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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

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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 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.

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

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.]

3.38
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]

3.39
safety data sheet
SDS
document specifying the properties of a substance, its potential hazardous effects for humans and the environment, and the precautions necessary to handle and dispose of the substance safely

[SOURCE: ISO 11139:2018, 3.239]

3.40
services
supplies from an external source needed for the function of equipment

EXAMPLE Electricity, water, compressed air, drainage.

[SOURCE: ISO 11139:2018, 3.252, modified — EXAMPLES added.]

3.41
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]

3.42
specify, verb
stipulate in detail within an approved document

[SOURCE: ISO 11139:2018, 3.259]

3.43
stage
<operating cycle> part of an *operating cycle* (3.25) with a specified function.

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

[SOURCE: ISO 11139:2018, 3.262]

3.44
sterilant
chemical or combination of chemicals used to generate a sterilizing agent

Note 1 to entry: For the purposes of this document this is water and hydrogen peroxide.

[SOURCE: ISO 11139:2018, 3.268, modified — Note 1 to entry added.]

3.45
sterile
free from viable microorganisms

[SOURCE: ISO 11139:2018, 3.271]

3.46
sterile barrier system
minimum package that minimizes the risk of ingress of microorganisms and allows aseptic presentation of the *sterile* (3.45) contents at the point of use

[SOURCE: ISO 11139:2018, 3.272]

3.47
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]

3.48
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]

3.49
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]

3.50
sterilization cycle
predetermined sequence of *stages* (3.43) performed in a sterilizer to achieve product free of viable microorganisms

[SOURCE: ISO 11139:2018, 3.279]

3.51
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]

3.52
sterilizer
equipment designed to achieve sterilization

[SOURCE: ISO 11139:2018, 3.287]

3.53
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]

3.54
test of sterility
technical operation performed as part of *development* (3.11), validation, or *requalification* (3.38) to determine the presence or absence of viable microorganisms on product or portions thereof

[SOURCE: ISO 11139:2018, 3.299]

3.55
type test
technical operation to verify conformity of an equipment type to a standard or specification, and to establish data for reference in subsequent tests

[SOURCE: ISO 11139:2018, 3.306]

3.56
usable chamber space
specified geometry within the chamber that is available to accept the load

[SOURCE: ISO 11139:2018, 3.311]

3.57
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]

3.58
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 elements

4.1 The development, validation and routine control of a sterilization process is a critical element in realization of health care products. 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 (see also E.4);

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

— control of product provided by external parties;

— calibration of all equipment, including instrumentation for test purposes;

— identification and traceability of product throughout the process; and

— control of non-conforming products.

NOTE 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.

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

5 Sterilizing agent characterization

5.1 General

5.1.1 The purpose of this activity is to define the sterilizing agent, demonstrate its microbicidal effectiveness, identify the factors that influence microbicidal effectiveness, assess the effects that exposure to the sterilizing agent has on materials, and identify requirements for safety of personnel and protection of the environment. This activity may be undertaken in a test or prototype system.

5.1.2 The final equipment specification (see 6.3.2) shall be relatable to the results of experimental studies, which might have been undertaken in the test or prototype equipment. For the purpose of this document the sterilizing agent shall be a mixture of VH202 and water vapor. Additional information on VH2O2 can be found in informative Annex I and[25].

5.1.3 The sterilizing agent characterization shall include a specification of the chemical composition of the sterilant and how the sterilizing agent is generated.

5.2 Sterilant and sterilizing agent

The sterilant specification shall be provided. The specification shall include conditions of storage of the sterilant for the duration of the stated shelf-life to ensure the sterilizing agent being applied is within its specification. The sterilant specification shall also include the maximum concentration of each sterilant component including any contaminant that could either affect the solution stability during its shelf-life or impact the safety of the sterilized product (see also 5.5.1).

NOTE H_2O_2/H_2O solutions contain stabilizers which can influence the sterilization activity.

5.3 Microbicidal effectiveness

Data shall be available to demonstrate the microbicidal effectiveness of the sterilizing agent in the VH2O2 process (see E.5.3). Microbiological efficacy data from multiple sources (e.g. testing, sterilizer manufacturer provided data, literature) may be used to satisfy these requirements based on its appropriateness to the process as determined by the party responsible for the sterilization process. These data shall be suitable to:

a) demonstrate the lethal action of the sterilizing agent against the reference microorganism, *Geobacillus stearothermophilus* spores, if the overkill method is used, or viable microorganisms selected in accordance with Annex A. Microorganisms should be presented on a non-cellulosic carrier;

NOTE 1 ISO 11138-1 gives general requirements for biological indicators (BIs).

NOTE 2 ISO 11138-6[3)] is under preparation. Once published, BIs conforming with ISO 11138-6 can be used for determination of the lethal action of the sterilizing agent against the reference microorganism. Until available, ISO 11138-1 can be used for guidance.

3) Under preparation. Stage at the time of publication: ISO/AWI 11138-6.

NOTE 3 The inactivation of *Geobacillus stearothermophilus* as a viable microorganism providing a specified resistance has been comprehensively documented in the literature. This literature provides knowledge of the manner in which H_2O_2 affects microbial inactivation.

b) establish an empirical mathematical relationship defining the microbial inactivation kinetics of identified resistant microorganisms so that the probability of a microorganism surviving exposure to a defined treatment can be predicted and is reproducible;

c) identify the process variables that affect the lethal action of the sterilizing agent and the interactions of these process variables in relation to this lethal action (see 6.2.3, also[23] and[31] provide additional information);

d) assess those factors that can influence the microbicidal effectiveness of the sterilizing agent based upon physical or chemical interactions and its delivery or distribution;

e) identify a means for terminating the microbicidal activity of the sterilizing agent (see D.2.6);

f) assess material properties that directly affect the inactivation kinetics of microorganisms[31].

5.4 Effects on materials

5.4.1 The effects of exposure to the VH2O2 process on the physical or chemical properties of product and packaging materials shall be assessed and the outcomes of tests shall be recorded (see 4.1).

NOTE The VH2O2 process includes material effects of the sterilizing agent, additives, processing conditions and chemical reaction products. See [22] for additional guidance on effects of the sterilizing agent on materials.

5.4.2 The following clauses require assessments to be performed during the sterilization process development phase. These assessments may be conducted on product or product prototypes. The results of these assessments may become part of the specifications (see Clause 6) and may be used for documented evidence of conformity with the requirements of this clause.

5.4.3 Experimental results or available information shall be used to study the effects of repeated exposure, if applicable, to the sterilization process on the properties of materials (e.g. those potentially used for product and packaging systems), using the combination of process parameters applicable to that device that maximize effects on materials.

5.4.4 The biological safety of materials following exposure to the sterilizing agent shall be assessed based on data established in accordance with ISO 10993-1.

5.4.5 Limits for the process residuals on/in product materials shall be based on a health-based risk assessment conducted in accordance with ISO 10993-17.

NOTE National limit values can be specified. See also EU Risk Assessment Report[24].

5.5 Safety and the environment

5.5.1 A safety data sheet shall be available for the sterilant. Measures needed to protect the health and safety of personnel using the process shall be specified.

WARNING — Hydrogen peroxide is corrosive and irritating to the eyes and skin and can pose a potential hazard to patients and operators.

5.5.2 The potential effect on the environment of any substance which could be released, either deliberately or accidentally, during or following use of the sterilant or sterilizing agent, shall be assessed and measured for the control of the substance(s) established. This assessment, including any potential effect and measures for control shall be recorded (see 4.1).

NOTE See Annex G.

5.5.3 Instructions and information concerning the processing of loads that are not dry before being processed shall be provided to process users.

WARNING — Mixtures of hydrogen peroxide with water, either as vapour, or as a liquid composition are likely to be corrosive to material surfaces and are irritating to the eyes and skin and can pose a potential hazard to patients and operators.

6 Process and equipment characterization

6.1 General

The sterilization process shall be defined in order to deliver an effective and reproducible process. This shall address the following:

a) process characterization;

b) equipment and process parameters;

c) control and monitoring.

NOTE EN 17180 is in development by CEN/TC 102 and specifies requirements for the design and performance of low temperature VH2O2 sterilizers.

6.2 Process characterization

6.2.1 The process parameters, together with their tolerances, shall be specified. These tolerances shall be based upon knowledge of the combination of process parameters yielding acceptable microbicidal effectiveness. Processing at such process parameters shall routinely yield a safe and functional product.

6.2.2 Process characterization, at a minimum, shall include:

a) identification of phases necessary for a VH2O2 sterilization process;

b) specification of defined process variables and corresponding parameters for each phase of the sterilization operation;

c) any restriction of the items and load configuration for a given operating cycle such as mass, geometry and materials.

6.2.3 The process specifications shall include:

a) a description of the operating cycle(s);

b) the process parameters including their tolerances;

c) the process and cycle parameters that are measured and used to verify the sterilization process shall include:

   1) time intervals and set points;

   2) temperature, (e.g. load, chamber and vaporizer);

   3) VH2O2 concentration (measured directly or indirectly);

   4) pressure.

d) any load preconditioning (e.g. temperature, moisture) that is required prior to exposure to the operating cycle to ensure effectiveness of the sterilization process;

e) restrictions on the load, e.g. configuration, temperature, material type, packaging system, size or mass of the sterilization load;

f) the location for chemical indicators (CIs) and/or BIs (BIs are used in batch release and verification) (see 8.5 and 8.6).

NOTE Annex F provides an example of a VH2O2 sterilization cycle.

6.2.4 Any treatment of product that is required following exposure to the sterilizing agent to ensure conformity to the requirements of this document shall be specified as part of the sterilization processes.

6.3 Equipment characterization

6.3.1 The sterilizer to deliver the process in a safe manner within the tolerances stipulated for the process parameters shall be specified.

6.3.2 The specification shall include, but is not limited to:

a) physical description of the sterilizer and necessary ancillary items, including materials of construction;

b) identification of the available operating cycles of the sterilizer, their intended use, and the cycle parameters established for each operating cycle;

c) specification of the sterilant (see 5.2) and the means by which the sterilizing agent is generated and delivered to the chamber;

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

e) fault(s) and failure(s) recognised by the sterilizer;

f) safety features, including those for personnel and environmental protection, including the means used to eliminate hydrogen peroxide from chamber effluent;

g) installation requirements, including those for the control of emissions, if applicable;

h) details of each service necessary for the correct function of the sterilizer;

i) the location of the reference measurement point(s);

j) the maximum rate of change of falling and rising pressure and tolerances for each operating cycle;

k) the specification for any air filtering or other filtering devices used to prevent contaminants from entering the chamber;

l) the maximum emissions of H_2O_2 from the equipment during normal operation, allowing verification to be made for conformity with local, regional, or national regulations (see Annex G).

6.3.3 Control and monitoring

The equipment specification shall confirm that means are provided to ensure that a failure in a control function does not lead to a failure in recording of process parameters such that an ineffective process appears effective. This may be achieved by:

a) the use of segregated systems for cycle control and recording;

b) independently measured monitoring data; or

c) a cross-check by the monitoring system to identify any discrepancies between control data and data from independent monitoring devices and, if applicable, to indicate them as a fault.

NOTE EN 17180, currently under development in CEN/TC 102, displays examples of suitable concepts for cycle control, monitoring, data processing and recording.

The specification shall include provisions to ensure that any failure of parts or functions of the sterilizer recognised by the control and monitoring system of the equipment is indicated and recorded.

7 Product definition

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

7.2 The product to be sterilized, including the sterile barrier system to be used and the manner in which product is to be presented to the sterilization process (load configuration), shall be specified. The functionality of medical devices after exposure to the sterilization process shall be assessed. The selection of medical devices used for functionality testing and the number of repetitive exposures shall be justified. Meeting this requirement could necessitate that appropriate information, including maintenance activities required by the medical device manufacturer, be provided to the organization undertaking the sterilization process by the manufacturer of the medical device and the manufacturer of the sterilization equipment.

NOTE Meeting this requirement encourages the organization undertaking the sterilization process to ask for appropriate available information from the manufacturer of the sterilization equipment and the manufacturer of the medical device. Information provided according to ISO 17664-1 can support this activity.

7.3 Packaging shall be designed to allow penetration of humidity and sterilizing agent as required and shall be suitable for use in VH2O2 processing. Packaging system material compatibility studies shall include an assessment if materials absorb or promote the decomposition of VH2O2 compromising the sterilization process. The sterile barrier system shall be specified and shall be in accordance with ISO 11607-1 and ISO 11607-2 (using ISO/TS 16775 as guidance if needed) considering the conditions for VH2O2 sterilization and the cycle parameters.

NOTE It is possible that cellulosic materials such as papers or nonwovens containing cellulose, or materials that have a high absorbance of VH2O2 will not be appropriate in VH2O2 sterilization processes.

7.4 The documentation available for product definition shall allow confirmation that the process as defined in Clause 8 is capable of reducing level(s) of process residual(s) on/in product or the packaging system below that (those) identified in accordance with ISO 10993-17 (see 5.4.5).

7.5 A specification shall be established that defines and controls the microbiological, organic and inorganic contamination levels of the product presented for sterilization to ensure that it does not compromise the effectiveness of the sterilization process.

7.6 The effectiveness of the procedure defined in accordance with 7.5 shall be established. For medical devices to be supplied for single use, this shall include an estimation of bioburden in accordance with ISO 11737-1. For medical devices to be processed, this shall include an assessment of the effectiveness of the specified cleaning and, if applicable, disinfecting processes.

7.7 If the product is assigned to a product family, the product and its packaging system shall be specified (see E.7.8).

7.8 The criteria for assigning a product to a product family shall be specified.

7.9 If a process challenge device (PCD) is intended to be used to represent a defined resistance to sterilizing the product in its sterile barrier system, it shall be specified (see 8.8).

8 Process definition

8.1 The purpose of this activity is to obtain a detailed specification for the sterilization process to be applied to a defined product (see Clause 7), without compromising the safety, quality and performance of that product.

8.2 The sterilization cycle applicable to the product defined in accordance with Clause 7 shall be specified.

8.3 The sterility assurance level (SAL) attained for the product during the specified sterilization cycle shall be established by one of the following methods:

a) 'bioburden' method (see Annex B);

b) 'BI/bioburden' method (see Annex C);

c) 'overkill' method (see Annex D).

