EO (環氧乙烷)滅菌標準(ISO11135:2014)

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2021/11/23

AGENDA

- EO (環氧乙烷)滅菌標準(ISO11135)解說
  EO滅菌確效規劃執行與例行管控

INTERNATIONAL ISO STANDARD 11135 Second edition 2014-07-15

- Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices

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Scope

- . This International Standard specifies requirements for the development, validation, and routine control of an ethylene oxide sterilization process for medical devices in both the industrial and health care facility settings, and it acknowledges the similarities and differences between the two applications

2 Normative references

- ISO 10012, *Measurement management systems — Requirements for measurement processes and measuring equipment*
- ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*
  ISO 11138-1:2006, *Sterilization of health care products — Biological indicators — Part 1: General requirements*

2 Normative references

- ISO 11138-2:2009, *Sterilization of health care products — Biological indicators — Part 2: Biological indicators for ethylene oxide sterilization processes*
- ISO 11140-1, *Sterilization of health care products — Chemical indicators — Part 1: General requirements*

2 Normative references

- ISO 11737-1, *Sterilization of medical devices — Microbiological methods — Part 1: Determination of a population of microorganisms on products*
- ISO 11737-2, *Sterilization of medical devices — Microbiological methods — Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process*
- ISO 13485:2003/Cor 1:2009, *Medical devices — Quality management systems — Requirements for regulatory purposes — Technical Corrigendum 1*

Terms and definitions

- bioburden
- population of viable microorganisms on or in product and/or sterile barrier system

chemical indicator

- test system that reveals a change in one or more pre-defined process variables based on a chemical or physical change resulting from exposure to a process

sterile

- free from viable microorganisms

sterile barrier system

- minimum package that prevents ingress of microorganisms and allows aseptic presentation of the product at the point of use

sterility

- state of being free from viable microorganisms

biological indicator

- test system containing viable microorganisms providing a defined resistance to a specified sterilization process

sterility assurance level, SAL

- probability of a single viable microorganism occurring on an item after sterilization
- NOTE 1 to entry: The term SAL takes a quantitative value, generally 10^{-6} or 10^{-3}. When applying this quantitative value to assurance of sterility, an SAL of 10^{-6} has a lower value but provides a greater assurance of sterility than an SAL of 10^{-3}.

Quality management systems 品質管理系統

- Documentation
-
  - 4.1.1 Procedures for development, validation, routine control, and product release from sterilization shall be specified.

- 4.1.2 Documents and records required by this International Standard shall be reviewed and approved by designated personnel (see 4.2.1). Documents and records shall be controlled in accordance with the applicable clauses of ISO 13485.

Management responsibility

- 4.2.1 The responsibility and authority for implementing and meeting the requirements described in this International Standard shall be specified. Responsibility shall be assigned to competent personnel in accordance with the applicable clauses of ISO 13485.

- 4.2.2 If the requirements of this international standard are undertaken by organizations with separate quality management systems, the responsibilities and authority of each party shall be specified.

Product realization

- 4.3.1Procedures for purchasing shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.
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- 4.3.2Procedures for identification and traceability of product shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.
- 4.3.3 A system complying with the applicable clause(s) of ISO 13485 or ISO 10012 shall be specified for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this International Standard.
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Measurement, analysis and improvement — Control of nonconforming product

- Procedures for control of product designated as nonconforming and for correction, corrective action, and preventive action shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.

Sterilizing agent characterization

- General
- The purpose of this activity is to define the sterilizing agent, demonstrate its microbicidal effectiveness, identify the factors that influence microbicidal effectiveness, assess the effects that exposure to the sterilizing agent has on materials, and identify requirements for safety of personnel and protection of the environment. This activity may be undertaken in a test or prototype system. Where this occurs, the final equipment specification (see 6.3) shall be relatable to the results of experimental studies undertaken in the test or prototype equipment. For the purposes of this International Standard, the sterilizing agent is EO.

Sterilizing agent

- The sterilizing agent specification shall include, if appropriate, conditions of storage to maintain the EO within its specification for the duration of the stated shelf life.

