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Report

AAMI TIR15:1997

Ethylene oxide sterilization equipment, process considerations, and pertinent calculations

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AAMI TIR No.15—1997

Ethylene Oxide Sterilization Equipment, Process Considerations, and Pertinent Calculations

Approved 4 August 1997

Abstract: This AAMI Technical Information Report (TIR) provides additional guidance to ANSI/AAMI/ISO 11135–1994, *Medical devices—Validation and routine control of ethylene oxide sterilization*. The topics covered under this TIR are sterilization equipment, considerations for preconditioning, calculations for relative humidity, calculations of ethylene oxide concentration, and flammability.

Keywords: ethylene oxide concentration, flammability, preconditioning, relative humidity, sterilization equipment, calculations

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ETHYLENE OXIDE STERILIZATION EQUIPMENT, PROCESS CONSIDERATIONS, AND PERTINENT CALCULATIONS

Introduction

This technical report is considered informative, and use of the terms "shall," "should," etc., should be considered within the context of this technical report only. That is, if the decision is made to use a particular method presented in this technical report, then the method should be followed in adherence with the requirements ("shall") and recommendations ("should") as set forth in this technical report.

1 Scope

This AAMI Technical Information Report (TIR) provides additional guidance to ANSI/AAMI/ISO 11135–1994, *Medical devices—Validation and routine control of ethylene oxide sterilization.* The topics covered under this TIR are sterilization equipment, considerations for preconditioning, calculations for relative humidity, calculations of ethylene oxide (EO) concentration, and flammability.

This TIR is not designed to be used as a stand-alone document. Therefore, the reader is advised to refer to the applicable sections of ANSI/AAMI/ISO 11135–1994 to ensure that the requirements specified within that document are followed.

2 Definitions

For the purposes of this AAMI Technical Information Report, the following definitions apply.

2.1 aerate/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. This may be performed within the sterilizer and/or in a separate chamber or room.

NOTE—During aeration, only EO desorbs from the load. However, ethylene chlorohydrin and ethylene glycol levels may remain stable, increase, or be converted to other byproducts.

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

2.3 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.

2.4 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 according to instructions.

2.5 conditioning: Treatment of product within the sterilization cycle, but prior to sterilant admission, to attain a predetermined temperature and relative humidity.

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

2.6 performance qualification: Obtaining and documenting evidence that the equipment as commissioned will produce acceptable product when operated according to the process specification.

2.7 preconditioning: Treatment of product prior to the sterilization cycle in a room or chamber to attain specified limits for temperature and relative humidity.

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

2.9 requalification: Single performance qualification study that provides evidence that the equipment continues to produce acceptable results when operated in accordance with the process specification.

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

2.11 sterilization process equipment: Preconditioning area (if used), chamber/sterilizer and aeration area, and their respective ancillary equipment.

2.12 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 a total process that consists of commissioning and performance qualification.

3 EO sterilization equipment

3.1 General requirements

3.1.1 Sterilization process equipment is to be designed, manufactured, installed, and calibrated to provide reproducible control of process conditions and safe operations as established by local or international regulations or standards.

3.1.2 Measuring instrumentation (for example: sensors, timers, recorders) utilized on sterilization process equipment shall be capable of successive measurements (real-time) of the sterilization cycle parameters.

3.1.3 The specified limits for the accuracy and repeatability of measuring instruments used for the process should comply with process requirements.

3.1.4 Provisions should be available to document all process control parameters.

3.1.5 When using flammable mixtures of ethylene oxide (EO):

a) Electrical accessories in the sterilizer room, gas storage area, aeration rooms, and emission control area should comply with Class I, Division 2, Group B electrical requirements as stated in National Fire Protection Association (NFPA) 70, *National Electrical Code* (1995) or equivalent.

b) The sterilizer interior should comply with Class I, Division 1, Group B electrical requirements stated within NFPA 70 or equivalent. The guidance within NFPA 560 (1995) should also be consulted.

c) All equipment and piping should be grounded in accordance with NFPA 70 or equivalent.

d) In facilities constructed after 1995 and where NFPA standards have jurisdiction by federal, state, local, or other regional department or individual (e.g., fire chief), the storage, handling, and use of ethylene oxide shall comply with NFPA 560: *Standard for the Storage, Handling, and Use of Ethylene Oxide for Sterilization and Fumigation.*

3.1.6 In certain abnormal situations (equipment malfunction, power failures, experimental cycles, etc.) when product exposed to ethylene oxide remains in a closed environment without proper ventilation (failure of chamber rear exhaust or aeration cell exhaust, etc.), attention should be paid to the possible accumulation of flammable or explosive amounts of ethylene oxide. This danger is possible regardless of the blend used.

3.1.7 The aeration chamber or room should be equipped with a means to remove sterilant gases to a level compliant with Occupational Safety Hazard Administration (OSHA) employee exposure regulations, *Occupational Exposure to Ethylene Oxide,* 29 CFR 1910.1047 (1994).

3.1.8 Electromagnetic interference, caused either by equipment and/or circumstances within the same facility (e.g., walkie-talkies) or external to the facility, should be evaluated for possible effects on the process. Provisions (proper grounding, shielded cables, filtered power supply, protective building materials, etc.) should be incorporated in the design of the facility to prevent such interference from influencing the process. Reference EN 50081 and EN 50082 for additional guidance on electromagnetic interference.

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3.2 Preconditioning area (outside sterilizer chamber)

3.2.1 If facilities are provided to heat and humidify the product, equipment should be available to adequately control and document the air temperature and the relative humidity (RH). ANSI/AAMI/ISO 11135–1994 expresses humidity only in terms of % RH, but humidity may also be recorded in other engineering units such as parts per million (ppm), dew point, grains of water, etc.

3.2.2 Uniform temperature and humidity distribution throughout the useable room/area should be achieved through assisted air circulation.

