Annex C
(informative)

Temperature sensors, RH sensors and biological indicator numbers

C.1 Temperature sensors

It is recommended to use one sensor per 2,5 m^3 during OQ to establish a thermal map of the room or chamber that captures potential hot or cold locations. Therefore, monitoring should include more than one plane and locations near doors.

For PQ, one temperature sensor is required per cubic metre of product volume. The minimum number of temperature sensors is three. For PQ, humidity sensors should be placed within the packaging (where possible) within the load. This can be achieved by placing the sensor within the sterile barrier system or amongst the unit packages.

The result of the calculation should be rounded to the next higher number.

Table C.1 provides guidance for determining the number of temperature sensors.

Table C.1 — Minimum recommended number of temperature sensors

Volume m^3	**Number for OQ** (usable chamber/room volume)			**Number for PQ** (product load volume)		
	Preconditioning	**Conditioning/ sterilization**	**Aeration**	**Preconditioning**	**Conditioning/ sterilization**	**Aeration**
≤ 1	3			3		
10	4			10		
15	6			15		
20	8			20		
25	10			25		
30	12			30		
35	14			35		
40	16			40		
50	20			50		
100	40			100		

EXAMPLE During OQ of a preconditioning room with a usable chamber volume of 70 m^3: 70/2,5 = 28.

EXAMPLE During PQ with a product load volume of 2 m^3: 2/1 = 2. The number of sensors to use is at least three (the minimum number of sensors to use).

C.2 Humidity sensors

The recommendation is to use one sensor per 2,5 m^3 to establish a humidity map of the area or product that captures potential variability in the humidity levels. The minimum number of sensors is two.

The result of the calculation should be rounded to the next higher number.

For PQ, humidity sensors should be placed within the packaging (where possible) within the load. This can be achieved by placing the sensor within the sterile barrier system or amongst the unit packages.

Table C.2 provides guidance for determining the number of humidity sensors.

Table C.2 — Minimum recommended number of humidity sensors

Volume m^3	Number for OQ (usable chamber/room volume)			Number for PQ (product load volume)		
	Preconditioning	Conditioning/ sterilization	Aeration	Preconditioning	Conditioning/ sterilization	Aeration
≤ 1	2			2		
10	4			4		
15	6			6		
20	8			8		
25	10		N/A	10		N/A
30	12			12		
35	14			14		
40	16			16		
50	20			20		
100	40			40		

EXAMPLE 1 During OQ for a usable chamber volume of 6 m^3: 6/2,5 = 2,4. The number of sensors to use is at least three.

EXAMPLE 2 During PQ for a product volume of 60 m^3: 60/2,5 = 24. The number of sensors to use is at least 24.

C.3 Biological Indicators

The minimum recommended number of BI/PCDs to use is as follows:

a) For MPQ with a product load volume of up to 10 m^3, use three BIs per m^3 of product volume, with a minimum of five BIs.

b) For MPQ with a product load volume above 10 m^3, use one additional BI per additional m^3 beyond 10m^3.

If BIs are used for routine control use half the number of BIs used during MPQ up to a maximum of 30.

The result of the calculation should be rounded to the next higher number.

Table C.3 provides guidance for determining the number of BI/PCDs.

The actual number of BI/PCDs to be used will depend on:

a) microbiological qualification method chosen (see Annex A or Annex B);

b) product volume;

c) type of chamber (developmental vs. production).

When using the Stumbo-Murphy-Cochran procedure and the Overkill Cycle Calculation approach the recommended number of BI/PCDs can be based on the product volume to be sterilized. When this approach is being used a minimum quantity of 10 BI/PCD's are indicated, see Reference [38].

Table C.3 — Examples of minimum recommended number of BI/PCDs

Product load volume m^3	**MPQ**	**Routine control** (if used)
≤ 1	5	3
10	30	15
15	35	18
20	40	20
25	45	23
30	50	25
35	55	28
40	60	30
50	70	30
100	120	30

EXAMPLE 1 For product load volume of 3 m^3: 3 × 3 = 9. The number of BIs to use is at least nine for MPQ. For routine control: 9/2 = 4,5. The number of BIs is at least five.

EXAMPLE 2 For a product load volume of 18 m^3: 10 × 3 + (18 − 10) × 1 = 38. The number of BIs to use is at least 38 for MPQ. For routine control: 38/2 = 19. The number of BIs is at least 19.