NOTE 1 EN 556-1 provides requirements for terminally sterilized medical devices designated as 'sterile'.

NOTE 2 ISO/TS 19930 and ANSI/AAMI ST67 provide guidance on identifying the aspects to be considered as part of a risk-based approach to selecting an SAL.

8.4 The sterilization cycle appropriate for a defined product shall be established. This shall be achieved by:

a) selecting the cycle parameters and demonstrating their attainment by measurements;

b) performing the defined process in a sterilizer that has undergone installation qualification (IQ) and operational qualification (OQ) procedures (see 9.2 and 9.3);

c) applying the sterilizing agent under conditions as established in accordance with one of the approaches outlined in Annexes B, C or D for each defined product (see Clause 7);

d) confirmation of the biological safety for the defined product after end of cycle, based on the results of the activities according to 5.4.4 and 5.4.5;

e) considering the influence of product materials and their surface characteristics on the inactivation kinetics of microorganisms[29] and therefore sterility of the load.

NOTE Information provided according to ISO 17664-1 can support this activity.

f) considering that the function of the product and packaging materials are not impaired (see 5.4.1 and 7.2).

8.5 Biological indicators used as part of the establishment of the sterilization process shall:

a) be in accordance with ISO 11138-1;

NOTE ISO 11138-6 is under preparation and will provide additional requirements and information when available.

b) contain *Geobacillus stearothermophilus* spores as the indicator microorganism; alternatively may,

1) contain a microorganism per Annex A and which is shown to be appropriate (see 5.3); or

2) contain a microorganism that is shown to be more resistant relative to product bioburden where a bioburden-based validation approach is used (Annex B).

c) be placed either at positions in product where it has been determined that sterilizing conditions are most difficult to achieve or within a PCD established per 8.8;

d) have established storage conditions to ensure their quality and composition remain within specification.

8.6 If CIs are used as part of the establishment of the sterilization process, they shall

a) be in accordance with ISO 11140-1;

b) be placed either at positions in product where it has been determined that sterilizing conditions are most difficult to achieve or within a PCD (see 8.8);

c) not be used as the sole means of establishing the sterilization process;

d) not be used as an indicator that the required SAL has been achieved;

e) have established storage conditions to ensure their quality and composition remain within specification.

8.7 If tests of sterility are performed during the establishment of the sterilization process, such tests shall be in accordance with ISO 11737-2.

8.8 If PCDs are used as part of the establishment of the sterilization process or routine monitoring, they shall be specified and their appropriateness shall be determined. PCDs shall present a challenge to the specified characteristics of the sterilization process that is equivalent to or greater than that at the position in product where it has been determined that sterilizing conditions are most difficult to achieve. The demonstration of the appropriateness of a PCD may be performed through comparative resistance studies utilizing tests of sterility in accordance with ISO 11737-2.

9 Validation

9.1 General

The purpose of validation process is to demonstrate by objective evidence, that the sterilization process established in the process definition (see Clause 8) can be delivered effectively and reproducibly to the sterilization load. Validation consists of a number of identified stages: IQ, OQ and performance qualification (PQ).

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

OQ is carried out either with unloaded sterilizer or using appropriate test materials to demonstrate the capability of the sterilizer to deliver the operating cycle in conformance with selected parameters that have been defined (see Clause 8).

PQ is the stage of validation that uses product to demonstrate that the sterilizer consistently operates in accordance with predetermined criteria, including process parameters, and the process yields product that is sterile and meets the specified requirements. PQ shall be carried out for each operating cycle or product to be qualified to demonstrate that the process conforms with identified acceptance criteria and is capable of delivering the required SAL to the product.

9.1.1 Prior to validation, documentation shall be reviewed for validity and applicability (see E.9.1.1).

NOTE Part of the documentation verification can also be considered as being part of IQ.

9.1.2 Each stage of validation shall be carried out in accordance with a documented procedure or protocol. Informative Annex J and Annex K provide guidance on recommended validation tests and test procedures.

9.1.3 It shall be verified that each item of equipment used during validation conforms with its specification.

9.1.4 Any modifications of product, equipment, or operating cycle carried out during validation shall be recorded and justified, and the specification(s) changed accordingly (see also 12.5).

9.1.5 Modifications to product, equipment or processes shall be conducted under a change control process by designated and trained personnel, and can require additional type testing, revalidation or re-certification in order to ensure that the process or equipment functions as intended.

9.1.6 The measuring chain for each test instrument used for validation shall be in accordance with the requirements in 4.1.

9.1.7 The correlation between readings indicated and recorded by instruments fitted to the sterilizer and readings registered by corresponding independent test instruments shall be verified.

9.1.8 Conformance with safety and operational specifications (see 6.3.2) shall be verified after installation at the site.

9.1.9 Documented results shall be evaluated in order to confirm that the installed sterilizer provides consistently and reproducibly the specified sterilization cycles. The evaluation shall include, at a minimum:

a) scheduled maintenance tests;

b) periodic tests during routine operation, as recommended by the user instructions;

c) documented technical corrective actions (repairs) upon system failures;

d) records from routine cycle monitoring.

These results may be used to confirm or improve current operating instructions which specify routine operation, periodic tests, scheduled maintenance activities, and finally propose the time point for the next re-qualification.

9.2 Installation qualification (IQ)

9.2.1 General

9.2.1.1 The location in which the sterilizer is to be installed, including any services required, shall be specified. Any special precautions and provisions shall be identified (e.g. safety equipment).

9.2.1.2 Instructions for installation shall be specified and shall include instructions pertinent to the health and safety of personnel.

9.2.1.3 The conditions for the storage of the sterilant to ensure that its quality and composition remain within specification shall be specified.

9.2.1.4 It shall be demonstrated that the sterilizer and any ancillary equipment is capable of operating as intended when operated at specified environmental conditions.

9.2.2 Equipment

9.2.2.1 Equipment to be used in the sterilization process, including any ancillary items, shall be specified.

9.2.2.2 The equipment documentation and installation protocol shall provide evidence that the sterilizer conforms to its specification as installed and that identified basic safety features and fault indications are operating as intended.

9.2.2.3 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 and failure 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.

9.3 Operational qualification (OQ)

9.3.1 Prior to OQ, the calibration status of all instrumentation (including any test instruments) used for monitoring, controlling, indicating, or recording shall be confirmed (see 4.2).

9.3.2 OQ shall demonstrate that the installed sterilizer (see Clause 6) is capable of delivering the specified process parameters within defined tolerances.

9.3.3 Results of the IQ shall be available prior to operational qualification (see 9.2.2).

9.3.4 OQ shall be carried out in accordance with a specified test programme (i.e. test protocol). The programme shall define requirements to be verified, test equipment, test procedures and acceptance criteria.

9.4 Performance qualification (PQ)

9.4.1 The manner of presenting the product for sterilization, including the orientation of product, shall be specified.

9.4.2 A product used in PQ shall be packaged equivalently or considered to be a greater challenge than that to be sterilized routinely. For each type of packaging, it is necessary to define all product families (if applicable) and select configurations to define loads used in PQ which are considered most difficult to be sterilized. The selection of products constituting each type of load shall be documented.

9.4.3 Data shall be generated to demonstrate the attainment of the defined physical or chemical conditions, within specified tolerances, throughout the sterilization load. Relationship(s) between the conditions occurring at positions used routinely to monitor the sterilization cycle and those conditions occurring throughout the sterilization load shall be established. This is achieved by determining the attainment of the specified condition(s) at predetermined positions throughout the sterilization load. Process or cycle parameters measured in PQ shall be correlated to parameters used for control, monitoring or recording in routine operation.

NOTE One or more test sensors for this purpose are typically located as closely as possible to the positions of the respective sterilizer chamber sensor probes.

Microbiological performance qualification studies shall comprise delivery of the sterilizing agent under conditions so designed that the extent of treatment is reduced relative to that in the sterilization process. Extrapolation of the outcomes of such reduced treatment(s) shall be used to predict that, upon application of the full sterilization process, the specified SAL is met. The approaches to process definition described in Annexes B, C, or D shall be employed in microbiological performance qualification studies. Justification of the selected method shall be documented.

9.4.4 Prior to performing PQ, the following shall be verified:

a) documentation confirms a successful IQ and OQ;

b) the test sterilization load used during PQ shall use product or similar items representative of that to be sterilized routinely. If multiple product families are compatible and assigned to the sterilization process the product family verified to represent the greatest challenge to the sterilization process shall be used in PQ;

c) the sterile barrier system is identical to or provides a challenge evaluated and considered greater than that intended for routine production or processing;

d) the condition of the product conforms with 6.2.3 d), 7.2, and 7.5;

e) the PQ load configuration conforms with 7.2 and has been evaluated and considered to be the most difficult to sterilize;

f) the size or mass of the PQ sterilization load conforms with 7.2.

9.4.5 For each of the following, studies shall be established to determine:

a) conformity to the sterilization cycle identified in Clause 8 and the range of parameters identified in 6.2.3 b);

b) the minimum and maximum cycle parameters and sensor locations, measured during the sterilization cycle;

c) the specified parameters of the sterilization processes determined from the sterilizer chamber pressure, temperature and H_2O_2 concentration and, if applicable, other variable for a specific design;

d) the response of the BIs (see 8.5);

e) the response of the CIs, if used (see 8.6);

f) the integrity of the sterile barrier system (see the ISO 11607 series).

9.4.6 Biological indicators employed during microbiological performance qualification shall be in accordance with 8.5.

9.4.7 If tests of sterility are performed on a product as part of PQ, such tests shall be performed in accordance with ISO 11737-2.

9.4.8 If CIs are used in PQ, they shall be in accordance with 8.6.

9.4.9 If PCDs are used in PQ, they shall be in accordance with 8.8.

9.4.10 The rationale for the number and locations of sensors used to demonstrate that requirements are met in the sterilization load shall be documented (see guidance in Annex H).

9.4.11 The PQ shall include a minimum of three qualification cycles, consecutive in the same study, in which all the specified acceptance criteria are met. If a failure can be attributed to factors not relevant to the effectiveness of the process being validated, this may be documented as unrelated to the performance of the process without requiring three further consecutive successful runs. Examples of this type of failure can include, but are not limited to, power failures, other loss of services, or failure of external monitoring equipment.

9.4.12 The levels of any process residues following exposure to the upper tolerances of the process parameters shall be demonstrated as being below the specified limits identified in the health-based risk assessment (see 5.4.5 and 7.4).

9.4.13 It shall be confirmed that the product meets its specified requirements for safety, quality and performance following application of the defined process within specified tolerances of the process parameters.

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 of the sterilization process and to approve the process specification.

9.5.2 Information gathered or produced during IQ, OQ and PQ shall be recorded and reviewed for acceptability. The results of this review shall be recorded (see 4.1).

9.5.3 The cycle specifications (see Clause 8), including the parameters and their tolerances [see 6.2.3 c)], shall be confirmed. This specification shall include the criteria for designating the sterilization process used for a particular sterilizer load as conforming, and shall document at least the following:

a) the product family(ies) that can be processed (if applicable);

b) the load configuration(s);

c) the size of the sterilization load or its mass;

d) the procedures for any conditioning of product;

e) a description of the sterile barrier system, including its assembly, as well as its validation and demonstration of compatibility with VH2O2 (see the ISO 11607 series);

f) the instructions for how to arrange the medical devices within a package containing multiple medical devices, if applicable;

g) the periodic tests (see 10.5);

h) the bioburden, if applicable;

i) any material type exclusions or limitations.

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 There shall be evidence through measurements, supplemented as necessary by BIs (see 10.8) or CIs (see 10.9), that the sterilization process was delivered within the defined tolerances (see 9.5.3).

10.3 Routine monitoring and recording shall be performed on each sterilization cycle.

10.4 Evidence of scheduled maintenance, current calibration status and validation shall be verified.

10.5 The operational status of the equipment shall be verified by evidence from periodic tests of factors such as (but not limited to) the following:

a) air leakage into the sterilizer chamber (if applicable);

b) automatic control (e.g. a test to verify that the operating cycle continues to function correctly);

c) sterilization process (e.g. a test to verify that the sterilization process remains reproducible).

10.6 The recorded data shall include the cycle parameters described in 6.2.3 c) and 9.5.3.

10.7 All records shall be retained in accordance with 4.1.

10.8 If BIs are used in routine monitoring, they shall be in accordance with 8.5.

10.9 If CIs are used in routine monitoring, they shall be in accordance with 8.6.

10.10 If PCDs are used in routine monitoring and control, they shall be in accordance with 8.8.

11 Product release from sterilization

11.1 A procedure for product release from sterilization shall be specified. This procedure shall define the criteria (see 9.5.3) for designating a sterilization process as conforming to its specification.

11.2 Parametric release shall only be used if the defined process/cycle parameters necessary for parametric release are controlled and monitored. The monitoring of these parameters shall be justified as sufficient to ensure specified microbiocidal effectiveness. For release of product, the parameters have to be delivered within specified tolerances established during the process validation. Records of process/cycle parameters shall be retained (see 4.1).

11.3 If BIs or CIs are used to monitor the sterilization process (see 8.5 and 8.6), the results of these indicators shall be included within the criteria for product release from sterilization.

NOTE BIs and CIs are widely used to support product release in health care facilities.

11.4 Procedures shall be established, implemented and maintained to ensure the integrity of the sterile barrier system is not compromised (see the ISO 11607 series). Visual inspection shall include the verification of all visible liquid process residues being removed from the load and the sterile barrier system.

11.5 If the criteria specified according to 9.5.3 are not met, the product shall be considered as non-conforming and handled in accordance with documented procedures (see 4.1).

12 Maintaining process effectiveness

12.1 General

The continued effectiveness of the system for ensuring the condition of the product presented for sterilization (see 7.2) shall be demonstrated (see 7.6).

12.2 Recalibration

The calibration status of all instrumentation (including any test instruments) used for monitoring, controlling, indicating, or recording shall be confirmed periodically (see 4.2).

12.3 Maintenance of equipment

12.3.1 Preventative maintenance shall be planned and performed in accordance with documented procedures. The procedure for each planned maintenance task and the frequency at which it is to be carried out shall be specified. Records of maintenance shall be retained (see 4.1).