3.2.3 During equipment commissioning, the air recirculation rate should be established and documented. Prior to periodic requalification, the air recirculation rate should be verified. If requalification does not occur on an annual basis, it is recommended that the air recirculation rate be verified annually.

3.2.4 The specified limits for the accuracy and repeatability of measuring instruments used for the preconditioning process should comply with process requirements.

3.2.5 The preconditioning areas should be accessible for cleaning and sanitation. Materials of construction and the cleaning process should be compatible. The cleaning process should be documented in accordance with good housekeeping practices and the manufacturer’s internal procedures.

3.2.6 ANSI/AAMI/ISO 11135, annex A.3.1.1, suggests facilities for segregation and identification of different sterilization loads in preconditioning. While such segregation may be designed into a facility, an acceptable alternative is to segregate and identify different loads in accordance with Quality System Regulations (QSRs) and internal quality systems.

3.2.7 Necessary equipment and connections (connections for sensors, for example) should be available and accessible to validate preconditioning areas.

3.2.8 The equipment design for the heating and humidification of the preconditioning area should avoid direct wetting of the product (for example, the use of manifolding or baffles). Steam traps, separators, and coalescing filters can be used to minimize the entrainment of water in the steam entering the preconditioning area.

3.2.9 Audible and/or visual alarms should be incorporated to alert the operators if the process approaches an out-of-specification condition.

3.2.10 Humidification by direct steam injection is preferred. In rare instances, local environmental conditions (e.g., desert) or particular product considerations (e.g., temperature sensitivity) may preclude the use of steam. In such cases, the sterilization load may be humidified without the addition of heat. However, process water must be microbiologically controlled (e.g., by filtration) and the system validated.

3.3 Sterilizer chamber

3.3.1 The sterilizer chamber surfaces that come in contact with EO should be of materials that, under the designed operating conditions, minimize:

a) corrosion by EO, its diluent gases, or steam;

b) reaction with EO or other compounds found as contaminants of EO;

c) the polymerization or decomposition of EO.

3.3.2 The sterilizer chamber should be accessible for cleaning. Materials of construction for the sterilizer chamber and the cleaning process should be compatible. The cleaning process should be documented in accordance with good housekeeping practices and the manufacturer’s internal procedures.

3.3.3 Sensors (e.g., pressure, temperature, gas concentration, relative humidity) should be designed for use in an ethylene oxide sterilization process.

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3.3.4 Auditory and/or visual alarms should be incorporated to alert the operators if the process approaches an out-of-specification condition.

3.3.5 The chamber should be designed to prevent inadvertent access to the load prior to cycle completion using mechanical means (interlocks). If a fault occurs during a sterilization cycle, access to the load shall necessitate the use of a special key, code, or tool.

3.3.6 When the chamber is used to condition a load, either statically or dynamically, equipment should adequately control and document the chamber temperature, chamber pressure, and the conditions necessary to achieve the required process conditions.

3.3.7 Since process conditions inside a chamber may approach the dew point of water, condensation on both product and equipment should be evaluated. Condensation, especially at ‘cold spots,’ will reduce the partial pressure of water vapor in the chamber, causing additional steam to be added in order to maintain a constant pressure during static conditioning. Excess condensation inside the chamber or on product/packaging can result in interference with the process and can contain dissolved ethylene oxide and derivatives. This dissolved EO may later be released when the load is allowed to dry in the aeration or storage areas, possibly creating a hazard to workers. In addition, condensate in the chamber or load may revaporize and drive the chamber headspace humidity level above validated levels.

3.3.8 The equipment design for the heating and humidification of the sterilizer chamber should avoid direct wetting of the load (e.g., the use of manifolding or baffles). Steam traps, separators, and/or coalescing filters should be used to minimize the entrainment of water in the steam entering the chamber. This facilitates proper heating and humidification of the load.

Water used for steam generation should be free of contaminants that can impair the sterilization process or harm the sterilizer or sterilization load.

NOTE—See 21 CFR 173.310 (1997) and 21 CFR 200.11 (1997) for a list of FDA-approved boiler additives.

3.3.9 Equipment should be selected that has adequate controls to deliver and monitor the selected parameters, such as

a) pressure control;

b) rate (e.g., sterilant injection, evacuation, etc.);

c) temperature control;

d) time;

e) gas concentration (e.g., weight, volume, pressure, and/or direct analysis);

f) humidity.

3.3.10 There should be proper equipment to ensure complete volatilization of the sterilant, thus avoiding nonuniformity in temperature and EO concentration. Common practice is to have the gas inlet temperature at or above the chamber temperature. Excessive heating of the inlet gas should be avoided to prevent problems associated with localized high temperatures within the chamber load.

3.3.11 There shall be equipment to quantify the amount of EO used. The methods of determining EO concentration are: chamber gas pressure monitoring, direct EO concentration measurement, and measurement of the weight or volume of sterilant injected. One method is required for routine processing. During validation, one method other than pressure monitoring is required (ANSI/AAMI/ISO 11135–1994, section 5.5.2.3).

3.3.12 During initial engineering studies, the sensor(s) used to monitor and control the chamber heating may be temporarily mounted in locations to determine the relationship to the chamber temperature profile. Additional monitoring sensors should be used during these thermal profiles to map the distribution of heat in the usable chamber volume. In addition to confirming that the chamber control system and ancillary equipment are properly functioning, such thermal studies will provide important information, as detailed below.

a) The minimum and maximum chamber temperatures throughout the cycle and their locations within the usable chamber volume will be determined. These locations should be included in the commissioning studies and subsequently translated into positions within the sterilizer for performance qualification studies.

b) The degree of temperature control will also be determined. This determination should include not only the extremes of temperature, but also the capability of the system to control a single point (or an average of multiple points) at a given temperature plus or minus some tolerance. A common tolerance is ± 5.4° F (± 3° C) during exposure. If this is achieved, it is more likely that an 18° F (10° C) range can be achieved within the sterilization load during performance qualification studies.