Annex D
(informative)

Guidance on the application of the normative requirements

The guidance given in this annex is not intended as a checklist for assessing compliance with this International Standard. This guidance is intended to assist in obtaining a uniform understanding and implementation of this International Standard by providing explanations and acceptable methods for achieving compliance with specified requirements. Methods other than those given in the guidance can be used, providing their performance achieves compliance with this International Standard

NOTE For ease of reference, the numbering of clauses in this annex corresponds to that in the normative parts of this International Standard.

D.1 Scope

No guidance offered.

D.2 Normative references

The requirements given in documents that are included as normative references are requirements of this International Standard only to the extent that they are cited in normative parts of this International Standard; the citation can be to a whole standard or limited to specific clauses in which case the referenced standard should be dated.

D.3 Terms and definitions

No guidance offered.

D.4 Quality management systems

NOTE As the scope of ISO 13485 focuses on manufacturers of medical devices, health care facilities can use other quality management standards applicable to their organization.

D.4.1 Documentation

Refer to ISO 13485.

D.4.2 Management responsibility

D.4.2.1 Requirements for responsibility and authority are specified in ISO 13485:2003, 5.5, and requirements for human resources are specified in ISO 13485:2003, 6.2.

In ISO 13485, the requirements for management responsibility relate to management commitment, customer focus, quality policy, planning, responsibility, authority and communication, and management review.

Each organization should establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities.

D.4.2.2 The development, validation and routine control of a sterilization process can involve a number of separate parties, each of whom is responsible for certain elements. It is important that the respective

procedures clearly outline the responsibilities for meeting the requirements of this International Standard. This is especially important where contractors are engaged to carry out specific functions.

Even where elements of the sterilization process are contracted out it is important to note that the medical device manufacturer is ultimately responsible for validation, release and distribution of sterilized product to the market. When a health care facility contracts out the sterilization of reusable medical devices, it is the health care facility's responsibility for validation and release of the sterilized product

Further guidance is available in ISO 14937:2009, E.4.2.2.

D.4.3 Product realization

NOTE In ISO 13485, the requirements for product realization relate to the product lifecycle from the determination of customer requirements, design and development, purchasing, control of production, and calibration of monitoring and measuring devices.

D.4.3.1 Requirements for purchasing are specified in ISO 13485:2003, 7.4. In particular, it should be noted that the requirements in ISO 13485:2003, 7.4 for verification of purchased product apply to product and services, that impact on process quality, received from outside the organization.

Purchasing procedures in a health care facility should ensure that reusable medical devices are supplied with validated instructions for cleaning, disinfection, sterilization and aeration as specified in ISO 17664. It should also be verified that the prescribed procedure for cleaning, disinfection, sterilization and aeration can be performed in the health care facility.

D.4.3.2 Requirements for identification and traceability are specified in ISO 13485:2003, 7.5.3.

For those facilities that do not fully comply with ISO 13485, such as health care facilities, procedures for identification of product and maintenance of traceability should include the labelling of each item or package prior to sterilization with a lot control identifier that includes the following information:

a) the sterilizer ID or code;

b) the date of sterilization;

c) the cycle number (i.e. the cycle run of the day or sterilizer);

d) the identity of the person who assembled the pack.

Including the identity of the person who assembled the pack allows for further investigation if a problem should arise. Lot identification information enables personnel to retrieve items sterilized in a specific cycle in the event of a recall and to trace problems to their source.

D.4.3.3 Requirements for calibration of monitoring and measuring instrumentation are specified in ISO 13485:2003, 7.6.

D.4.4 Measurement, analysis and improvement — Control of non-conforming product

Procedures for control of non-conforming product and corrective action are specified in ISO 13485:2003, 8.3 and 8.5.2, respectively.

D.5 Sterilizing agent characterization

D.5.1 General

No guidance offered.

D.5.2 Sterilizing agent

EO is a highly penetrative gas that will permeate most packaging materials and polymeric materials. Widely recognized compositions include pure EO and mixtures with carbon dioxide or nitrogen.

NOTE For EO gas mixtures with carbon dioxide, nitrogen or other inert gas blends, EO molecular diffusion rates into polymer materials can be affected by the volume percent of EO gas molecules within the sterilant, which can result in longer EO exposure times to achieve the desired microbiological spore log reduction.

The storage conditions and shelf life for EO should be in accordance with the EO manufacturer's recommendations and all applicable regulations. This is particularly important with premixed gas mixtures where stratification might be an issue.

D.5.3 Microbicidal effectiveness

No guidance offered.

D.5.4 Material effects

No guidance offered.

D.5.5 Safety and the environment

D.5.5.1 EO is toxic, flammable and explosive; therefore, extreme caution should be used during its handling and use. The explosive limits are 2,6 % to 100 % EO by volume in air.