12.3.2 Equipment shall not be used to process a product until specified maintenance tasks have been satisfactorily completed and recorded.

12.3.3 The maintenance scheme, maintenance procedures and maintenance records shall be reviewed periodically by a designated person. The results of the review shall be recorded (see 4.1).

12.4 Requalification

12.4.1 Requalification of a sterilization process, carried out for a defined product and specified equipment, shall be performed at defined intervals. The extent and frequency to which requalification is carried out shall be justified.

NOTE Recommendations to the extent and frequency of requalification in the technical documentation can be considered.

12.4.2 Requalification procedures shall be specified and records of requalification shall be retained (see 4.1).

12.4.3 Requalification data shall be reviewed against specified acceptance criteria in accordance with documented procedures. Records shall be retained (see 4.1) of reviews of requalification data together with corrections made and corrective actions taken if specified acceptance criteria are not met (see 4.1).

12.5 Assessment of change

12.5.1 Any change in the sterilization equipment that could affect delivery of the sterilization process shall be assessed. If the effectiveness and safety of the sterilization process is judged to be potentially affected, a repeat of part or all of IQ, OQ or PQ shall be carried out (see Clause 9). The outcome of this assessment, including the rationale for decisions reached, shall be recorded (see 4.1).

12.5.2 Any change in product, its package, or the presentation of product for sterilization shall be assessed for the effect on the appropriateness of the sterilization process. Based on the nature of the change, parts of the process definition (see Clause 8) or PQ (see 9.4) shall be undertaken. The outcome of the assessment, including the rationale for the decisions reached, shall be recorded (see 4.1).

Annex A
(normative)

Factors to be considered in selection of microorganisms for demonstrating microbicidal effectiveness

A.1 General

As described in 5.3, microbicidal effectiveness studies will demonstrate the lethal action of the sterilizing agent against viable microorganisms providing a specified resistance. *Geobacillus stearothermophilus* spores are recommended as such a representative microorganism of known high resistance to VH2O2, based on a long history of documented evidence.

However, there can be applications where another microorganism is selected. Hence, this annex presents the factors to be considered in selecting microorganisms, alternative to *Geobacillus stearothermophilus* spores, used in demonstrating the microbicidal effectiveness of a sterilizing agent. Table A.1 gives examples of microorganisms that can be included in such studies. Table A.1 is not exhaustive.

A.2 Identification of reference microorganism

The data obtained in the demonstration of microbicidal effectiveness identifies a suitable reference microorganism to be employed as a representative model of known, high resistance during sterilizing agent characterization and, if applicable, process definition studies.

NOTE Generally, a bacterial spore is selected.

A.3 Selection of microorganisms

In selecting microorganisms to be used in demonstrating the microbicidal effectiveness of a sterilizing agent, the following shall be considered:

a) microorganisms with known high resistance to the sterilizing agent or an expectation of a high resistance from information in the scientific literature or a knowledge of the mode of action of the sterilizing agent;

b) microorganisms with known resistance to well-characterized sterilization processes;

c) types of microorganisms (aerobic and anaerobic Gram-positive and Gram-negative bacteria, bacterial spores, mycobacteria, fungi including sporing forms, yeasts, parasites and viruses);

d) resistance of the microorganism relative to the microbiological challenge of the product being sterilized in the process;

e) ability to recover and culture microorganisms during testing;

f) any biological hazard associated with the microorganism being considered;

g) microorganisms present on the materials of construction of the product and in the environment in which the product is manufactured;

h) microorganisms that have been isolated during determinations of bioburden undertaken on a typical product to be processed and, if applicable, microorganisms likely to be present on a re-usable medical device as a result of its prior use on a patient.

Record the microorganisms selected and the rationale for their choice (see 4.1). These microorganisms can be designated by a recognised culture collection reference or other identifier that allows the source to be traced.

NOTE 1 The information with respect to microorganisms given in A.3 b) is to provide a comparison with other sterilization processes and to ensure that well-characterized microorganisms are included in the studies.

NOTE 2 Inactivation of viruses or parasites [see A.3 c)] is a particular consideration in processes used to sterilize products containing material of animal origin (see Reference [14]), as well as when processing medical devices in health care facilities.

NOTE 3 It should be understood that measured resistances of microorganisms in part depend on factors other than their genus and species, for example, the method of deposition, the arrangement on the carrier material, and the specific carrier material used (e.g. Reference [31]).

In considering the information obtained with respect to microorganisms given in A.3 e), it should be noted that the resistance of microorganisms isolated from product can be modified by recultivation.

Table A.1 — Examples of potential test microorganisms

Bacterial spores	*Bacillus atrophaeus* *Geobacillus stearothermophilus* *Clostridium sporogenes*
Vegetative bacteria	*Staphylococcus aureus* *Salmonella choleraesuis* *Pseudomonas aeruginosa*
Fungi	*Trichophyton mentagrophytes* (conidia) *Candida* spp.
Mycobacteria	*Mycobacterium terrae*
Non-lipid viruses	Hepatitis A Parvovirus Poliovirus type 1 (attenuated)
Lipid viruses	*Herpes simplex*
Parasites	*Cryptosporidium parvum*
NOTE 1 This table is not intended to be a comprehensive list of microorganisms that have to be evaluated, and it cannot be assumed to cover all the factors specified above for any particular sterilization process. This table is informative only. NOTE 2 Viral culture can use any suitable cell line which is traceable and for which the number of passage(s) is known.	

Annex B
(normative)

Approach 1 — Process definition based on inactivation of the microbial population in its natural state (bioburden method)

B.1 General

This approach requires knowledge of the resistance and population of the naturally occurring product bioburden and potential manufacturing environmental contaminants. In accordance with 7.1, bioburden representative of production should be determined in accordance with ISO 11737-1 and routinely evaluated for resistance to the sterilization process. The bioburden approach is not suitable for health care facilities sterilizing reusable medical devices as the bioburden of such devices is likely to be variable and not consistent.

In the evaluation of natural product bioburden, it is important to consider the potential contribution(s) made by all steps of the manufacturing process, and to document this in a risk assessment. An example would be evaluation/consideration of water used in the manufacturing process.

The methods described in ISO 11137-2 are examples of how process definition can be achieved based on inactivation of the microbial population in its natural state.

B.2 Product selection

Use of a bioburden-based method for process definition requires that product bioburden counts and types are known and controlled over time and that knowledge of the product bioburden resistance is comprehensive. Implementation of an ongoing bioburden monitoring program is required to use this method.

A product selected for studies on process definition should be representative of routine production. Alternatively, isolates obtained from process resistance screening of bioburden or environmental isolates can be cultivated and used to inoculate a defined population onto representative product samples.

B.3 Procedure

B.3.1 Expose the product to the sterilizing agent in predetermined increment(s) of the anticipated sterilization process. Establish the required accuracy and precision of increments, and control and monitor the delivery of the sterilizing agent to meet defined limits.

B.3.2 Following exposure to the sterilizing agent, subject products individually to a test of sterility in accordance with ISO 11737-2.

B.3.3 To define the sterilization process, use data providing the relationship between the proportion of products exhibiting no growth in tests of sterility and the extent of exposure to the sterilizing agent. Guidance on the mathematics involved can be found in ISO 11138-7.

B.4 Maintaining process effectiveness

Confirm the continued appropriateness of the sterilization process at defined intervals using a product representative of routine production (see 12.4). The method requires on-going monitoring

of microorganism type(s), population, and resistance of the bioburden and control to defined levels established in the validation. It is common practice to conduct bioburden or microbial limits tests on each lot and or batch presented for sterilization. Bioburden is a critical characteristic of the defined process and bioburden testing is conducted to demonstrate bioburden is within defined limits prior to product release.

Annex C
(normative)

Approach 2 — Process definition based on inactivation of reference microorganisms and knowledge of bioburden (BI/ bioburden method)

C.1 General

This approach has been referred to as the "combined BI/bioburden method". Use of a bioburden-based method for process definition requires that product bioburden counts and types are known and controlled over time and that knowledge of the product bioburden resistance is comprehensive. Guidance on this approach is in ISO 11138-7.

Microorganisms can exhibit log-linear inactivation kinetics when tested in constant exposure conditions. However, because it is difficult for VH2O2 processes to maintain constant concentration over time, the rate of kill can vary during different stages of the process. A knowledge of the inactivation kinetics can be obtained as in 5.3 b). Linear inactivation kinetics are not always observed with H_20_2 processes. In addition to this, the nature of the inactivation kinetics can be influenced by the product. For linear and non-linear kinetics, the extent of treatment can be defined conservatively as twice that employed in D.2.4 or D.2.5.

C.2 Procedure

C.2.1 Establish the location(s) within product at which sterility is most difficult to achieve.

C.2.2 Create a challenge to the sterilization process by using microorganisms with a known resistance to VH2O2. This microbiological challenge (BI) comprises a known population of these microorganisms with known D value. Place BIs in the product or create BIs by inoculating the product with these microorganisms at locations where sterilizing conditions are considered most difficult to achieve (e.g. lumens, mated surfaces, lubricated areas, materials that negatively interact with hydrogen peroxide). If the location(s) of the microbiological challenge is other than the most difficult-to-sterilize within the product, its relationship to the most difficult location(s) shall be established. Enumeration of the inoculation solution or inoculated product should be verified (see ISO 11138-7).

NOTE Establishment of recovery efficiency is described in ISO 11737-1.

C.2.3 Package the challenge in the same manner as product produced routinely and include it within the sterilization load or use a configuration that presents a greater challenge to the microbiological inactivation by the sterilization process.

C.2.4 Treat the sterilization load with the sterilizing agent under conditions selected to deliver less lethality than those conditions to be used routinely, such that not all the reference microorganisms have been inactivated. The level of treatment identified should be carried out in triplicate to demonstrate reproducibility.

C.2.5 Establish that the microbicidal or microbiostatic action(s) of the sterilization process have been appropriately neutralized prior to the estimation of survivors.

NOTE See ISO 11138-1:2017, Annex B, for information on a method to determine growth inhibition.

C.2.6 Determine the number of microorganisms surviving, either by direct enumeration or estimated by a most probable number technique.

C.2.7 Calculate the rate of inactivation of the reference microorganisms.

C.2.8 From a knowledge of the bioburden (established in accordance with 7.1) and the rate of inactivation of the reference microorganisms, determine the extent of treatment required to achieve the specified SAL. In the calculation of SAL by extrapolation, the linearity of the inactivation should be assessed in accordance with ISO 11138-7.

C.3 Maintaining process effectiveness

C.3.1 Confirm the continued appropriateness of the sterilization process at defined intervals using product representative of routine production (see 12.4).

C.3.2 The method requires on-going monitoring and control of the bioburden type(s), population, and resistance using product representative of routine production. It is common practice to conduct bioburden testing periodically. Bioburden is a critical characteristic of the defined process and bioburden testing is conducted to demonstrate that the bioburden is within defined limits.

Annex D
(normative)

Approach 3 — Conservative process definition based on inactivation of reference microorganisms (overkill method)

D.1 General

This approach to process definition has been widely employed, particularly for products to be processed in health care facilities and industrial sterilization of single-use devices. An overkill approach to process definition is based on the inactivation of reference microorganisms and has been widely used whereby sterilization processes qualified in this manner are often conservative and use a treatment that can exceed that required to achieve an SAL of 10^{-6}. Further guidance on this approach can be found in ISO 11138-7.

Microorganisms can exhibit log-linear inactivation kinetics when tested in constant exposure conditions. However, because it is difficult for VH2O2 processes to maintain constant concentration over time, the rate of kill can vary during different stages of the process. A knowledge of the inactivation kinetics can be obtained as in 5.3 b). Linear inactivation kinetics are not always observed with H_20_2 processes. In addition to this, the nature of the inactivation kinetics can be influenced by the product. For linear and non-linear kinetics, the extent of treatment can be defined conservatively as twice that employed in D.2.4 or D.2.5.

A conservative (overkill) process definition may be validated through use of either of the approaches given in a) and b) below.

a) Half-cycle approach (see D.2.4): a total of three consecutive experiments resulting in a total inactivation of a challenge (see D.2.4.2) with a population of not less than 10^6 spores per BI/PCD/inoculated product. The specified exposure of the sterilization cycle shall be at least double of this minimum (half-cycle) exposure condition. When a PCD is used the relative resistance of the PCD and the inoculated product (or product bioburden) shall be demonstrated using a fractional cycle (less than the half-cycle exposure condition).

b) Cycle calculation approach (see D.2.5): the routine processing parameters that deliver minimally a 12-log reduction of the BI. After fractional sterilizing agent exposures with all other parameters remaining the same, the lethality of the process can be determined by using one of the following methods:

   1) survivor curve method;

   2) fraction-negative method.

NOTE A standard for a BI for hydrogen peroxide is under development[5].

D.2 Procedure

D.2.1 Determine the position(s) within product where it is most difficult to achieve sterilizing conditions.

D.2.2 Create a challenge to the sterilization process by using microorganisms with known high resistance to VH2O2. This microbiological challenge (BI) comprises a known population of these microorganisms with a known D value. Place BIs in the product or create BIs by inoculating product with these microorganisms at locations where sterilizing conditions are considered most difficult to

achieve (e.g. lumens, mated surfaces, lubricated areas, materials that negatively interact with hydrogen peroxide). If the location(s) of the microbiological challenge is other than the most difficult-to-sterilize within the product, its relationship to the most difficult location(s) shall be established. Enumeration of the inoculation solution or inoculated product should be verified. Establishment of recovery efficiency is described in ISO 11737-1.

NOTE 1 ISO 11737-2 gives additional information on how to perform a test of sterility on a product.

NOTE 2 Placing of a BI within a product is likely to alter its apparent resistance characteristics in comparison to the resistance noted on the labelling. This can require adjusting the half-cycle exposure period to compensate for the additional resistance cause by the placement of the BI in the product or load. It is possible that similar adjustments will be needed when the test microorganism suspensions are used to prepare inoculated product.

