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

Stérilisation des produits de santé — Chaleur humide — Exigences pour le développement, la validation et le contrôle de routine d'un procédé de stérilisation des dispositifs médicaux

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Foreword

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

ISO draws attention to the possibility that the implementation of this document may involve the use of (a) patent(s). ISO takes no position concerning the evidence, validity or applicability of any claimed patent rights in respect thereof. As of the date of publication of this document, ISO had not received notice of (a) patent(s) which may be required to implement this document. However, implementers are cautioned that this may not represent the latest information, which may be obtained from the patent database available at www.iso.org/patents. ISO shall not be held responsible for identifying any or all such patent rights.

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

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

This first edition cancels and replaces ISO 17665-1:2006, ISO/TS 17665-2:2009 and ISO/TS 17665-3:2013, which have been technically revised.

The main changes compared to the previous editions are as follows:

— combined ISO 17665-1, ISO/TS 17665-2 and ISO/TS 17665-3 into a single standard.

A list of all parts in the ISO 17665 series can be found on the ISO website.

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.

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Introduction

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, can, prior to sterilization, have microorganisms on them, albeit in low numbers. Such medical devices are non-sterile. The purpose of sterilization is to inactivate the microbiological contaminants and thereby transform the non-sterile medical devices into sterile ones.

The kinetics of inactivation of a pure culture of microorganisms by physical and/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 organisms exist during treatment. It follows that the sterility of any one product in a population subjected to sterilization processing cannot be ensured and the expression of sterility of a processed population is defined in terms of the probability of there being a viable microorganism present on a product item.

The process variables for a moist heat sterilization process, i.e. those which contribute towards microbial lethality, are exposure to adequate temperature for a prerequisite time in the presence of moisture. Moist heat sterilization can be utilised as a saturated steam process, where saturated steam is allowed to directly contact all surfaces to be sterilized, or as a contained product sterilization process, where steam, steam mixed with air or other gas, or hot water under pressure are used as the heating medium in order to generate moist heat within the sealed contained product. The term saturated steam describes a theoretical state in which water and vapour are in equilibrium and that no other gases are present. In practice theoretical saturated steam state conditions are not achieved. Mixtures of steam and NCGs, albeit in very low levels, will be supplied to the sterilizer and employed as the sterilizing agent, moist heat.

This document describes requirements that, if met, will provide a moist heat sterilization process intended to sterilize medical devices, which has appropriate microbicidal activity. Furthermore, conformance with the requirements, ensures this activity is both reliable and reproducible so that predictions can be made, with reasonable confidence, that there is a low level of probability of there being a viable microorganism present on product after every sterilization process is complete. 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 given in 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, monitored and recorded sterilization process is not the only factor associated with the provision of reliable assurance that the product is sterile and, in this regard, suitable for its intended use. Attention is therefore given to a number of factors including:

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

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

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

d) the control of equipment and processes;

e) the control of personnel and their hygiene;

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f) the manner and materials in which the product is packaged;

g) the conditions under which product is stored.

The type of contamination on a product to be sterilized varies and this has an impact upon the effectiveness of a sterilization process. It is preferable that products that have been used in a health care setting and that are being presented for sterilization in accordance with the instructions for use (see ISO 17664-1) be regarded as special cases. There is the potential for such products to possess a wide range of contaminating microorganisms (bioburden) and either residual inorganic or organic contamination, or both, in spite of the application of a cleaning process. Hence, particular attention is given to the validation and control of the cleaning and disinfection processes used during processing. The ISO 15883 series provides requirements for and information on automated cleaning and disinfection processes.

This document describes the requirements for ensuring that the activities associated with the process of moist heat sterilization are performed properly. The requirements are the normative parts of this document with which conformance is claimed. The guidance given in the informative Annexes is not intended as checklists for assessing conformance with the requirements of this document. The guidance in the informative Annexes is intended to assist in obtaining a uniform understanding and implementation of the requirements in this document by providing explanations, rationales, examples and methods that are regarded as being suitable means for conforming with the requirements. 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, equipment maintenance, product definition, process definition, installation qualification (IQ), OQ and PQ, during which, along with other characteristics, compatibility of product and materials will be ascertained. 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. It is possible that performing these different activities will involve a number of either separate individuals or organizations, or both, each of whom undertake one or more of these activities. This document does not specify the particular individuals or organizations who are responsible for carrying out the activities.

The requirements of this document are applicable to all settings where moist heat sterilization of medical devices is carried out. However, this document or part of it can be applied to the moist heat sterilization of other products.

Medical devices processed in an industrial setting can, in certain circumstances, be manufactured using standardised processes that result in product with a known and controlled bioburden prior to sterilization. Medical devices processed in health care facilities can include a wide variety of product with varying levels of bioburden. Appropriate and thorough cleaning and, where necessary for safe handling, decontamination processes, are used prior to presenting product for sterilization. Mixed product loads are common in facilities reprocessing medical devices with throughput volumes dictated by historical and predicted demand for sterile product.

Annex A provides guidance on the principles of moist heat sterilization and provides a rationale for the requirements. Specific guidance for health care facilities is given in Annex F and for industrial applications, in Annex H. The numbering and structure of the clauses in Annex F and Annex H correspond to the numbering and structure of the clauses in the normative requirements section of this document.

An overview of the purpose of each normative section is provided at the beginning of Clauses 5 to 12 (see ISO 14937). Table A.1 summarises the purpose of each normative section and suggests the roles and responsibilities for the organisations and personnel involved in each element of the development, validation and routine control of a moist heat sterilization process and moist heat sterilizer.

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

1 Scope

This document provides requirements for the development, validation and routine control of moist heat sterilization processes for medical devices. It also contains guidance which is intended to explain the requirements set forth in the normative sections. The guidance given is intended to promote good practice related to moist heat sterilization processes according to this document. The application within industrial and health care settings is considered.

