Draft for Public Comment

Form 36

DPC: 24/30485888 DC

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Date: 11 January 2024
Origin: International

Latest date for receipt of comments: 06 February 2024

Project No. 2020/02025

Responsible committee: CH/198 Sterilization and Associated Equipment and Processes

Interested committees:

Title: Draft BS EN ISO 11135 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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Introduction

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For international standards, comments will be reviewed by the relevant UK national committee before sending the consensus UK vote and comments to the international committee, which will then decide appropriate action. If the international standard is approved, it is usual for the text to be published as a British Standard.

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UK Vote

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Template for comments and secretariat observations

Date: xx/xx/20xx	Document: ISO/DIS xxxx

1	2	(3)	4	5	(6)	7
MB	Clause No./ Subclause No./Annex **(e.g. 3.1)**	Paragraph/ Figure/Table/Note	**Type of comment**	**Commend (justification for change) by the MB**	**Proposed change by the MB**	**Secretariat observations on each comment submitted**
	3.1	Definition 1	ed	Definition is ambiguous and needs clarifying.	Amend to read '...so that the mains connector to which no connection...'	
	6.4	Paragraph 2	te	The use of the UV photometer as an alternative cannot be supported as serious problems have been encountered in its use in the UK.	Delete reference to UV photometer.	

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DRAFT International Standard

ISO/DIS 11135.2

ISO/TC **198**

Secretariat: **ANSI**

Voting begins on:
2024-01-11

Voting terminates on:
2024-03-07

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

Stérilisation des produits de santé — Oxyde d'éthylène — Exigences de mise au point, de validation et de contrôle de routine d'un processus de stérilisation pour des dispositifs médicaux

ICS: 11.080.01

This document is circulated as received from the committee secretariat.

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Published in Switzerland

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO document should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 204, *Sterilization of medical devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

This third edition cancels and replaces the second edition (ISO 11135:2014), which has been technically revised. It also replaces Amendment ISO 11135:2014/Amd 1:2018.

The main changes are as follows:

— addition of informational guidance in Annexes B, D, E, G, H, J and K;

— more defined requirements for microbiological performance qualification (MPQ) in Annex F;

— incorporation of relevant elements of ISO/TS 21387:2020 into Annexes A and H.

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Introduction

A sterile medical device is one that is free of viable microorganisms. Medical devices produced under standard manufacturing conditions in accordance with the requirements for quality management systems (see for example ISO 13485) may, prior to sterilization, have microorganisms on them, albeit in low numbers. Such medical devices are non-sterile. The purpose of sterilization is to inactivate the microbiological contaminants and thereby transform the non-sterile medical devices into sterile ones.

The kinetics of inactivation of a pure culture of microorganisms by physical and chemical agents used to sterilize medical devices can generally best be described by an exponential relationship between the numbers of microorganisms surviving and the extent of treatment with the ethylene oxide (EO); inevitably this means that there is always a finite probability that a microorganism may survive regardless of the extent of treatment applied. For a given treatment, the probability of survival is determined by the number and resistance of microorganisms and by the environment in which the organisms exist during treatment. It follows that the sterility of any one medical device in a population subjected to sterilization processing cannot be guaranteed and the sterility of a processed population is defined in terms of the probability of there being a viable microorganism present on a medical device.

This document describes requirements that, if met, will provide an EO sterilization process intended to sterilize medical devices, which has appropriate microbicidal activity. Furthermore, conformance with the requirements ensures that validations conducted following this document provide products that meet the defined requirements for sterile products with a high degree of confidence. The specification for this probability is a matter for regulatory authorities and can vary from country to country (see for example EN 556-1 and ANSI/AAMI ST67).

Generic requirements of the quality management systems for design and development, production, installation and servicing are given in ISO 9001 and particular requirements for quality management systems for medical device production are given in ISO 13485. The standards for quality management systems recognize that, for certain processes used in manufacturing or reprocessing, the effectiveness of the process cannot be fully verified by subsequent inspection and testing of the product. Sterilization is an example of such a process. For this reason, sterilization processes are validated for use, the performance of the sterilization process monitored routinely, and the equipment is maintained and calibrated.

Exposure to a properly validated, accurately controlled sterilization process is not the only factor associated with the provision of reliable assurance that the product is sterile and, in this regard, suitable for its intended use. Attention is therefore given to a number of considerations including:

— the microbiological status of incoming raw materials and components or both;

— the validation and routine control of any cleaning and disinfection procedures used on the product;

— the control of the environment in which the product is manufactured or reprocessed, assembled and packaged;

— the control of equipment and processes;

— the control of personnel and their hygiene;

— the manner and materials in which the product is packaged;

— the conditions under which product is stored.

The type of contamination on a product to be sterilized varies and this impacts upon the effectiveness of a sterilization process. Products that have been used in a health care setting and are being presented for resterilization in accordance with the manufacturer's instructions (see ISO 17664-1) are a special case.

Health care facilities differ from medical device manufacturers in the physical design of processing areas, in the equipment used, and in the availability of personnel with adequate levels of training and experience. The primary function of the health care facility is to provide patient care; medical device reprocessing is just one of a myriad of activities that are performed to support that function.

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In terms of the initial condition of medical devices, medical device manufacturers generally sterilize large numbers of similar single-use medical devices. Health care facilities, on the other hand, handle and process both new medical devices and reusable medical devices of different types and with varying levels of bioburden. They are therefore faced with the additional challenges of cleaning, evaluating, preparing and packaging a medical device prior to sterilization. In this document, alternative approaches and guidance specific to health care facilities are identified as such.