NOTE 3 Product design does not always allow a BI to be positioned in the most difficult-to-sterilize location of the product. In this circumstance it can be appropriate to place the BI in a location to which the relationship with the most difficult-to-sterilize location can be established. Additionally, in many medical devices the most difficult-to sterilize location contains a low number of microorganisms, and therefore the challenge population can be more closely linked to the bioburden of the product.

A PCD that has demonstrated an equivalent or greater microbiological resistance to the sterilization cycle than the product may be used for verification of conformance with these requirements.

D.2.3 Package the challenge in the same manner as product produced routinely and include it within the sterilization load.

D.2.4 Half-cycle approach

D.2.4.1 Expose the sterilization load to VH2O2 under conditions designed to deliver less lethality than the specified sterilization cycle.

D.2.4.2 Identify the extent of treatment that inactivates a minimum of 1 x 10^6 microorganisms at the selected position(s).

D.2.4.3 If the inactivation of the microorganisms has been confirmed following D.2.4.2, determine the extent of treatment for the sterilization process by doubling of exposure conditions to a predicted probability of a surviving microorganism of less than 10^{-6}, taking into account the nature of the inactivation kinetics effected by the sterilizing agent and the number and resistance of the microorganism on the BI/inoculated product.

D.2.5 Cycle calculation approach

Cycle calculation approach may be followed using fraction-negative or quantal methods. Growth or non-growth is observed relative to the number exposed.

A common reference method in accordance with the ISO 11138 series is the Limited Holcomb-Spearman-Karber Procedure (LHSKP). Two other commonly used statistical methods, the Holcomb-Spearman-Karber Procedure (HSKP) and the Stumbo-Murphy-Cochran Procedure (SMCP), may be used under particular conditions (see ISO 11138-7:2019, Annex C). The inactivation rate determined by the methods described here shall be used to assure at least a 12-log reduction of the BI or PCD with the tested process parameters. The full sterilization cycle shall be equal to or exceed this calculated process.

a) Limited Holcomb-Spearman-Karber Procedure (LHSKP): This procedure can be used if the successive exposure conditions differ by a constant time interval and if an identical number of replicates is exposed at each exposure time interval. ISO 11138-1 specifies at least 20 replicates at each interval for the LHSKP (see ISO 11138-1:2017, Table 1 and Figure A.4).

b) Holcomb-Spearman-Karber Procedure (HSKP): This method is similar to the LHSKP but uses the generic formula which does not require use of the same number of replicates nor that constant time intervals be used.

c) Stumbo-Murphy-Cochran Procedure (SMCP): The formula for the SMCP requires one result in the fraction-negative range, consisting of time, the number of units negative for growth, and the number of replicates, at one exposure time within the fraction-negative range, and the initial number of microorganisms per replicate. To obtain a higher level of confidence using the SMCP, the D value should be calculated as the average of at least three runs in the fraction-negative range in order to confirm reproducibility.

For further details on procedures and worked examples, see ISO 11138-7:2019, C.11.3.4.

D.2.6 For any of the approaches being adopted, establish that the VH2O2 microbicidal or microbiostatic action(s) have been appropriately neutralized prior to the estimation of the number of survivors.

NOTE The enzyme catalase effectively eliminates any remaining residues of H_2O_2.

ISO 11138-1:2017, Annex B, can provide information to verify effective neutralization.

D.3 Maintaining process effectiveness

The continued appropriateness of the sterilization process is confirmed at defined intervals by repeating a single qualification according to 12.4.

Annex E
(informative)

Guidance on application of this document

NOTE 1 For ease of reference, the numbering of clauses in this annex corresponds to that in the normative part of this document. The main headings in this annex follow the clause headings and numbering in the main document. Below the main headings the subheadings and their numbering are not consistent with the subheadings and the numbering in the main document.

NOTE 2 The guidance given in this annex is not intended as a checklist for assessing conformance with this document. This guidance is intended to assist in obtaining a uniform understanding and implementation of this document by providing explanations and acceptable methods for achieving conformance with specified requirements. It highlights important aspects and provides examples. Methods other than those given in the guidance can be used, providing their performance achieves conformance with this document.

E.1 Scope

E.1.1 No guidance offered.

E.1.2.1 No guidance offered.

E.1.2.2 No guidance offered.

E.1.2.3 No guidance offered.

E.1.2.4 No guidance offered.

E.1.2.5 The VH2O2 sterilization process does not ensure sterilization efficacy for contained product. This does not necessarily prevent sterilization of the container's surface. In this case, the container surface is considered part of the product for sterilization. The regional EN 868 series of standards is one of the ways that can be used to conform with ISO 11607-1 and ISO 11607-2.

E.1.2.6 No guidance offered.

E.2 Normative references

No guidance offered.

E.3 Terms and definitions

No guidance offered.

E.4 Quality management system elements

E.4.1 Requirements for the control of documents and records are specified in national and international standards (e.g. ISO 13485:2016, 4.2.3 and 4.2.4). In ISO 13485, the requirements for

documentation relate to the generation and control of documentation (including specifications and procedures) and records.

Requirements for responsibility and authority and for human resources are specified in national and international standards (e.g. ISO 13485:2016, 5.5 and 6.2). In ISO 13485, the requirements for management responsibility are related to management commitment, customer focus, quality policy, planning, responsibility, authority and communication, and management review.

The level of qualification, training and experience required by personnel will depend upon the activities being performed. General guidance on training as part of the overall quality management system is given in ISO 9004.

Particular qualifications and training are appropriate for personnel with the following responsibilities: microbiological testing; chemical analysis and formulation; installation of equipment; equipment maintenance; physical PQ; routine sterilizer operation; calibration; process design; equipment specification.

The development, validation and routine control of a sterilization process are likely to involve a number of separate parties, each of whom is responsible for certain elements. This document does not require particular elements to be carried out by specific parties but does require that the party accepting particular responsibilities is defined and that this definition of responsibilities is documented. This documented definition of responsibilities should be within the quality management system(s) of the identified parties and can form part of a contractual relationship.

Table E.1 lists the elements of this document and, for illustration only, names parties that can be responsible for identified activities. It should be noted that

— it is possible that the elements listed will not occur sequentially, as the design and testing programme can be iterative in part;

— responsibilities for the elements can vary from case to case.

The organization accepting responsibilities for defined elements is required to assign these elements to appropriately trained and qualified personnel.

Table E.1 — Elements of sterilizing agent characterization, sterilization process development, validation and routine control

Element	Purpose	Components	Responsible party
Quality management system	To provide a structure to control all stages of the sterilization process	Personnel and training Documentation Records Review procedures Corrective action	All parties with respect to the elements undertaken
Sterilizing agent characterization	To define the sterilizing agent and its microbicidal effectiveness	Sterilizing agent definition Microbicidal effectiveness Material effects Safety and environment	Developer of the sterilizing agent or sterilization process

[a] If the product manufacturer provides information on the VH2O2 process in the processing instructions for the medical device.

Table E.1 *(continued)*

Element	Purpose	Components	Responsible party
Process/equipment characterization	To define the sterilization process and the equipment necessary to carry it out	Process description Equipment specification Ancillary equipment and service definition Cycle parameters and tolerances	Sterilizer manufacturer, in collaboration with the developer of the sterilization process, if appropriate
Product definition	To define the product to be sterilized	Product specification Packaging materials Product quality prior to sterilization	Manufacturer of product[a] to be sterilized (and sterilizer manufacturer, depending on claims made for sterilizing equipment)
Process definition	To obtain a detailed specification for the sterilization process to be applied	Development Biological safety Process residuals Product compatibility Limits on resterilization Cycle parameters and tolerances to be applied	Manufacturer of product[a] to be sterilized, in collaboration with the sterilizer manufacturer and, if appropriate, the health care facility
Validation	To demonstrate that the defined sterilization process can be delivered effectively and reproducibly to the sterilization load	IQ OQ PQ Review and approval of validation	Organization with responsibility for sterilizing the product (either product manufacturer or health care facility), in collaboration with the sterilizer manufacturer, if appropriate Product manufacturer or health care facility, in collaboration with the organization sterilizing the products and contract laboratory, if appropriate
Routine monitoring and control	To demonstrate that the validated sterilization process has been delivered within defined tolerances to all products within a sterilization load	Sterilization load configuration Process monitoring Record generation Record retention	Product manufacturer or health care facility and contract laboratory, if appropriate
Product release from sterilization	To review records of routine control procedures and determining the disposition of a particular sterilization load	Record review Indicator testing (if any) Product disposition Corrective action (if any)	Product manufacturer or health care facility
Maintaining process effectiveness	To ensure the continued acceptability of the validated sterilization process	Product quality prior to sterilization Calibration Equipment maintenance Requalification and assessment of change	Product manufacturer or health care facility, together with organization sterilizing the product, if appropriate

[a] If the product manufacturer provides information on the VH2O2 process in the processing instructions for the medical device.

In order to illustrate the variety of possible allocations of responsibility, three sample scenarios are presented below. These scenarios are not intended to be all-inclusive.

Scenario 1 — Health care facility: in this scenario, the user of the sterilization process is a health care facility. Three parties are involved in complying with this document: the health care facility, the sterilizer manufacturer and the medical device manufacturer. The assignment of responsibilities and the means used to undertake these responsibilities can be as follows.

— Quality management system elements: each party has its own quality management system. The limits of responsibility of each party are laid down in formal contracts.

— There can be applicable national regulations for operation, routine monitoring and control of sterilization processes.

— Sterilizing agent characterization: the health care facility has agreed to a contract to purchase a sterilization system from a sterilizer manufacturer; this sterilizer manufacturer accepts responsibility for sterilizing agent characterization and has the resultant data on file. The health care facility has access to these data and, prior to making the decision to purchase, has reviewed the sterilizer manufacturer's data and the data available in the published scientific literature.

— Process/equipment characterization: the sterilizer manufacturer has undertaken the process/equipment characterization, developed the equipment specification and has the necessary regulatory approval to place the product on the market. The health care facility reviews the equipment specification in conjunction with the sterilizer manufacturer to confirm that the services and infrastructure necessary to operate the sterilization equipment are available.

— Product definition: the health care facility has identified the medical devices that it intends to process. The instructions for processing these medical devices provided by the medical device manufacturer include instructions for cleaning and disinfection as well as for sterilization. The medical device manufacturer has undertaken process definition studies in collaboration with the sterilizer manufacturer in order to substantiate the processing instructions provided. The health care facility reviews the data on the effectiveness of its cleaning processes and confirms they are adequate for the particular device(s) and sterilization process.

— Process definition: the sterilizer manufacturer and the medical device manufacturer have collaborated to define the sterilization process for the particular medical devices and have included the relevant instructions within each of their instructions for use. The necessary regulatory approvals have been obtained. The health care facility reviews the documentation and confirms that it has the capability to follow these instructions.

— Validation: the health care facility contracts with the sterilizer manufacturer to undertake IQ and OQ in accordance with documented procedures. The health care facility reviews and approves the IQ, OQ protocol and reports. The health care facility undertakes PQ and then reviews and approves the validation exercise. Calibration and maintenance can be performed under contract by sterilizer manufacturer or health care facility.

— Routine monitoring and control: The health care facility undertakes the routine control and monitoring in accordance with its documented procedures. Procedure includes methods for verification that cycle parameters are within specified limits. Monitoring of process parameters is often supported by either BIs or CIs, or both.

— Product release from sterilization: the health care facility undertakes product release from sterilization in accordance with its documented procedures.

— Maintaining process effectiveness: the health care facility accepts responsibility for maintaining process effectiveness. It contracts with the sterilizer manufacturer to undertake planned preventive maintenance and calibration. It defines procedures for requalification. The health care facility defines procedures for the periodic reassessment of the effectiveness of the cleaning and disinfection processes.

Scenario 2 — Medical device manufacturer using in-house facilities: in this scenario, the user of the sterilization process is a manufacturer of single-use medical devices who is installing in-house facilities for sterilization. The parties involved are the medical device manufacturer and the sterilizer manufacturer. The allocation of responsibilities and the means used to undertake these responsibilities can be as follows.

— Quality management system elements: each party has its own quality management system. The limits of responsibility of each party are laid down in formal contracts.

— Sterilizing agent characterization: the sterilizer manufacturer has undertaken the sterilizing agent characterization and made the data available to the medical device manufacturer.

— Process/equipment characterization: the sterilizer manufacturer has developed an equipment specification, including a control system for the equipment, which is capable of being programmed to deliver a predefined process.

— Product definition: the medical device manufacturer is responsible for the specification of the product and its manufacture.

— Process definition: the medical device manufacturer defines a process for the particular medical device(s) to be sterilized. The medical device manufacturer initiates experimental studies to assess the biological safety and product compatibility.

— Validation: the medical device manufacturer undertakes validation using the sterilization equipment to be used routinely, confirming that it is capable of delivering the defined sterilization process.

— Routine control and monitoring: this is carried out by the medical device manufacturer in accordance with documented procedures.

— Product release from sterilization: this is carried out by the medical device manufacturer in accordance with documented procedures.

— Maintaining process effectiveness: this is carried out by the medical device manufacturer in accordance with documented procedures.

Scenario 3 — Medical device manufacturer using a sterilization subcontractor: in this scenario, the user of the sterilization process is a manufacturer of single-use medical devices who is using a sterilization subcontractor to deliver the sterilization process. Additionally, the medical device manufacturer is using a contract laboratory to undertake defined testing as part of the product release procedures. The parties involved are the medical device manufacturer, the sterilization subcontractor, and the contract laboratory. The allocation of responsibilities and the means used to undertake these responsibilities can be as follows:

— Quality management system elements: each party has its own quality management system. The limits of responsibility of each party are laid down in formal contracts.

— Sterilizing agent characterization: the sterilization subcontractor has licensed the sterilization process from a separate organization that characterized and developed the sterilization process. The process developer has undertaken the sterilizing agent characterization and made the resultant data available to the sterilization subcontractor and the medical device manufacturer.

— Process/equipment characterization: the sterilization subcontractor has developed an equipment specification, including a control system for the equipment, which is capable of being programmed to deliver a predefined process. A sterilizer manufacturer has been contracted to manufacture and install the specified equipment.

— Product definition: the medical device manufacturer is responsible for the specification of the product and its manufacture.