Microbicidal effectiveness

- Microbicidal effectiveness data shall be developed if it is proposed to use the EO outside of the range of compositions that are widely recognized or if a novel diluent is to be used.

Material effects

- The effects of EO on a wide variety of materials used to manufacture medical devices have been comprehensively documented, and such documentation is of value to those designing and developing medical devices that are to be sterilized by EO. This International Standard does not require the performance of specific studies on material effects but does require performance of studies of the effects of EO on product (see Clause 7).

Safety and the environment

- 5.5.1 Either a material safety data sheet (MSDS) or analogous safety information shall be made available for EO and its diluents (if any). Measures necessary to protect the health and safety of personnel shall be identified.

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

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

Process and equipment characterization

- 6.6.1The purpose of this activity is to define the entire sterilization process and the equipment necessary to deliver the sterilization process safely and reproducibly.

Process characterization

Process characterization, at a minimum, shall include:

- identifying the phases that are necessary for an EO sterilization process;
- identifying the process variables for each phase; and
- documenting the process variables.

- The phases of the sterilization process include:

- preconditioning (if used);
- the sterilization cycle; and
- aeration (if used).

7. Product definition

- 7.1.1The purpose of this activity is to define the product to be sterilized, including the microbiological quality of the product prior to sterilization and the manner in which product is packaged and presented for sterilization.

- 7.1.2 Product definition shall be performed prior to the introduction of a new or modified product, package or loading configuration. A demonstration of equivalence (with reference to the challenge to the sterilization process) to a previously validated product, package, or loading configuration shall be considered to meet the requirement to perform product definition. Any demonstration of equivalence shall be documented.

- 7.1.3 Product shall be designed to allow removal of air, if applicable, and penetration of heat, humidity, and EO during the sterilization process, and removal of EO at the end of the process.

- 7.1.4 Packaging shall be designed to allow removal of air and penetration of heat, humidity, and EO during the sterilization process, and removal of EO at the end of the process.

- 7.1.5 The load configuration shall be designed to allow removal of air and penetration of heat, humidity, and EO during the sterilization process, and removal of EO at the end of the process.

- 7.1.6 It shall be demonstrated that the specified sterilization process is effective in sterilizing the most difficult-to- sterilize location within the product. This can be achieved by performing process definition and validation of a new product; or through the demonstration of equivalence to a previously validated product or internal process challenge device (internal PCD) used to qualify the product SAL when exposed to the specified sterilization process (See 8.6 and D.8.6).

7.2 Product safety, quality and performance

- 7.2.1 It shall be confirmed that the product and its packaging meet specified requirements for safety, quality, and performance following the application of the defined sterilization process, using the process parameter tolerances that have been determined to have the greatest impact on the product/package.

- 7.2.2 If multiple sterilization cycles are permitted, the effects of such processing on the product and its packaging shall be evaluated.

- 7.2.3The biological safety of product following exposure to the sterilization process shall be established in accordance with the applicable parts of the ISO 10993 series.

- 7.2.4 Means shall be established to reduce EO residual levels such that the processed products comply with the requirements of ISO 10993-7.

7.3 Microbiological quality

- 7.3.1 A system shall be specified and maintained to ensure that the microbiological quality and cleanliness of the product presented for sterilization are controlled and do not compromise the effectiveness of the sterilization process.

- 7.3.2 For single use medical devices, an estimation of bioburden at a defined interval shall be performed in accordance with ISO 11737-1. For reusable medical devices, an assessment of the effectiveness of the specified cleaning process and, if applicable, disinfecting process, shall be performed.

7.4 Documentation

- The results of product definition shall be documented by the manufacturer of the device.

8 Process definition

- 8.1 The purpose of this activity is to obtain a process specification that can be applied for the sterilization of the defined product (see Clause 7) during the validation studies.

- 8.2 The sterilization process applicable for the defined product shall be established. The defined product includes new or modified product, packaging, or loading configurations.

