerating them. Following exposure to fractional cycles with graded time increments, the BIs or inoculated carriers are removed from the PCD and sterility tested. For this method to be useful in calculating the D-value, the sterility test must result in fractional growth of the sterility test samples (i.e., some positive and some negative). The drawback to this method is the loss of accuracy in calculating the final D-value from the data when compared with the enumeration method. Additionally, more fractional cycles are required to support this method than to support the enumeration method.

Regardless of the method used to determine lethality, it is assumed that:

a) the organism population is homogeneous;

b) the process parameters, with the exception of time, are constant from run to run;

c) a semi-logarithmic survivor curve exists; and

d) the recovery medium will support growth of damaged and fully viable indicator organisms, processed in fractional studies, as demonstrated by growth promotion and recovery testing.

6.3.2 Steps required by both methods

a) Process challenge devices (see section 3.18 for definition) are prepared by placing a BI challenge in the most-difficult-to-sterilize location of the PCD (as determined by a sterilization specialist or by resistance studies) using organisms of a known population and resistance.

   NOTE—If external PCDs are used for routine processing prior to the approval of parametric release, including them in a fractional study may provide data regarding the resistance relationship between the external PCD and the internal PCDs.

b) An adequate number of samples should be used to address the potential variation of gas/humidity penetration that exists among different individual test samples. See section 6.4 for the number of samples to be used per cycle.

c) The PCDs should be exposed to process parameters that provide less lethality than the proposed production process. The parameter data recorded during these studies should be used to determine the minimum production process and load parameters. The production process parameters will be equal to or greater than those employed during the process development studies. For each fractional cycle, all process

parameters should remain constant with the exception of time. Equally graded time increments should be used.

NOTE—Section 11.3.3.b of ANSI/AAMI/ISO 14161, *Sterilization of health care products—Biological indicators—Guidance for the selection, use, and interpretation of results,* provides guidance for calculating the D-value using the Holcomb–Spearman–Karber procedure, which does not require evenly graded time increments.

d) The PCDs should be removed from the load as quickly as possible following completion of the cycle. This action will minimize the impact of postexposure kill (latent lethality) caused by residual EO within the PCD. This time should be consistent from run to run. Safety controls should be implemented and followed when handling non-aerated material.

The following sections provide more specific directions for the methods identified for use in the development process. A more detailed description of the methods for calculating D-values may be found in Chapter 6 of *Disinfection, Sterilization, and Preservation* (Block 2000). In addition, section 6.5 of this TIR provides additional guidance regarding locations, whether the sterilization is performed in a small pilot unit or in a larger production chamber.

6.3.3 Method A: Survivor curve construction—Enumeration of the BIs

Method A consists of exposing the inoculated PCDs to graded EO exposure times, removing the BIs from the PCDs, and counting (enumerating) the number of surviving organisms on each BI. This method generates a survivor count that can be used in developing a survivor curve.

Five or more graded EO exposure times must be performed. For the performance of this method to be acceptable, all of the exposure times used should result in recoverable populations. Exposure times should be chosen such that they are evenly spaced starting with zero and with the longest time producing a remaining population of 1 to 100 organisms per sample.

NOTE—The starting population (zero EO exposure cycle) should be determined on BIs exposed to all stages of the process before EO injection.

The spore log reduction at each exposure time should be calculated by subtracting the log of the population at that time from the log of the population at zero time. Linear regression analysis should be used to calculate the D-value of the microbial population of the PCD from the slope of the resulting line. For example, the linear correlation of the line should be greater than 0.878 (0.811 if six exposure times are used, 0.754 if seven exposure times are used), corresponding to a level of significance of 0.05. (See *Statistics, a First Course*, Freund, John E., Prentice Hall Inc., 1970.)

6.3.4 Method B: Fraction negative

Method B requires using sets of PCDs in a minimum of seven fractional cycles that apply graded exposures to ethylene oxide with all parameters except time remaining constant. The time intervals for this study should be of equal increments.

NOTE—Section 11.3.3.b of ANSI/AAMI/ISO 14161, *Sterilization of health care products—Biological indicators—Guidance for the selection, use, and interpretation of results*, provides guidance for calculating the D-value using the Holcomb–Spearman–Karber procedure, which does not require evenly graded time increments.

The results from the PCD BI sterility testing should result in:

— 1 EO exposure time that results in growth of all the PCD BIs;

NOTE—A zero exposure time cycle may provide a baseline for establishing successive EO exposure times.

— 4 EO exposure times that result in fractional growth of the PCD BIs;

NOTE—These results establish the quantal region and the resulting fraction negative data will be used to calculate the D-value for the process.