1.1 Inclusions

Moist heat sterilization processes covered by this document include, but are not limited to:

a) saturated steam sterilization in which air is removed by passive purging (gravity displacement principle);

b) saturated steam sterilization in which air is removed by active air removal (dynamic air removal, pre-vacuum/fractionated vacuum principle);

c) contained product sterilization in which heat transfer is achieved by steam or steam-air mixtures;

d) contained product sterilization in which heat transfer is achieved by water sprays;

e) contained product sterilization in which heat transfer is achieved by water immersion.

NOTE 1 See Annex D where the processes are explained further.

NOTE 2 Although the scope of this document is limited to medical devices, it specifies requirements and provides guidance that can be applicable to other health care products and industrial applications.

1.2 Exclusions

1.2.1 This document does not specify requirements for development, validation, and routine control of a process for inactivating the causative agents of spongiform encephalopathies such as scrapie, bovine spongiform encephalopathy and Creutzfeldt-Jakob disease.

NOTE 1 See ISO 22442-1, ISO 22442-2 and ISO 22442-3.

NOTE 2 Specific regulations have been produced in particular countries for the processing of materials potentially contaminated with these agents.

1.2.2 This document does not apply to those sterilization processes that are based on a combination of moist heat with other biocidal agents (e.g. formaldehyde) as the sterilizing agent.

1.2.3 This document does not detail a specified requirement for designating a medical device as “sterile.”

NOTE National or regional requirements can designate medical devices as “sterile.” See, for example, EN 556-1 or ANSI/AAMI ST67.

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

NOTE There can be applicable national or regional regulations for operational safety.

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 11138-1:2017, *Sterilization of health care products — Biological indicators — Part 1: General requirements*

ISO 11138-3:2017, *Sterilization of health care products — Biological indicators — Part 3: Biological indicators for moist heat sterilization processes*

ISO 11140 (all parts), *Sterilization of health care products — Chemical indicators*

ISO 11607-1, *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
air detector
device designed to detect the presence of non-condensable gases in the chamber or in a stream of steam and condensate

[SOURCE: ISO 11139:2018, 3.9]

3.2
automatic controller
device that directs the equipment sequentially through required stages of the cycle in response to programmed cycle parameters

[SOURCE: ISO 11139:2018, 3.18]

3.3
bioburden
population of viable microorganisms on or in a product and/or sterile barrier system

[SOURCE: ISO 11139:2018, 3.23]

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3.4
biological indicator
test system containing viable microorganisms providing a defined resistance to a specified sterilization process

[SOURCE: ISO 11139:2018, 3.29]

3.5
calibration
operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by the 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]

3.6
chamber
part of equipment in which a load is processed

[SOURCE: ISO 11139:2018, 3.36]

3.7
chemical indicator
test system that reveals change in one or more pre-specified process variables based on a chemical or physical change resulting from exposure to a process

[SOURCE: ISO 11139:2018, 3.43]

3.8
conditioning
treatment of product prior to the exposure stage to attain a specified temperature, relative humidity, or other process variable throughout the load

[SOURCE: ISO 11139:2018, 3.58]

3.9
contained product
load for which the ambient media within a chamber do not come into direct contact with the item to be processed

Note 1 to entry: The environment within the sterilizer is used for heating and cooling purposes only, not for achieving the sterilization effect, e.g. a solution in a sealed bottle.

3.10
contained product sterilization
validated process where indirect contact of a heating medium on the external surfaces of contained product is used to create moist heat internally to achieve the specified requirements for sterility within the contained product

Note 1 to entry: The environment within the sterilizer is used for heating and cooling purposes only, not for achieving the sterilization effect, e.g. a solution in a sealed bottle.

[SOURCE: ISO 11139:2018/Amd1:2024, 3.332, modified — Note 1 to entry added.]

3.11
correction
action to eliminate a detected nonconformity

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

[SOURCE: ISO 11139:2018, 3.64]

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3.12
corrective action
action to eliminate the cause of a nonconformity and to prevent recurrence

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

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

[SOURCE: ISO 11139:2018, 3.65]

3.13
cycle parameter
value of a cycle variable including its tolerance used for control, monitoring, indication, and recording of an operating cycle

[SOURCE: ISO 11139:2018, 3.72]

3.14
cycle variable
property used to control, monitor, indicate, or record an operating cycle

[SOURCE: ISO 11139:2018, 3.74]

3.15
***D* value**
D_{10} value
time or dose required under stated conditions to achieve inactivation of 90 % of a population of the test microorganisms

Note 1 to entry: For the purposes of this document, *D* value refers to the exposure period necessary to achieve 90 % reduction.

Note 2 to entry: The definition of *D* value assumes that a plot of $\log_{10}$ of population versus time of exposure is linear within accepted tolerances.

[SOURCE: ISO 11139:2018, 3.75, modified — Notes to entry have been added.]

3.16
development
act of elaborating a specification

[SOURCE: ISO 11139:2018, 3.79]

3.17
equilibration time
period between the attainment of defined sterilization process parameters at the reference measurement point and the attainment of the specified sterilization process parameters at all points within the load

Note 1 to entry: For the purposes of this document the process parameter to which this definition refers is temperature.

Note 2 to entry: Equilibration time is also known as sterilization time lag.

[SOURCE: ISO 11139:2018, 3.105, modified — Notes to entry have been added.]

3.18
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]

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3.19
establish
determine by theoretical evaluation and confirm by experimentation

[SOURCE: ISO 11139:2018, 3.107]

3.20
evaluation
systematic and objective comparison of the measured results either with one another or with a specification to be met in initial, intermediate and final tests

Note 1 to entry: Evaluation analyses the level of achievement of both expected and unexpected results by examining the results chain, processes, contextual factors and causality using appropriate criteria. An evaluation provides credible, useful evidence-based information that enables the timely incorporation of its findings, recommendations and lessons into the decision-making processes of organizations and stakeholders.