The requirements are the normative parts of this document, including Annexes E and F, with which conformance is claimed. The guidance given in the informative annexes (A, B, C, D, G, H, I and J) is not normative and is not provided as a checklist for auditors. These annexes provide explanations and methods that are regarded as being suitable means for complying with the requirements for industry and health care facilities.

The guidance in annexes is intended for people who have a basic knowledge of the principles of EO sterilization. Methods other than those given in the guidance can be used if they are effective in achieving conformance with the requirements of this document.

The development, validation and routine control of a sterilization process comprises a number of discrete but interrelated activities, e.g. calibration, maintenance, product definition, process definition, installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). While the activities required by this document have been grouped together and are presented in a particular order, this document does not require that the activities be performed in the order in which they are presented. The activities required are not necessarily sequential, as the programme of development and validation can be iterative. It is possible that performing these different activities will involve a number of separate individuals and/or organizations, each of whom undertakes one or more of these activities. This document does not specify the particular individuals or organizations to carry out the activities.

Patient safety should be considered by minimizing exposure to EO and its by-products during product use. ISO 10993-7 specifies limits for EO and ethylene chlorohydrin (ECH); however, no exposure limits are set for ethylene glycol (EG) because risk assessment indicates that when EO residues are controlled, it is unlikely that biologically significant residues of EG would be present.

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

1 Scope

1.1 Inclusions

This document specifies requirements for the development, validation and routine control of an EO 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.

Among the similarities are the common need for quality systems, staff training, and proper safety measures. The major differences relate to the unique physical and organizational conditions in health care facilities, and to the initial condition of reusable medical devices being presented for sterilization.

Although the scope of this document is limited to medical devices, it specifies requirements and provides guidance that can be applicable to other health care products.

1.2 Exclusions

1.2.1 This document does not specify requirements for the development, validation and routine control of a process for inactivating the causative agents of spongiform encephalopathies such as scrapie, bovine spongiform encephalopathy and Creutzfeldt-Jakob disease. Specific recommendations have been produced in particular countries for the processing of materials potentially contaminated with these agents.

NOTE See ISO 22442-1 and ISO 22442-3.

1.2.2 This document does not detail a specified requirement for designating a medical device as sterile.

NOTE National or regional requirements for designating medical devices as “sterile” can apply (for example, EN 556–1 or ANSI/AAMI ST67).

1.2.3 This document does not specify a quality management system for the control of all stages of production of medical devices.

NOTE The effective implementation of defined and documented procedures is necessary for the development, validation and routine control of a sterilization process for medical devices. Such procedures are commonly considered to be elements of a quality management system. It is not a requirement of this document to have a full quality management system during manufacture or reprocessing. The necessary elements are referenced at appropriate places in the text (see, in particular, Clause 4). Attention is drawn to the standards for quality management systems (see ISO 13485) that control all stages of production or reprocessing of medical devices. National or regional regulations for the provision of medical devices can require the implementation of a full quality management system and the assessment of that system by a third party.

1.2.4 This document does not specify requirements for occupational safety associated with the design and operation of EO sterilization facilities.

NOTE EO is toxic, flammable and explosive. National or regional regulations exist in some countries concerning safety requirements for the handling of EO and for premises in which EO is used.

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1.2.5 This document does not cover sterilization by injecting EO or mixtures containing EO directly into packages or a flexible chamber.

NOTE See ISO 14937 for validation of these types of EO processes.

1.2.6 This document does not cover analytical methods for determining levels of residual EO and its reaction products.

NOTE 1 For further information see ISO 10993-7.

NOTE 2 National or regional regulations specifying limits for the level of EO residues present on or in medical devices can apply.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

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

ISO 11138-2, *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*

ISO 11737-1, *Sterilization of health care products — Microbiological methods — Part 1: Determination of a population of microorganisms on products*

ISO 11737-2, *Sterilization of health care products — Microbiological methods — Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
aeration
part of the sterilization process during which the sterilizing agent and/or its reaction products desorb from the health care product until predetermined levels are reached

Note 1 to entry: This can be performed within the sterilization chamber and/or in a separate chamber or room.

[SOURCE: ISO 11139:2018, 3.7]

3.2
aeration area
either a chamber or a room in which aeration occurs

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3.3
batch
defined quantity of a product intended or purported to be uniform in character and quality produced during a specified cycle of manufacture

[SOURCE: ISO 11139:2018, 3.21]

3.4
bioburden
population of viable microorganisms on or in product and/or sterile barrier system

[SOURCE: ISO 11139:2018, 3.23]

3.5
biological indicator
test system containing viable microorganisms providing a specified resistance to a specified sterilization process

[SOURCE: ISO 11139:2018, 3.29]

3.6
calibration
operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication

[SOURCE: ISO 11139:2018, 3.31]

3.7
chamber
part of equipment in which a load is processed

[SOURCE: ISO 11139:2018, 3.36]

3.8
chamber volume
enclosed space of a chamber, including the volume of nozzles to the first connection or weld, and excluding the volume of permanent internal parts

[SOURCE: ISO 11139:2018, 3.318.1]

3.9
change control
assessment and determination of the appropriateness of a proposed alteration to product, process, or equipment

[SOURCE: ISO 11139:2018, 3.39]

3.10
chemical indicator
test system that reveals a change in one or more pre-specified process variables based on a chemical or physical change resulting from exposure to a process

[SOURCE: ISO 11139:2018, 3.43]

3.11
conditioning
treatment of product prior to the exposure phase to attain a specified temperature, relative humidity, or other process variable throughout the load

Note 1 to entry: This part of the sterilization cycle can be carried out either at atmospheric pressure or under vacuum.