— Process definition: the sterilization subcontractor defines a process for the particular medical device(s) to be sterilized in consultation with the medical device manufacturer. The medical

device manufacturer initiates experimental studies to assess the biological safety and product compatibility.

— Validation: the sterilization subcontractor undertakes IQ and OQ in accordance with documented procedures. The medical device manufacturer or sterilization subcontractor then undertakes PQ using the installed sterilization equipment, confirming that the equipment is capable of delivering the defined sterilization process. The medical device manufacturer reviews and approves the validation exercise. A contract laboratory can perform microbiological testing in accordance with methods agreed with the medical device manufacturer.

— Routine control and monitoring: this is carried out by the sterilization subcontractor and the contract laboratory in accordance with documented procedures agreed with the medical device manufacturer.

— Product release from sterilization: this is carried out by the medical device manufacturer in accordance with documented procedures, on the basis of records provided by the sterilization subcontractor and the contract laboratory.

— Maintaining process effectiveness: the sterilization subcontractor carries out equipment maintenance and calibration in accordance with documented procedures. The medical device manufacturer maintains the quality of the product prior to sterilization and takes responsibility for requalification; the sterilization subcontractor carries out any necessary repetition of part or all of IQ or OQ.

Product realization

NOTE 1 In ISO 13485, the requirements for product realization relate to the product lifecycle from the determination of customer requirements, design and development, purchasing, control of production, and calibration of monitoring and measuring devices.

Requirements for purchasing are specified in national and international standards (e.g. ISO 13485:2016, 7.7).

Requirements for identification and traceability are specified in national and international standards (e.g. ISO 13485:2016, 7.5.3).

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

In ISO 13485, the requirements for measurement, analysis and improvement relate to process monitoring, control of non-conforming product, analysis of data and improvement (including corrective and preventive actions).

NOTE 2 Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence.

Procedures for control of non-conforming products and corrective action are specified in national and international standards (e.g. ISO 13485:2016, 8.3 and 8.5.2).

E.4.2 Requirements for calibration of monitoring and measuring devices are specified in national and international standards (e.g. ISO 13485:2016, 7.6).

E.5 Sterilizing agent characterization

E.5.1 No guidance offered.

E.5.2 The storage conditions and shelf life for the sterilant should be in accordance with the manufacturer's information being aware of any safety and environmental requirements and regulations. Additional information can be found in G.2.2.

E.5.3 Many chemicals and processes can be shown to have antimicrobial activity. Not all, however, meet the criteria for a sterilizing agent. The intent and approach of the studies on microbicidal effectiveness are to:

— provide a definition of the sterilizing agent and the associated process and equipment sufficient to establish and maintain reproducible parameters for studies on microbicidal effectiveness; this activity should be documented;

— develop and validate methods for the growth of microorganisms and their inoculation onto carriers for exposure to the sterilizing agent; these procedures include recovery and enumeration of microorganisms from the carriers and estimation of the fraction of exposed carriers rendered sterile; the necessity for neutralization of residues of the sterilizing agent should be considered (see the guidance in 5.3 e);

— characterize the microbicidal activity of the sterilizing agent in regard to concentration/potency, exposure time/dose, or other variables that could affect the microbicidal activity using the highly resistant microorganism(s);

— define the kinetics of microbial inactivation; confirm that the lethal action can be extrapolated to predict the probability of a microorganism surviving exposure to a defined treatment using the inactivation data obtained with the highly resistant microorganism(s).

Guidance specific to 5.3 a): If the reference microorganism, *G. stearothermophilus*, is not used, qualitative studies can be used to test the activity of VH2O2 against a range of microorganisms. The purpose of these studies is two-fold:

— to demonstrate that a range of different types of microorganism is sensitive, to some degree, to the action of VH2O2;

— to choose one or more highly resistant microorganisms for more quantitative inactivation studies.

Further information can be found in the Bibliography.

Guidance specific to 5.3 b): quantitative microbial inactivation studies are undertaken to demonstrate that the sterilizing agent, when applied in a defined manner, can reliably yield calculable numbers of surviving microorganisms. These studies generally involve the use of graded exposure to the sterilizing agent to generate survival data defining the inactivation of the previously identified highly resistant microorganism(s). To define the upper section of the microbial survival curve, direct enumeration methods are generally used. For the section of the curve where there is a low number of survivors occurring, fraction negative data are employed. In the construction of such survival curves, the practical lower limit of estimation of average numbers of surviving microorganisms due to constraints of number of samples is 0,01 or 10^{-2}. The extent of treatment to provide a probability of a surviving microorganism lower than this limit is inferred by extrapolation.

The empirical relationship can, for example, be defined in an equation or represented as a graph relating extent of treatment to the numbers and probability of surviving microorganisms. The relationship can also be presented in a tabulation of values.

In situations where the survival curve is log-linear, i.e. a plot on semi-log paper yields a straight line and extrapolation is readily performed, a curve that is concave in relation to the X-axis can, when fitted with a straight line, yield a somewhat conservative estimate of the extent of treatment needed to attain a defined probability of survival of a microorganism. In VH2O2 processes the sterilizing agent is applied typically as a dose per part cycle, rather than using constant concentration conditions. This can result in a microbial inactivation curve that is convex in relation to the X-axis. In such case the “half cycle” concept can be used, see Annex D (Half-cycle approach). However, special care should be taken to apply appropriate neutralization methods directly after stop of the half cycle (see guidance specific to 5.3 e).

Demonstration of the lethal action of the sterilizing agent over a range sufficient to define the microbial inactivation kinetics requires an adequate number of viable microorganisms to be initially present on and recoverable from carriers. In studies requiring quantitative enumeration of surviving microorganisms from carriers exposed to graded treatments of the sterilizing agent, the numbers of

microorganisms recovered from exposed carriers are compared to those recovered from the unexposed controls to construct survivor curves relating log proportion of microorganisms surviving to the extent of treatment.

NOTE 1 Microbial inactivation and failure to recover viable test microorganisms from the surface of an inoculated carrier exposed to the sterilizing agent are not always distinguishable. In this context, use of tracer agents (such as radiolabelled microorganisms) can be useful.

Microbial inactivation studies require the use of test methods validated for the specific sterilizing agent. During the design and validation of the test methods, particular attention should be paid to test conditions that result in spurious data arising from, for example, inadequate recovery conditions, the occurrence of microbiostasis, and false positives. Loss of viability of surviving microorganisms should be considered arising from, for example, transport of test materials to a contract laboratory. Development of the test methods or their performance can be carried out in-house or in a contract laboratory.

Selection of test microorganisms for microbial inactivation studies should be justified. Methods to be qualified can include:

a) growth, maintenance, and enumeration of the selected test microorganism;

b) preparation of consistent inocula of test microorganisms;

c) inoculation of microorganisms onto carriers;

d) quantitative assessment of inactivation of microorganisms on carriers exposed to a sterilizing agent and recovery of microorganisms from carriers following exposure to a sterilizing agent.

Inoculation onto carriers should be carried out in a defined and reproducible manner. The effects of drying the inoculum and storage of the carriers (under defined conditions) upon microorganism viability and resistance to the sterilizing agent should be considered. The carriers should neither inhibit nor potentiate the action of the sterilizing agent upon the inoculated microorganisms.

NOTE 2 See also NOTE 1.

Guidance specific to 5.3 c): studies on sterilizing agent characterization can be performed with laboratory, prototype or routine production-type equipment. For each situation, sufficient definition of the sterilizing agent and equipment is required in order to ensure reproducible conditions.

Consideration should be given to a reproducible set-up and operation of equipment and the monitoring and control of variables that can affect the outcome of the microbial inactivation studies.

The set-up for each study should be documented; any changes to the set-up and their effect on the outcome of microbial inactivation studies should be assessed and documented. Operation of the sterilizer and the performance of studies should preferably be conducted in accordance with a previously written procedure. Data defining the conditions of exposure to the sterilizing agent should be recorded together with the microbiological and any other test measurements.

Guidance specific to 5.3 d): Examples include interactions with materials, residues from manufacturing, cleaning or disinfection and the nature of the load such as its design and materials of construction.

Guidance specific to 5.3 e): Before commencing any investigation of microbial inactivation, it is necessary to ensure that the results of the investigation are not influenced adversely by microbicidal or microbiostatic effects due to carry-over of the sterilizing agent or its residual derivatives into the recovery system; such effects can be reduced by:

a) dilution of the sterilizing agent;

b) removal of the sterilizing agent;

c) neutralization of the microbicidal or microbiostatic action of the sterilizing agent by reaction with an appropriate agent (e.g. catalase).

The choice of neutralizing system is influenced by the nature of the sterilizing agent. The effectiveness of the chosen neutralizing agent should be demonstrated prior to the commencement of inactivation studies.

Guidance specific to 5.3 f): See [31]

E.5.4 Effects on materials and medical devices

E.5.4.1 The manufacturers of the medical devices can be asked to provide information on material effects.

E.5.4.2 No guidance offered.

E.5.4.3 No guidance offered.

E.5.4.4 No guidance offered.

E.5.4.5 No guidance offered.

E.5.5 Safety and the environment

E.5.5.1 No guidance offered.

E.5.5.2 Suitable treatment systems should be utilized for any emissions. Reference [24] provides an evaluation of relevant risks related to safety when using VH2O2. Further guidance is given in Annex G.

E.5.5.3 Presence of water on a load prior to sterilization can lead to an aborted cycle. Water will evaporate during the vacuum step and will increase the vacuum time, which can raise an alarm with some sterilizers. In addition, the water will absorb the heat from the medical device during the evaporation process and can create a cold spot that can lead to hydrogen peroxide condensation found on the load at the end of the sterilization process. Finger burn is one of the most common complaints reported.

E.6 Process and equipment characterization

E.6.1 No guidance offered.

E.6.2 Process characterization

E.6.2.1 No guidance offered.

E.6.2.2 Some critical process variables can be found in ISO 11140-1.

E.6.2.3 If VH2O2 is supplied to the process by defined doses the initial concentration of H_2O_2 can decrease due to spontaneous decomposition or consumption by chemical reactions or adsorption at surfaces.

Concentration values are typically provided as absolute values in g/l or Mol/l. However, also relative concentrations can be provided in % (wt/wt or V/V), which can be converted equivalent into each other, if the physico-chemical conditions (T, V, p) are specified.

Residual moisture on product surfaces (e.g. due to insufficient drying before sterilization) can affect the process efficacy.

E.6.2.4 No guidance offered.

E.6.3 This clause describes the requirements for a VH2O2 sterilizer. EN 17180 (under development) provides essential information and support for the equipment (sterilizer) characterization.

Ranges in product load temperatures (too cool or too warm) can adversely affect the performance of the VH2O2 cycle. During the VH2O2 sterilization process, temperatures can be cooler inside the product load as compared to the temperature of the sterilizer chamber walls and the temperature recorded on the sterilizer cycle printout.

E.7 Product definition

E.7.1 This clause describes product considerations that are addressed when evaluating a sterilization process. The sterilization process has to yield a sterile, safe and functional product. Certain process conditions can adversely affect the integrity of medical devices and packages. Some packaging materials and devices can impede the sterilization process. Therefore, the effects of the sterilization process on materials and design characteristics and on packaging configurations and materials are evaluated. This evaluation is usually conducted during product development. Generally, health care facilities follow the instructions for the product, the sterile barrier system and the sterilizer.

Sterilization process support: a successful and repeatable VH2O2 sterilization process can be supported with the following specifications:

a) effective cleaning, disinfection and drying of the product (if processing is intended or if applicable) including re-usable sterile barrier systems, if used (e.g. rigid sterilization containers) to control bioburden;

b) processes to minimize cleaning and disinfection residuals that promote decomposition of VH2O2;

c) effective environmental controls to minimize bioburden during handling;

d) loading configurations (e.g. number of products, stacking, combinations of products, size of sterile barrier system) to avoid overload in the chamber;

e) materials to be avoided, because they absorb or promote the decomposition of VH2O2.

NOTE Cellulosic materials such as papers or nonwovens containing cellulose, or materials that have a high absorbance of VH2O2, are sometimes not appropriate in VH2O2 sterilization processes.

E.7.2 The product can be subjected to various environmental stresses during sterilization, such as pressure changes, elevated temperature, and changes in relative humidity. The product can also react with the sterilizing agent or any diluent(s). The product design has to ensure that functionality and safety are not compromised by exposure to the anticipated range of sterilization conditions. Typically, the maximum conditions would represent the most severe challenge to the product, including the package. If applicable, the effects of multiple exposures to the sterilization process are evaluated.

If the product has to be resterilized, either as part of its intended use or in the event of an inadequate sterilization process being delivered, the suitability of product and packaging for resterilization and the effect of repeated exposures to the sterilization process on product functionality and potential increase in residual levels should be investigated.

Design tolerances and configuration: these are important in ensuring effective delivery of the sterilizing agent and its distribution.

Materials composition: it is important to select materials that exhibit adequate resistance to chemical and physical changes caused by the sterilizing agent or any diluents over the anticipated

range of sterilization conditions. Properties of materials required to satisfy requirements for product performance, e.g. physical strength, permeability, physical dimensions and resilience, are evaluated after sterilization to ensure that the materials are acceptable for use. Degradation effects (such as crazing, embrittlement and phase separation) due to exposure to the sterilization process should be identified and resistant materials specified. Materials should also allow sufficient sterilizing agent transmission or permeation to ensure that target surfaces and materials are sterilized. The materials should allow desorption of the sterilizing agent (if applicable) within a reasonable time and retain biocompatibility. Methods for determining residuals of the sterilizing agent should be selected and validated during product development. If applicable, the effects of exposure to multiple sterilization processes are evaluated.

E.7.3 The major function of a package for a sterilized medical device is to ensure that the medical device remains sterile throughout its defined shelf-life. During sterilization, the package is intended to withstand the process conditions without a negative effect on overall product quality (e.g. generation of particulates, breach of sterile barrier or failure to achieve the required SAL).

Packaging considerations are addressed in more detail in ISO 11607-1 and ISO 11607-2.

When selecting a sterile barrier system for a product that is to be sterilized, the following design aspects should be considered with respect to the VH2O2 sterilization process. Those portions of the sterile barrier system or product components intended to maintain product sterility (e.g. closures or seals) should be demonstrated to maintain their integrity during and following exposure to the sterilization process.