- 8.3 Process definition activities shall be performed in a sterilization chamber (developmental chamber or production chamber) that has undergone Installation Qualification (IQ) and Operational Qualification (OQ) procedures (see 9.2 and 9.3).

- 8.4 Documentation and records shall support the validity of process parameters and associated process variables as defined in the process characterization (see 6.2)

- 8.5 The rate of microbiological inactivation provided by the specified sterilization cycle for a specific microbiological challenge shall be determined, using one of the methods described in Annexes A or B or by an alternative method that demonstrates the product has achieved the required sterility assurance level (SAL).

8.6 Biological indicators (BIs) used as part of the establishment of the sterilization process shall

- comply with ISO 11138-2:2006, Clause 5 and 9.5;
- be shown to be at least as resistant to EO as is the bioburden of product to be sterilized; and
- be placed within an appropriate PCD.

- The appropriateness of the PCD used for process definition, validation, or routine monitoring and control shall be determined. The PCD shall present a challenge to the sterilization process that is equivalent or greater than the challenge presented by the natural bioburden at the most difficult to sterilize location within the product.

- 8.7 Commercially supplied biological indicators used in the definition of the sterilization process shall comply with the requirements in 8.6 and all applicable clauses of ISO 11138-1.

- 8.8 If chemical indicators are used as part of the definition of the sterilization process, these shall comply with ISO 11140-1.

- 8.9 If tests of sterility are performed during the definition of the sterilization process, they shall comply with ISO 11737-2.

9 Validation

9.1 General

9. Validation

- 9.1.1 The purpose of validation is to demonstrate that the sterilization process established in the process definition (see Clause 8) can be delivered effectively and reproducibly to the product within the sterilization load. Validation consists of a number of identified stages: installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). Testing shall not commence until the procedures and/or protocols have been approved.

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- Protocol Study
  - Refer to the Protocol

- 9.1.2 IQ is undertaken to demonstrate that the sterilization equipment and any ancillary items have been supplied and installed in accordance with their specification.

- 9.1.3 OQ is undertaken to demonstrate the ability of the equipment to meet the performance requirements of its design specification.

- 9.1.4 PQ is the stage of validation that uses product to demonstrate that the equipment consistently operates in accordance with predetermined acceptance criteria and the process yields product that is sterile and meets the specified requirements.
- IQ and OQ may be a one-time exercise for the specific equipment being employed for a sterilization process. PQ should be carried out for each new process and/or product to be validated to demonstrate that the process complies with identified acceptance criteria and is capable of delivering the required SAL to the product.

9.2 Installation qualification, IQ

- 9.2.1 Equipment
- 9.2.1.1 Equipment to be used in the sterilization process, including any ancillary items, shall comply with its design specifications.
- 9.2.1.2 Sterilization equipment shall comply with the applicable safety standards.

- 9.2.1.3 The operating procedures for the equipment shall be specified. These operating procedures
- shall include, but are not limited to
- a) step-by-step operating instructions,
- b) fault conditions, the manner in which they are indicated, and actions to be taken,
- c) instructions for maintenance and calibration, and
- d) details of contacts for technical support.

9.2.2 Installation qualification

- 9.2.2.1 Installation of the equipment and all associated services shall be in accordance with the architectural and engineering drawings. The installation shall comply with all pertinent national, regional and local regulations.
- 9.2.2.2 Instructions for installation shall be specified and shall include instructions pertinent to the health and safety of personnel.
- 9.2.2.3 Conditions for the safe storage of EO shall be specified to ensure that its quality and composition remain within specification.

- 9.2.2.4 Prior to IQ, the calibration status of any test instrumentation used during the IQ shall be confirmed.
- 9.2.2.5 Drawings of the equipment as installed, plumbing and other ancillary equipment shall be finalized during IQ.
- 9.2.2.6 Changes made to systems during the IQ shall be assessed for their impact on the design and process specification and documented in the design history file.