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Note 2 to entry: See *preconditioning* (3.45).

[SOURCE: ISO 11139:2018, 3.58]

3.12
control
regulation of variables within specified limits

[SOURCE: ISO 11139:2018, 3.63]

3.13
correction
action to eliminate a detected nonconformity

Note 1 to entry: A correction can be made in advance of, in conjunction with, or after a corrective action.

[SOURCE: ISO 11139:2018, 3.64]

3.14
corrective action
action to eliminate the cause of a nonconformity and to prevent recurrence

Note 1 to entry: There can be more than one cause for a nonconformity.

Note 2 to entry: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence.

[SOURCE: ISO 11139:2018, 3.65]

3.15
cycle parameter
value of a cycle variable including its tolerance used for control, monitoring, indication, and recording of an operating cycle

[SOURCE: ISO 11139:2018, 3.72]

3.16
cycle variable
property used to control, monitor, indicate, or record an operating cycle

[SOURCE: ISO 11139:2018, 3.74]

3.17
***D* value**
D_{10} value
time or dose required under stated conditions to achieve inactivation of 90 % of a population of the test microorganisms

[SOURCE: ISO 11139:2018, 3.75]

3.18
dew point
temperature at which the saturation water vapour pressure is equal to the partial pressure of the water vapour in the atmosphere

Note 1 to entry: Any cooling of the atmosphere below the dew point would produce water condensation.

[SOURCE: ISO 11139:2018, 3.80]

3.19
EO dwell time
holding time of an EO process from the end of EO injection and inert gas (if used) to the start of EO evacuation

Note 1 to entry: See f) of Figure A.1.

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3.20
equilibration time
period between the attainment of defined sterilization process parameters at the reference measurement point and the attainment of the specified sterilization process parameters at all points within the load

[SOURCE: ISO 11139:2018, 3.105]

3.21
establish
determine by theoretical evaluation and confirm by experimentation

[SOURCE: ISO 11139:2018, 3.107]

3.22
exposure phase
cycle stage between the introduction of the sterilizing or disinfecting agent into the chamber and when the agent is removed

Note 1 to entry: For the purposes of an EO process, this is illustrated in e) through g) of Figure A.1.

[SOURCE: ISO 11139:2018, 3.111]

3.23
fault
situation in which one or more of the process or cycle parameters is/are outside its/their specified tolerance(s)

[SOURCE: ISO 11139:2018, 3.116]

3.24
fractional cycle
operating cycle in which the exposure phase is reduced compared with that specified for the sterilization cycle

Note 1 to entry: For EO processes, the EO dwell time within the exposure phase is reduced.

[SOURCE: ISO 11139:2018, 3.123]

3.25
gas concentration
weight of a specific gas in a given volume

Note 1 to entry: Concentration can be expressed as mg/l or g/m^3.

[SOURCE: ISO 11139:2018, 3.125]

3.26
half cycle
test cycle in which the extent of treatment is reduced by 50 % as compared with an operating cycle

Note 1 to entry: A cycle in which the EO dwell time is reduced by 50 % compared to that specified in the sterilization process.

[SOURCE: ISO 11139:2018, 3.129]

3.27
health care facility
governmental and private organization and institution devoted to the promotion and maintenance of health, and the prevention and treatment of diseases and injuries

EXAMPLE Hospital, nursing home, extended care facility, free-standing surgical centre, clinic, medical office, dental office.

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3.28
health care product
medical device, including in vitro diagnostic medical device, or medicinal product, including biopharmaceutical

[SOURCE: ISO 11139:2018, 3.132]

3.29
holding time
period during which process parameters are maintained, within their specified tolerances

[SOURCE: ISO 11139:2018, 3.133]

3.30
humidity
measure of water vapour present in a gas

Note 1 to entry: Humidity is usually expressed as absolute humidity (i.e. vapour pressure density), relative humidity, or dew point.

[SOURCE: ISO 11139:2018, 3.136]

3.30.1
absolute humidity
AH
measure of water vapour in the air, regardless of temperature

Note 1 to entry: It is expressed as grams of moisture per cubic meter of air (g/m^3).

[SOURCE: ISO 11139:2018, 3.136.1]

3.30.2
relative humidity
RH
measure of water vapour in the air expressed as a percentage of the maximum for a given temperature

Note 1 to entry: It is expressed as a percent.

[SOURCE: ISO 11139:2018, 3.136.2]

3.31
inoculated carrier
supporting material on or in which a specified number of viable test microorganisms has been deposited

[SOURCE: ISO 11139:2018, 3.144]

3.32
load
product, equipment, or materials to be processed together within an operating cycle

[SOURCE: ISO 11139:2018, 3.155]

3.33
load volume
space occupied by product and any packaging and carrier(s)

[SOURCE: ISO 11139:2018, 3.318.3]

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3.34
master product
health care product or procedure set used to represent the most challenging to sterilize item in a product family or processing category

[SOURCE: ISO 11139:2018, 3.160]

3.35
medical device
instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, or software material, or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

— diagnosis, prevention, monitoring, treatment, or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of, or compensation for an injury;

— investigation, replacement, modification, or support of the anatomy, or of a physiological process;

— supporting or sustaining life;

— control of conception;

— disinfection of medical devices;

— providing information by means of in vitro examination of specimens derived from the human body;

and does not achieve its primary intended action by pharmacological, immunological, or metabolic means, but which may be assisted in its intended function by such means

Note 1 to entry: Products which may be considered to be medical devices in some jurisdictions, but not in others include:

— items specifically intended for cleaning or sterilization of medical devices;

— pouches, reel goods, sterilization wrap, and reusable containers for packaging of medical devices for sterilization;

— disinfection substances;

— aids for persons with disabilities;

— devices incorporating animal and/or human tissues;

— devices for in vitro fertilization or assisted reproduction technologies.