   If this degree of temperature control cannot be achieved during the engineering studies, opportunities to enhance process control should be considered prior to validation.

   Some product configurations may yield excessively wide temperature distributions when profiling the chamber with product, even though the empty chamber profiles were acceptable. This can sometimes be resolved by using a different pallet configuration (e.g., chimney, lowered pallet height, etc.). Product temperature ranges beyond 18° F (10° C) should be evaluated to determine the effect, if any, on the efficacy of the sterilization cycle.

c) Since relative humidity is a result of water vapor pressure and temperature, it can significantly differ in various parts of the chamber as a result of temperature differences. As suggested in ANSI/AAMI/ISO 11135, annex A.2.2, “The product design should ensure that functionality and safety are not compromised by exposure to the anticipated range of sterilization conditions.”

d) The relationship between the position of the controlling temperature sensor(s) and the characteristics of the heat distribution throughout the usable chamber volume are determined. If the data obtained during chamber profiling (with and/or without product) are acceptable, they may become part of the chamber commissioning file, but only if the controlling temperature sensors remain in these original location(s). If these controlling sensors should be moved, either inadvertently or to affect the chamber performance, then all previously performed thermal profiles may need to be repeated to evaluate the change. For example, if a controlling sensor located in the colder area of the chamber (usually close to the door) calls for a quantity of heat sufficient to bring the monitoring sensors within ± 5.4° F (± 3° C) of the setpoint during sterilant dwell in an empty chamber, then moving this controlling sensor to the hottest area of the chamber (near the ceiling) may reduce the chamber’s call for heat, yielding a temperature distribution outside the ± 5.4° F (± 3° C) range.

3.3.13 When the relationship between the controlling temperature sensors and the thermal profiles of the chamber is known and accepted, then the sensors should be permanently mounted in such a way as to allow routine maintenance and calibration. Verifying the position of these sensors should be part of the routine maintenance program of the chamber.

3.3.14 Temperature, humidity, and sterilant gas distribution should be maintained uniformly throughout the chamber. Uniform distribution can be achieved through assisted circulation.

The boundaries of the usable sterilization chamber and the dimensions of the load should be defined to preclude adverse effects from the proximity of the sterilization load with the inside of the sterilizer chamber. These may include obstruction of the circulating gases by product interference, uneven heating of the load due to direct wall contact, and interference of process instrumentation by product.

3.3.15 Sterilizer measurement and control systems may use electronic microprocessor-based technology. The software application programs that are used to execute and control the sterilization process shall be validated and documented. Modifications to the programs shall be documented, approved, and maintained by either the user or the software supplier. This documentation should consist of detailed procedures that demonstrate the logical correctness of the programs during both process-simulated conditions and actual sterilizer use. Any subsequent changes shall be similarly documented, approved, and validated. The performance and reliability of the system should be evaluated during production.

3.3.16 EO liquid feed filters are not recommended. If they are used, employee exposure and environmental concerns should be considered when filters are replaced and discarded.

3.3.17 The EO liquid feed system piping, from the supply line to the vaporizer, should be capable of being cleaned with hot water and then dried with nitrogen gas to minimize accumulation of EO polymer in the line. Polymer buildup in the supply line or vaporizer may alter the flow rate and temperature of the gases entering the vessel. EO polymer may also alter the effectiveness of flame and detonation arresters, safety valves, and rupture disks.

3.3.18 Automatic feed gas regulation is preferred to avoid the inherent risks of over pressurization. These risks include but are not limited to:

a) damage to the chamber and valves as a result of the pressure exceeding the maximum rating of the equipment;

b) damage to the product/packaging contained in the chamber as a result of high pressures that exceed acceptable tolerances;

c) process deviations resulting from excessively high pressures and gas concentrations;

d) sterilant gas-related residuals that exceed validated levels;

e) employee exposure during product transfer to aeration resulting from higher than anticipated levels of EO contained within the load;

NOTE—If the parameter for maximum gas quantity is exceeded, the number of postevacuations may be insufficient to reduce the chamber EO concentration to safe levels. EO gas removal is facilitated during the postevacuation phases. Each evacuation removes a known (calculated) quantity of the EO present in both the chamber atmosphere and product and replaces it with nitrogen or air. A total number of necessary postevacuations is calculated in order to render the vessel atmosphere safe for product removal because the parameters for the postevacuations are based on the maximum amount of sterilant gas expected to be found following dwell.

f) overpressurization of the chamber with EO that may result in a flammable mixture, thus compromising the facility safety status. (For additional information, refer to the publication *Ethylene Oxide*, Union Carbide Corporation, 1993.)

3.3.19 When more than one type of gas is stored and dispensed in a facility, administrative and/or engineering controls are required to ensure the introduction of the appropriate gas into the chamber.

3.3.20 Provisions should be made for nitrogen and air inbleed filters to protect product and equipment.

If compressed air comes in contact with the load, it should be produced or treated to ensure that it is dry, free from oil, and filtered.

When products are sterilized outside their final sterile packaging, provisions should be made for the use of bacterial retentive filters in accordance with manufacturer's quality system.

3.3.21 Aeration area: If facilities are provided to aerate the product after gas exposure, equipment should be available to continuously control and document air temperature. There should be provisions for periodically checking the air flow and/or exchange rate during aeration to confirm conformance to original validated performance specifications. If the flow of fresh air into the aeration facility and/or the air flow vented from the facility is altered, the temperature profile of the area may go out of validated tolerances. This could impact the proper off-gassing of processed product and/or create a worker exposure problem. In addition, inadvertent alteration of the air flow to and from the aeration facility may result in noncompliance with the requirements of the National Emissions Standard for Hazardous Air Pollutants (NESHAP;[EPA 1997]).

3.3.22 The specified limits for accuracy and repeatability of measuring instruments used for the aeration process should comply with process requirements.