9.3 Operational qualification, OQ

- 9.3.1 Prior to OQ, the calibration of all instrumentation (including any test instruments) used for monitoring, controlling, indicating or recording of the sterilization process shall be confirmed (see 4.3.3).
- 9.3.2 OQ shall demonstrate that the installed equipment is capable of meeting its operating specification.

9.4 Performance qualification, PQ

- 9.4.1
- OQ shall demonstrate that the installed equipment is capable of meeting its operating specification.
- Performance qualification, PQ General
- 9.4.1.1 PQ consists of both microbiological and physical performance qualification and is performed in the equipment used to sterilize the product.

- 9.4.1.2 PQ shall be performed on the introduction of new or modified products, packaging, load configuration, equipment or process parameters, unless equivalence to a previously validated product, packaging, load configuration, equipment or process has been documented. (See 7.1.2, 7.1.6 and 12.5.)
- 9.4.1.3 PQ shall use product, or material representative of that to be sterilized routinely, to demonstrate that the equipment consistently operates in accordance with acceptance criteria and that the process produces product that meets the intended SAL.

- 9.4.1.4 The manner of presenting product for sterilization, including the load configuration of a product, shall be specified.
- NOTE If saleable product has been used during validation, 7.2 provides information concerning the product quality for patient use and 11.4 provides information concerning the requirements for the release of sterile product.
- 9.4.1.5 The load used for PQ shall be representative of that to be sterilized routinely and shall be defined based upon the most challenging routine load.

- 9.4.1.6 For establishments that have widely varying load configurations, the extent to which the variation affects the sterilization process shall be evaluated. It shall be demonstrated that all product exposed to a sterilization process achieves the required SAL.
- 9.4.1.7 If material other than product is used, it shall present at least as great a challenge to the sterilization process as the product.

- 9.4.1.8 If loads are reused for the validation cycles, they shall be aerated between exposures to meet the regulations for worker safety and to ensure that EO residues in the load do not affect the biological challenge in the next microbiological PQ study.
- 9.4.1.9 If chemical indicators are used as part of PQ, these shall comply with ISO 11140-1, and shall be used in conjunction with microbiological and physical monitoring.

- 9.4.1.10 Biological indicators used in PQ shall comply with the applicable clauses of ISO 11138-1:2006 and ISO 11138-2:2009, Clause 5 and 9.5.

9.4.2 Performance qualification — Microbiological

- 9.4.2.1 The microbiological PQ (MPQ) shall demonstrate that, on application of the sterilization process, the specified requirements for sterility are met. Studies shall be performed in the production chamber using defined process parameters selected to deliver less lethality than the specified sterilization process.
- 9.4.2.2 MPQ shall confirm the effectiveness of the defined process for the product/load combination in a production chamber.

- 9.4.2.3 The lethality of the cycle shall be determined using one of the methods described in Annex A or Annex B or by an alternative method that demonstrates achievement of the required product SAL.
- 9.4.2.4 If process definition was determined in a developmental chamber, the MPQ shall include at least three fractional or three half cycles in the production chamber that confirm the data from the developmental chamber.

- 9.4.2.5 If the overkill half cycle approach [see B.1.2 a)] is used, then there shall be no positive internal PCDs from the half cycle runs.
- Positive external PCDs during the half cycle are acceptable if they have demonstrated greater resistance than the internal PCDs providing a “worst-case challenge” for routine processing. However, all internal PCDs should test negative.

- 9.4.2.6 If the overkill cycle calculation approach [see B.1.2 b)] or the BI/bioburden approach (see Annex A) is used, there may be some surviving internal PCDs, but the calculated SAL shall meet the specified value (See ISO 14161).

9.4.3 Performance qualification — Physical

- 9.4.3.1 Physical PQ (PPQ) shall demonstrate
- a) that the specified acceptance criteria are met throughout the load for the duration of the proposed routine process specification, and
- b) reproducibility of the process.