[SOURCE: ISO 11139:2018, 3.166]

3.36
microorganism
entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

[SOURCE: ISO 11139:2018, 3.176]

3.37
monitoring
continual checking, supervising, critically observing, or determining the status, in order to identify change from the performance level required or expected

[SOURCE: ISO 11139:2018, 3.180]

3.38
operating cycle
complete set of stages of a process that is carried out, in a specified sequence

Note 1 to entry: Loading and unloading are not part of the operating cycle.

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[SOURCE: ISO 11139:2018, 3.188]

3.39
overkill approach
method of defining a sterilization process that achieves a maximal sterility assurance level (SAL) for product substantially less than 10^{-6}

[SOURCE: ISO 11139:2018, 3.190]

3.40
parametric release
declaration that product is sterile based on records demonstrating that the sterilization process variables were delivered within specified tolerances

Note 1 to entry: This method of process release does not include the use of biological indicators.

[SOURCE: ISO 11139:2018, 3.193]

3.41
preconditioning
treatment of product, prior to the operating cycle, to attain specified values for temperature, relative humidity, and/or other process variables

[SOURCE: ISO 11139:2018, 3.200]

3.42
process challenge device
PCD
item providing a defined resistance to a cleaning, disinfection, or sterilization process and used to assess performance of the process

Note 1 to entry: For the purpose of this document, an item can be product, surrogate product or other device that is inoculated directly or indirectly.

Note 2 to entry: In this document, a distinction is made between an internal PCD and an external PCD. An internal PCD is used to demonstrate that the selected product SAL is achieved. A PCD located within the confines of the product or product shipper case is an internal PCD, whereas a PCD located between shipper cases or on the exterior surfaces of the load is an external PCD. An external PCD is an item designed to be used for microbiological monitoring of routine production cycles.

[SOURCE: ISO 11139:2018, 3.205]

3.43
process challenge location
PCL
site chosen within a load as the position at which the least microbiological inactivation is expected to be delivered

[SOURCE: ISO 11139:2018, 3.206]

3.44
process control
specific activities to ensure process requirements are achieved

[SOURCE: ISO 11139:2018, 3.209]

3.45
process parameter
specified value for a process variable

Note 1 to entry: The specification for a process includes the process parameters and their tolerances.

[SOURCE: ISO 11139:2018, 3.211]

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3.46
process variable
chemical or physical attribute within a cleaning, disinfection, packaging, or sterilization process, changes in which can alter its effectiveness

EXAMPLE Time, temperature, pressure, concentration, humidity, wavelength.

[SOURCE: ISO 11139:2018, 3.213]

3.47
processing category
collection of different product or product families that can be processed together

[SOURCE: ISO 11139:2018, 3.215]

3.48
product
tangible result of a process

EXAMPLE Raw material(s), intermediate(s), sub-assembly(ies), health care product(s).

[SOURCE: ISO 11139:2018, 3.217]

3.49
product family
group or subgroup of product characterized by similar attributes determined to be equivalent for evaluation and processing purposes

[SOURCE: ISO 11139:2018, 3.218]

3.50
qualification
activities undertaken to demonstrate that utilities, equipment, and methods or modes are suitable for their intended use and perform properly

Note 1 to entry: Qualification of equipment and/or processes generally includes installation qualification, operational qualification, and performance qualification.

[SOURCE: ISO 11139:2018, 3.220]

3.50.1
installation qualification
IQ
process of establishing by objective evidence that all key aspects of the process equipment and ancillary system installation comply with the approved specification

[SOURCE: ISO 11139:2018, 3.220.2]

3.50.2
operational qualification
OQ
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[SOURCE: ISO 11139:2018, 3.220.3]

3.50.3
performance qualification
PQ
process of establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements

[SOURCE: ISO 11139:2018, 3.220.4]

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3.50.4
requalification
repetition of part or all of validation for the purpose of confirming the continued acceptability of a specified process

[SOURCE: ISO 11139:2018, 3.220.5]

3.51
reference load
specified load created to represent combinations of items that provide defined challenge(s) to a process

Note 1 to entry: Reference load may also be referred to by other descriptions such as dunnage, dummy or simulated load.

[SOURCE: ISO 11139:2018, 3.226]

3.52
reference microorganism
microbial strain obtained from a recognized culture collection

[SOURCE: ISO 11139:2018, 3.228]

3.53
reusable medical device
medical device designated or intended by the manufacturer as suitable for reprocessing and reuse

Note 1 to entry: This is not a medical device that is designated or intended by the manufacturer for single use only.

[SOURCE: ISO 11139:2018, 3.236]

3.54
services
supplies from an external source needed for the function of equipment

Note 1 to entry: For the purposes of this document, services can include electricity, water and process gases.

[SOURCE: ISO 11139:2018, 3.252]

3.55
single-use medical device
medical device labelled or intended to be used on one individual during a single procedure

[SOURCE: ISO 11139:2018, 3.255]

3.56
specify
stipulate in detail within an approved document

[SOURCE: ISO 11139:2018, 3.259]

3.57
stabilization period
elapsed time from the attainment of the minimum specified exposure conditions until the end of the specified time to achieve steady state conditions

[SOURCE: ISO 11139:2018, 3.261]

3.58
stage
<operating cycle> part of an operating cycle with a specified function

EXAMPLE Air removal stage, plateau period, drying stage, final air admission stage.

