INTERNATIONAL STANDARD

ISO 22441

First edition
2022-08

Sterilization of health care products — Low temperature vaporized hydrogen peroxide — Requirements for the development, validation and routine control of a sterilization process for medical devices

Stérilisation des produits de santé — Vapeur de peroxyde d'hydrogène à basse température — Exigences pour la mise au point, la validation et le contrôle de routine d'un procédé de stérilisation pour dispositifs médicaux

Reference number
ISO 22441:2022(E)

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Published in Switzerland

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Foreword

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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 documents 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).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

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*.

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.

Introduction

This document specifies the requirements for the development, validation and routine control of sterilization processes using a vaporized composition of water and hydrogen peroxide (H_2O_2) as the sterilizing agent. Vaporized hydrogen peroxide (VH2O2) sterilizers process typically below 60 °C and are primarily used for the sterilization of thermolabile or moisture-sensitive medical devices in health care facilities but can also be used for sterilization of other reusable medical devices that have been established as compatible with VH2O2 processes. The sterilizers operate automatically using pre-set cycles. VH2O2 sterilizer processes can also be used by medical device manufacturers during commercial production.

NOTE 1 Work is underway within CEN/TC 102 to develop a standard for requirements for VH2O2 sterilizers (EN 17180[1)]). It is intended that applicable test procedures to demonstrate conformity (e.g. type tests and works tests) will be included.

A sterile medical device is one that is free of viable microorganisms. International Standards that specify requirements for validation and routine control of sterilization processes require, when it is necessary to supply a sterile medical device, that adventitious microbiological contamination of a medical device prior to sterilization be minimized. Even so, medical devices produced under standard manufacturing conditions in accordance with the requirements for quality management systems (see, for example, ISO 13485) can, prior to sterilization, have microorganisms on them. 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 microorganisms by physical or chemical agents used to sterilize medical devices generally can best be described by an exponential relationship between the number of microorganisms surviving and the extent of treatment with the sterilizing agent; inevitably this means that there is always a finite probability that a microorganism can 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 microorganisms 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 a sterilization process by VH2O2 with appropriate microbicidal activity intended to sterilize medical devices. Furthermore, conformance with the requirements ensures that the sterilization process is both reliable and reproducible so that predictions can be made, with reasonable confidence, that there is a small probability of there being a viable microorganism present on a medical device after sterilization. Specification of 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 system 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 provided in national and international standards (e.g. ISO 13485). The standards for quality management systems recognise that, for certain processes used in manufacturing, 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 is monitored routinely and the equipment is maintained.

Exposure to a properly validated, accurately controlled sterilization process is not the only factor associated with the provision of reliable assurance that a processed medical device is sterile and, in this regard, suitable for its intended use. Attention should also be given to a number of factors including:

a) the microbiological status of incoming raw materials or components;

1) Under preparation.

b) the validation and routine control of any cleaning and disinfection procedures used on the medical device;

c) the control of the environment in which the medical device is manufactured, assembled and packaged;

d) the control of sterilizer and processes;

e) the control of personnel and their hygiene;

f) the sterile barrier system(s) including any protective packaging as applicable;

g) the conditions under which the medical device is transported and stored;

h) the material and design of the medical devices being processed.

The type of contaminants on a medical device to be sterilized varies, and this influences the effectiveness of a sterilization process. Medical devices used in a health care facility and that are being presented for sterilization in accordance with the manufacturer's instructions (see ISO 17664-1) should be regarded as special cases. There is the potential for such medical devices to possess a wide range of contaminating microorganisms and residual inorganic or organic contaminants in spite of the application of a cleaning process. Hence, the validation and control of the cleaning and disinfection processes used during processing are critical.

The guidance given in Annexes E, F, G, H, I, J and K on the application of this document is informative and is not provided as a checklist for auditors. The guidance provides explanations and methods in relation to the application of the document that are regarded as being a suitable means for conforming with the requirements of this document. 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 comprise a number of discrete but interrelated activities, e.g. calibration, maintenance, product definition, process definition, installation qualification, operational qualification and performance qualification. 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 that they are presented. The activities required are not necessarily sequential, as the programme of development and validation can be iterative. The responsibility for carrying out the activities required by this document vary from case to case. This document requires that the responsibilities of the various parties be defined (see 4.1) but does not specify to whom the responsibilities are allocated. E.4 provides guidance on allocation of responsibility.