The ability of the protective packaging to protect product during customary handling and distribution should be demonstrated (see ISO 11607-1 for information about performance testing). If the protective packaging is to be exposed to the sterilization process, it should be demonstrated that the protective packaging can withstand the process without losing its ability to protect the product. Furthermore, it should be demonstrated that the protective packaging does not affect the attainment of sterilizing conditions during the sterilization process and that resterilization, if applied, has no effect on the protective packaging and product. See ISO 17664-1.

E.7.4 If the health-based risk assessment conducted in accordance with 7.4 identifies residues of the sterilizing agent for which acceptable limits have to be set, process definition should aim to minimize the presence of such residues on or in the product while meeting the specified SAL. Additionally, it is possible that a post-treatment will have to be defined to further reduce the level of residues to meet specified limits. If a post-treatment is required, it is defined and validated as part of the sterilization process.

E.7.5 This includes activities in the lifecycle of a processed product (e.g. lubrication).

E.7.6 The intention is that bioburden be stable and low, taking into account the nature of the raw materials, product and manufacturing or processing procedures prior to sterilization. This can be achieved by employing a quality management system throughout the manufacturing of the medical device or a defined and controlled cleaning process of demonstrated effectiveness, prior to sterilization. Equipment to be used in cleaning and disinfecting reusable medical devices is specified in the ISO 15883 series. They also include methods to demonstrate the effectiveness of a cleaning and disinfecting process.

Medical devices that are supplied for single use and intended to be sterilized prior to use can use a bioburden-based method or overkill approach to establish the sterilization process. When using a bioburden-based method, a knowledge of the bioburden would be established in accordance with ISO 11737-1. In the case of reusable medical devices, where an overkill method is used, control of the bioburden is important prior to processing to ensure that the bioburden is below acceptable values, for example by use of prior processing through a validated washer-disinfector process, where a quantitative knowledge of the bioburden might not be known or be necessary.

E.7.7 No guidance offered.

E.7.8 A product family is a collection of products determined to be similar or equivalent for validation purposes. Although product families can be used for other reasons (VH2O2 residuals, bioburden, or biocompatibility) for VH2O2 sterilization, a product family usually refers to products that have been grouped together for the purposes of determining that the required SAL has been delivered to the products during the microbiological PQ.

A product family can consist of various combinations of similar products. For example, a product family can contain a series of devices that differ only in their sizes or a variety of products that are made in the same environment with the same material. When products are grouped into families it is important that they are grouped based on a rationale that is appropriate for the VH2O2 sterilization process.

The product definition process should also consider whether this is a new design, or whether it is part of an existing product family. The following should be considered as part of product definition:

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

b) intended use of the medical device;

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

d) design characteristics that would affect the choice of sterilization process (e.g. batteries, optical fibres, electronic integrated circuits);

e) maintenance activities such as lubrication

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

g) required SAL;

h) packaging;

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

j) compatibility with VH2O2 and processing conditions.

The use of product families makes the validation process simpler since all products in the family would be determined to represent an equivalent or lesser challenge to the specified characteristics of the sterilization process than the representative product or PCD. The product family can be represented by a master product that should be selected based on the worst-case conditions being examined. These worst-case conditions would be a set of conditions encompassing upper and lower processing limits and circumstances that pose the greatest chance of process or product failure (when compared to ideal conditions). Such conditions do not necessarily induce product or process failure.

In addition to product families, processing categories can also be used in VH2O2 sterilization routinely once the PQ has been completed. A processing category is a collection of product families that can be dissimilar in the details used to establish the product family, such as material of construction or packaging, or manufacturers, but each of the product families within a processing category should be qualified in a common sterilization process. For example, a collection of products (e.g. intravenous sets) can constitute a product family and can be placed in a processing category that includes a separate collection of products (e.g. a family of syringes). The commonality within the processing category can be the PCD that represents the microbial challenge for the products in that group. All products within this processing category should present an equivalent or lesser challenge to the sterilization process when compared with the master product, representative member, or PCD which is placed within the product sterile barrier system.

The review for product equivalence can be conducted within each product family or processing category. Alternatively, a master product or representative member can be selected for the qualification study.

If a new or modified product or change to the packaging system is demonstrated to be equivalent to an existing medical device or specified characteristics of a PCD for which sterilization characteristics are already known, the new or modified product can be considered part of a product family or a processing category.

E.7.9 A PCD, as used in this document, in which a microbiological challenge is located, provides a defined resistance to the process.

The appropriateness of the PCD used for process definition, validation or routine monitoring and control shall be established. The PCD shall present a challenge to the sterilization process that is equivalent or greater than the challenge presented by the bioburden at the most difficult to sterilize location within the product (see E.8.8).

E.8 Process definition

E.8.1 Process definition is undertaken to define the process parameters for a sterilization process that will achieve the specified SAL for a defined product without adversely affecting product functionality. Therefore, process definition includes at least two pieces of work: one directed at assessing the effect (if any) of a range of candidate values for the process and cycle variables on the product and packaging, and the other directed at defining the process parameters that will achieve the specified SAL for the product.

As sterilization does not typically improve product performance, a careful selection of values and tolerances for each process and cycle variable should be undertaken during process definition. In general, those variables which, when increased, significantly improve sterilization effectiveness without adversely affecting product performance should be maximized during process definition. Conversely, those variables which, when increased, adversely affect product performance without significantly improving sterilization effectiveness should be minimized during process definition. In addition, if a threshold exists above which significant adverse effects on product or packaging are observed, it should be documented.

While it is desirable to evaluate the sterile barrier system in the process definition studies, this cannot always be possible. In most cases, the sterile barrier system to be used in routine operation can and should be used in the process definition studies, as it could influence the rate of achievement of the sterilizing conditions. If experimental sterilization equipment is used to perform these studies, it cannot always be possible to accommodate the packaging system that can also influence the attainment of sterilizing conditions. Furthermore, the effectiveness of the sterilization process can be affected by the, e.g. load configuration, material type(s), mass, density. For these reasons, it is desirable to perform the process definition studies where possible in equipment that will accommodate the sterilization load. While the influence of the sterilization load will be assessed during validation, it is recommended that it be evaluated as early in development as is practical.

The use of energy and the disposal and handling of chemicals and indicators used during testing and validation should be considered during planning and performing testing.

E.8.2 The sterilization cycle can be established from at least one of the following:

a) sterilization literature and updated scientific knowledge about this specific sterilization process;

b) similarity with a product that is already assigned to a product family (if applicable);

c) data supplied by the medical device manufacturer (see ISO 17664-1);

d) data supplied by the packaging material manufacturer or sterilizer manufacturer.

The sterilization process will be defined based on the inactivation of microorganisms. These microorganisms can be either natural contamination on the product or reference microorganisms that present at least as great a challenge to the sterilization process as does the bioburden on the product.

There are, however, a number of stages in the determination of process effectiveness that should be performed in order to have confidence in the selection of the process parameters. If BIs are to be used, the stages include the selection of the BI, the determination of the most difficult-to-sterilize location, the assessment of lethality at this location, and the evaluation of the influence of packaging and load characteristics.

From the range of values for the process and cycle variables studied, a single value with its tolerance should be defined for all but one of the process variables. Typically, the process variable that is not defined is time. A series of studies is performed to generate a survivor curve, which is extrapolated to enable the process to be fully defined. The form of the survivor curve can be different from that observed during earlier sterilizing agent characterization studies. For instance, the survivor curve observed during characterization can have been a straight line. This can be expected when the process parameters are fully achieved at the start of the exposure phase and fully depleted at the end of the exposure phase. When measuring inactivation at the most difficult-to-sterilize location, however, it is possible that the process parameters will not be fully achieved at process start or fully depleted at the end of the process. This is certainly the case for processes which involve heating or gas penetration. In such cases, the effectiveness of the sterilizing agent will increase with time, and the survivor curve will be concave with respect to the X-axis. However, at no time should the inactivation rate be greater than that observed in the characterization studies. Conversely, if the process parameters decay with time, the microbicidal effects of the sterilizing agent will deteriorate, and the survivor curve will be convex in respect of the X-axis. In this case, there is greater risk in predicting end points, and it is recommended that other values for the process variables be evaluated.

E.8.3 No guidance offered.

E.8.4 No guidance offered.

E.8.5 If *Geobacillus stearothermophilus* spores are not to be used as the indicator microorganism, a review of the data obtained from the microbial inactivation studies (see E.5.3) should be conducted to select a BI. The BI should have a relatively high resistance to the sterilizing agent when compared to other microorganisms. In addition, the challenge presented by the BI should be compared to that of the product bioburden and, if the challenge is greater than that of the product bioburden, it can be considered as appropriate for process definition and subsequent validation studies. While it is not necessary to determine the D value for each bioburden isolate, it is important to assess the more resistant portion of the bioburden population. Relative inactivation can be assessed via graded exposures to the sterilizing agent.

Once the BI has been selected, an appropriate location within the product at which the BI can be placed is established. Establishment of the location can be based on an expert understanding of the process and a documented rationale for why a given location will be the last to fully achieve the sterilizing conditions. If this cannot be done with certainty, then a number of locations that are likely to be difficult to sterilize should be evaluated. A BI should be placed at each of these locations within the product and the product exposed to a fraction of the sterilization process. The location that consistently yields the greatest number of survivors should be chosen.

The cycle calculation approach can be used if an exposure parameter, such as time or dose, can be used to express the inactivation kinetics. If other cycle steps, such as additional gas injection (air spike), are added after sterilizing agent injection, more than one parameter is modified, and the use of this approach is not recommended. See ISO 11138-7 for additional information on the cycle calculation approach and associated methods.

E.8.6 No guidance offered.

E.8.7 No guidance offered.

E.8.8 Where PCDs are used for demonstration of the microbiological inactivation of the sterilization process, their appropriateness in providing a defined resistance to the sterilization process is

demonstrated such that the resistance is equivalent or greater than that of the product itself in its sterile barrier system. This demonstration can be achieved by either of the following two methods.

a) Perform a comparative resistance study of the PCD and the product with its typical microbiological challenge using a fractional process. Tests of sterility in accordance with ISO 11737-2 are employed to demonstrate that the PCD is either microbiologically equivalent or more challenging to the process than the product itself.

b) Perform a comparative resistance study of the PCD and the product with an artificial inoculum of a BI in the worst-case location of the product. Establishment of the location can be based on an expert understanding of the process and a documented rationale for why a given location will be the last to fully achieve the sterilizing conditions. If the selection of an appropriate location cannot be achieved with certainty, a number of locations that are likely to be difficult to sterilize should be evaluated. A BI should be placed at each of these locations within the product and the product exposed to a fraction of the sterilization process. The location that consistently yields the greatest number of survivors should be chosen.

If the PCD that is used for part of routine release is different from that used in the microbiological PQ, it should be at least as resistant to the process as the PCD used in the microbiological PQ. Attention is given to the impact of packaging and the removal of sterilant from the PCD.

E.9 Validation

E.9.1 General

The object of validation is to document the evidence required to provide a high degree of assurance that a specific process will consistently produce product meeting the required SAL. Product sterilized in the validated process should be shown to meet predetermined specifications and quality characteristics related to product functionality and safety (i.e. through product compatibility studies).

Validation of the sterilization process should be performed according to an approved written document (e.g. protocol) that defines the testing procedures and the acceptance criteria, prior to initiation of testing. This document should be reviewed by a sterilization specialist(s).

The elements of validation, as defined in this clause, are

— IQ;

— OQ;

— PQ.

IQ and OQ should be performed by qualified personnel (see 4.1). For healthcare facilities, the qualified personnel can be provided by the sterilizer manufacturer. Microbiological test data can be available from the sterilizer manufacturer for general loads.

This means describing and documenting the following:

a) the validation steps that need to be performed;

b) the way in which these validation steps will be performed, along with a listing of responsible individuals, departments or outside contractors;

c) the criteria for successful validation.

There is an option of contracting with an outside service to perform this validation; however, there is still the responsibility to ensure that the validation conforms with the requirements of this document.

The use of energy and the disposal and handling of chemicals and indicators used during testing and validation should be considered during planning and performing testing.

E.9.1.1 Documentation review can include:

a) standard operation procedures for the sterilization process, including documentation for routine operation, process control, monitoring, product release, and for scheduled maintenance of the equipment;

b) qualification and training status of personnel;

c) user manual and technical documentation of the VH2O2 sterilizer and its accessories;

d) verification that supplies and consumables for the sterilizer conform to their specifications;

e) documented evidence that the safety functions operate as intended;

f) validated efficacy of the cleaning and disinfecting process for the products to be sterilized;

g) verification of compatibility of the products and their packaging to VH2O2 sterilization processes;

h) packaging lists and configuration schemes of the products intended to be processed in routine operation;

i) specifications and configuration schemes of products intended to be used for performance qualification;

j) microbiological quality of the product prior to sterilization, where appropriate (bioburden).

E.9.1.2 No guidance offered.

E.9.1.3 No guidance offered.

E.9.1.4 No guidance offered.

E.9.1.5 Items to consider are:

a) calibration traceable to a national or international standard;

b) a valid maintenance certificate (if appropriate);

c) a calibration status verified according to the technical and applicable management requirements;

d) verification of calibration carried out at a value(s) used to control the sterilization process.

E.9.1.6 No guidance offered.

E.9.1.7 This is required because after final inspection tests at the manufacturing site, equipment can have been affected by packaging, transportation or installation activities.

E.9.1.8 No guidance offered.

E.9.1.9 No guidance offered.

E.9.2 Installation qualification (IQ)

For new equipment, IQ begins with specifying the design, delivery and installation requirements. IQ is based on specifications that ensure that the construction and installation requirements are met. IQ should be documented, and the documentation should include drawings and details of all the construction materials, the dimensions and tolerances of the chamber in which the load will be placed (if applicable), support services, and any supplies.

IQ should be approved prior to OQ of the equipment.

E.9.2.1 General

E.9.2.1.1 The supporting documentation for IQ should include descriptions of the physical and operational characteristics of the equipment (including ancillary equipment). Examples of relevant documents include design specifications, the list of items on the original purchase order, user requirements specifications and functional design specifications.