— 2 EO exposure times that result in complete inactivation, no growth, of all PCD BIs.

The D-value can be calculated from the quantal region sterility test results. Section B.7 of ANSI/AAMI/ISO 11135:1994 describes the method for calculating a fraction negative D-value. The upper 95 % confidence level from the resulting D-value is then used to calculate the minimum EO exposure time for the desired SAL.

6.3.5 Sterilization cycle development process troubleshooting

The following actions may be taken in the event that all positives, all negatives, and/or slope linearity cannot be obtained.

6.3.5.1 Obtaining all positives

6.3.5.1.1 Methods to obtain all positives with a new process

If there is some or all kill in the zero gas time exposure study, the sterilization process is probably very robust, and reevaluating the sterilization parameters used in the cycle development process is recommended. The process may be modified either by reducing the gas concentration or reducing the processing temperature. The new parameters should then be used to complete process development. Following data generation, the more robust cycle or the cycle used during the study may be implemented for routine processing, if the requirements for product functionality, package functionality, and EO residual levels have been achieved and if the applicable Quality Management documentation for parametric release of the product has been completed.

6.3.5.1.2 Methods to obtain all positives in an existing cycle

Some or all kill in a zero time EO gas exposure cycle may occur. This result indicates that the EO process provides a high level of lethality to the product. It may also indicate a high level of residual EO activity with devices constructed of materials that retain and slowly release EO during the aeration phase of the process. In these cases, problems in obtaining all positives may be addressed in the following ways:

— the biological indicator resistance and/or population may be increased to generate the zero time data;

— the use of BIs with multiple populations may provide an understanding concerning the inactivation kinetics for the PCD;

— the cycle parameters may be modified to a shorter ramp for gas inject and evacuation to provide less time at gas exposure;

— the cycle temperature may be reduced; and

— the gas exposure pressure may be modified.

Once data generation is completed, the more robust cycle may be implemented for routine processing when the requirements for product functionality, package functionality, and EO residual levels have been achieved and when the applicable Quality Management documentation has been completed for parametric release of the product.

6.3.5.2 Obtaining a linear slope in the lethality curve

When slope linearity cannot be achieved, the following should be evaluated:

— Determine if the load temperature is uniform and optimal for sterilization. If not, enhance the preconditioning and conditioning phase temperature of the process as well as increase the sterilization process temperature.

— Determine if the load humidity is uniform and optimal for sterilization. If not, enhance the preconditioning and conditioning phase humidity of the process as well as increase the sterilization process humidity.

— Increase the gas concentration or gas dwell period if compatible with product and package functionality.

6.3.5.3 Obtaining all negatives

When all negative results cannot be obtained within a reasonable exposure time for the cycle, the following conditions may be responsible and should be evaluated:

— incomplete humidification of the load/samples;

— incorrect inoculation (inoculated products only); and

— inconsistencies in delivered conditions in portions of the chamber.

If total kill still is not achieved, the process should be reviewed, and increases in temperature and EO concentration or rearrangement of the load to better facilitate sterilant penetration should be considered. Caution should be exercised so as not to compromise the integrity of the product or package being sterilized.

6.4 Sampling considerations for process development studies

Selection of a sample number for a lethality study should take into consideration the method used (Method A or Method B), and whether the samples are distributed throughout the load or are concentrated in one location. Use of a single location may improve consistency of results between samples. If a single location is used, it should be a location where lethality is less likely to be enhanced. See section 6.5.1 for site selection guidance options.

Because Method A results in enumeration of surviving spores for each sample, calculating a lethality rate with a small number of samples is possible. However, calculating a lethality rate using Method B requires enough samples so that a significant number of those samples exhibit growth and so that four graded quantal results may be obtained.

For each fractional cycle run, a minimum of five samples is suggested for Method A, and 10 to 20 samples are suggested for Method B.

NOTE—When sample requirements are defined, consideration should be given as to whether any of the fractional cycles will also be used as microbiological performance qualification cycles. These studies are used to map the delivered lethality throughout the production sterilizer and, therefore, specific numbers are recommended. The number of samples should be based on the production chamber volume per annex B.

6.5 Performance of Method A or B in a pilot or a production chamber

6.5.1 Four ways that Method A or B may be performed

It is recommended that section 7.2 be reviewed before a method is selected. The data developed in these studies may be used to meet some requirements listed in section 7.2.