[SOURCE: ISO 9022-1:2016, 2.10, modified — Added "systematic and objective" at the beginning of the definition and Note 1 to entry has been added.]

3.21
exposure stage
cycle stage between the introduction of the sterilizing or disinfecting agent into the chamber and when the agent is removed or neutralised

Note 1 to entry: For the purposes of this document the exposure stage only includes that part of the process for which microbial lethality is claimed.

[SOURCE: ISO 11139:2018 & Amd 1:2024, 3.111, modified — Note 1 to entry has been added]

3.22
F_o value
measure of microbiological lethality delivered by a moist heat sterilization process expressed in terms of the equivalent time, in minutes, at a temperature of 121,1 °C with reference to microorganisms with a z value of 10 °C

[SOURCE: ISO 11139:2018, 3.113.1, modified — 10 K was replaced by °C (by convention, z value is expressed in °C).]

3.23
F_{BIO} value
expression of the resistance of a biological indicator calculated as the product of the logarithm to base 10 of the initial population of microorganisms and the D value

[SOURCE: ISO 11139:2018, 3.113.2, modified — "to base 10" added to the definition]

3.24
$F_{BIOLOGICAL}$ value
expression of the delivered lethality of a process, measured in terms of actual kill of microorganisms on or in a biological indicator challenge system

Note 1 to entry: $F_{BIOLOGICAL}$ can be calculated by multiplying the D_{121} value by the difference between the log to the base ten of the starting population and the log to the base ten of the enumerated population after processing.

3.25
fault
situation in which one or more of the process or cycle parameters is/are outside its/their specified tolerance(s)

[SOURCE: ISO 11139:2018, 3.116]

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3.26
health care facility
HCF
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 specialized treatment facilities.

[SOURCE: ISO 11139:2018 and Amd 1:2024, 3.339]

3.27
health care product
medical device, including in vitro diagnostic medical device, or medicinal product, including biopharmaceutical

[SOURCE: ISO 11139:2018, 3.132]

3.28
holding time
<moist heat sterilization> period for which the temperatures at the reference measurement point and all points within the load are continuously within the sterilization temperature band

[SOURCE: ISO 11139:2018 & Amd 1:2024, 3.133.1]

3.29
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]

3.30
load
product, equipment or materials to be processed together within an operating cycle

[SOURCE: ISO 11139:2018, 3.155]

3.31
load configuration
distribution and orientation of a load

Note 1 to entry: For the purposes of this document the definition refers to the placement of a load in the chamber and includes fixed chamber parts and the numbers and types of product presented for sterilization.

[SOURCE: ISO 11139:2018, 3.156, modified — Note 1 to entry has been added.]

3.32
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]

3.33
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;

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— 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 and Amd 1:2024, 3.166]

3.34
microorganism
entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

[SOURCE: ISO 11139:2018, 3.176]

3.35
moist heat
thermal energy in the presence of moisture used as the sterilizing agent to achieve the specified requirements for sterility

3.36
non-condensable gas
NCG
air and/or other gas which will not liquefy under the conditions of a saturated steam sterilization process

[SOURCE: ISO 11139:2018, 3.183, modified — Added “sterilization” and abbreviation NCG.]

3.37
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]

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

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

[SOURCE: ISO 11139:2018, 3.188]

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

[SOURCE: ISO 11139:2018, 3.190]

3.40
packaging system
combination of a sterile barrier system and protective packaging

[SOURCE: ISO 11139:2018, 3.192]

3.41
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]

3.42
plateau period
equilibration time plus the holding time

[SOURCE: ISO 11139:2018, 3.195]

3.43
porous
<sterilizer load> permeable to water, air or other fluids

[SOURCE: ISO 11139:2018, 3.197]

3.44
preconditioning
treatment of product, prior to the operating cycle, to attain specified values for temperature, relative humidity, and/or other process variables

[SOURCE: ISO 11139:2018, 3.200]

3.45
preventive action
action to eliminate the cause of a potential nonconformity or other potential undesirable situation

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

Note 2 to entry: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence.

[SOURCE: ISO 11139:2018, 3.203]

3.46
process challenge device
PCD
item providing a defined resistance to a cleaning, disinfection, or sterilization process and used to assess performance of the process

Note 1 to entry: For the purpose of this document, the item can be product, simulated product or other reference device. The item can contain a physical indicator, biological indicator or chemical indicator.

[SOURCE: ISO 11139:2018, 3.205, modified — Note 1 to entry has been added.]

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3.47
process parameter
specified value for a process variable

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

[SOURCE: ISO 11139:2018, 3.211]

3.48
process variable
chemical or physical attribute within a cleaning, disinfection, packaging, or sterilization process, changes in which can alter its effectiveness

Note 1 to entry: For the purposes of this document, process variables are conditions within a sterilization process, changes in which alter microbicidal effectiveness, i.e. exposure time and temperature in the presence of moist heat.

[SOURCE: ISO 11139:2018, 3.213, modified — EXAMPLES have been deleted and Note 1 to entry has been added.]

3.49
product
tangible result of a process

EXAMPLE Raw material(s), intermediates, sub-assembly(ies), healthcare product(s).

[SOURCE: ISO 11139:2018, 3.217]

3.50
product family
group or subgroup of product characterized by similar attributes determined to be equivalent for evaluation and processing purposes

Note 1 to entry: See Annex G.

[SOURCE: ISO 11139:2018, 3.218, modified — Note 1 to entry has been added.]