E.9.2.1.2 Guidance can be found in IEC 61010-2-40.

E.9.2.1.3 No guidance offered.

E.9.2.1.4 No guidance offered.

E.9.2.2 Equipment

E.9.2.2.1 The user should be aware of local regulations when choosing a location in which the equipment is to be installed. The safety tests for the sterilizer should include at least the following:

— checking the safety of the sterilization chamber and mobile opening;

— checking the safety of the user when handling the sterilant container;

— checking the safety of the user with respect to the presence of liquid inside the sterilization chamber;

— safety requirements for any part of the sterilizer or load where a risk for burn hazard could exist;

— checking the doors interlock with cycle(s);

— verification of emergency stops (if applicable);

— verification that the basic safety functions operate as intended.

Some of these safety tests can be performed using non-destructive fault simulations. The device documentation should provide instructions on how to perform such tests. Examples of non-destructive (reversible) manipulations to check basic functions of the fault detection system that are intended to provoke failures and failure messages are given below:

a) power fail;

b) start of cycle with chamber door not (properly) locked;

c) leak provoked by an item being deposited on the sealing surface of the chamber door;

d) failure of sterilant supply, e.g. container/bottle/cartouche not connected;

e) refill an empty sterilant supply container/bottle/cartouche with water, re-connect it to the sterilizer, and start an operating cycle;

f) interrupt a running cycle;

g) significant overload of the chamber.

E.9.2.2.2 The storage conditions for VH2O2 sterilant should be in accordance with the sterilant manufacturer's recommendations, being aware of applicable regulations.

E.9.2.2.3 The verification of the control system should include at least the following:

a) configuration;

b) access codes;

c) cycles parameters range;

d) saving / printing data;

e) archiving / backup / restore data;

f) traceability and operations tracking log;

g) analog and digital inputs and outputs;

h) remote interface;

i) program creation and modification;

j) process controller and independent data management;

k) verification of fault detection and alarm system.

E.9.3 Operational qualification (OQ)

OQ consists of documented testing of the equipment over its defined and installed operating range to verify consistent operation. OQ should be documented and approved prior to PQ of the process. The documentation should include details of alarm systems, monitoring systems with response tolerance and accuracy requirements, the operational limits of all critical process variables, and safety checks. As part of demonstrating the capability of the sterilizer to deliver the operating cycle in conformance with selected parameters, test materials including PCDs can be employed for such OQ activities.

E.9.3.1 The following information should be documented for all instrumentation used for monitoring, controlling, indicating or recording:

a) equipment identification;

b) calibration schedule;

c) actual completion date for each calibration, as well as who performed it;

d) the next scheduled calibration date.

E.9.3.2 OQ for VH2O2 equipment comprises test cycles either with an empty sterilizer chamber or using appropriate test material to demonstrate the capability of the equipment to deliver the range of operating parameters and operating limits contained in the cycle specifications. This range of parameters and operating limits should include the initial sterilization process that has been defined in process definition (see 8). OQ should also determine the performance of associated ancillary systems.

E.9.3.3 No guidance offered.

E.9.3.4 No guidance offered.

E.9.4 Performance qualification (PQ)

Performance Qualification involves the assessment of a number of product outcomes following processing. Outcomes being assessed include microbiological inactivation, product and packaging functionality and sterilizing agent desorption.

A key element of performance qualification is the provision of objective evidence that the defined process consistently achieves the required sterility assurance level. This is achieved through the performance of one of the approaches defined in Annexes B, C, or D. The overkill half-cycle method (Annex D) is the most common approach using the BI, *Geobacillus stearothermophilus* due to the conservative nature of the method.

PQ should be carried out for each product family to be qualified to demonstrate the process conforms with identified acceptance criteria and is capable of achieving the required SAL to the product. IQ and OQ can be a one-time exercise or repeated as needed.

E.9.4.1 PQ consists of documented trials and tests to establish confidence that the finished product produced by the specified process in the specified sterilizer meets the requirements for safety, quality and performance. Use of product items, presented in the same manner as that to be used routinely, is an important element of PQ. Material in addition to the product items used in PQ can be used to make up the sterilization load. It is recommended that qualified personnel perform PQ.

In specifying the presentation of product, the load configuration, both the composition of the load and the placement of items within the load, should be considered. This refers to the positioning of baskets, packs, and rigid containers. For each type of product load, it can be helpful to define product families to reduce the number of product loads to test in the PQ. Select product loads which are considered most difficult to be sterilized. The rationale of the selection of product loads should be documented.

Typical load parameters to be defined might include stacking configuration, overall density, dimensions, material composition, and use and type of packaging system. Load configuration should be documented for each sterilizer. If routine sterilization consists of product loads that are less than the full chamber, then the PQ should incorporate the minimum load.

E.9.4.2 Product used in PQ is packaged in the same manner as that to be used routinely, but other material that is used in PQ might not need to be packaged in this manner. Changing process variables that can affect the quality of the product package should form part of the testing.

E.9.4.3 Criteria used to select products constituting each type of load for PQ should take into account at least:

a) sterilizing agent absorption: material, mass, size;

b) sterilizing agent diffusion: form (length, diameter for lumens for example), packaging.

PQ is performed with a load challenge equivalent or greater than the routine maximum load. Load challenge can be real or simulated (see Clause 7). In both cases evidence is provided that the level of challenge is equivalent to or greater than routine.

If PCDs are used to represent specific characteristics of a product or part of them, their definition will follow the same logic. Local regulation can require using a real product instead of a PCD.

Data to be generated are intended to demonstrate the attainment of the defined physical or chemical conditions, within specified tolerances, throughout the sterilization load. Established relationship(s) between the conditions occurring at positions used routinely to monitor the sterilization cycle and those conditions occurring throughout the sterilization load are intended to verify indirectly those specified parameters at the load which cannot be measured directly during routine operation. This is achieved by determining the attainment of the specified condition(s) at predetermined positions throughout the sterilization load.

Sensors measuring process or cycle parameters can be placed with each BI inside the products or PCDs when possible. Measurement of process parameters inside products or PCDs provides information correlating to biological performance.

E.9.4.4 The product and load used during PQ should be at least as difficult to sterilize as the most challenging load expected during normal production. The load can consist of product or materials that

have characteristics similar to those of a load to be sterilized routinely. Changes in the load configuration can affect the lethality of a sterilization process. It is important that the acceptable load configurations be specified (see Clause 7). If multiple load configurations are allowed, the load configuration used in the PQ studies should represent the most difficult-to-sterilize configuration or should have a known relationship to the most difficult-to-sterilize configuration. Some variations in the load size can be justified as having no significant impact.

E.9.4.5 No guidance offered.

E.9.4.6 No guidance offered.

E.9.4.7 No guidance offered.

E.9.4.8 No guidance offered.

E.9.4.9 No guidance offered.

E.9.4.10 For microbiological inactivation studies, if a PCD is used as a substitute for product it should be shown to provide an equivalent or greater challenge than the product. For example, in the substitution for microbiological inactivation, the appropriate use of a PCD can be demonstrated through comparative resistance assessment with a fractional process [see E.8.8 a)].

E.9.4.11 No guidance offered.

E.9.4.12 No guidance offered.

E.9.4.13 Appropriate elimination of sterilization residues for operator and patient safety is demonstrated using a product in worst case conditions.

E.9.5 Review and approval of validation

E.9.5.1 Typically the validation report is approved by the designated responsible person(s) as defined in the validation protocol.

E.9.5.2 Any discrepancies observed during the validation process should be documented, and their effect on the results of the validation should be determined and documented.

E.9.5.3 No guidance offered.

E.10 Routine monitoring and control

E.10.1 Routine monitoring and control of sterilization processes are based primarily on measurements of the process and cycle parameters during the sterilization process. Supplementation of these measurements by the use of BIs or CIs can be required.

Procedures for routine monitoring and control are needed to ensure that the defined parameters of the sterilization process are within established limits during PQ. These procedures should describe tests and checks, and the frequency with which these tests and checks should be carried out.

E.10.2 In addition, routine monitoring positions for taking measurements are defined, as are the locations where any BIs or CIs are to be placed, if used. The appropriateness of routine monitoring positions, and any PCDs that are used, should have been demonstrated (see 9.4.4).

BIs, CIs, and visual inspection of the sterilized product (see Clause 11) are widely used for routine control and monitoring in health care facilities. Typically, BIs are used in industrial sterilization unless parametric release has been validated and approved. There can be regional differences in the frequency of use of BIs and CIs. There are also regional differences in the use of parametric release. Refer to local guidance (if available) on routine monitoring and control, and product release. Any recommendations provided in the validation report should also be considered.

E.10.3 If a product is resterilized because the initial exposure to the sterilization process was outside of its specification (see also E.7.2), records of the initial sterilization process should be included or referenced in the sterilization records.

E.10.4 No guidance offered.

E.10.5 No guidance offered.

E.10.6 No guidance offered.

E.10.7 No guidance offered.

E.10.8 No guidance offered.

E.10.9 No guidance offered.

E.10.10 No guidance offered.

E.11 Product release from sterilization

E.11.1 If a sterilization process operating within specified tolerances has been demonstrated to be both effective and reproducible, confirmation that the process parameters were within specification limits is taken as evidence of the adequacy of the process.

Various pharmacopoeias specify tests for sterility (see ISO 11139:2018, 3.298) that can be applied to a sample withdrawn from a batch of product that has been exposed to a sterilization process. The value of conducting such tests for sterility is limited because of the insensitivity of the method. For product release, this document does not recommend the conduct of a test for sterility. However, should a manufacturer specify such testing as part of the criteria for product release from sterilization, a product is treated as non-conforming and handled accordingly if the test criteria are not satisfied.

E.11.2 Parametric release should only be applied when all process and cycle parameters are defined and monitored and when defined process parameters fall within the specified tolerances. The appropriateness of parametric release should be established during the development and validation of the sterilization process and should follow an established procedure.

The use of parametric release should consider the following factors:

a) maintaining control and consistency on the presentation of product and sterile barrier systems for VH2O2 sterilization which includes the methods used for cleaning, rinsing, and drying of both devices and sterile barrier systems;

b) maintaining control and consistency of the product load configurations which can contain a diversity of devices (including loaned instrumentation), different material compositions, diverse sterile barrier systems, and variety of accessories.

Adequate resources and expertise should be in place to effectively implement and maintain control of parametric release which can include defining the factors to control, testing to be conducted, and documentation required for the implementation and routine requalification of parametric release. Visual inspection is part of the monitoring for parametric release and can include check of CIs.

NOTE No BI testing is required for parametric release.

E.11.3 If BIs are to be used in product release, records of the physical process and cycle parameters and results of indicator testing are reviewed to demonstrate the effective delivery of the sterilization process. Guidance on the selection, use and interpretation of results of BIs is contained in ISO 11138-7. Failure to meet the process specification or failure of an indicator to meet its specified requirements should lead to the affected product being placed in quarantine and the cause of failure investigated. Actions taken during the investigation should be documented and the outcome of the investigation should be recorded.

If the process or cycle parameters are outside their specified tolerances, product should be evaluated in accordance with non-conforming product procedures. The decision reached as to the disposition of the product is recorded.

E.11.4 No guidance offered.

E.11.5 No guidance offered.

E.12 Maintaining process effectiveness

E.12.1 No guidance offered.

E.12.2 No guidance offered.

E.12.3 The technical documentation of the equipment can provide maintenance information.

E.12.4 Requalification

E.12.4.1 All or part of IQ, OQ, PQ is performed after certain events such as major repair or relocation or periodically to guard against unreported or inadvertent changes. Following such an event, the content of the requalification is defined by risk analysis. The interval between periodic requalifications should be determined by the nature of the sterilization process and by the amount of process data available. The interval can be varied taking into account historical data that demonstrate process reproducibility and conformance with established specifications for process parameters. Typically, requalification would be performed for a specified sterilization load or for a defined or simulated product. However, if requalification detected a process change, it is possible that PQ will need to be performed. It can be recommended to perform PQ once a year. In the event of changes in load or anything else that can affect the process performance, it is possible that additional PQ will need to be performed, see E.12.5.1.

E.12.4.2 Previous validation and requalification results should be considered in deciding the requalification procedure.

E.12.4.3 Data from requalification should be compared with records of the original validation (and any subsequent requalification) to confirm that the original performance has been retained. This comparison is facilitated by a common format for validation and requalification reports.

E.12.5 Assessment of change

NOTE A change control is employed to determine when operational or performance qualification testing is necessary. Requalification is needed if significant changes are made in the sterilization equipment (hardware or software), or process (see E.12.5.1), or to product or packaging (see E.12.5.2) that can influence sterilization effectiveness.

E.12.5.1 The following are examples (not necessarily all-inclusive) of changes to the sterilization equipment that can necessitate PQ unless data are available to demonstrate equivalency prior to and after such changes.

a) Equipment:

— changes that could affect the ability to maintain specified process parameters or a modification to the sterilizing agent or its presentation;

— replacement/modification of a part which can cause a process parameter to change;

— replacement/modification of a part which can cause an increase in leakage into the sterilizer chamber;

— any change to services and the outcome of maintenance on a service.

b) Process:

— alterations in the process that can substantially change the manner in which process parameters are achieved and controlled (e.g. new or modified process control software);

— any change to a critical process parameter directly or indirectly affecting sterilization process performance.

c) Product loading or density:

— changes in the previously validated loading configurations that can affect sterilizing agent penetration into the load.

E.12.5.2 The following are examples (not necessarily all-inclusive) of changes to a product, its package, or the presentation of product for sterilization that can necessitate PQ unless data are available to demonstrate equivalency prior to and after such changes.

a) Product:

— a change in the product material, source of materials, the composition or thickness of the product material, product assembly, construction or design tolerances that can influence the effectiveness of the sterilization process.