Table 1—Site selection of BI sample

Method	BI sample location in the sterilizer	Recommendations
Pilot chamber	Single location or throughout the load	Problems may be associated with transferring the data to a production chamber. However, a small pilot chamber may provide better control of process parameters than a large chamber, making it easier to achieve Method A or B fractional exposure results. The site selection guidance options listed in the remainder of this table may also be applied to selecting a site in the pilot vessel. If a single location is used, it should be a location where lethality is less likely to be enhanced.
Production chamber	Single location—selected site	This site is chosen without load temperature/humidity profile data. The site is selected on the basis of the potential effects of the load geometry and composition on temperature/humidity penetration throughout the load, which has been judged by a sterilization specialist to be representative of the entire load. Placement of all sterility test samples in one selected site may compensate for variations in temperature/humidity in different sites in the load. Additional lethality studies may be required to verify this location as representative of the entire load.
Production chamber	Single location—worst case site in load with regard to delivered lethality	This site is in a production chamber with all BIs in a single location in the load demonstrated to be the most difficult to sterilize. The survivor curve should be generated in an area of the sterilizer delivering the least lethality. Microbiological and/or parameter profile data may be used to select this location.
Production chamber	Spread throughout the load	This site is in a production chamber with BIs spread throughout the validation load. Spreading the BIs throughout the chamber may result in a survivor curve that is more representative of the lethality delivered throughout the load.

CAUTION—Performing Method A or B in a production-size vessel may result in inaccurate D-value and exposure time calculations because of the delivered lethality during the sterilant charge and removal phases of the test cycles. See section 6.3.5 for troubleshooting guidance.

6.5.2 Establishing relationship between pilot chamber and production chamber

The development of the microbial inactivation curves described in section 6.3 is not always possible in production chambers because of the size of the chamber and the time required to inject and remove ethylene oxide in the chamber. These long injection and vacuum times limit the ability to obtain the required fractional recovery of indicator organisms. These inactivation curves may be developed in a pilot chamber that can deliver equivalent parameters used in the production chamber. Suggested methods for demonstrating a relationship between the data developed in the pilot chamber and a production chamber involve a physical profile comparison and/or density comparison. Compare the sterilization conditions delivered in the pilot chamber with the physical profile obtained in a production chamber.

6.5.2.1 Parameter comparison

It may be possible to establish the relationship between the studies performed in a pilot and production chamber by comparing the following:

— temperature set point and range within the preconditioning room (if used);

— relative humidity set point and range within the preconditioning room (if used);

— preconditioning time;

— temperature set point and range within the sterilization chamber;

— relative humidity set point and range within the sterilization chamber;

— gas concentration set point and range within the sterilization chamber (if gas analysis equipment is available on the pilot chamber);

— gas dwell time;

— pressure vacuum/transfer depths and rates;

— microbial lethality;

— temperature set point and range within the aeration room (if used); and

— temperature and relative humidity range within the load.

The lowest temperature location(s) in the load or the slowest-to-heat locations are generally considered to be the worst-case or most-difficult-to-sterilize locations. If these conditions and locations are known for the production chamber, they should be simulated in the pilot chamber.

Comparison requirements may vary because of the specific sterilization cycle and equipment used. The sterilization specialist will have to determine the applicability of data developed in a pilot vessel on a case-by-case basis.

6.5.2.2 Product/load comparison

If a pilot chamber is being used, the load density (mass/volume) should be representative of the routine sterilization unit density.

Example: A ten-pallet load weighing a total of 5,000 lbs and occupying 1,000 ft^3 would have a density of 5 lbs/ft^3. A pilot chamber sample container weighing 5 lbs and occupying 1 ft^3 would have the same density of 5 lbs/ft^3.

The ratio of pilot load volume to usable pilot chamber volume also should be representative of the ratio of load volume to chamber volume used in the production chamber.

Example: A ten-pallet load occupying 1,000 ft^3 of a 2,000 ft^3 chamber would fill 50 % of the chamber volume. A pilot chamber sample container occupying 1 ft^3 of a 2 ft^3 pilot chamber would fill an equivalent 50 % of the pilot chamber volume.

The comparison of pilot and production loads should be based on equivalency of the load not only in terms of its weight to volume, but also in terms of the challenge that the product and load configuration presents to the sterilization process.

Example: A large or heavy sealed device requiring only surface sterilization may have a greater density, but present less challenge to the sterilization process, than a device with a lumen and complex product geometry.

CAUTION—Duplicating the density and sterilizer volume in a pilot chamber may not reproduce all of the effects on the sterilization process that are created by a production load. The penetration of many layers of a routine production pallet load may affect the delivered lethality. Therefore, it may take longer to attain the same lethality observed in the pilot chamber.

6.6 Calculation of the sterilization cycle

The data obtained from Method A or B is used to establish the minimum EO gas exposure time required for the sterilization process. Note that kill curves (lethality rates or D-values) are specific to the process parameters, chamber, loading configuration, and PCD placement within the load used for the study.