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

[SOURCE: ISO 11139:2018, 3.226]

3.52
reference measurement point
location of the sensor controlling the operating cycle

[SOURCE: ISO 11139:2018, 3.227]

3.53
reference microorganism
microbial strain obtained from a recognized culture collection

[SOURCE: ISO 11139:2018, 3.228]

3.54
reproducibility
condition of measurement, out of a set of conditions that includes different locations, processors, measuring systems, and replicate measurements on the same or similar objects

Note 1 to entry: The different measuring systems may use different measurement procedures.

Note 2 to entry: A specification should give the conditions changed and unchanged to the extent practical.

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3.55
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]

3.56
saturated steam
water vapour in a state of equilibrium between its liquid and gas phases

[SOURCE: ISO 11139:2018, 3.241]

3.57
saturated steam sterilization
validated process which involves the direct contact of saturated steam as the sterilizing agent on product surfaces to achieve the specified requirements for sterility

[SOURCE: ISO 11139:2018 and Amd 1:2024, 3.368]

3.58
services
supplies from an external source, needed for the function of equipment

EXAMPLE Steam, electricity, water, compressed air, drainage.

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

3.59
specify
stipulate in detail within an approved document

[SOURCE: ISO 11139:2018, 3.259]

3.60
spore log reduction
SLR
negative exponent to the base 10 describing the decrease in the number of spores

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

[SOURCE: ISO 11139:2018, 3.260]

3.61
sterile
free from viable microorganisms

[SOURCE: ISO 11139:2018, 3.271]

3.62
sterile barrier system
SBS
minimum package that minimizes the risk of ingress of microorganisms and allows aseptic presentation of the sterile contents at the point of use

[SOURCE: ISO 11139:2018, 3.272]

3.63
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.

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[SOURCE: ISO 11139:2018, 3.274]

3.64
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.

Note 2 to entry: The term SAL takes a quantitative value, generally 10^{-6} or 10^{-3}. When applying this quantitative value to assurance of sterility, an SAL of, for example, 10^{-6} has a lower value but provides a greater assurance of sterility than an SAL of 10^{-3}.

[SOURCE: ISO 11139:2018, 3.275, modified — Note 2 to entry has been added.]

3.65
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]

3.66
sterilization cycle
predetermined sequence of stages performed in a sterilizer to achieve product free of viable microorganisms

[SOURCE: ISO 11139:2018, 3.279]

3.67
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]

3.68
sterilization temperature
minimum temperature on which the evaluation of the sterilization efficacy is based

[SOURCE: ISO 11139:2018, 3.286]

3.69
sterilizing agent
physical or chemical entity, or combination of entities having sufficient microbicidal activity to achieve sterility under defined conditions

[SOURCE: ISO 11139:2018, 3.288]

3.70
temperature band
<moist heat sterilization> temperature range, the minimum of which is the sterilization temperature

Note 1 to entry: The upper limit of the temperature band can be specified in standards and/or can take into account product compatibility.

[SOURCE: ISO 11139:2018, 3.293.1, modified — Note 1 to entry added.]

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3.71
test for sterility
technical operation defined in a pharmacopoeia performed on product following an aseptic process or exposure to a sterilization process

[SOURCE: ISO 11139:2018, 3.298]

3.72
test of sterility
technical operation performed as part of development, validation or requalification to determine the presence or absence of viable microorganisms on product or portions thereof

[SOURCE: ISO 11139:2018, 3.299]

3.73
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]

3.74
verification
confirmation, through 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, monitoring or reviewing documents.

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

[SOURCE: ISO 11139:2018, 3.314]

3.75
works test
series of technical operations performed prior to delivery to demonstrate compliance of a piece of equipment with its specification

[SOURCE: ISO 11139:2018, 3.325]

3.76
***z* value**
change in temperature of a thermal sterilization or disinfection process that produces a tenfold change in *D* value

Note 1 to entry: It is expressed in degrees Celsius (°C).

[SOURCE: ISO 11139:2018, 3.326]

4 General

4.1 The development, validation and routine control of a sterilization process is a critical element in product realization of a health care product. To ensure the consistent implementation of the requirements specified in this document, the necessary processes shall be established, implemented and maintained.

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Processes of particular importance in relation to the development, validation and routine control of a sterilization process include but are not limited to:

— control of documentation, including records;

— assignment of management responsibility;

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

— control of product provided by external parties;

— identification and traceability of product throughout the process;

— control of non-conforming product.

NOTE ISO 13485 covers all stages of the lifecycle of medical devices in the context of quality management systems for regulatory purposes. National and/or regional regulatory requirements for the provision of health care products 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.

NOTE ISO 10012 specifies requirements for a system of calibration and ISO 13485 includes requirements for the control of monitoring and measuring equipment.

5 Sterilizing agent characterization

5.1 Sterilizing agent

5.1.1 The purpose of this activity is to:

a) define the sterilizing agent;

b) demonstrate its microbicidal effectiveness;

c) identify the factors that influence microbicidal effectiveness;

d) assess the effects that exposure to the sterilizing agent has on materials;

e) identify requirements for safety of personnel and protection of the environment.

This activity may be undertaken in a test or prototype system. Where this occurs, the final equipment specification shall be relatable to the results of experimental studies undertaken in the test or prototype equipment.

5.1.2 For the purposes of this document, the sterilizing agent shall be moist heat. A specification for the sterilizing agent shall be documented.

NOTE See definitions of moist heat (3.35), saturated steam sterilization (3.57) and contained product sterilization (3.10) with regard to the sterilizing agent.

5.1.3 Limiting values for any contaminants contained within the sterilizing agent shall be included in the sterilizing agent specification. Contaminants contained within the sterilizing agent shall not impair the efficacy of the sterilization process or the safety of the product for its intended use.

NOTE See A.5.4 and C.10 for guidance on contaminants which can be considered.