Like other standardized low temperature sterilization processes such as ethylene oxide (ISO 11135) or low temperature steam and formaldehyde (ISO 25424), the VH2O2 sterilization processes are specified by physical and chemical parameters and can be verified using physical, chemical and microbiological means.

Sterilization processes to which this document applies should consider not only technical issues but also the environmental impact. Activities required by this document can contribute to an environmental burden that can be minimised by planning and combining tests. Additional information regarding environmental impact is provided in Annex G.

NOTE 2 Specifications on operating safety are addressed in IEC 61010-1, IEC 61010-2-040 and are not included in this document. IEC 60204-1 can also apply.

NOTE 3 Requirements on occupational safety are not specified in this document (see 1.2.4).

This document has two distinct applications:

— for manufacturers of VH2O2 sterilizers and users of VH2O2 sterilization processes in the health care facility;

— for manufacturers of VH2O2 sterilizers and users of VH2O2 sterilization processes in the manufacture of healthcare products.

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1 Scope

1.1 Inclusions

1.1.1 This document provides requirements for the development, validation and routine monitoring and control of a low temperature sterilization process for medical devices using vaporized hydrogen peroxide (VH2O2) as the sterilizing agent.

1.1.2 This document is intended to be applied by process developers, manufacturers of sterilization equipment, manufacturers of medical devices to be sterilized, organizations performing process validation of VH2O2 sterilization, and organizations responsible for sterilizing medical devices.

NOTE VH2O2 sterilizers can be used in both health care and industrial facilities, and this document acknowledges the similarities and differences between the two applications.

1.2 Exclusions

1.2.1 Processes that use other sterilizing agents, or hydrogen peroxide solution in combination with other chemicals as the sterilizing agent are not addressed in this document.

NOTE See ISO 14937 for guidance on validation of such processes.

1.2.2 This document does not specify requirements for development, validation and routine control of a process for inactivating the causative agents of spongiform encephalopathies, e.g. 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 Some VH2O2 sterilizers have processes that demonstrate some level of inactivation of the causative agents of spongiform encephalopathies, e.g. scrapie, bovine spongiform encephalopathy and Creutzfeldt-Jakob Disease. However, this inactivation is process, cycle, and test protocol specific, therefore this inactivation is outside the scope of this document, and no specific test methods are provided (see [14], [26], and [30] for more information).

1.2.3 This document does not specify requirements for designating a medical device as sterile.

NOTE See for example EN 556–1 or ANSI/AAMI ST67.

1.2.4 This document does not specify requirements for occupational safety associated with the design and operation of VH2O2 sterilization equipment.

NOTE For further information on safety, see examples in the Bibliography. National or regional regulations can also exist.

1.2.5 This document does not apply to the contents of contained product, i.e. product for which the environment within the sterilizer chamber during any stage of the sterilization process does not come into direct contact with the product, such as a solution in a sealed bottle.

1.2.6 This document does not cover hydrogen peroxide decontamination systems for use in rooms, enclosures or environmental spaces.

NOTE These decontamination systems operate at ambient conditions (e.g. temperature and pressure) and in general utilise an approach that is different to that of VH2O2 sterilization processes addressed in this document.

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 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

ISO 11138-1:2017,[2)] *Sterilization of health care products — Biological indicators — Part 1: General requirements*

ISO 11140-1, *Sterilization of health care products — Chemical indicators — Part 1: General requirements*

ISO 11607-1:2019, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 11607-2, *Packaging for terminally sterilized medical devices — Part 2: Validation requirements for forming, sealing and assembly processes*

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
bioburden
population of viable microorganisms on or in product and/or *sterile barrier system* (3.46)

[SOURCE: ISO 11139:2018, 3.23]

2) ISO 11138-1 gives general requirements for biological indicators, including information that can be used for guidance on test microorganism selection. Specific requirements will be given in a new document, ISO 11138-6 under preparation, current stage ISO/AWI 11138-6.

3.2
biological indicator
BI
test system containing viable microorganisms providing a specified resistance to a specified sterilization process

[SOURCE: ISO 11139:2018, 3.29]

3.3
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]

3.4
chamber
part of equipment in which a load is processed

[SOURCE: ISO 11139:2018, 3.36]

3.5
change control
assessment and determination of the appropriateness of a proposed alteration to product, process, or equipment

[SOURCE: ISO 11139:2018, 3.39]

3.6
chemical indicator
CI

test system that reveals change in one or more pre-specified *process variables* (3.33) based on a chemical or physical change resulting from exposure to a process

[SOURCE: ISO 11139:2018, 3.43]