The D-value can be used to calculate the final cycle exposure time. If an overkill cycle is desired, the D-value is used to calculate the desired time needed to achieve the defined sterility assurance level for the product.

Example: The D-value for a PCD consisting of a prep kit has been established to be 15 minutes. The desired SAL for the tray is 10^{-6}. Therefore, the total exposure time would be 12 logs $\times$ 15 min, or 3 h.

NOTE—D-values developed by Method B and calculated using the method listed in section B.7 of ANSI/AAMI/ISO 11135:1994 determines the upper 95 % confidence-level D-value.

6.7 Documentation of the process development

Whether Method A or B is used, one should ensure that all required parametric release parameters are documented. One should document any deviations to the protocol and perform additional tasks as required. One should declare that the process has or has not met the success criteria of the protocol, on the basis of the test results.

7 Validation

Validation studies must comply with the requirements of the normative portions of ANSI/AAMI/ISO 11135:1994. The following steps are required in the validation study.

7.1 Commissioning (IQ/OQ)

Installation qualification (IQ) studies involve obtaining and documenting evidence that equipment has been provided and installed in accordance with its specifications and that it functions within predetermined limits when operated in accordance with operational instructions. (See also validation, ANSI/AAMI/ISO 11135:1994.)

Commissioning involves the generation, collection, and documentation of evidence demonstrating that the design specifications of the sterilizer and all ancillary equipment are appropriate for their intended use.

Operational qualification (OQ) studies are performed according to a protocol and are intended to demonstrate that the equipment will consistently perform in the selected environment over all intended ranges as set forth in the specification. OQ studies are performed without the product. All OQ studies should be completed and approved before proceeding with the phases of physical and microbiological qualification.

7.2 Performance qualification (PQ)—Microbiological

The recommendations presented in this section may be used to validate new or modified EO sterilization processes undergoing conversion to parametric release. These recommendations may not be required for established EO processes, provided that they have been shown to be reproducible by accepted validation/revalidation procedures per ANSI/AAMI/ISO 11135:1994 and provided that all other requirements for establishing parametric release have been met.

In addition to the successful completion of Method A or B in a pilot or production chamber and calculating a minimum gas exposure time, performance qualification is performed in the loaded chamber to demonstrate the following for the specified load configuration:

a) The cycle is effective in achieving the specified sterility assurance level;

b) The required parameters are achieved at all monitored locations in the production load; and

c) The cycle is reproducible in the production chamber.

The way in which the above additional requirements should be demonstrated depends on the way in which Method A or B was performed. The number of samples used in the production chamber should comply with ANSI/AAMI/ISO 11135:1994.

a) If Method A or B was performed in a pilot chamber or with all BI samples in a single selected location in the production chamber load, then three all-kill fractional cycles should be performed with BI samples spread throughout the load in the production chamber.

b) If Method A was performed in the production chamber load, then at least three all-kill fractional cycles should be performed. (See note below.)

c) If Method B was performed in the production chamber with the BI samples spread throughout the load or located in a single location previously demonstrated to be the most difficult to sterilize (i.e., previous validation studies), then only one additional all-kill fractional cycle is required. This fractional cycle in combination with the two all-kill fractional cycles performed as a part of the Method B study provides for the total of three all-kill fractional cycles needed to demonstrate reproducible achievement of the specified SAL.

NOTE—It is assumed that the all-kill cycles confirm the endpoint of the log reduction curve previously determined during cycle development. Because Method A does not require all-kill cycles, three all-kill fractional cycles are required during performance qualification to confirm the endpoint of the log reduction curve and to demonstrate reproducibility. The two all-kill cycles of Method B, in addition to one all-kill cycle during performance qualification, are sufficient to demonstrate reproducibility, provided that the conditions specified in (c) above are met. If the performance qualification all-kill fractional cycles do not confirm the endpoint of the log reduction curve determined during cycle development, then the log reduction curve endpoint requires adjustment. In this case, three all-kill cycles must be conducted to show reproducibility.

No all-kill cycles will be required for processes previously validated by Method C of ANSI/AAMI/ISO 11135:1994, provided that:

a) The inactivation curve developed by Method A or B indicates that the current exposure time, previously validated by Method C of ANSI/AAMI/ISO 11135:1994, is sufficient to deliver the required SAL; and

b) The process and load configurations are not modified.

7.3 Load configuration

The combination of product type, packaging, load density, number of pallets, and configuration shall constitute a sterilization parameter. This parameter will be identified and documented before starting the parametric release validation.

The critical relationship between the product, packaging, load density, and configuration, relative to the sterilizing environment, shall be established during the validation and shown to be reproducible. This relationship data will be used to create the load configuration parameter for routine, production cycle, and parametric release. The parameter will be verified and documented after each sterilization cycle.