3.3.23 The aeration area should be accessible for cleaning. Materials of construction and the cleaning process should be compatible. The cleaning process should be compliant with good housekeeping practices and internal procedures.

3.3.24 There should be provisions for identifying different loads within the aeration area.

3.3.25 Necessary equipment and connections (i.e., connections for sensors) should be available and accessible to validate the aeration area.

3.3.26 Temperature uniformity should be achieved through assisted air circulation.

3.3.27 Auditory and/or visual alarms should be incorporated to alert the operators if an out-of-specification condition occurs.

3.4 EO handling, storage, and dispensing

3.4.1 U.S. Department of Transportation regulations for the transportation of EO 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 Environmental Protection Agency (EPA) labeling regulations and OSHA process safety management (if applicable). NFPA 560 regulations may apply to facilities constructed after 1995.

3.4.2 There should be controls 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 cylinder should be reviewed against inhouse gas acceptance criteria prior to use.

NOTE—The gas supplier(s) should be included in a manufacturer certification program. The gas supplier(s) that are included in a manufacturer certification program need to meet the standards defined for a certified supplier.

3.5 Calibration and maintenance

3.5.1 Documented calibration and preventative maintenance programs, consistent with Food and Drug Administration (FDA) Quality System Regulation 21 CFR 820 (FDA, 1997) and/or other national standards or regulations, should be used on instruments that control, monitor, and record the sterilization process.

3.5.2 Equipment should be designed and installed with provisions for periodic maintenance, calibration verification, and correction.

3.5.3 Equipment to be maintained and/or calibrated on a routine basis may include but is not limited to the following preconditioning, chamber, and aeration equipment:

a) gaskets and seals;

b) monitoring gauges;

c) EO monitoring equipment (i.e., environmental and/or chamber);

d) door safety interlocks;

e) safety pressure relief valves and rupture disks;

f) filters (for periodic replacement);

g) volatilizers/vaporizers;

h) chamber jacket recirculation system;

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i) chamber jacket system (for corrosion and insulation);

j) audible and visual alarms;

k) temperature and humidity sensor equipment;

l) boiler system for steam and heat supply (i.e., steam quality and quantity);

m) evacuation equipment;

n) weigh scales;

o) valves;

p) pressure transducers;

q) timers;

r) recorders.

3.6 Safety

3.6.1 When EO sterilization and aeration equipment are selected, provisions should be made for compliance with federal, state, and local health and environmental protection regulations. These regulations include but are not limited to the following:

a) *Occupational exposure to ethylene oxide*, 29 CFR 1910.1047 (1994)—defines EO personnel exposure monitoring, exposure limits, documentation requirements, and controls. While not required by OSHA, monitoring the areas of potential EO exposure is recommended (area monitoring).

b) *Process safety management of highly hazardous chemicals*, 29 CFR 1910.119 (OSHA, 1994)—defines the requirements for facilities storing more than 5,000 lbs of ethylene oxide in one location.

c) *National Emissions Standard for Hazardous Air Pollutants* (NESHAP), 40 CFR Parts 9 and 63, provides limits for EO emissions (EPA, 1997). In some locations, state and/or other local authorities have established lower limits. Construction and operating permits for EO sterilizers should be obtained and pollution control equipment installed to meet federal, state, and local regulations.

3.6.2 Ethylene oxide should be used with caution because it is toxic, potentially flammable, and explosive. Additional guidance is available through NFPA 560 (1995) and other similar guidelines and should be consulted to review flammability and safety requirements.

4 Determination of minimum product temperature prior to preconditioning

4.1 General

ANSI/AAMI/ISO 11135–1994 states in section 5.5.2.1(b) that a minimum temperature of product permitted to enter preconditioning (if used) shall be established. Load temperature prior to entrance to preconditioning should be determined at the lowest temperature zone. Caution should be exercised when placing excessively cold product into preconditioning. The sudden change in temperature may cause product damage and/or condensation and water damage.

4.2 Simulation of anticipated process conditions

Process validation considers the worst conditions to which the load will ever be exposed. Anticipated load temperature extremes during transportation, handling, and storage should be evaluated for impact on the sterilization process. These anticipated load temperature extremes may be simulated during validation in different manners consisting of, but not limited to, the following techniques:

a) Use of cold storage—For example, the product load is stored under refrigeration or deliberately induced cold temperature. The temperature of the storage area should be less than or equal to the lowest temperature the product is expected to be exposed to throughout the year. Product temperature data are recorded during the storage time. The time in storage should be equal to or greater than the maximum time any product load is expected to exist under such conditions, or the maximum product temperature while in storage becomes the minimum acceptable product temperature for a load to be admitted to the preconditioning phase. This applies to preconditioning or to conditioning when preconditioning is not employed.

b) Mathematical temperature modeling (e.g., linear regression analysis)—Assume that at the time of validation the lowest product load temperature point is 60° F prior to entering preconditioning. Once in preconditioning, data are recorded, yielding a temperature profile for the worst case position showing that the load temperature increases to 100° F by the end of preconditioning. Once the temperature over time data are graphed, the linear part of the time/temperature relationship (which is generally the beginning few hours of preconditioning where the difference between load temperature and preconditioning area temperature is the greatest) may be used to extrapolate the necessary preconditioning times for sterilization loads at temperatures lower than 60° F. Using this technique to calculate a minimum preconditioning time will yield a time that is greater than that actually required.

c) Seasonal validation (reference: ANSI/AAMI/ISO 11135–1994, annex B, section B.3.1.2.)—A preconditioning validation can target those seasons that present the most extreme temperature and humidity conditions. For example, a validation conducted during the coldest part of the year (which would also present the lowest ambient humidity level) could yield minimum preconditioning parameters valid for routine production cycles during the entire year. However, in cases of validations performed during the summer season, it is advisable to validate the preconditioning process with simulated cold storage or to repeat the preconditioning validation at least once during the winter to confirm the validity of the parameters.