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5.2 Microbicidal effectiveness

If moist heat is used outside of the range of conditions that are widely recognised, then the microbicidal effectiveness shall be established and documented.

NOTE The microbial inactivation achieved by moist heat and its use in sterilization processes has been comprehensively documented and is available in the published literature (see [43] and [61]). If moist heat is used outside of the range of conditions that are widely recognised then its ability to achieve microbial inactivation can be established using the approach described in Annex B (e.g. bioburden or bioburden/biological indicator or overkill approach) or in ISO 14937:2009, 5.3.

5.3 Effects on materials

The effect of exposure to moist heat on the physical and/or chemical properties of materials and on their biological safety shall be assessed.

NOTE The effects of moist heat on a wide variety of materials used to manufacture medical devices have been comprehensively documented (see [28]) and such documentation is of value to those designing and developing medical devices that are to be sterilized by moist heat. Studies of the effects of a moist heat process on a product are implemented during the product design stage. See Clauses 6, 7 and 8. Table A.1 outlines the roles and responsibilities for each normative section and Annexes F and H give guidance for health care facilities and industrial settings.

5.4 Environmental consideration

Moist heat is not normally considered as having a significant environmental effect. However, the potential impact on the environment of the operation of the sterilization process shall be assessed and any measures necessary to protect the environment shall be identified. This assessment, including potential impact (if any) and measures for control (if identified), shall be documented.

6 Process and equipment characterization

6.1 General

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

6.2 Process characterization

6.2.1 The process variables for moist heat sterilization shall be time and temperature in the presence of moist heat sufficient to ensure microbial inactivation. All sterilization processes shall be specified.

NOTE Pressure is not a process variable in a moist heat sterilization process since it has no bearing on microbial inactivation. Pressure is a cycle variable which is employed to control the operating cycle.

6.2.2 Process characterization, at a minimum, shall include:

a) identifying the type of moist heat sterilization cycle to be used and documenting the process variables and the process parameters and their tolerances;

NOTE 1 See the Scope, 6.3 and 6.4 for types of moist heat sterilization cycle and Annex D for examples of moist heat sterilization cycles.

b) identifying the cycle variables for the selected moist heat sterilization cycle and documenting the cycle variables, cycle parameters and their tolerances;

NOTE 2 The data developed in product definition (see Clause 7) can impact the characterization of the sterilization process.

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NOTE 3 This clause considers all cycle variables and their cycle parameters, 6.2.2 d) considers specific cycle variables and cycle parameters used to ensure efficacy, safety and reproducibility of the sterilization cycle.

c) description of each operating cycle, including specified process parameters and their tolerances;

d) the specific cycle variables and their cycle parameters used to ensure process efficacy, safety and reproducibility including their tolerances (see A.6.1);

e) the process variables and cycle variables that are measured and used to verify that the sterilization cycle will be delivered;

f) the products, including their SBS and packaging system, product families and representative load configurations that can be sterilized;

NOTE 4 Information on the product characteristics and product families can be found in Annex C.

g) any restrictions on the load, such as size, mass and configuration, as applicable;

h) requirements for the preconditioning of the load prior to sterilization, if such preconditioning is necessary to ensure the efficacy of the sterilization process (e.g. equilibration of the load at a specified temperature and humidity);

i) requirements for the post sterilization cycle treatment, if such treatment is included in the sterilization process specification (e.g. allowing the load to cool in a controlled environment);

j) the location of the reference measuring point;

k) the minimum frequency of use of process monitoring tools, e.g. physical sensors, biological indicators, chemical indicators, process challenge devices (PCDs);

l) the maximum quantity of each contaminant that can be present in any liquid, air, gas or steam admitted to the chamber if the contaminant can adversely affect the product, its SBS or packaging system or the efficacy of the sterilization cycle, e.g. the maximum amount of water that can be suspended in the steam entering the chamber shall be specified if that can cause an adverse effect on the product or its SBS or packaging system.

NOTE 5 Properly engineered steam traps and separators can be used to remove water from the steam prior to injection into the chamber.

NOTE 6 The level of risk to the process and load associated with the presence of contaminants can depend upon the point in the process when maximum quantities occur.

6.2.3 The acceptable SAL for the process shall be specified.

NOTE 1 The specification for SAL can be based on the determination of the population and resistance of any bioburden which can be on the product at the start of the sterilization process.

NOTE 2 If a 10^{-6} SAL is specified for a product and an overkill approach with recognised time and temperature combinations for moist heat sterilization (see Table A.2) is used to achieve the SAL, then the maximum SAL for the product will be substantially less than 10^{-6}.

NOTE 3 See Annex B for guidance on the establishment and evaluation of a sterilization process primarily based on microbiological inactivation methods.

6.3 Saturated steam sterilization processes

In addition to the requirements in 6.1 and 6.2, the specification for a saturated steam sterilization process shall include:

a) the holding time and the minimum and maximum temperatures (and their locations) measured during this time for the reference load(s) in the chamber, including fixed chamber parts and specific loading accessories (e.g. trolleys, frames) intended for routine operation.

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b) the maximum difference between the temperature measured at the reference measuring point and the temperature determined from the measured chamber pressure using steam table values [see Annex E, Table E.1 and Formula (E.1)] during the holding time;

NOTE 1 The comparison between the measured temperature and that calculated from measured chamber pressure according to steam tables cannot be regarded as a substitute for the monitoring devices or procedures specified in 6.3 c), d) or e).