EO sterilization users who intend to vary or mix product types, packaging, load/pallet configurations, and densities must establish and validate the specific degree of variance acceptable for achieving the specified SAL and the maintainability of all sterilizing parameters throughout the modified load. The limits for load parameters such as package size, package weight, materials, and pallet density should be determined and included in the validation plan.

7.4 Performance qualification—Physical

Full-length sterilization cycles should be run with temperature, relative humidity (RH), and EO sensors to verify reproducibility of the process and to assess the impact of the cycle on the product and packaging functionality and residue levels. This performance qualification may be done in actual production loads, with release of the loads contingent on verification of reproducibility and on BIs included in the load.

During the full-length cycle studies, a gas concentration profile for the entire gas dwell period should be developed and assessed to determine how the gas concentration changes over the period.

NOTE—Section 5.2 addresses the frequency and timing of EO analyses required during routine cycles.

Finished devices that have been used to validate a parametric release process should be exposed to a sterilization process that the above studies or prior qualifications support as a full cycle. Until parametric release has been approved for that cycle, BIs should be used to release such loads, provided that the requirements of conventional release have been met.

7.5 Revalidation

Revalidation must be performed to ensure that process changes have not occurred and to demonstrate that the original validation program remains effective. Minimally, a single revalidation study or cycle is performed on an annual basis. The revalidation study must be documented (see ANSI/AMMI/ISO 11135:1994, section 5.6) and should include, but not be limited to, the following elements:

a) A review of the chamber performance and engineering changes of the past year to ensure that the commissioning process is still valid. This check should include a review of the annual empty chamber temperature profile study and the relative humidity profiles of the preconditioning areas.

b) Reconfirmation of the delivered SAL of the sterilization process through microbiological studies.

c) Reconfirmation of the bioburden trends and resistance that were previously established and documented.

NOTE—These revalidation requirements are specific to parametric release and are in addition to the standard revalidation requirements for conventional release. Refer to ANSI/AAMI/ISO 11135:1994 for additional revalidation guidance.

8 Routine processing

Additional requirements during routine processing have been identified for process parameters in ANSI/AAMI/ISO 11135:1994. Careful attention should be given to the additional requirements for the establishment of specifications for processing in section 7.2.2 and for routine control and monitoring in section 7.2.4 of the standard. Further guidance for process monitoring may be found in section D.2 of the standard.

9 Product release

9.1 General

For parametric release, the routine release of product as sterile is based on a demonstration of conformity of the physical processing parameters to all specifications established during the validation. Product release is based on a documented review of processing records rather than on testing of product sterility or process challenge devices. Qualified individuals should perform documentation reviews. Note that this discussion is limited to release of the devices as sterile. Testing of characteristics other than sterility may be required after sterilization.

9.2 Written procedures

When parametric release is used for routine release of product, procedures shall be written that:

— identify the documents and process parameters that are to be reviewed;

— define acceptance criteria for each process parameter;

— designate the individual(s) who is (are) authorized to sign release documents; and

— outline the steps to be taken when nonconformity is found.

9.3 Electronic records and signatures

Routine release of a product following sterilization may be based on a review of electronic records in lieu of paper records. Likewise, required signatures may be made electronically. In these cases, the requirements of the regulation on Electronic Records; Electronic Signatures (Title 21, *Code of Federal Regulations*, Part 11) shall be met in order to ensure the authenticity, integrity, and retrievability of the records.

Annex A
(informative)

Gas analysis issues

A.1 Gas analysis hardware concerns

To validate and practice the parametric release method, users of ethylene oxide must install, validate, and maintain measurement systems to perform direct sterilizer analysis of water vapor (relative humidity) and EO. Several technologies already exist for the direct analysis of water vapor and EO.

The most common technologies for measuring EO are chromatographic and spectroscopic. The main technology for measuring water vapor is thin film sensors. Other technologies are under development and may soon be available. It is critical that personnel with the proper education, training, and experience be involved in the design, selection, operation, and maintenance of such equipment.

Design of the gas analysis system, selection and installation of each component, and maintenance practices must be carefully planned in such a way that they do not interfere with the accuracy of the analysis. In addition, certain designs require that the user address safety concerns such as potential worker exposure and the flammability of the sterilant.