4.3 Special situations

Situations may exist where direct placement of cold loads into preconditioning may result in excessive water condensation, resulting in product damage. In these cases, warehouse storage after cold storage can be validated if load temperature monitoring is continued at warehouse conditions until acceptable load temperatures are attained. Such validated storage times should become part of the sterilization process specifications. This additional warehouse storage, prior to preconditioning, may be required only during cold portions of the year.

4.4 Other considerations

4.4.1 Individual load probing

Factoring extreme shipping/storage conditions into a validation can result in longer than usual minimum preconditioning times. Extreme shipping conditions are a rare occurrence. Therefore, the long preconditioning times are not always necessary and can be avoided. First a minimum product temperature parameter, prior to entrance into preconditioning, is established during process validation. Then, as part of monitoring and control of routine production, each load should be probed prior to entering preconditioning and the temperature compared to values verified during validation. In the case of a load that does not meet the minimum specification, it should remain in storage until the coldest load area comes into specification.

4.4.2 Loads difficult to heat

The minimum acceptable temperature for a load to achieve before transfer to the sterilizer should be reproducible from cycle to cycle. It is advisable to validate a minimum acceptable product temperature at the end of preconditioning that is as close as possible to the targeted process (chamber) temperature. However, this may not be possible in the case of extremely dense or difficult to heat product types. In such cases it is acceptable to validate a product temperature at the end of preconditioning that is below process temperature. It is critical, however, that the load areas exhibiting the lowest temperatures receive adequate microbiological challenge. Refer to AAMI TIR 16, *Process Development and Performance Validation for EO sterilization—Microbiological aspects* (to be published).

5 Calculation of percent relative humidity

5.1 Calculation of chamber RH from difference in total pressure resulting from addition of steam

In instances where the direct measurement of relative humidity is not possible, the relative humidity in the chamber can be calculated on the basis of the difference in total pressure resulting from the addition of steam and the sterilizer chamber temperature.

The following assumptions are made.

a) The chamber is empty;

b) Gauge readings are in absolute pressure;

c) Initial humidity present inside the chamber is insignificant (partial pressure is less than 0.1 pounds per square inch (psi)).

Definition of variables

P_t = Recorded terminal pressure at the end of steam injection
P_i = Recorded initial evacuation pressure
T_{dc} = Recorded temperature at the end of steam injection
P_{ss} = Saturated steam pressure at T_{dc} (from steam table (ASME 1983))
P_w = Partial pressure of water vapor prior to each steam injection (for dynamic conditioning only)
P_2 = Recorded pressure after steam injection prior to evacuation stage where P_3 is determined.
P_3 = Recorded pressure after evacuation following steam injection stage where P_2 was determined

The formula for determining the relative humidity in the chamber based on the difference in total pressure resulting from the addition of steam and the sterilizer chamber temperature is:

$$\%RH = \frac{(P_t - P_i)}{P_{ss}} \times 100 \qquad [1]$$

5.2 Dynamic conditioning

5.2.1 General

In deep vacuum cycles, dynamic environmental conditioning (DEC) is considered an improvement because it displaces virtually all the air from the sterilizer and load and replaces it with steam. The advantage of DEC is that it will improve the humidification and heating rates.

The two common methods for achieving dynamic environmental conditioning are Method A (pulse/purge) and Method B (continuous).

5.2.2 Method A (pulse/purge)

5.2.2.1 The pulse/purge method is when, after an initial deep evacuation, steam is injected and then re-evacuated to a predetermined set-point. This process is repeated until the desired process conditions are achieved. Use the following formula:

$$\text{New } P_w = \frac{P_2}{P_3} \text{ x Old } P_w \qquad [2]$$

a) Record the initial evacuation pressure using inHgA (P_i).

b) Steam pulse to a higher pressure and record the terminal pressure at the end of steam injection (P_t or P_2).

c) Calculate the new partial pressure of water vapor (inHgA) as follows:

$$\text{New } P_i = (P_t - \text{Previous } P_i) + P_w$$

d) Draw vacuum to a lower pressure (P_3).

e) Steam pulse to a higher pressure.

f) Calculate the partial pressure of water vapor (inHgA).

5.2.2.2 One of the ways of executing Method A is the following:

Assume temperature = 120° F. Then, $P_{ss} = 3.45$ inHgA.

Step 1: Draw an initial vacuum to 2 inHgA. Assume water vapor is negligible at this point. If water vapor is not negligible, replace zero value for P_w with the true value.

$$P_i = 2 \text{ inHgA} \qquad P_w = 0$$

Step 2: Pulse steam to a total pressure of 3 inHgA.

$$P_2 = 3$$

Step 3: Using equation [2] , calculate new P_w:

$$= (P_2 - P_i) + \text{old } P_w$$
$$= (3 - 2) + 0$$
$$= 1 \text{ inHgA}$$

And calculate new %RH, using equation [1]:

$$\text{New \%RH} = \frac{1.00\,\text{inHgA}}{3.45\,\text{inHgA}} \text{x}\,100 = 29.00\%$$

Step 4: Draw vacuum to 2.0 inHgA

$$P_3 = 2 \text{ inHgA}$$

Step 5: Calculate new P_w

$$\text{New } P_w = \frac{P_3}{P_2} \text{ x old } P_w = \frac{2\,\text{inHgA}}{3\,\text{inHgA}} \text{x}\,1\,\text{inHgA} = 0.67\,\text{inHgA}$$

$$\text{New RH} = \frac{0.67\,\text{inHgA}}{3.45\,\text{inHgA}} \text{x}\,100 = 19.4\%$$

Step 6: Pulse to 3 inHgA with steam

$$\begin{aligned} &= (P_2 - P_3) + \text{old } P_w \\ &= (3 - 2) + 0.67 \\ &= 1.67 \text{ inHgA} \end{aligned}$$

$$\text{New} \quad \%\text{RH} = \frac{1.67\,\text{inHgA}}{3.45\,\text{inHgA}} \text{ x } 100 = 48.40\%$$

Continue pulsing and evacuating as many times as desired, calculating the changing partial pressures of water vapor and the changing relative humidities for each step.