[SOURCE: ISO 11139:2018, 3.262]

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3.59
sterilant
chemical or combination of chemicals used to generate a sterilizing agent

[SOURCE: ISO 11139:2018, 3.268]

3.60
sterilant/sterilizing agent injection
introduction of sterilant/sterilizing agent into the evacuated chamber until the set operating pressure has been attained or the specified quantity of sterilant/sterilizing agent has been delivered

Note 1 to entry: For the purposes of an EO process, this is illustrated in e) of Figure A.1.

[SOURCE: ISO 11139:2018, 3.269]

3.61
sterilant/sterilizing agent injection time
duration of the stage beginning with the first introduction of the sterilant/sterilizing agent into the chamber and ending when addition of sterilant/sterilizing agent ceases

[SOURCE: ISO 11139:2018, 3.270]

3.62
sterile
free from viable microorganisms

[SOURCE: ISO 11139:2018, 3.271]

3.63
sterile barrier system
SBS
minimum package that minimizes the risk of ingress of microorganisms and allows aseptic presentation of the sterile contents at the point of use

[SOURCE: ISO 11139:2018, 3.272]

3.64
sterility
state of being free from viable microorganisms

Note 1 to entry: In practice, no such absolute statement regarding the absence of microorganisms can be proven.

[SOURCE: ISO 11139:2018, 3.274]

3.65
sterility assurance level
SAL
probability of a single viable microorganism occurring on an item after sterilization

Note 1 to entry: It is expressed as the negative exponent to the base 10.

[SOURCE: ISO 11139:2018, 3.275]

3.66
sterilization
validated process used to render product free from viable microorganisms

Note 1 to entry: In a sterilization process, the nature of microbial inactivation is exponential and thus the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

[SOURCE: ISO 11139:2018, 3.277]

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3.67
sterilization cycle
predetermined sequence of stages performed in a sterilizer to achieve product free of viable microorganisms

[SOURCE: ISO 11139:2018, 3.279]

3.68
sterilization process
series of actions or operations needed to achieve the specified requirements for sterility

Note 1 to entry: This series of actions includes pre-treatment of product (if necessary), exposure under specified conditions to the sterilizing agent, and any necessary post treatment. The sterilization process does not include any cleaning, disinfection, or packaging operations that precede sterilization.

[SOURCE: ISO 11139:2018, 3.284]

3.69
sterilization specialist
person(s) with technical knowledge of the sterilization technology being utilized.

3.70
sterilizer
equipment designed to achieve sterilization

[SOURCE: ISO 11139:2018, 3.287]

3.71
sterilizing agent
physical or chemical entity, or combination of entities, having sufficient microbicidal activity to achieve sterility under specified conditions

[SOURCE: ISO 11139:2018, 3.288]

3.72
surrogate product
item designed to represent product in process simulations and which is comparable with the actual product

[SOURCE: ISO 11139:2018, 3.291]

3.73
survivor curve
graphical representation of the inactivation of a population of microorganisms with increasing exposure to a microbicidal agent under stated conditions

[SOURCE: ISO 11138-1:2017, 3.16]

3.74
terminal sterilization
process whereby a product is sterilized within its sterile barrier system

[SOURCE: ISO 11139:2018, 3.295]

3.75
test for sterility
technical operation specified in a pharmacopoeia performed on product following an aseptic process or exposure to a sterilization process

[SOURCE: ISO 11139:2018, 3.298]

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3.76
test of sterility
technical operation performed as part of development, validation, or requalification to determine the presence or absence of viable microorganisms on product or portions thereof

[SOURCE: ISO 11139:2018, 3.299]

3.77
usable chamber space
specified geometry within the chamber that is available to accept the load

Note 1 to entry: The volume allowed for gas circulation around the load inside the chamber is not included as usable space.

[SOURCE: ISO 11139:2018, 3.311]

3.78
validation
confirmation process, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The objective evidence needed for a validation is the result of a test or other form of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The word "validated" is used to designate the corresponding status.

Note 3 to entry: The use conditions for validation can be real or simulated.

[SOURCE: ISO 11139:2018, 3.313]

3.79
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

Note 1 to entry: The objective evidence needed for a verification can be the result of an inspection or of other forms of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The word "verified" is used to designate the corresponding status.

[SOURCE: ISO 11139:2018, 3.314]

4 Quality management system

4.1 The development, validation and routine control of a sterilization process is a critical element in product realization of health care product. To ensure the consistent implementation of the requirements specified in this document, the necessary processes need to be established, implemented and maintained. Processes of particular importance in relation to the development, validation and routine control of a sterilization process include but are not limited to:

— control of documentation, including records,

— assignment of management responsibility,

— provision of adequate resources, including competent human resources and infrastructure,

— control of product provided by external parties,

— identification and traceability of product throughout the process, and

— control of non-conforming product.

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NOTE 1 ISO 13485 covers all stages of the lifecycle of medical devices in the context of quality management systems for regulatory purposes. National or regional regulatory requirements for the provision of health care product can require the implementation of a full quality management system and the assessment of that system by a recognized conformity assessment body.

NOTE 2 Where the development, validation and routine control of a sterilization process involve a number of separate parties, E.4.2.2 and Table E.1 of ISO 14937:2009 offer guidance on who should take responsibility for the respective elements.