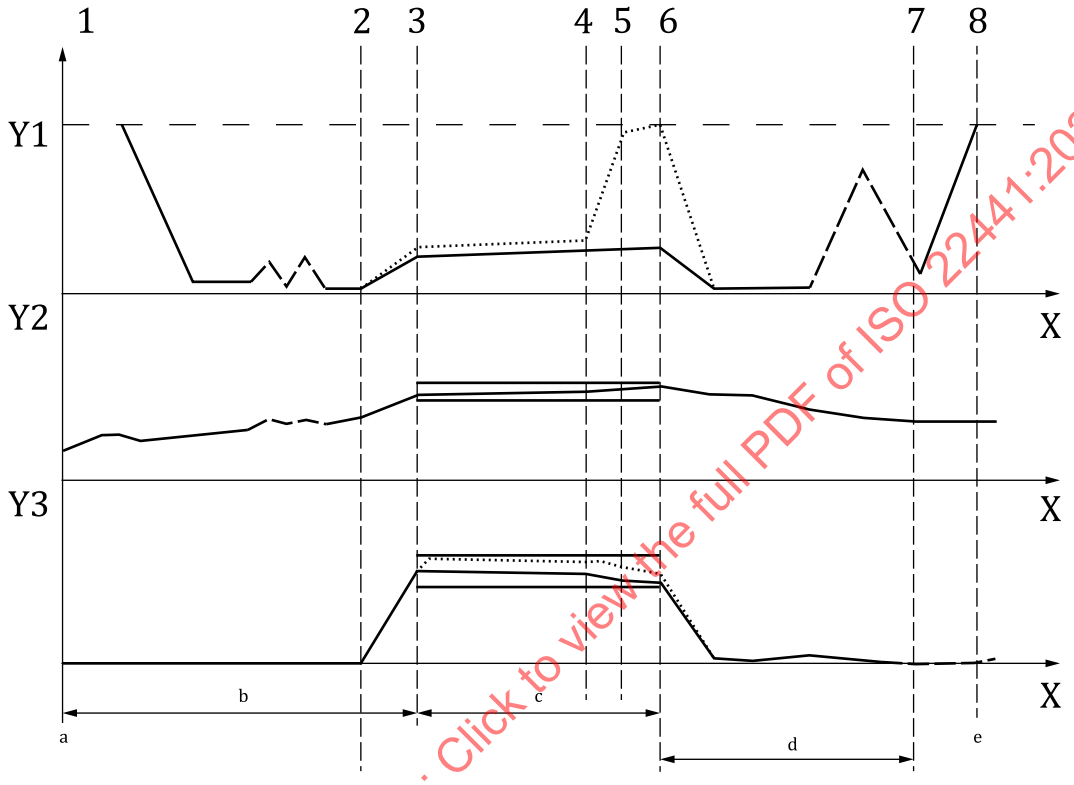
b) Packaging:

— a change in packaging design that can significantly affect physical properties of the package and attainment of sterilizing conditions;

— any change of packaging or packaging procedure.

Annex F
(informative)

Schematic example of a VH2O2 sterilization cycle



Key

Y1	pressure	1	start of the sterilization cycle
Y2	temperature	2	start of exposure phase
Y3	concentration	3	start of holding time
X	time	4	start of air/inert gas injection pulse(s) (if applicable)
		5	end of air/inert gas injection pulse(s) (if applicable)
a	start of cycle	6	end of holding time and start of purging stage
b	conditioning stage	7	end of purging stage and start of air admission
c	holding time	8	“cycle complete”
d	purging stage		
e	end of cycle		

Figure F.1 — Schematic example of a VH202 sterilization cycle conforming to EN 17180

Annex G
(informative)

Environmental aspects

G.1 General environmental aspects

The environmental aspects addressed by this document are related to the development, installation, validation, and operation of the sterilizer during the entire life cycle. Factors such as operating frequency, load capacity and configuration can have a significant outcome on the environmental aspects of operation of the process. During the development, installation, validation and operation of low temperature VH202 sterilization processes, the environmental aspects can be summarised as follows:

a) installation and final disposal of the sterilizer and associated equipment;

b) emissions to air of hydrogen peroxide and its reaction products;

c) contamination of processed items by residues;

d) use and disposal of raw materials for operation such as sterile barrier systems, biological or CIs;

NOTE 1 ISO 11607-1:2019, Annex D provides guidance on environmental aspects of sterile barrier system and packaging systems

e) energy consumption such as electricity use.

Some of these environmental aspects are related to the sterilizer (equipment) design and performance (e.g. tightness of system components containing process chemicals, performance of the operating cycles regarding desorption of hydrogen peroxide and its reaction products), hence are considered in the respective sterilizer (equipment specifications), e.g. EN 17180 (under preparation). Therefore, the overall impact of the sterilizer operation on the environment should be considered.

NOTE 2 Occupational safety and health requirements are a matter for regional or national jurisdiction, hence are not specified in this document (see 1.2.4).

G.2 Hydrogen peroxide properties and classification

G.2.1 Physico-chemical properties

Hydrogen peroxide (H_2O_2) at room temperature is a clear, very pale blue liquid, which is normally used as an aqueous solution. Aqueous solutions are usually stabilised with additives to prevent decomposition over time.

Hydrogen peroxide is not flammable, however, there is a potential hazard by chemical reaction with combustible materials and reducing agents, as hydrogen peroxide is a powerful oxidiser.

Some physical and chemical properties of hydrogen peroxide solutions are given in Table G.1

Table G.1 — Physical and chemical properties of hydrogen peroxide-water solutions

H_2O_2	35 % w/w	50 % w/w	70 % w/w	90 % w/w
Melting point	−33 °C	−52 °C	−40 °C	−11 °C
Boiling point	108 °C	114 °C	125 °C	141 °C
Density (g/cm^3 at 25 °C)	1,128 2	1,191 4	1,283 9	1,386 7
Vapour pressure (partial) at 30 °C	48 Pa	99 Pa	200 Pa	-
Vapour pressure (total) at 30 °C	-	2,4 kPa	1,47 kPa	0,67 kPa
Saturated vapour concentration at 25 °C	-	787 mg/m^3	1,685 mg/m^3	3,049 mg/m^3
NOTE Data taken from Table 1.2 in [24] "European Union Risk Assessment Report Hydrogen Peroxide", Office for Official Publications of the European Communities, Final Report, 2003, CAS No: 7722-84-1, EINECS No: 231-765-0.				

G.2.2 Classification

Globally, classification criteria and labelling requirements for dangerous substances are specified by the United Nations Globally Harmonised System of Classification and Labelling of Chemicals (GHS).

These criteria are incorporated into most national regulations worldwide (e.g. US/OSHA, Japan/JIS, Russia/GOST) and into the European Regulation (EC) No 1272/2008 on classification labelling and packaging of substances and mixtures (CLP Regulation). According to Annex VI, part 3, Table 3.1 of the CLP Regulation hydrogen peroxide solutions (CAS No 7722-84-1) within the application range as being relevant for VH2O2 sterilization are classified as given in Table G.2.

Table G.2 — EC-Regulation classifications of hydrogen peroxide-water solutions

Hazard class	Specific concentration limits	Hazard category	Hazard statement
Oxidising liquid	50 % ≤ C < 70 %	2	H272 Can intensify fire; oxidiser
Skin corrosion	50 % ≤ C < 70 %	1B	H314 Causes severe skin burns and eye damage
Skin irritation	35 % ≤ C < 50 %	2	H315 Causes skin irritation
Eye damage	50 % ≤ C < 70 %	1B	H314 Causes severe skin burns and eye damage
Specific target organ toxicity (STOT)	C ≥ 35 %:	SE 3	H335 Can cause respiratory irritation.
Acute toxicity (oral)	C ≥ 50 %	4	H302 Harmful if swallowed.
Acute toxicity (inhalation)	C ≥ 50 %	4	H332 Harmful if inhaled

The CLP Regulation does not classify hydrogen peroxide solutions as carcinogenic, mutagenic, or dangerous for the environment.

G.3 Environmental impact

National regulations can specify limits for the exposure of humans to airborne hydrogen peroxide concentrations.

The environmental impact of the operation of a VH2O2 sterilization process includes:

a) the design and material selection of accessories and consumables for operating the sterilizer;

b) performing testing (type tests, works tests, validation tests);

NOTE Planning of testing can allow some tests to serve multiple requirements, minimising the number of operating cycles that are necessary.

c) packaging, transportation, unpacking and installation of the sterilizer;

d) the supply and treatment of the feed water and wastewater (if applicable);

e) generation of noise, vibration and heat emissions;

f) operation of the sterilizer;

g) maintenance activities including the extent of repair, testing, inspection, cleaning, including the use of protecting and cleaning agents;

h) product preparation prior to loading the sterilizer (cleaning, washing, disinfecting, packaging and use of sterile barrier systems), including use of energy and other services;

i) use and disposal of BIs and CIs;

j) consumption of electricity and other services including ventilation and cooling;

k) the release of fluids and other substances to the environment.

Planning of the activities specified in this document can help to minimise the environmental aspects. Table G.3 shows how clauses of this document address requirements or recommendations intended to decrease the environmental impact of operation of a VH2O2 sterilization process.

The potential effect (as listed above) on the environment of the operation of the sterilization process together with the relevant hazard classifications should be assessed and measures to protect the environment should be identified. The assessment, including potential impact and measures for control should be documented.

Table G.3 — Clauses of this document addressing environmental aspects

Environmental aspects (inputs and outputs)	Product life-cycle			
	Production and preproduction Stage A	Distribution (including packaging) Stage B	Use Stage C	End of life cycle Stage D
	Addressed in clause of this document	Addressed in clause of this document	Addressed in clause of this document	Addressed in clause of this document
1 Resource use	Introduction (with additional clause) 5.5 8.3 8.4 9.4.8 9.4.10 10.6 E.8.1 E.9.1 For Annex E: with additional verbiage to E.8.1 and E.9.1	—	Introduction (with additional clause) 5.5 8.3 8.4 9.4.8 9.4.10 10.6 E.9.1 For Annex E: with additional verbiage to E.8.1 and E.9.1	—
NOTE Clauses referenced in the stage A column are invariably repeated in the stage C column, as this document requires testing procedures during both stages of the life cycle.				

Table G.3 *(continued)*

Environmental aspects (inputs and outputs)	Product life-cycle			
	Production and preproduction Stage A	Distribution (including packaging) Stage B	Use Stage C	End of life cycle Stage D
	Addressed in clause of this document	Addressed in clause of this document	Addressed in clause of this document	Addressed in clause of this document
2 Energy consumption	Introduction 5.5 E.8.1 E.9.1 For Annex E: with additional verbiage to E.8.1 and E.9.1	—	Introduction 5.5 E.9.1 For Annex E: with additional verbiage to E.8.1 and E.9.1	2
3 Emission to air	Introduction 5.1 5.5 6.3.2 E.8.1 E.9.1 For Annex E: with additional verbiage to E.8.1 and E.9.1	—	Introduction 5.1 5.5 6.3.2 E.9.1 For Annex E: with additional verbiage to E.8.1 and E.9.1	—
4 Emission to water	Introduction 5.5.2	—	Introduction 5.5.2	—
5 Waste	Introduction 5.1 5.5 6.3.2 8.3 8.4 9.4.8 9.4.10 10.6 E.8.1 E.9.1	—	Introduction 5.1 5.5 6.3.2 8.3 8.4 9.4.8 9.4.10 10.6 E.9.1	—
6 Noise	—	—	—	—

NOTE Clauses referenced in the stage A column are invariably repeated in the stage C column, as this document requires testing procedures during both stages of the life cycle.

Table G.3 *(continued)*

Environmental aspects (inputs and outputs)		Product life-cycle			
		Production and preproduction Stage A	Distribution (including packaging) Stage B	Use Stage C	End of life cycle Stage D
		Addressed in clause of this document	Addressed in clause of this document	Addressed in clause of this document	Addressed in clause of this document
7	Migration of hazardous substances	Introduction 5.1 5.5 6.3.2 8.3 8.4 9.4.8 9.4.10 10.6 E.8.1 E.9.1	—	Introduction 5.1 5.5 6.3.2 8.3 8.4 9.4.8 9.4.10 10.6 E.9.1	—
8	Impacts on soil	Introduction	—	Introduction	—
9	Risks to the environment from accidents or misuse	Introduction 4.2 5.1 5.2 5.5 6.1 6.3.2 9.2.2.3 E.9.1	—	Introduction 4.2 5.1 5.2 5.5 6.1 6.3.2 9.2.2.3 E.9.1	—

NOTE Clauses referenced in the stage A column are invariably repeated in the stage C column, as this document requires testing procedures during both stages of the life cycle.

Annex H
(informative)

Justification for the number of temperature sensors and biological indicators (BIs)

H.1 Background

During OQ and PQ activities (see Clause 9), it can be necessary to perform mapping of the sterilizer chamber to ensure homogeneity of the process conditions.

H.2 Justification

The need for OQ or PQ mapping as well the nature of which variables are to be mapped (e.g. temperature or microbiological efficacy) can be determined by

a) evidence-supported recommendation of the manufacturer of the sterilizing equipment;

NOTE The need for OQ or PQ mapping can vary according to chamber volume.

b) risk analysis by the organization in charge of process implementation (user).

H.3 Examples of OQ and PQ mapping

OQ and PQ mapping can include the following process variables:

— Temperature: It is possible that temperature fluctuation will not be as critical to the VH2O2 process efficacy as heat-based sterilization processes, although demonstration of the process working under a controlled variable range can be necessary and can be monitored during OQ and/or PQ. An established OQ thermal map of the chamber can identify potential hot or cold locations. Therefore, monitoring should include more than one geometric plane and locations near doors. The minimum number of temperature sensors is determined according to the usable chamber space (see Table H.1).

Table H.1 — Recommended minimum number of temperature sensors

Volume (L)	Number for OQ	Number for PQ
	Usable chamber space	Product load volume
<100	3	3
100 to 1 000	12	12
>1 000	12	24

— Microbiological efficacy mapping: Microbiological efficacy can be mapped by using appropriate PCDs. During performance qualification, the distribution of the sterilizing agent is assessed with PCDs (containing BIs) distributed throughout the sterilization load or material representative of the sterilization load volume.

The user should document the placement of the chosen PCDs in the sterilizer chamber, within the sterilization load. Other considerations to be addressed in PCD placement within the sterilization load are, e.g. loading patterns, load density and geometry, process challenge locations, placement of physical and/or chemical sensors or probes, potential stratification of physical elements, the effect of packaging.