- The PPQ shall include a minimum of three planned qualification cycles, consecutive in the same study, in which all the specified acceptance criteria are met. PPQ may be conducted during the MPQ. If PPQ is performed in parallel with at least three MPQ runs, then a minimum of one additional PPQ run shall be performed using the full routine process specification.
- If a failure can be attributed to factors not relevant to the effectiveness of the process being validated, this may be documented as unrelated to the performance of the process without requiring three further consecutive successful runs. Examples of this type of failure may include, but are not limited to, power failures, other loss of services, or failure of external monitoring equipment.

- 9.4.3.2 PPQ shall confirm the process such that:
- a) the minimum temperature of product to enter the sterilization process and/or the defined conditions required to achieve it shall be established;
- b) at the end of the defined preconditioning time (if used), the sterilization load temperature and humidity have been established;
- c) the specified maximum elapsed time between the completion of preconditioning (if used) and the commencement of the sterilization cycle is appropriate;

- d) at the end of the defined conditioning time, if used, the sterilization load temperature and humidity have been established;
- e) the chamber humidity was recorded if parametric release was to be used;
- f) gaseous EO has been admitted to the sterilizer chamber;
- g) pressure rise and the quantity of EO used or concentration of EO in the sterilizer chamber have been established [see 9.5.4 f)]. If parametric release is to be used, also see 9.5.5 b);

- h) during the sterilization cycle, the temperature and humidity (if recorded) of the chamber and, where applicable, other process parameters have been established;
- i) the temperature of the product load during exposure has been established;
- j) during aeration (if used), the temperature of the sterilization load has been established.

9.5 Review and approval of validation

- 9.5.1 The purpose of this activity is to undertake and document a review of the validation data to confirm the acceptability against the approved validation procedures/protocol for the sterilization process and to approve the process specification.
- 9.5.2 Information gathered or produced during product definition, process definition, IQ, OQ and PQ, including results from incubation of biological indicators, shall be recorded and reviewed for acceptability. The results of this review shall be recorded.

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

- 9.5.4 The validation report shall describe or reference specific qualified product, defined load configurations and the documented specification for the EO sterilization process and shall address:
- NOTE For practical purposes, rates can be determined as the time taken (with tolerances) to attain a specified pressure change.

- a) the minimum temperature of product to enter the sterilization process and/or the defined conditions required to achieve the minimum required temperature;
- b) preconditioning (if used):
  - 1) time in chamber/area, temperature and humidity of chamber/area;
  - 2) temperature and humidity of the sterilization load;
  - 3) maximum elapsed time between removal of the load from preconditioning and commencement of the sterilization cycle;

- c) vacuum levels and rate of evacuation (if used):
- 1) holding time under vacuum (if used);
- NOTE The rate of evacuation is commonly specified as either a minimum allowed evacuation time, a maximum allowed evacuation time or as an acceptable range of evacuation times, rather than the specific time for each run.

- d) inert gas flushing (if used):
  - 1) pressure (ΔP or terminal pressure) and rate (ΔP/time) of attainment of pressure associated with inert gas/steam;
  - 2) depth (ΔP or terminal pressure) and rate (ΔP/time) of attainment of vacuum;
  - 3) number of times of repetition and any variations in successive repetitions;

- e) conditioning and/or humidity dwell phases (if used):

1) pressure levels and/or rate of attainment of vacuum or relative humidity levels (whichever is being controlled and monitored);

2)number of steam pulses/vacuum (if used);

- 3) time;
- 4) chamber temperature;
- 5) temperature and humidity of the sterilization load at the end of conditioning;

- f) EO injection and exposure:
  - 1) EO injection pressure rise (ΔP), EO injection time and terminal pressure of EO injection phase;
  - 2) evidence that the gaseous EO has been admitted to the sterilization chamber by the pressure rise and by one of the following;
    - i) Mass of EO used (see D.10.2 i);
    - ii) Direct measurement of the concentration of EO;
    - iii) Volume of EO used.