Where practical, EO sterilization cycles should operate within the non-flammable region throughout the complete sterilization cycle in order to minimize the risk of explosion. This requires the removal of air from the chamber prior to the introduction of EO gas. For 100 % EO sterilization processes this can be achieved by pulling a deep vacuum or by pulling several partial vacuums, each of which is followed by injection of an inert gas, e.g. nitrogen. This purges air from the chamber allowing EO gas to be injected into the chamber in a safe manner. On completion of the EO gas exposure phase it is necessary to remove the EO gas from the chamber until the level of gas is below the 2,6 % explosive limit. This is achieved by pulling several post-vacuums, each of which is followed by a nitrogen backfill.

The use of non-flammable sterilant blends can improve safety by decreasing the risk of fire or explosion. They can also facilitate compliance with country-specific equipment safety requirements. Non-flammable blends are produced by mixing the highly flammable EO gas with one or more inert gases. The flammability of such a mixture can be assessed by measuring the relative proportions of EO, air, diluent gas (e.g. CO_2, etc.), inert gas (e.g. nitrogen) and water vapour in the sterilizer. Caution should be exercised to ensure no separation of the EO blend can occur as this might lead to safety and quality issues.

Ethylene oxide sterilizers should be installed in a dedicated room. The operating controls for the sterilization equipment should be mounted outside the room so that operators can set or change program parameters without entering the sterilization room. All airflow from the sterilizer access area should be exhausted to the outdoors and comply with applicable requirements.

Prior to removing product from a sterilizer, precautions should be taken to ensure that operators are not exposed to levels of EO above relevant worker exposure limits [permissible exposure limit (PEL)/ short term exposure limit STEL)] due to the outgassing of the load. When products sterilized with inert EO-gas mixtures are not immediately removed from the sterilizer at the end of a cycle the EO concentrations in the sterilizer might result in personnel safety issues.

D.5.5.2 Principles of an environmental management system can be applied to the EO sterilization process. ISO 14001 provides a specification for an environmental management system. ISO 14040 provides guidance on designing a life cycle assessment study.

D.5.5.3 Effluent gas should be discharged through an EO gas treatment system, such as a catalytic oxidizer, wet acid scrubber or thermal oxidizer in compliance with local permit requirements or emission control legislation.

When choosing a diluent, the ozone depleting potential of the diluent as well as the disposal of any by-products should be taken into consideration.

D.6 Process and equipment characterization

In health care facilities, process and equipment characterization are generally the responsibility of the sterilizer manufacturer. The management of the health care facility should have controls in place to ensure that the equipment it purchases conforms to national, regional and local regulations and is suitable for use to sterilize products that require EO sterilization. The management of the health care facility should ensure that the facility has the infrastructure necessary to correctly operate the sterilizing equipment and to achieve effective sterilization of medical devices.

D.6.1 General

No guidance offered.

D.6.2 Process characterization

D.6.2.1 No guidance offered.

D.6.2.2 The resistance of microorganisms to deactivation by EO is affected by their moisture content. At low levels of humidity, below 30 %, microbial resistance may increase with decreased humidity for some products. For this reason it is common practice to control and monitor the humidity of the atmosphere to which the product is exposed in order to attempt to equilibrate the moisture content of the microorganisms with the local conditions. Consideration should be given to the packaged product to ensure that excessive relative humidity will not impact the product functionality and package integrity. One of the ways to assist in addressing the humidity in the product is to precondition product at a defined temperature and humidity. Such preconditioning can reduce the duration of the sterilization cycle. For health care facilities, excessive moisture content can also be caused by inadequate drying after cleaning.

Product heating and humidification are used to establish reproducible product temperature and moisture content prior to EO exposure. Studies establishing minimum residence time in preconditioning cells/rooms ensure that the required conditions are attained in the sterilization load. Precautions should be taken to prevent excessive water condensation on the sterilization load.

Although it is common practice to perform preconditioning in a separate chamber, room or cell, sterilization cycles can be designed to attain the required temperature and humidity ranges within the load during a conditioning phase in the sterilization chamber. To minimize the risk of excessive condensation, it is recommended that the load temperature should be maintained above the process environmental dewpoint temperature during the preconditioning and conditioning phases of the sterilization process.

The actual temperature and humidity ranges within the sterilization load at the end of preconditioning should be demonstrated during PQ.