NOTE—It is possible, with enough pulses and a large enough air pressure at the start of dynamic conditioning, to exceed the saturation pressure of water vapor and cause condensation on the load.

5.2.3 Method B (continuous)

5.2.3.1 Method B is an alternative method for executing DEC whereby steam is injected into the sterilizer and evacuated simultaneously. This method may be preferred because of product, package, load configuration, or load storage conditions.

Minimum suggested equipment for controlling Method B are proportional control valves (for steam and/or vacuum), a pressure transducer, and a process controller. Method B can also be performed manually, however, the precision of execution is then dependent on the operator.

A manifold or multiport steam inlet and vacuum outlet should be considered to obtain uniform conditioning across the load. Other vital components are the chamber jacket, vacuum system, and steam supply. The jacket provides the heat sink for stabilizing the internal chamber environment. Ideally, the vacuum system should be capable of removing 1 chamber volume per minute. The steam supply should be capable of delivering saturated steam at a rate comparable to the vacuum system.

The final theoretical relative humidity (Load %RH) in the chamber can be calculated using the following formula:

$$\text{Load }\%\text{RH} = \frac{P_t}{P_{ss}} \times 100 \qquad [3]$$

where:

P_t = chamber pressure at the end of DEC

P_{ss} = saturated steam pressure at T_0

T_0 = recorded chamber temperature at the end of DEC

5.2.3.2 One of the ways of executing Method B is the following.

Step 1: Select the final temperature and relative humidity of the load. Use these values to calculate P_t;

Step 2: Pull initial vacuum to P_t;

Step 3: Inject steam into the chamber while the vacuum system continues to evacuate the chamber;

Step 4: Control the steam injection rate to maintain a dynamic chamber pressure of P_t (± 0.1 inHg if possible);

Step 5: When the load temperature becomes stable, DEC is accomplished.

6 Calculation of EO concentration

6.1 Introduction

The theoretical calculation of the concentration of ethylene oxide in a sterilizer, after the initial charge of gas and at temperature equilibrium, is based on the Ideal Gas Law (PV = nRT). The following assumptions are made.

a) The chamber is empty.

b) The mixture of ethylene oxide, water vapor, and air (and the diluent gas when used) behaves as an ideal gas.

c) The label information on the cylinders containing the gas is accurate, and the percentage by weight of the mixture of gas remains constant during admission to the sterilizer.

d) Gauge readings are in absolute pressure.

6.2 Definition of variables

Variables are defined as follows:

C = EO concentration

R = Gas constant

P = Difference in total pressure due to ethylene oxide (EO) and diluent gases (DG)

T = Absolute temperature of EO/diluent gas mixture giving pressure P

K = Constant for a given diluent

M = Molecular weight of diluent gas

E = Weight percentage of EO in diluent mixture

V =Volume

n = number of moles of gas

6.3 Calculations

Table 1—List of constants and molecular weights of some common EO/diluent combinations

EO/Diluent and Molecular Weights Constants

EO/Diluent	K (mg/gm mole)[1]	K (lb/lb mole)[2]
8.5% EO/91.5% CO_2	3.74×10^3	3.74
12% EO/88% CFC-12	1.20×10^4	12
8.6% EO/91.4% HCFC-124	9.942×10^3	9.942
10% EO/90% HCFC Mixture	9.99×10^3	9.99
20% EO/80% CO_2	8.80×10^3	8.80
100% EO	4.40×10^4	44
10% EO/27%HCFC-22/63%HCFC-124	9.989×10^3	9.989

Molecular Weights

Ethylene Oxide (EO)	44.0
CFC-12	120.9
HCFC-124	136.5
HCFC-22	86.5
Carbon Dioxide	44.0

[1] Use when calculating mg/l
[2] Use when calculating lb/ft^3

The ethylene oxide concentration is calculated on the basis of the difference in total pressure resulting from the addition of ethylene oxide plus carrier or diluent gas, and from the sterilizer chamber temperature. The difference in total pressure due to the addition of ethylene oxide and diluent gas can be expressed as:

$$P = P_{EO} + P_{DG} = \left(\left(\frac{n}{v} \right)_{EO} + \left(\frac{n}{v} \right)_{DG} \right) RT \qquad [4]$$

Rearranging the Ideal Gas Law expression, equation [1], allows for the calculation of ethylene oxide concentration, regardless of the EO single diluent combination, using the following equation:

$$C = \frac{K \text{ x } P}{R \text{ x } T} \qquad [5]$$

where:

$$K = \frac{4.4 \text{ x } 10^4 \, (M)\,(E)}{(M)(E) + 44\,(100 - E)}$$

6.4 Example calculations — Determining EO concentration in terms of pounds per cubic foot (lb/ft^3)

Assume a process that uses 8.5% EO and 91.5% CO_2. After gas injection, the rise in pressure was 2.89 kg/cm^2.

NOTE—This does not include pressure rise due to moisture preconditioning.