4.2 A process shall be specified for the calibration and maintenance of all equipment, including instrumentation for test purposes, used in meeting the requirements of this document.

5 Sterilizing agent characterization

5.1 General

The purpose of this activity is to define the sterilizing agent, demonstrate its microbicidal effectiveness and identify the factors that influence microbicidal effectiveness, assess the effects that exposure to the sterilizing agent on materials, and identify requirements for safety of personnel and protection of the environment. This activity can 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 document, the sterilizing agent is EO.

5.2 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.

5.3 Microbicidal effectiveness

The inactivation of microorganisms by EO and the use of EO in sterilization processes have been comprehensively documented in the literature. This literature provides knowledge of the manner in which the process variables affect microbial inactivation. Reference to these general studies on microbial inactivation is not required by this standard.

5.4 Material effects

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

5.5 Safety and the environment

5.5.1 Either a safety data sheet (SDS) or analogous safety information should be made available for EO and its diluents (if any).

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.

NOTE There can be applicable local, national and international requirements regarding the emission and disposal of EO and its diluents as well as any by-products.

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6 Process and equipment characterization

6.1 General

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

6.2 Process characterization

6.2.1 Process characterization, at a minimum, shall include:

a) identifying the phases that are necessary for an EO sterilization process;

b) identifying the process variables for each phase;

c) documenting the process variables.

NOTE The data developed in product definition (see Clause 7) can impact the characterization of the sterilization process.

6.2.2 The phases of the sterilization process include:

a) preconditioning (if used);

b) the sterilization cycle;

c) aeration (if used).

6.2.3 The process variables for preconditioning (if used) include:

a) time;

b) temperature;

c) humidity;

d) transfer time from preconditioning to the sterilization chamber.

6.2.4 The process variables for the sterilization cycle include:

a) time;

b) temperature;

c) humidity;

d) EO concentration;

e) pressure.

6.2.5 The process variables for aeration (if used) include:

a) time;

b) temperature.

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6.3 Equipment characterization

6.3.1 The specification for the equipment to be used shall be developed and documented. This specification shall include:

a) the preconditioning area (if used);

b) the sterilization chamber;

c) the aeration area (if used).

NOTE Some aspects of the equipment design can be influenced by national or regional regulatory requirements or standards (e.g. EN 1422, ANSI/AAMI ST24, JIS T 7323).

6.3.2 At a minimum, the specification shall include:

a) description of the equipment, together with any necessary ancillary items;

b) description of the means by which the gaseous sterilizing agent is delivered to the chamber;

c) description of the means by which any other gas(es), including steam, are delivered to the chamber;

d) description of instrumentation for monitoring, controlling and recording the sterilization process, including sensor characteristics and their locations;

e) fault(s) recognized by the sterilizing equipment;

f) safety features, including those for personnel and environmental protection;

g) installation requirements, including specifications for required services and requirements for the control of emissions.

6.3.3 Software used to either control or monitor, or both, the process shall be prepared and validated. Results of the validation shall be documented to demonstrate that the software meets its design specification.

NOTE For further information, see ISO/IEC 90003.

6.3.4 The means of monitoring and controlling the process variables shall be determined and specified.

6.3.5 Means shall be provided to ensure that failure in a control function does not lead to failure in recording of process variables such that an ineffective process appears effective.

7 Product definition

7.1 General

7.1.1 The purpose of this activity is to define the product to be sterilized, including the microbiological quality (see 7.3) 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 load configuration. A demonstration of equivalence (with reference to the challenge to the sterilization process) to a previously validated product, package or load configuration shall be considered to meet the requirement to perform product definition (see Annex K). Any demonstration of equivalence shall be documented.

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7.1.3 Product, product packaging system and load configuration shall be designed to allow removal of air, if applicable, and penetration of heat, humidity and EO to the product during the sterilization process, and removal of EO from the product at the end of the process.

7.1.4 It shall be demonstrated that the specified sterilization process is effective in sterilizing the most challenging location or locations of the product for sterilization conditions to be achieved. This can be achieved by performing process definition and validation of a new product; or through the demonstration of equivalence (see Annex J) to a previously validated product, or internal PCD used to qualify the product SAL when exposed to the specified sterilization process (see 8.6 and Annex B).

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 taking into consideration the process parameter tolerances that have been determined to have the greatest effect 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.

7.2.3 Means shall be established to reduce EO residual levels such that the processed products conform with the requirements of ISO 10993-7 before release to market (see Clause 11).

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 is controlled and does not compromise the effectiveness of the sterilization process.

NOTE Guidance on testing for bacterial endotoxins is provided in ISO 11737-3, ANSI/AAMI ST72 and the applicable pharmacopeia.

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.

NOTE Requirements for information to be provided for the reprocessing of critical and semi-critical resterilizable devices are given in ISO 17664-1.

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 load 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) (see 9.2 and 9.3).

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

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 outlined in Annexes F or by an alternative method that demonstrates the product has achieved the required SAL.

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

a) conform with all the applicable clauses of ISO 11138-2;

b) be shown to present a greater or equal microbiological challenge to the EO process than the bioburden of product to be sterilized; and

c) be placed within an appropriate PCD.

The appropriateness of the PCD used for process definition, validation, or routine monitoring and control shall be established. The PCD shall present a microbiological challenge to the sterilization process that is equivalent or greater than the microbiological challenge presented by the natural bioburden on all surfaces of the product. See Annex B for guidance on establishing the appropriateness of a PCD.

NOTE For guidance on the selection, use, and interpretation of BIs, see ISO 11138-7.