NOTE 2 See A.6.1.2.5 and Annex E for guidance on assigning a limit to the difference.

c) a description of and justified procedure for the steam penetration test used to verify that the level of residual NCG does not prevent the presence of the validated level of moist heat on the surfaces to be sterilized, for the product family(ies) known to restrict the penetration of steam by virtue of their material composition, mass, design or load configuration;

NOTE 3 The presence of residual NCG in the chamber can arise from:

— NCGs carried into the chamber in the steam supply;

— air leakage into the chamber during periods of vacuum;

— NCG remaining as a result of an inadequate air removal stage of the operating cycle.

d) a description of:

1) the PCD suitable for the sterilization process and not fitted to the sterilizer to demonstrate a specific characteristic of the sterilization process (e.g. air removal and steam penetration); or

2) for dynamic air removal cycles, the monitoring system fitted to the sterilizer for the detection of NCGs (e.g. an air detector), including its sensor location(s), and how to interpret its results;

NOTE 4 The specification for a saturated steam sterilization process normally includes a description of a PCD not fitted to the sterilizer [6.3 d) 1)] or a monitoring system fitted to the sterilizer [6.3 d) 2)] both used for the detection of NCG during each operating cycle. Specified, established and validated alternative methods for the detection of NCGs, particularly in an industrial setting where sterilization processes and load configurations are specified in detail, are also possible (but see E.2.3).

e) the reference load(s) to be used to confirm or judge the effectiveness of the sterilization process for an identified load [see 6.2.2 f)];

f) dryness of the reference load determined by a change in mass or by presence of perceptible moisture.

6.4 Contained product sterilization processes

In addition to the requirements in 6.1 and 6.2, the sterilization process specification shall include the following information for the load configuration justified to be the most difficult to sterilize:

a) details of the product(s) and its container(s) or, if applicable, reference product(s);

b) the size of the load and its location, orientation and support system within the chamber;

c) the temperature profiles and the locations from which they were determined for the period of the sterilization cycle for which lethality is claimed, and which shall be measured in the reference load and in the free space surrounding the load;

d) the maximum and minimum temperature and rates of change for the period of the sterilization cycle for which lethality is claimed;

e) the method for establishing the location where the maximum and minimum temperature can be measured.

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6.5 Equipment

6.5.1 Equipment used to deliver the sterilization process shall be specified. The specification shall include:

a) unique identification (e.g. manufacturer, model and serial number) and physical description of the equipment, together with any necessary ancillary items;

b) the materials of construction of any part of the equipment and any ancillary items that are used to contain and transport steam or any other gas or liquid into the chamber;

c) characteristics of filters (if used);

d) a record of cycle parameters that is independent from the process control (see ISO/TS 22421:2021, Annex B);

e) for each measuring chain used for control and recording;

   1) a description of the measuring chain;

   2) the characteristics and location of the sensor;

   3) the measurement range, resolution and accuracy.

f) where applicable, the rates of pressure change capability during each stage of the cycle;

   NOTE 1 The specification for the rates of pressure change during each stage of the operating cycle can be important as this can influence the integrity of a medical device and an SBS, or influence diffusive steam penetration into complex devices.

g) the fault(s) and failures recognised by the monitoring system, together with any visual, audible or recorded warnings or indications;

h) the safety features;

   NOTE 2 The specification can include safety features for the protection of personnel and the environment.

   NOTE 3 In some jurisdictions specific safety features can be required.

i) information and test results which can allow the user to establish the conformity of the equipment to local, regional, or national regulations applicable for installation and operation of the equipment including those for emissions into the environment;

   NOTE 4 Citation of appropriate standards can be included.

j) a description and acceptance criteria for the test to be used to determine the level of air leakage into the chamber if vacuum is used during the operating cycle;

k) a description of the device (e.g. air detector), if fitted, including its settings used to detect non-condensable gas that can be present in steam supplied to the chamber or remain in the chamber after the air removal stage of the sterilization cycle.

6.5.2 The operating procedures for the equipment and ancillary items shall be specified. The specification shall include:

a) the means by which allowed changes to the automatic controller programmes can be made;

b) step-by-step operating instructions;

c) action to be taken in case of a fault or failure indication;

d) the means by which an error in the results of a measurement for control, indication and/or recording can be identified, e.g. if a sensor becomes damaged an open circuit error will be reported;

e) the contact for technical support if applicable.

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6.5.3 The installation requirements for the equipment shall be specified. The specification shall include:

a) the location, space and the environment in which the equipment is to be installed;

b) installation instructions;

c) any restriction or precautions to be considered for intended operation of the equipment (e.g. required space for load carriers, maintenance access, ventilation);

d) details of each service necessary for the correct function of the equipment, including (if applicable);

   1) means of disconnecting services to the sterilizer;

   2) minimum and maximum pressure of services including, e.g. compressed air, water, steam;

   3) minimum and maximum temperature of services including, e.g. water;

   4) minimum and maximum flow rate for each service;

   5) any filtration requirements for each service, e.g. water, compressed air, steam;

   6) electrical requirements, e.g. phase requirements, minimum and maximum voltage and maximum current (amperes), expressed as phase to neutral or phase to phase, for the electrical supply;

   7) maximum level of NCG and liquid water in steam;

   8) maximum quantity of each contaminant which can be found in fluids supplied to the sterilizer, e.g. compressed air, water, steam.

e) the load bearing structures that are to support the principal heavy components of the equipment;

f) the materials of construction for the parts that transport steam, gas, air and water into the space in which the sterilizer is to be installed and into the sterilizer.

6.5.4 The load support system, if used, in the chamber shall be specified. This specification shall ensure that the system shall not inhibit the attainment of sterilizing conditions throughout the load or cause damage to product including its SBS or packaging system.

6.5.5 The sterilizer specification shall provide a description of how a failure in a control function does not lead to a failure in recording of process parameters resulting in an ineffective process appearing effective.

NOTE This can be achieved by monitoring systems which evaluate and compare data from process control, independent cycle recording, equipment specifications and hardware status indications for fault detection, indication and initiation of consecutive safety measures, as applicable.

6.5.6 The software used to control or monitor the process shall be prepared in accordance with a documented system that provides documented evidence that the software meets its design intention.