A.2 Chromatographic technology

Chromatographic systems require that the gas sample be removed from the sterilizer and then carried to the analyzer hardware for processing. In the case of nonflammable sterilant gases, the actual analyzer can be located adjacent to the sterilizer, simplifying sample delivery. In the case of flammable gases (100 % EO, for example), the analyzer should be rated as intrinsically safe, isolated from the sterilizer room atmosphere (pressurized NEMA cabinet), or remotely located outside the room housing the sterilizer. Gas sample delivery must be carefully planned, because sample capture may have to take place while the sterilizer is under deep vacuum. In addition, where process conditions inside the sterilizer may allow the gases to exist as vapors, once they are removed from the sterilizer the change in pressure and temperature may cause them to condense, thus compromising the accuracy of the analysis. The system, therefore, will require a sample pump capable of overcoming the sterilizer vacuum and able to deliver a constant flow of analyte gas to the chromatograph. The pump must not allow any gas to leak out to the surrounding area, and the pump manufacturer must certify that the pump was designed for use with flammable (100 % EO) and/or corrosive gases (any concentration of EO). All lines connecting the sterilizer to the sample pump, and the sample pump to the chromatograph, must be heat traced to a temperature higher than that of the process in order to avoid condensation. The temperature of the heat tracing must be monitored and controlled to specified tolerances in order to maintain calibration accuracy. Following analysis, all gases should either be routed through a return line, bringing them back to the sterilizer, or be safely vented to an emissions control device.

A.3 Spectroscopic technology

Spectroscopic systems exist in two forms. One type involves a remotely located gas cell, a heat-traced feed line, and a return line. Analyte gas is continuously pumped through the feed line into the gas cell and then back to the sterilizer. Analyte determination occurs inside the gas cell without destroying the sample. This system uses a pump, as does the chromatographic system. The major difference, however, is that with sealed gas cells, the gas analysis hardware can function at the same process pressure as the sterilizer, thus reducing the stress on the sample pump. All sample lines and the gas cell must be properly heat traced to avoid condensation. When sterilant flammability is a concern, the analyzer and sample pump must be intrinsically safe in order to be placed in the sterilizer room. However, by extending the length of the heated-traced sample lines, these systems may be remotely located outside the sterilizer room. Caution should be taken, as remote isolation of the measurement system may result in EO condensing in the sample line or reduction in the efficiency of the sample pump.

A second type of spectroscopic instrument design does not require the gas sample to be physically removed from the sterilizer. A portion of the instrument, sometimes referred to as a probe, is mounted through a sterilizer wall penetration and collects spectroscopic data directly from the sterilizer atmosphere. This data is then transmitted to the analyzer for processing and reporting. The analyzer may reside either in proximity to the sterilizer or outside the sterilizer room. Data transfer may be accomplished electronically or optically. Analyte determination is non-destructive. Because the need for sample pumps and sample lines is eliminated, the actual analysis can be performed regardless of process conditions.

The probe (portion of the analyzer residing inside the sterilizer) must be properly constructed and rated if used with flammable mixes of EO. It must also be proven compatible with all process gases and conditions. Because

condensation of process gases will interfere with the accuracy of spectroscopic analyzers (especially optically-based units), some components penetrating inside the sterilizer may have to be heated to a temperature higher than that of the process.

A.4 Component selection

In designing any type of gas analysis system, all materials and components must be evaluated for compatibility with the anticipated range of operating pressures and temperatures, as well as with the chemical characteristics of all process gases. Generating a well-researched functional specification document can ensure that the system operates safely and effectively. Trace contaminants may come from O-rings, seals, or other components that may be present in the system. Employing metal-to-metal and glass-to-metal seals rather than elastomer seats is preferred. The system design also should exclude greased fittings and soldered joints, which represent potential sources of contamination. When tubing is installed, tube-type fittings or brazed joints should be required to provide leak-tight connections. Valve types should be selected to ensure the best control of gas flow. All fittings should be of the highest quality and sealed only with instrument-grade PTFE tape. Pipe sealant chemicals and low-grade tapes may bleed contaminants into the gas stream. Brazing alloy used for soldering should be flat stick silver solder containing 15 % silver. Methyl acetylene propadiene should be used instead of acetylene. The design also should prohibit the use of flux in soldering connections. In specifications for tube-fitting components, a requirement should be included to purchase all components from the same manufacturer or of the same brand. Nuts, ferrules, and bodies from different manufacturers may have different angles and depth specifications.

A.5 Calibration

Electronic sensors for measuring and recording RH can be calibrated, or the standardization verified, by the use of saturated salt solutions or qualified RH generation systems. Lists of salt solutions can be found in available chemical handbooks. The National Institute for Standards and Testing (NIST) also recommends a list. The salt solutions in the NIST list are characterized by relatively stable humidity over large temperature ranges. The suppliers of self-contained temperature/humidity sensors can supply recalibration services.