If the temperature at the end of gas injection was 134° F, then:

$$P = 2.89 \frac{\text{kg}}{\text{cm}^2} = 2.8 \text{ atm}$$

$$T = 134\,°F = 56\,°C = 329\,°K$$

$$R = 1.3140 \frac{\text{atm ft}^3}{\text{lb moles }°K} \text{ (See table 2 for gas constants.)}$$

$$K = 3.74 \frac{\text{lb}}{\text{lb mole}}$$

$$C = \frac{K \text{ x } P}{R \text{ x } T} = \frac{(3.74)\,(2.80)}{(1.314)\,(329)} = 0.0242 \text{ lb/ft}^3$$

Using equation [5], the EO concentration is:

6.5 Example calculations — Determining EO concentration in terms of mg/l

Assume a process that uses 8.6% EO and 91.4% HCFC-124. After gas injection, the rise in pressure was 40.5 inHg. If the temperature at the end of gas injection was 55° C, then:

$$P = 40.5 \text{ inHg} = 1.35 \text{ atm}$$

$$T = 55\ °C = 328\ °K$$

$$R = 0.08205 \frac{\text{atm l}}{\text{gm moles }°K} \text{ (See table 2 for gas constants.)}$$

$$K = 9.94 \times 10^3 \frac{\text{mg}}{\text{gm mole}}$$

Using equation [5], the EO concentration is:

$$C = \frac{K \text{ x } P}{R \text{ x } T} = \frac{(9.94 \text{ x } 10^3)\,(1.35)}{(0.08205)\,(328)} = 498.6 \text{ mg/l}$$

6.6 Gas constants

Table 2 — Gas constants (R)*

Pressure	Volume	Temperatures	R
atm	cc	°K	82.057
atm	liters	°K	0.08205
atm	cu. ft.	°K	l.3140
bar	liters	°K	0.08314
kg/m^2	liters	°K	847.80
kg/cm^2	liters	°K	0.08478
mmHg	liters	°K	62.361
mmHg	cu. ft.	°K	998.90
inHg	liters	°K	2.4549

NOTE—1 atm = 760 mmHg = 29.92 inHg = 14.70 psia = 1.013 bar = 1.033 kg/cm^2 = 101.3 kPa (KN/m^2)
1 liter = 1000 cc = 0.03532 ft^3
°K = °C + 273

* It is important to maintain the proper units when using equation [5] and the above gas constants.

6.7 Derivation of equation [5]

Since most operations record the pressure change during EO gas injection, equation [5] was derived to allow the calculation of EO concentration from the pressure rise due to EO gas injection, with or without a single diluent gas such as carbon dioxide or Freon 12. The purpose of this equation is to provide a simple and rapid method for calculating EO concentration for production sterilizers as well as for experimental facilities.

The pressure rise can be expressed as in equation [4]:

$$P = P_{EO} + P_{DG} = \left(\frac{n}{v}\right)_{EO} RT + \left(\frac{n}{v}\right)_{DG} RT = \left[\left(\frac{n}{v}\right)_{EO} + \left(\frac{n}{v}\right)_{DG}\right] RT$$

The above formula can be expressed in mg/l:

$$\left(\frac{n}{v}\right)_{EO} = \frac{gm}{MW_{EO}} = \frac{10^{-3}}{44}\left(\frac{mg}{l}\right)_{EO}$$

$$\left(\frac{n}{v}\right) = \frac{gm}{MW_{DG}} = \frac{10^{-3}}{MW_{DG}}\left(\frac{mg}{1}\right)_{DG} = \frac{10^{-3}}{M}\left(\frac{mg}{l}\right)_{DG}$$

where:

MW_{EO} = molecular weight ethylene oxide = 44.0
MW_{DG} = molecular weight of diluent gas = M

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Then pressure rise can be rewritten as:

$$P = \left[\frac{10^{-3}}{44}\left(\frac{mg}{l}\right)_{EO} + \frac{10^{-3}}{M}\left(\frac{mg}{l}\right)_{DG}\right] RT \qquad [7]$$

Since the weight percent EO (Wt % EO) is usually known and the sterilizer volume remains constant, the expression derived above can be rewritten as:

$$\mathrm{Wt\ \%\ EO} = \frac{\left(\frac{mg}{l}\right)_{EO}}{\left(\frac{mg}{l}\right)_{EO} + \left(\frac{mg}{l}\right)_{DG}} \times 100$$

Solving for:

$$\left(\frac{mg}{l}\right)_{DG} : \left(\frac{mg}{l}\right)_{DG} = \frac{\left(\frac{mg}{l}\right)_{EO} 100 - \left(\frac{mg}{l}\right)_{EO} \mathrm{Wt\ \%\ EO}}{\mathrm{Wt\ \%\ EO}} = \left(\frac{mg}{l}\right)_{EO}\left(\frac{100 - \mathrm{Wt\ \%\ EO}}{\mathrm{Wt\ \%\ EO}}\right)$$

Substituting the above for:

$$\left(\frac{mg}{l}\right)_{DG}$$

Equation [7] becomes

$$P = \left[\frac{10^{-3}}{44}\left(\frac{mg}{1}\right)_{EO} + \frac{10^{-3}}{M}\left(\frac{mg}{l}\right)_{EO}\left(\frac{100 - \mathrm{Wt\ \%\ EO}}{\mathrm{Wt\ \%\ EO}}\right)\right] RT \qquad [8]$$

Solving for:

$$\left(\frac{mg}{l}\right)_{EO} \text{ in Equation [8]}$$

$$P = RT\left[\frac{10^{-3}}{44} + \frac{10^{-3}}{M}\left(\frac{100 - \mathrm{Wt\%EO}}{\mathrm{Wt\%EO}}\right)\right]\left(\frac{mg}{l}\right)_{EO}$$

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Let Wt % EO = E and rewrite:

$$P = RT\left[\frac{10^{-3}}{44} + \frac{10^{-3}}{M}\left(\frac{100 - E}{E}\right)\right]\left(\frac{mg}{1}\right)_{EO}$$

Then rewrite:

$$P = 10^{-3}\,RT\left[\frac{1}{44} + \frac{(100 - E)}{(M)(E)}\right]\left(\frac{mg}{1}\right)_{EO} = 10^{-3}\,RT\left[\frac{(M)(E) - 44(100 - E)}{44(M)(E)}\right]\left(\frac{mg}{1}\right)_{EO}$$

Then,

$$\left(\frac{mg}{l}\right)_{EO} = \frac{10^{3}P}{RT}\left[\frac{44(M)(E)}{(M)(E) + 44(100 - E)}\right]$$

7 Calculations for use of flammability curve

7.1 Calculation of the flammability curve depends on the following assumptions:

a) Water vapor, like nitrogen, is inert. It does not enhance the combustion of ethylene oxide.

b) The goal is to operate the sterilizer at all times in the nonflammable zone.

c) The constituent gases are well mixed and behave as ideal gases.

d) The flammability chart with data obtained at the highest anticipated chamber pressure is used (i.e., usually this is the exposure pressure. If the chamber is likely to be operated at 1 atm, then the 1 atm chart is used).