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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 before sterilization, and the manner in which the product is packaged and presented for sterilization.

7.2 Product and, as applicable, product family(ies) to be sterilized shall be specified.

NOTE For health care facilities, see F.7.2.

7.3 The criteria for defining and assigning a product to a product family shall be specified (see Annex G for guidance).

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7.4 The SBS or packaging system that is assigned to a product family shall be specified and conform to ISO 11607-1 and ISO 11607-2.

7.5 A system shall be defined, documented and maintained to ensure that the condition of the product presented for sterilization is controlled and does not compromise the effectiveness of the sterilization process, e.g. preconditioning the product in a controlled temperature and humidity environment. Also see A.7.5.

NOTE Microbiological, organic and inorganic contamination can be considered when defining the system. See C.10.2 and Annexes F and H for further guidance.

7.6 If biological indicators are used for evaluation of a contained product sterilization process, evidence of any effect the composition of the contained product can have on the measured resistance (*D* value) of a biological indicator used to evaluate the sterilization process shall be established.

7.7 A dedicated PCD shall be specified. Alternatively, a reference device identified as an appropriate challenge and its SBS or packaging system, shall be specified. For example, product that can be used to represent a specific characteristic(s) of the product.

7.8 The limiting value(s) for each process and cycle variable to which the product and its SBS or packaging system (if used) can be exposed, shall be specified.

NOTE 1 Exceeding the limiting values can have an adverse effect on either the performance of the product or its packaging, or both.

NOTE 2 If an SBS is not used (e.g. sterilization of a load in a dental office where the items are used immediately after processing) sterility will not be maintained once the sterilizer door is opened.

7.9 If the level of moisture present in the product and/or its packaging system prior to sterilization can affect the efficacy of the sterilization process, the limiting value(s) shall be specified.

7.10 The safety, performance and stability of a product in its SBS or packaging system, and where applicable, product potency, after exposure to the sterilization process, shall continue to meet documented specifications.

7.11 If the product is a reusable medical device, the instructions for use shall be consulted for any limitations relating to end-of-life indicators or the number of processing cycles which they can be subjected to (see ISO 17664-1).

7.12 If the integrity of the product can be affected by a contaminant(s) or process residue (e.g. moisture) remaining on the product or packaging after sterilization, the contaminant or process residue shall be specified along with the maximum acceptable limit allowed.

7.13 An operating procedure shall be specified to ensure that the condition of the product and, if used, its SBS or packaging system presented for sterilization will not compromise the effectiveness of the sterilization process. This procedure shall include at least the following elements:

a) cleaning and where applicable disinfection of re-useable product by a validated process;

   NOTE When processing reusable product, cleaning and disinfection will also reduce the risk of infectious hazards to operators.

b) cleaning and, where applicable, disinfection of re-useable SBSs where used, using a validated process;

c) cleaning of single use product during manufacturing, where applicable, by a validated process;

d) any further preconditioning prior to the sterilization cycle identified as necessary for specific product;

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e) characteristics and limitations of load configurations;

f) if required, verification of the integrity of the SBS before exposure to the sterilization process;

g) an estimation of bioburden in accordance with ISO 11737-1 when a sterilization process is established using the bioburden approach.

7.14 The integrity of the SBS or packaging system after exposure to the sterilization process shall be ensured.

NOTE The integrity of the SBS can be ensured by using either a validation approach or a post process test approach.

8 Process definition

8.1 The purpose of this activity is to define the sterilization process by providing a detailed specification for the sterilization cycle to be applied to defined product without compromising the safety, quality and performance of that product.

8.2 The sterilization process shall be specified, including process variables and process parameters and their tolerances. During the establishment of this sterilization process, process parameters and appropriate cycle parameters shall be measured and used, to confirm reproducibility.

8.2.1 If a saturated steam sterilization cycle is to be used, during the holding time the maximum difference between the temperature measured at the reference measuring point and the temperature measured at the surfaces in or on the product to be sterilized shall be specified.

EXAMPLE A temperature difference of 2 K can be considered acceptable. Alternatively, maximum temperature difference is determined based on risk assessment for product attribute.

8.2.2 If an existing validated sterilization process, including the sterilization cycle, is intended to be used to sterilize defined product, process and equipment documentation shall be reviewed to ensure the identified variables in 6.2, 6.3 and 6.4 have been included in the process specification for routine production.

8.3 The sterilization process shall be established from at least one of the following:

a) data supplied in the instructions for use accompanying the medical device (see ISO 17664-1), the sterilizer and, if used, the SBS;

NOTE This is the common approach for process definition in health care facilities.

b) similarity with a product that is already assigned to a product family (see Annex G);

c) development of an operating cycle that will deliver the specified SAL.

8.4 The SAL to be achieved by the sterilization process on and/or within a product shall be specified and shall meet a pre-defined requirement. National specifications for the SAL can apply.

NOTE The SAL specified can be a range with the maximum value representing the maximal SAL required to be achieved by the sterilization process.

8.4.1 The SAL attained on and/or within the product during the sterilization process shall be by means of one of the following;

a) established by knowledge of the bioburden and its resistance (see B.2 and B.3);

b) determined by an “overkill” method (see B.4);

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c) defined by demonstrating that during the holding time all parts of the product that are intended to be sterile are exposed to process parameters selected from an official national or regional pharmacopoeia;

NOTE This is a common approach in a health care facility.

8.4.2 The SAL attained on and/or within the product during the sterilization process shall be deemed to be equal to or exceed the requirements specified in 8.4.1 c) provided that:

a) the product is assigned to a relevant product family;

b) a relevant sterilization process is specified;

c) the equilibration time does not exceed the maximum for products assigned to the same product family.