8.7 Commercially supplied BIs used in the definition of the sterilization process shall conform with all applicable clauses of ISO 11138-1 and ISO 11138-2.

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

Chemical indicators shall not be used as the sole means of establishing the sterilization process and shall not be used as an indicator that the selected SAL has been achieved.

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

9 Validation

9.1 General

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: IQ, OQ and PQ. Testing shall not commence until the associated procedures or protocols have been approved.

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 design specification.

9.1.3 OQ is undertaken to demonstrate the ability of the equipment to meet the performance requirements of its functional 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 user requirements specified.

PQ should be carried out for each new processor product, or both, to be validated, to demonstrate that the process conforms with identified acceptance criteria and is capable of delivering the selected SAL to the product.

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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 conform with its design specifications.

9.2.1.2 Sterilization equipment shall conform to the applicable safety and environmental 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;

d) details of contacts for technical support.

9.2.2 Installation qualification (IQ) specifications

9.2.2.1 Installation of the equipment and all associated services shall be in accordance with the architectural and engineering drawings.

NOTE Pertinent national, regional and local regulations can apply.

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 or change management system.

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.

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 General

9.4.1.1 PQ consists of both microbiological and physical PQ and is performed in the equipment used to sterilize the product.

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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, 7.1.4 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 loads, 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 selected SAL.

9.4.1.7 If material other than product is used to comprise the PQ load, it shall present at least as great a challenge to the sterilization process as the challenge presented by product.

9.4.1.8 If loads are reused for the PQ cycles, they shall be aerated between exposures and returned to ambient conditions to meet the regulations for worker safety and to ensure that EO remaining 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 conform with ISO 11140-1, and shall be used in conjunction with microbiological and physical monitoring.

9.4.1.10 BIs used in PQ shall conform with the applicable clauses of ISO 11138-1 and ISO 11138-2.

9.4.2 Performance qualification (PQ) — 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 outlined in Annex F or by an alternative method that demonstrates achievement of the selected product SAL.

9.4.2.4 If process definition was determined in a developmental chamber, full MPQ shall be carried out in the production chamber. The number of cycles to complete a full MPQ are dependent on the method used. Requirements for MPQ are defined in Annex F.

9.4.2.5 If the overkill half cycle method is used, then there shall be no positive internal PCDs from the half cycle runs.

NOTE Positive external PCDs during the half cycle can be accepted (see A.9.4.2.5).

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9.4.2.6 If the overkill cycle calculation method or the BI/bioburden method is used, the calculated SAL shall meet the specified value. See Annex F.

9.4.2.7 The conditions used for recovery of BIs in qualification studies, including duration of incubation, shall be established, and documented. Refer to ISO 11138-7 and ISO 11138-8 for additional guidance on biological indicator incubation times.

9.4.3 Performance qualification (PQ) — Physical

9.4.3.1 Physical PQ (PPQ) shall demonstrate;

a) that the specified acceptance criteria are met for the duration of the proposed routine process specification;

b) reproducibility of the process.

The PPQ shall include a minimum of three planned qualification cycles in the production chamber, in which all the specified acceptance criteria are met. PPQ can 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 an EO dwell time of at least that of the routine process specification.

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

9.4.3.2 PPQ shall establish:

a) the minimum temperature of product to enter the sterilization process or the defined conditions required to achieve it;

b) preconditioning (if used):

   1. time, temperature and humidity of chamber or area for the preconditioning phase;

   2. temperature and humidity of the sterilization load at the end of preconditioning;

   3. the specified maximum elapsed time between the completion of preconditioning (if used) and the commencement of the sterilization cycle is appropriate;

c) sterilization:

   1. vacuum levels and rate of evacuation (if used);

   2. holding time under vacuum (if used);

      NOTE For practical purposes, rates can be determined as the time taken (within tolerances) to attain a specified pressure change.

   3. pressure and rate of attainment of pressure associated with inert gas/steam;

   4. depth and rate of attainment of vacuum;

   5. inert gas flushing (if used);

   6. number of times of repetition and any variations in successive repetitions;

   7. conditioning and/or humidity dwell phases (if used):

      i. pressure levels and rate of vacuum or relative humidity levels (whichever is being controlled and monitored);

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ii. number of steam pulses/vacuum (if used);

iii. time;

iv. chamber temperature;

v. temperature and humidity of the sterilization load at the end of conditioning;

vi. if parametric release is being used, sterilization chamber humidity by measurement at the end of conditioning.

8. EO injection and dwell:

i. EO injection pressure, EO injection time and terminal pressure of EO injection phase;

ii. evidence that the gaseous EO has been admitted to the sterilization chamber by the pressure and by one of the following:

— mass of EO used;

— measurement of the concentration of EO;

— volume of EO used.

iii. EO injection pressure, EO injection time and terminal pressure of EO injection phase;

iv. Sterilization chamber temperature. If parametric release is being qualified, temperature recorded from a minimum of two separate monitoring locations;

v. EO dwell time;

vi. temperature of the sterilization load during EO dwell time;

vii. an indication of the satisfactory operation of the sterilization chamber gas circulation system (if used) during EO dwell;

viii. if parametric release is being used, the minimum value for the EO concentration determined from measurement of chamber atmosphere using analytical methods to establish the process specification for routine processing. The measurement intervals should be sufficient to verify the required conditions throughout EO dwell.

9. post exposure flushing (if used):

i. depth and rate of attainment of vacuum;

ii. pressure and rate of attainment of pressure associated with inert gas/air/steam;

iii. number of times of repetition and any variations in successive repetitions.