3.7
conditioning
treatment of product prior to the *exposure phase* (3.15) to attain a specified temperature, relative humidity, or other *process variable* (3.33) throughout the load

[SOURCE: ISO 11139:2018, 3.58]

3.8
cycle parameter
value of a *cycle variable* (3.9) including its tolerance used for control, monitoring, indication, and recording of an *operating cycle* (3.25)

[SOURCE: ISO 11139:2018, 3.72]

3.9
cycle variable
property used to control, monitor, indicate, or record an *operating cycle* (3.25)

[SOURCE: ISO 11139:2018, 3.74]

3.10
***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]

3.11
development
act of elaborating a specification

[SOURCE: ISO 11139:2018, 3.79]

3.12
environmental control
application of engineering and/or procedural systems to maintain conditions in a defined space within specified limits

[SOURCE: ISO 11139:2018, 3.102]

3.13
equipment maintenance
combination of all technical and associated administrative actions intended to keep equipment at a state in which it can perform its required function, or restore it to such a state

[SOURCE: ISO 11139:2018, 3.106]

3.14
establish
determine by theoretical evaluation and confirm by experimentation

[SOURCE: ISO 11139:2018, 3.107]

3.15
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 purposes of this document, VH2O2 is used as the sterilizing agent.

[SOURCE: ISO 11139:2018, 3.111]

3.16
fault
situation in which one or more of the process or *cycle parameters* (3.8) is/are outside its/their specified tolerance(s)

[SOURCE: ISO 11139:2018, 3.116]

3.17
health care facility
dedicated setting where health care professionals deliver services for care of patients

EXAMPLE Hospitals, free standing ambulatory surgical centres, nursing homes, extended care facilities, medical, dental and physician offices or clinics and other specialised treatment facilities.

3.18
health care product(s)
medical device, including in vitro diagnostic medical device, or medicinal product, including biopharmaceutical

[SOURCE: ISO 11139:2018, 3.132]

3.19
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]

3.20
load
product, equipment, or materials to be processed together within an *operating cycle* (3.25)

[SOURCE: ISO 11139:2018, 3.155]

3.21
load configuration
distribution and orientation of a load

[SOURCE: ISO 11139:2018, 3.156]

3.22
measuring chain
series of elements of a measuring instrument or measuring system, which constitutes the path of the measurement signal from the input (quantity subject to measurement) to the output (the result of the measurement)

[SOURCE: ISO 11139:2018, 3.165]

3.23
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]

3.24
microorganism
entity of microscopic size, encompassing bacteria, fungi, protozoa, and viruses

[SOURCE: ISO 11139:2018, 3.176]

3.25
operating cycle
complete set of *stages* (3.43) 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.

[SOURCE: ISO 11139:2018, 3.188]

3.26
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]

3.27
packaging system
combination of a *sterile barrier system* (3.46) and *protective packaging* (3.35)

[SOURCE: ISO 11139:2018, 3.192]

3.28
parametric release
declaration that product is *sterile* (3.45) based on records demonstrating that the sterilization *process variables* (3.33) were delivered within specified tolerances

[SOURCE: ISO 11139:2018, 3.193]

3.29
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]

3.30
preconditioning
treatment of product, prior to the *operating cycle* (3.25), to attain specified values for temperature, relative humidity, and/or other *process variables* (3.33)

[SOURCE: ISO 11139:2018, 3.200]

3.31
process challenge device
PCD
item providing a defined resistance to a cleaning, disinfection, or sterilization process and used to assess performance of the process

[SOURCE: ISO 11139:2018, 3.205]

Note 1 to entry: For the purpose of this document, item means a simulation of a product, a test device, or an inoculated product.

3.32
process parameter
specified value for a *process variable* (3.33)

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

[SOURCE: ISO 11139:2018, 3.211]

3.33
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]

3.34
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]

3.35
protective packaging
configuration of materials designed to prevent damage to the *sterile barrier system* (3.46) and its contents from the time of their assembly until the point of use

[SOURCE: ISO 11139:2018, 3.219]

3.36
reference measurement point
location of the sensor controlling the *operating cycle* (3.25)

[SOURCE: ISO 11139:2018, 3.227]

3.37
reference microorganism
microbial strain obtained from a recognized culture collection

Note 1 to entry: Recognized culture collection is defined as a depository authority under the Budapest Treaty on *The International Recognition of the Deposit of Microorganisms for the Purpose of Patent and Regulation.* See ISO 11139:2018, 3.222.

[SOURCE: ISO 11139:2018, 3.228, modified — Note 1 to entry added.]