- 3) sterilizer chamber temperature;
- 4) exposure time;
- 5) temperature of the sterilization load;
- 6) an indication of the satisfactory operation of the chamber gas circulation system (if used) during exposure;

- g) post exposure flushing (if used):
  - 1) depth (ΔP or terminal pressure) and rate (ΔP/time) of attainment of vacuum;
  - 2) pressure (ΔP or terminal pressure) and rate (ΔP/time) of attainment of pressure associated with inert gas/air/steam;
  - 3) number of times of repetition and any variations in successive repetitions;

- h) aeration (if used):
  - 1) time and temperature within the chamber and/or room;
  - 2) pressure changes (if any) within the chamber and/or room;
  - 3) rate of change of air or other gas;
  - 4) temperature of the sterilization load.

- 9.5.5 If parametric release is to be used, the validation report shall also specify:
- a) the value and tolerances for chamber humidity by direct measurement during conditioning;
- b) the value and tolerances for the EO concentration determined from direct analysis of chamber atmosphere using analytical methods to establish the process specification for routine processing. The sampling shall be conducted at defined intervals sufficient to verify the required conditions throughout EO exposure.

- c) temperature of the chamber; recorded from two separate monitoring locations.

- 9.5.6 A process specification including the process parameters and their tolerances shall be established for routine processing based upon the documentation generated during the validation. This process specification shall also include the criteria for designating EO processed product as conforming product and approved for release.

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- 10 Routine monitoring and control

- 10.1 The purpose of routine monitoring and control is to demonstrate that the validated and specified sterilization process has been delivered to the product.

- 10.2 Data shall be recorded and retained for each sterilization cycle to demonstrate that the sterilization process specification has been met. These data shall include at least the following:
- NOTE For practical purposes, rates can be determined as the time taken (with tolerances) to attain a specified pressure change.

- a) the minimum temperature of product entering the sterilization process and/or the defined conditions used to acclimate the load;
- b) temperature and humidity within the preconditioning area (if used), monitored and recorded from a specified position;
- c) time of commencement of preconditioning and of removal of load from preconditioning (if used) of each sterilization load;

- d) elapsed time between removal of the sterilization load from preconditioning (if used) and the commencement of the sterilization cycle;
- e) chamber humidity during conditioning and/or humidity dwell phases by pressure, pressure rise (ΔP) and/or direct monitoring;
- f) conditioning time;

- g) indication of the satisfactory operation of the chamber gas circulation system (if used) during EO injection and during exposure;
- h) temperature and pressure in the chamber throughout the sterilization cycle;

- i) If pressure is used as the primary control measure, the requirement for the secondary measure is only to confirm admission of EO to the chamber by at least one of the following:
  - 1) the mass of EO used (see D.10.2 i);
  - 2) the direct measurement of the concentration of EO in the sterilizer chamber;
  - 3) volume of EO used;

- j) EO-injection time
- k) inert gas injection, if used;
- l) exposure time;
- m) time taken to evacuate the chamber;
- n) time and pressure changes during post exposure flushing;
- o) time, temperature, pressure changes (if any) during aeration.

- 10.3 If biological indicators are used in routine monitoring, they shall comply with 8.6 and 8.7.
  If the PCD that is used for routine release is different from that used in the MPQ, it should be at least as resistant to the process as is the PCD used in the MPQ.

- 10.4 If chemical indicators are used in routine monitoring, they shall comply with 8.8.
  Chemical indicators shall not replace biological indicators for product release or be used to support a rationale to release a load parametrically.

- 10.5 If parametric release is performed, the following additional data shall be recorded and retained:
- a) temperature in the chamber from a minimum of two locations throughout the sterilization cycle;
- b) chamber humidity during conditioning as determined by direct measurement;
- c) the EO concentration, determined from direct analysis of chamber atmosphere using analytical methods at defined intervals sufficient to verify the required conditions throughout the exposure time.

11 Product release from sterilization

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

- confirmation that the data recorded during routine processing meet the sterilization process specification; and
- confirmation of no growth of the test organism from any biological indicator (if used).

- 11.2 If a process does not fulfil all of the conformance criteria above, the cause shall be investigated. If repair or alteration to the equipment is required, the necessary qualification shall be performed before this process can be used again.