Analytical instruments such as gas chromatographs or spectrophotometers present a more difficult challenge. Such instruments can be factory calibrated but should have that standardization verified after installation. Relative humidity can be verified by the use of calibrated electronic sensors located at the instrument sampling point. Confirmation of EO sensor standardization can be conducted in one of several ways. Some instrument suppliers can provide a standard that can be placed in the system to confirm maintenance of calibration. An alternate method is to standardize the EO monitor against known EO concentrations in an empty chamber or sample cell. Two methods of determining EO concentration:

a) use of the ideal gas law, which is based upon pressure change and gas temperature; and

b) use of the weight of gas added and the volume of the system.

Either the ideal gas law or gas weight/system volume can be used to verify calibrations if the following are confirmed:

a) correct analysis of the EO in the storage container;

b) uniform EO mixture in the chamber; and

c) accurate measurement of chamber pressure, chamber temperature at the sampling location, gas weight added, and the volume of the system occupied by the gas.

Confirmation of EO concentration through the use of both the ideal gas law and weight/volume calculations is recommended. In an empty chamber, the three approaches (gas law, weight/volume, and direct analysis) must correlate. Correlation requirements should be defined and justified by the user.

Annex B
(informative)

Sensor monitoring tables

B.1 Commissioning (IQ/OQ) (empty)

Table B.1—Sterilization

Chamber volume		ANSI/AAMI/ISO 11135:1994	EN 550
m^3	ft^3	Number of temperature probes	
2.5	90	10	10
5	175	10	10
10	350	20	20
15	530	20	20
20	705	20	25
25	885	20	30
30	1,060	20	35
35	1,235	20	40
50	1,765	20	55
100	3,500	20	105

Rules for determining number of probes—

ANSI/AAMI/ISO 11135:1994

If $m^3 < 5$, then 10 temperature probes.

If $m^3 \geq 5$ and < 10, then ($m^3 + 5$) = temperature probes.

If $m^3 \geq 10$, then 20 temperature probes.

EN 550

If $m^3 > 5$, then ($m^3 + 5$) = temperature probes.

Aeration commissioning: Same number of temperature probes as used above for preconditioning.

B.2 Performance qualification (with product)

Table B.2—Preconditioning and/or conditioning

Product load volume		ANSI/AAMI/ISO 11135:1994		EN 550	
m^3	ft^3	Number of temperature probes	Number of humidity sensors	Number of temperature probes	Number of humidity sensors
2.5	90	5	2	5	2
5	175	4*	2	4	2
10	350	8	4	8	4
15	530	12	6	12	6
25	885	20	10	20	10
35	1,235	28	14	28	14
50	1,765	40	20	40	20
100	3,500	40	20	40	20

* Although 4 is correct, it is recommended that 5 temperature probes be used for compliance with the nominal volume less than or equal to 2.5 m^3.

Rules for determining number of sensors—

ANSI/AAMI/ISO 11135:1994 and *EN 550*

If $m^3 < 2.5$, then 5 temperature probes and 2 humidity sensors.

If $m^3 \geq 5$ and < 50, then ($m^3 \times 0.8$) = temperature probes and ($m^3 \times 0.4$) = humidity sensors.

If $m^3 \geq 50$, then 40 temperature probes and 20 humidity sensors.

Table B.3—Sterilization

Product volume		ANSI/AAMI/ISO 11135:1994		EN 550	
m^3	ft^3	Number of temperature probes	Number of biological indicators	Number of temperature probes	Number of biological indicators
2.5	90	10	20	10	20
5	175	10	20	10	20
10	350	20	30	20	30
15	530	20	35	20	35
20	705	20	40	25	40
25	885	20	45	30	45
30	1,060	20	50	35	50
35	1,235	20	55	40	55
50	1,765	20	70	55	70
100	3,500	20	120	105	120

Rules for determining number of probes—

ANSI/AAMI/ISO 11135:1994

If $m^3 < 5$, then 10 temperature probes.

If $m^3 \geq 5$ and < 10, then $(m^3 + 5)$ = temperature probes.

If $m^3 \geq 10$, then 20 temperature probes.

EN 550

If $m^3 > 5$, then $(m^3 + 5)$ = temperature probes.

Rules for determining number of BIs—

ANSI/AAMI/ISO 11135:1994 and *EN 550*

If $m^3 < 5$, then 20 BIs.

If $m^3 > 5$ and < 10, then $[(m^3 – 5)\ 2] + 20$ = BIs.

If $m^3 > 10$, then $(m^3 + 20)$ = BIs.

Aeration: No guidance for number of temperature probes. Because probes are in the product for sterilization, the same number as in Table B.3 would apply.