10. aeration (if used):

i. time and temperature within the chamber and/or room;

ii. temperature of the sterilization load for a defined period of the phase;

iii. pressure levels and rate of evacuation within the chamber and/or room, if applicable;

iv. rate of change of air or other gas, if applicable.

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.

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9.5.2 Information gathered or produced during product definition, process definition, IQ, OQ and PQ, including results from incubation of BIs, 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

a) specific qualified product(s);

b) defined loads;

c) the documented specification for the EO sterilization process based on data gathered according to 9.3.4.2.

9.5.5 The validation report or quality system shall also include provision for future review, change assessment and requalification.

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.

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 process 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 change in the specified parameter (e.g. pressure).

a) the defined conditions of the sterilization load prior to entering the sterilization process;

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 by pressure rise (ΔP) or humidity by direct measurement for conditioning;

f) conditioning parameters;

g) if using parametric release, chamber humidity during or at the end of conditioning as determined by direct measurement;

h) indication of the satisfactory operation of the chamber gas circulation system (if used) during EO dwell;

i) temperature (recorded from two separate locations if using parametric release) and pressure in the chamber throughout the sterilization cycle;

j) pressure rise (ΔP) or terminal pressure of EO injection;

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k) if parametric release is used, the EO concentration, determined from measurement of chamber atmosphere at defined intervals sufficient to verify the required conditions after EO injection and throughout the exposure time (see H.2.3.4.4);

l) If pressure is used as the primary control measure, a secondary measure is required only to confirm admission of EO to the chamber, using at least one of the following:

   1. the mass of EO used;

   2. the direct measurement of the concentration of EO in the sterilization chamber;

   3. volume of EO used;

m) EO injection time;

n) inert gas injection and final pressure, (if used);

o) EO dwell time;

p) time taken to evacuate the chamber after EO dwell;

q) time and pressure changes during post exposure flushing;

r) time, temperature, pressure changes during aeration, (if used).

10.3 If BIs are used in routine monitoring, they shall conform with 8.6 and 8.7.

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

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:

a) confirmation that the data recorded during routine processing as given in 10.2 meet the sterilization process specification;

b) if used for routine release, confirmation of no growth of the test organism from the validated biological indicator.

NOTE Formal release of sterile product to the market can require results from other tests (e.g. EO residuals, endotoxin, physical testing).

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 either a product test for sterility or meeting the sterilization process specification. Additionally, a process that has failed to meet the sterilization process specification shall not be released based on biological indicator test results alone.

The non-conformity shall be addressed per documented procedures.

11.4 If saleable product is used in PQ studies, the requirements for release of this product for distribution shall be established before the start of the PQ activities. The effect of repeated exposures to the sterilization

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processes on product and packaging functionality, and levels of residual EO and reaction products should be assessed prior to release.

If saleable product is used in MPQ studies, then procedures shall be established to ensure the product is subjected to a full EO dwell time sterilization process and formal review of its acceptance prior to release to market.

NOTE See Annex E for the requirements for release of saleable product used in PQ studies.

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) 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 Clause 4.

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.

NOTE National, regional or local requirements can apply.

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 4.2).

12.2.4 The maintenance schedule, 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 The sterilization process shall be reviewed annually to establish the extent of requalification necessary. This shall include an assessment of the whether reconfirmation of the product SAL through microbiological studies is required. 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 the possibility that the sterilization process is no longer capable of achieving the selected product SAL, the cause shall be investigated and corrective or preventive action, or both, 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 selected SAL can no longer be achieved then a new MPQ/PPQ shall be performed to re-establish the selected SAL. The investigation and subsequent actions shall be documented.

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12.3.4 Review of requalification data, reports and resulting corrective actions (if required) shall be documented and retained.

12.4 Assessment of change

12.4.1 Changes to manufacturing operations, product including microbiological quality, load or load configuration, sterilization equipment and the sterilization process shall be assessed for their impact on the effectiveness of the sterilization process.

12.4.2 The impact of the change shall be assessed and confirmed as appropriate for its impact on

12.4.2.1 The appropriateness of the internal and/or external PCD in relation to the bioburden of the product (see 8.6 and Annex B).

12.4.2.2 The product definition including load and load configuration.

12.4.2.3 The qualified sterilization process definition and the efficacy of the process (see 8.2).

12.4.3 The magnitude of any changes identified in 12.4.2 shall be considered in determining the extent to which process definition, IQ, OQ or PQ is re-evaluated or re-executed.

12.4.4 The outcome of the assessment, including the rationale for decisions reached, shall be documented and retained.

12.5 Assessment of equivalence

12.5.1 Process equivalence

Process equivalence is a documented evaluation that the same sterilization process can be delivered by two or more pieces of sterilization process equipment thin defined parameters.

Sterilization processes using equipment that delivers the same process parameters, having undergone IQ and OQ, shall be qualified either

a) in the same manner as the original chamber; or

b) using a reduced PQ that demonstrates the delivery of the required temperature and humidity conditions in the load and the required microbiological lethality. The rationale for this reduced qualification shall be recorded and documented.

See Annex J for further guidance.

The influence of different geographical locations on the product or load properties shall be determined.

12.5.2 Product equivalence

Product equivalence is a process of formally including a candidate product into an existing validated EO processing category or EO product family.

A product can be added to a validated process if deemed equivalent to or a lesser challenge than an existing qualified master product or internal PCD. A technical review shall be performed comparing the candidate product with the master product or internal 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.

See Annex J for further guidance.

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