CAUTION—These calculations are based on an empty chamber and do not take into account EO retained by the load or additional EO added after initial pressure is attained.

7.2 Add the partial pressure of all components present to obtain a total pressure. All pressures shall be in the same units (e.g., inHgA, PSIA, etc.). The equation is

$$P_{total} = P_{water} + P_{nitrogen} + P_{air} + P_{EO} \qquad [9]$$

7.3 Calculate the percent of each component by dividing the partial pressure of that component by the total pressure, then multiplying by 100. The next example is for percent air.

$$\%\,air = \frac{P_{air}}{P_{total}} \times 100$$

7.4 As stated in the assumptions, all components other than air and EO are inert diluents. Add these percents together to obtain the total percent inert diluent.

7.5 Determine if sterilization cycle steps may be in the flammable zone by plotting the percents on the flammability triangle for each phase. Reference: *Ethylene Oxide*, Union Carbide Corporation, 1993.

7.6 If vacuums are drawn, the volume percentage of the components does not change (there is no selective removal of any component). However, the partial pressures do change in direct proportion to the pressure changes. Thus, the partial pressures for each component shall be adjusted by the following method:

$$P_{\text{new}} = P_{\text{old}} \times \frac{P_{\text{vacuum}}}{P_{\text{original}}} \qquad [10]$$

7.7 When a new component is added, add the increased partial pressure to the partial pressure calculated in section 7.6.

7.8 Go to section 7.1 to perform the sequence of calculations for the new mixture.

7.9 An example follows:

a) Desired exposure conditions are as follows:

   1) soft cycle (shallow vacuum);
   2) EO concentration is 500 mg/l (9.16 inHgA);
   3) RH is 50% (2.60 inHgA);
   4) temperature is 135° F;
   5) start pressure is 1 atm (29.92 inHgA).

b) Following the steps outlined above (7.1 to 7.7), the partial pressures and volume percents for air, nitrogen, and steam (which are inert) and EO have been calculated for each phase of the cycle.

   1) Pre-evacuation to 13.4 inHgA. After pre-evacuation #1 the chamber still contains 100% air by volume. However, the partial pressure is reduced.
   2) Nitrogen flush #1: Add nitrogen from 13.4 to 29.9 inHgA. The partial pressure of air is still 13.4 inHgA, while the partial pressure of nitrogen is 16.5 inHgA. Therefore the volume percentage is calculated by dividing the individual partial pressure by the total pressure. For example, the partial pressure of nitrogen and steam is 16.5. The total pressure is 29.9. The volume percentage for nitrogen and steam is (16.5/29.9) x 100 = 55.2%.
   3) For each phase of the cycle prior to EO injection, continue to calculate the partial pressures and volume percentages accordingly.

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Table 3—Flammability review, partial pressures, and volume percentage

Flammability Review		**Partial Pressures**			**Volume %**			
Cycle Steps	inHgA	P_{air}	$P_{N2+Steam}$	P_{EO}	V_{air}	$V_{N2+Steam}$	V_{EO}	Total
Pre-evacuation #1	13.4	13.40	0.0	0.0	100	0%	0%	100%
Nitrogen Flush #1	29.9	13.40	16.50	0.0	44.82	55.18	0%	100%
Pre-evacuation #2	13.4	6.01	7.39	0.0	44.82	55.18	0%	100%
Nitrogen Flush #2	29.9	6.01	23.89	0.0	20.08	79.92	0%	100%
Pre-evacuation #3	13.4	2.69	10.71	0.0	20.08	79.92	0%	100%
Steam Injection	16.1	2.69	13.41	0.0	16.72	83.28	0%	100%
EO Injection	25.3	2.69	13.41	9.20	10.64	53.00	36.36	100%
Post-evacuation #1	13.4	1.43	7.10	4.87	10.64	53.00	36.36	100%
Nitrogen Flush #1	29.9	1.43	23.60	4.87	4.77	78.94	16.30	100%
Post-evacuation #2	13.4	0.64	10.58	2.18	4.77	78.94	16.30	100%
Nitrogen Flush #2	29.9	0.64	27.08	2.18	2.14	90.56	7.30	100%
Post-evacuation #3	13.4	0.29	12.14	.98	2.14	90.56	7.30	100%
Nitrogen Flush #3	29.9	0.29	28.64	.98	.96	95.77	3.27	100%
Post-evacuation #4	13.4	0.13	12.83	0.44	.96	95.77	3.27	100%
Air Inbleed #1*	29.9	16.63	12.83	0.44	55.61	42.92	1.47	100%
Post-evacuation #1	13.4	7.45	5.75	0.20	55.61	42.92	1.47	100%
Air Inbleed #2	29.9	23.95	5.75	0.20	80.11	19.24	0.66	100%

- In this cycle, after the first air inbleed, the chamber contains a nonflammable amount of ethylene oxide (1.47%). However, the amount of nitrogen is high enough to cause worker protection concerns. The chamber should not be opened until the second air inbleed has been completed. A useful tool is to add to the end of the cycle a phase during which the chamber rear exhaust is activated while through another port fresh air is allowed to enter the chamber, thus flushing the headspace prior to employee entry.

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Annex A

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