Where applicable, a maximum time between removal of the load from preconditioning and the start of the sterilization cycle needs to be established. A transfer time of 60 min or less is common practice.

a) When product enters the sterilization chamber without preconditioning, consideration should be given to the possibility of excessive condensation in product and packaging.

b) Residues of EO and its reaction products can be hazardous. It is essential for the manufacturer of the product to be sterilized to be aware of the possible occurrence of residues in the product. Temperature, dwell time, forced heated air circulation, load characteristics, product and packaging

materials all affect the efficiency of aeration, and the set points and tolerances should be taken into account when evaluating residual levels as outlined in ISO 10993-7. Aeration can be performed within the sterilizer, in a separate area(s), or in a combination of both. For health care facilities it is usual to perform aeration in a chamber rather than in a room due to the hazards of exposure to EO. In health care facilities, reprocessed items sterilized with EO need to be thoroughly aerated prior to handling or use, according to the medical device and the rigid sterilizer container manufacturer's recommendations. Inadequately aerated items and packaging will release EO, which can injure patients and health care facility personnel.

D.6.2.3 Transfer time refers to each transfer step during preconditioning and final transfer of product into the sterilizer to the start of cycle.

D.6.2.4 The following is a list of phases that can be included in a sterilization cycle along with the performance factors that might be considered for each phase:

a) air removal:

   1) depth (ΔP or terminal pressure) and rate (ΔP/time) of attainment of vacuum;

b) chamber leak test (performed either under vacuum for subatmospheric cycles or under vacuum and at pressure for superatmospheric cycles), if applicable:

   1) stabilization period and/or hold time;

   2) pressure change;

c) inert gas addition (if used);

   1) pressure (ΔP or terminal pressure) and rate (ΔP/time) of attainment of pressure on admission of the inert gas.

d) conditioning (if used);

   1) during the conditioning phase, pressure rise (ΔP or terminal pressure) or % relative humidity and rate (ΔP/time) of attainment of pressure on injection of steam;

   2) number of steam pulse/vacuum stages, if applicable;

e) EO injection:

   1) pressure, pressure rise (ΔP) and rate (ΔP/time) of attainment of specified pressure on admission of EO and correlation of methods used to monitor EO concentration;

   2) pressure, pressure rise (ΔP) and rate (ΔP/time) of attainment of specified pressure on admission of any inert gasses (if used);

f) maintenance of specified conditions for the exposure time:

   1) pressure differential used to apply sterilant or inert gas make-ups (if used);

   2) chamber temperature;

g) EO removal:

   1) depth (ΔP or terminal pressure) and rate (ΔP/time) of attainment of vacuum to remove EO;

h) flushing (if used):

   1) pressure rise and rate of attainment of pressure;

   2) depth (ΔP or terminal pressure) and rate (ΔP/time) of attainment of vacuum to remove EO;

3) number of times of repetition and any variations in successive repetitions;

i) air/inert gas admission:

1) pressure (ΔP or terminal pressure) and rate (ΔP/time) of attainment of pressure on admission of the inert gas or air;

2) number of times of repetition and any variations in successive repetitions;

3) equilibration to atmospheric pressure using air admission.

D.6.2.5 Recirculation velocity should be specified when assessing product residual levels.

D.6.3 Equipment characterization

D.6.3.1 The following factors should be considered when characterizing the equipment:

a) Preconditioning area characterization.

Preconditioning can be performed in a separate preconditioning area (chamber, cell or room). Humidification by steam is necessary because humidifiers that operate by dispersion of unheated water as an aerosol (e.g. spinning disc humidifiers and nebulizers) can be a potential source of microbial contamination.

The preconditioning area (if used) should have the following performance and monitoring capabilities:

— adequate air circulation to ensure the uniformity of temperature and humidity in the usable space, and to ensure that uniformity is maintained in a loaded room or chamber;

— airflow detection equipment, alarm systems or indicators monitoring the circulation system to ensure conformance to predetermined tolerances;

— means of recording time of load entry into and removal from the preconditioning area;

— means of monitoring cell/room temperature and humidity;

— means of controlling cell/room temperature and humidity.

b) Sterilizer characterization.

The sterilization chamber should have the following performance and monitoring capabilities:

— means of monitoring time, chamber pressure, temperature and humidity (if humidity additions are controlled by sensor readings);

— means of controlling time, chamber pressure, temperature and humidity, if humidity additions are controlled by sensor readings (when sensors are fixed on the equipment, ensure that a correlation is made during IQ or OQ to the pressure rise);

— if humidity is not controlled by sensor readings, means to monitor and control steam additions;

— if parametric release is used, analytical instrumentation for the direct analysis of humidity during conditioning and EO concentration during EO exposure time (also see 9.5.5 and D.9.5.5);

— a system controlling the admission of gaseous EO to the chamber;

— means to demonstrate that gaseous EO is injected into the chamber. This can be done by measuring the temperature of the EO gas flowing from the vaporizer to the sterilizer chamber. This system can control EO concentration during EO exposure time.