- 11.3 Product shall be considered as non-conforming and handled in accordance with the applicable clauses of ISO 13485 if one or more of the conformance criteria of 11.1 are not fulfilled. In the event of a positive BI, it is not acceptable to release product based on acceptable results of a product test for sterility.

- 11.4 If saleable product is used in validation studies, the requirements for release of this product for distribution shall be generated before the start of the validation activities. It is important to assess the effect of repeated exposures to the validation/sterilization processes on product and packaging functionality, and levels of residual EO and/or reaction products prior to release.

12 Maintaining process effectiveness

- 12.1 General
  - 12.1.1 The continued effectiveness of the system for ensuring the condition of the product presented for sterilization (see 7.3.1) shall be demonstrated.
  - 12.1.2 The accuracy and reliability of the instrumentation used to control and monitor the sterilization process shall be verified periodically in accordance with 4.3.3.

12.2 Maintenance of equipment

- 12.2.1 Preventative maintenance shall be planned and performed in accordance with documented procedures. All procedures shall follow manufacturers' recommendations, as well as any pertinent national, regional, or local requirements.
- 12.2.2 Equipment shall only be used to process product after all specified maintenance tasks have been satisfactorily completed and recorded.
- 12.2.3 Records of maintenance shall be retained (see 4.1.2).

- 12.2.4 The maintenance scheme, maintenance procedures, and maintenance records shall be reviewed at specified intervals by a designated person, and the results of the review shall be documented.

12.3 Requalification

- 12.3.1 IQ, OQ, PQ, and subsequent requalification(s) shall be reviewed annually to determine the extent of requalification that is necessary. This shall include an assessment of the need to reconfirm the product SAL through microbiological studies. The outcome of this review, including the rationale for decisions reached, shall be documented.

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

- 12.3.3 If requalification indicates that the sterilization process might no longer be capable of achieving the required product SAL, the cause shall be investigated and corrective and/or preventive action shall be taken. As part of the investigation, the effect on the achievement of the specified SAL for previously processed loads of product shall be considered and a risk assessment undertaken on their suitability for use. If the investigation shows that the required SAL can no longer be achieved then a new MPQ/PPQ shall be performed to re-establish the required SAL. The investigation and subsequent actions shall be recorded.

- 12.3.4 Records of reviews of requalification data, reports, and resulting corrective actions (if required) shall be retained (see 4.1.2).

12.4 Assessment of change

12.4.1 Changes to manufacturing operations, product, sterilization equipment, and/or the sterilization process shall be assessed for their effect on the effectiveness of the sterilization process.

- 12.4.2 The appropriateness of the internal and/or external PCD in relation to the bioburden of the product shall be reconfirmed as a result of change (see 8.6 and 10.3) as appropriate.

12.4.3 The load and load configuration shall be re-evaluated following a change for its appropriateness, and the results of this re-evaluation shall be documented in accordance with 4.1.2.

- 12.4.4 The qualified sterilization process shall be reviewed whenever there has been a change to the sterilization process, the sterilization equipment, or product that could alter the efficacy of the process (see 8.2).
- 12.4.5 The magnitude of the change shall be considered in determining the extent to which process definition, IQ, OQ, or PQ is undertaken.
- 12.4.6 The outcome of the assessment, including the rationale for decisions reached, shall be documented.

12.5 Assessment of equivalence

- Process equivalence

- A) Sterilization equipment that delivers the same process parameters, having undergone IQ and OQ, shall be qualified either in the same manner as the original chamber, or
- B)using a reduced MPQ that demonstrates the delivery of the required level of microbiological lethality and PPQ to demonstrate temperature and humidity uniformity of the load and control by the production chamber. The rationale for this reduced qualification shall be recorded and documented.

- 12.5.2 Product

- A product may be added to a validated process if deemed equivalent to or a lesser challenge than an existing qualified product or internal PCD. A technical review shall be performed comparing the candidate product with the product or PCD that was used to validate the existing EO process. The outcome of the technical review, including the rationale for decisions reached, shall be documented. The requirements of 7.2 still need to be addressed for the product.