Annex C
(informative)

Factors influencing accuracy and decisions regarding the direct analysis of EO concentration

The use of a single-point analysis for direct measurement of gases is based on the definition of a gas, which includes the premise that a gas occupies the entire volume of the container that holds it. A number of other factors, however, can influence uniformity of the gas concentration.

C.1 Ideal gas law

Calculation of the concentration of the components of a gas or gas mixture is based on the ideal gas law:

$PV = nRT$

where:

P = partial pressure of the desired gas within the chamber

V = volume of the chamber

n = number of moles of gas

T = chamber temperature in Kelvin

R = constant, which depends on the units used for the other parameters

or

$C = (K \times P)/(R \times T)$

where:

C = concentration in mg/L

K = a constant, which varies with the specific gas mixture

P = pressure in atmospheres

R = gas constant = $0.08205(L \times atm)/(mol \times degK)$

T = temperature in Kelvin

Typical values for K, in units of mg/mole, are:

4.405×10^4 for pure EO

9.989×10^3 for 10 % EO/27 % HCFC-22/63 % HCFC-124

The ability to accurately measure the gas concentration depends on:

a) accurate determination of the gas being added for both composition and weight;

b) uniform mixing of the gases in the chamber;

c) accurate determination of the chamber temperature;

d) uniformity of pressure and temperature in the chamber; and

e) selective absorption of gases by the sterilization load.

C.2 Gas composition and weight

EO gas or gas mixtures are generally stored as liquefied gases in cylinders or drums. They are delivered to the sterilization chamber through a volatizer to heat the liquid and convert it to a gas. The container is typically located

on a scale that measures the weight of the container and the liquefied gas. Weight loss from the container is equal to the weight of the gas added to the system. Large-volume EO containers can weigh several hundred pounds and are typically set on scales with large calibration tolerances. Delivery of small charges of EO together with a large calibration tolerance may result in large fluctuations in gas concentration calculations. The sensitivity of the gas scale and the volume of gas makeups should be evaluated when calculating gas concentration by weight. The gas mixture 8.5 % EO with 91.5 % CO_2 may present a problem in delivering uniform small charges from the container because the gases stratify within the container. This problem has not been reported for other mixtures.

C.3 Chamber pressure

The chamber pressure should be uniform to meet the definition of a gas, but the use of circulation blowers can produce small, localized pressure changes. Placing the direct analysis sampling point in the recirculation line can have advantages such as the likelihood that the mixture would be more uniform. However, the possible impact of local pressure increases should be considered.

C.4 Chamber temperature

The magnitude of temperature spread in the chamber should be considered in calculating the comparison of concentration results. The use of absolute temperatures in the ideal gas law will usually minimize the effect of temperature spread in the calculation.

C.5 System volume

If the gas weight and chamber volume are used to calculate the EO concentration, the volume occupied by the gas should be accurately known. The volume of piping external to the chamber that is also occupied by the gas should be added to the calculated chamber volume. This additional volume includes the recirculation piping and the gas addition piping.

C.6 Chamber atmosphere

The simplest gas atmosphere is a one-component system (e.g., 100 % EO). No sterilization process is a true one-component system. Residual air and water vapor from in-chamber humidification are always present. A deep vacuum EO process using 100 % EO is the closest to the ideal one-component gas and will therefore result in the least concern regarding EO uniformity. Shallow vacuum processes, which can leave as much as half of the chamber atmosphere (either air or nitrogen), present more of a potential for problems with uniformity. The use of gas mixtures and diluents presents additional potential concerns. (See also C.7.) Therefore, a time delay can occur between the addition of the EO or EO mixture and the achievement of uniform EO concentration in the chamber, particularly if the EO is added at a single point versus a manifold or if the EO is put into the recirculation system. The time after addition(s) of EO should be evaluated to achieve accurate readings.

Vertical stratification of gas mixtures in EO sterilization processes has been reported with poor or absent recirculation systems. Adequate mixing of the chamber atmosphere is considered sufficient to avoid the possibility of this occurrence. The location of the direct analysis sampling point at an extreme vertical location (e.g., top or bottom of the chamber) can also test for this potential situation. (Results for direct analysis at these locations can be compared to an independent calculation such as the ideal gas law or weight/volume. A good correlation would eliminate the possibility of stratification. If stratification existed, the correct value at this point would require locations in the chamber with both higher and lower values.)

C.7 Selective absorption

Products that are being EO sterilized can selectively adsorb or absorb EO from gas mixtures. This is the result of several phenomena, including the solubility of EO in the product and the solubility of EO in the condensed water that may be present following the humidification process. If this occurs, gas addition weight or chamber pressure will not reflect the correct gas concentration. In this situation, developing a history of data may be necessary before establishing the ability of direct analysis to confirm correct EO addition.