— means to detect and alert deviations to cycle parameters so that remedial action can be taken in a timely fashion.

c) Aeration area characterization.

An aeration area (chamber, cell or room) can be used to remove EO residuals from product/packaging. Temperature uniformity, fresh air make-up and air re-circulation throughout the area are important to ensure consistent and reproducible results. The aeration area should have the following performance and monitoring capabilities:

— airflow detection equipment, alarm systems or indicators monitoring the air handling system to ensure that it operates within predetermined tolerances and maintains adequate airflow in a loaded room or chamber;

— equipment to re-circulate air;

— means of monitoring room temperature;

— means of controlling room temperature.

D.6.3.2 The equipment specification should be reviewed to ensure that regulatory and safety requirements are met, technical specifications are appropriate, and services and infrastructure necessary to operate the equipment are available.

The following items should be considered when preparing the equipment specification:

a) If the EO supply to the sterilizer is from a bulk storage tank that is periodically replenished, then the tank should be equipped with a means of removing samples for analysis, a means of emptying the tank of EO and a provision for cleaning in the event of contamination or excessive accumulation of polymers.

b) The system for admission of EO to the sterilizer should be equipped with a vaporizer to prevent liquid EO from being admitted to the sterilizer chamber.

c) The temperature of the EO gas flowing from the vaporizer to the sterilizer chamber should be measured to demonstrate that gaseous EO has been produced.

d) Steam is utilized to humidify the load and is not intended to be a sterilant. The consistency of steam supply can be determined by the periodic analysis of the boiler feed water or condensate.

e) A minimum of two probes to measure chamber temperature should be used. Large volume chambers can be fitted with more than two probes so as to ensure that the monitoring/control system captures data that reflects the temperature throughout the chamber during use.

NOTE The purpose of two separate probes is to prevent the failure of one sensor from causing an out-of-specification process from being erroneously accepted. Comparing two separate temperature sensors will detect that one of the sensors has failed. A dual element temperature probe can be used to meet this need.

f) It is important to maintain uniform conditions within the sterilizer chamber during processing. This can be achieved by forced gas circulation. If used, a gas circulation system should be equipped with a monitoring device to indicate when circulation is ineffective as devices that solely monitor "power on" to the fan or pump are not sufficient.

g) Areas used for storage of cylinders, tanks or cartridges of EO or EO gas mixtures should be secured and ventilated.

h) Where ambient conditions are subject to temperature variation greater than the range recommended by the supplier, storage areas for the containers of EO should include provision for temperature control.

It might not be possible to calibrate controlling and monitoring instruments under actual processing conditions, e.g. humidity sensors. Calibration results for these instruments should be correlated against qualification studies. Processing conditions can have a detrimental effect on some types of sensors, e.g. humidity sensors. Sensors might require replacement after repeated exposure to processing conditions due to irreversible deterioration of materials currently used as sensing elements. It might be necessary

to implement a program of more frequent maintenance for these sensors than that recommended by the sensor manufacturer/supplier.

D.6.3.3 No guidance offered.

D.6.3.4 No guidance offered.

D.6.3.5 If there is an undetected failure of a control or monitoring function, a sterilization load could be released without having met its required processing parameters. To prevent this from happening, it is general practice to have redundant sensors for many critical process parameters. The common options for utilizing these redundant sensors include:

a) use one sensor for control, and another sensor for monitoring and reporting;

b) use two sensors, or their average value, for both monitoring and control; this system needs to generate an automatic fault condition if the difference between the two sensors exceeds a defined value;

c) use dual element sensors for both monitoring and control; this system needs to generate an automatic fault condition if the difference between the two elements exceeds a defined value.

D.7 Product definition

D.7.1 General

D.7.1.1 Product definition involves documentation of essential information about the medical device to be sterilized (i.e. the new or modified product).

Product definition for a medical device includes the medical device itself, the sterile barrier system containing the device, and any accessories, instructions, or other items included in the packaging system. It also includes a description of the intended functionality of the medical device, and the available manufacturing and sterilization processes. The product definition process should also consider whether this is a new design, or whether it is part of an existing product family.

The following should be considered as part of product definition:

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

b) intended use of the medical device;

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

d) design characteristics that would affect the choice of sterilization process (e.g. batteries, fibre-optics, computer chips);

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

f) required sterility assurance level (SAL);

g) packaging;

h) loading configuration; requirements for a specific load or mixed loading configurations, or range of acceptable loading configurations;

i) compatibility with EO or gas mixture and processing conditions (preconditioning, sterilization and aeration processes).