8.5 The sterilization process shall not expose the product and its SBS or packaging system (if used) beyond the limiting process and cycle parameters or contaminants.

8.6 If a saturated steam sterilization process is to be used, the level of residual air and NCG at the commencement of the holding time shall not prevent the attainment of moist heat on all surfaces of the product intended to be sterilized, including the surfaces in cavities, lumens and tubing.

8.7 If biological indicators are used to establish the sterilization process:

a) they shall conform with ISO 11138-1 and ISO 11138-3;

b) the microorganism, population, resistance and method of presentation shall be identified and shall take into account the expected or established product bioburden;

c) the location of biological indicators within the sterilization load and acceptance criteria post-exposure to the sterilization process shall be specified.

8.7.1 The selected biological indicator or inoculated product may have populations and resistance values lower than the minimum values specified in ISO 11138-3:2017, Clause 9 in order to obtain a specified BI microbiological challenge, but they shall otherwise meet the requirements of ISO 11138-1 and ISO 11138-3 (also see Annex B).

NOTE The BI microbiological challenge is calculated as the product of the logarithm to the base ten of the initial population of microorganisms and the D value (BI microbiological challenge = log N_0 × D_{121}-value ; see F_{BIO}).

8.7.2 The method of presentation can include inoculated product or the placement of inoculated carrier(s) within the product.

NOTE 1 Conformance of the biological indicator to ISO 11138-1 and ISO 11138-3 does not apply to the inoculation of the PCD/reference device.

NOTE 2 A test for the ability to sterilize defined medical devices includes test specifications is given in Clauses 6 and 7.

8.8 For contained product, the effect of the product and its packaging system on the resistance of the test microorganism when exposed to the proposed sterilization process shall be known and considered for evaluation.

NOTE For contained products, the nature of the product (e.g. 5 % dextrose solution) and the packaging (e.g. a flexible intravenous infusion bag) can alter the resistance of the test microorganism.

8.9 If chemical indicators are used as part of the establishment of the sterilization process;

a) they shall conform to the relevant part(s) of the ISO 11140 series;

b) they shall be appropriate for their intended purpose;

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c) the location of chemical indicators within the load shall be specified;

d) the acceptance criteria shall be specified;

e) they shall not adversely affect the medical device by reaction, contamination and/or transfer before, during or after the sterilization process.

8.10 If a PCD is to be used to assess the efficacy of the specified characteristics of a sterilization process, the validity of the PCD, test methodology(ies) and acceptance criteria shall be established and documented.

8.11 For a sterilization process established by microbiological methods (see B.2, B.3 and B.4), the following apply:

a) bioburden determination shall be performed in accordance with ISO 11737-1 if the bioburden (B.2) or bioburden / biological indicator (B.3) approaches are used;

b) when the bioburden method (B.2) is followed, tests of sterility shall be performed in accordance with ISO 11737-2;

c) product used in establishing the process shall be representative of that to be processed routinely;

d) equipment used shall be capable of reproducibly delivering a combination of process parameters with less lethality than the routine sterilization process (unless the full cycle overkill approach described in B.4.6 is used), such that the level of inactivation of microorganisms results in a population that allows extrapolation with regard to the total result.

NOTE These approaches are more commonly used in an industrial setting.

8.12 If, after exposure to the sterilization process, treatment of the product and its packaging is required in order to maintain sterility, this treatment shall be specified.

8.13 Calibration, equipment maintenance, performance test(s) and acceptance criteria (where applicable) intended to ensure that the sterilization process remains reproducible shall be specified.

9 Validation

9.1 General

9.1.1 The purpose of this activity, is to demonstrate that the sterilization process established in the process definition can be delivered effectively and reproducibly to the load. Validation consists of several identified stages: installation qualification (IQ), operational qualification (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 equipment or using appropriate test materials to demonstrate the capability of the equipment to deliver the sterilization process that has been defined. PQ is the stage of validation that uses product to demonstrate that the equipment consistently operates in accordance with predetermined criteria and the process yields product that is sterile and meets the specified requirements.

9.1.2 Each stage of validation shall be carried out in accordance with a documented procedure.

NOTE 1 Carrying out all the elements of validation (IQ, OQ, PQ) cannot be regarded as a substitute for routine monitoring as specified in Clause 10.

NOTE 2 For further information and examples see C.14, F.9.1.2, F.9.2, and H.9.1.2.

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

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9.1.4 Any modifications to product, packaging, equipment, or sterilization process carried out during validation shall be recorded and justified, and the specification(s) changed accordingly (see Clause 12).

NOTE Modifications can invalidate regulatory conformity status for sterilizer equipment in some jurisdictions.

9.1.5 The measuring chain for each test instrument used for validation shall have:

a) documented evidence of calibration, traceable to a national standard and equipment maintenance in accordance with the instructions for use;

b) a calibration status verified according to the technical and applicable management requirements carried out at a value(s) used to control the sterilization process and judge the results of the test in which the measuring chain is used.

NOTE National calibration reference standards are often mutually recognized and traceable to international reference standards with recognized fixed points.

9.1.6 The correlation between readings from sterilizer instruments and independent test instruments for validation at the similar sensor locations shall be confirmed.

9.1.7 If the equipment could have been affected by packaging, transportation or installation activities after certified final inspection tests at the manufacturing site, conformance with related specifications shall be verified during validation (IQ and OQ).

9.1.8 During IQ, OQ or PQ, as applicable, it shall be verified that fault recognition and operational safety systems function and conform with their performance specifications. Verification can be carried out as far as possible without compromising the safety, functional integrity and certified conformity of the sterilizer.

NOTE Suitable procedures for testing the fault recognition and operational safety systems can be available in the sterilizers technical documentation.

9.1.9 If an existing sterilizer with a validated sterilization process is to be used to process a new product, the IQ and OQ stages of the existing validation may be accepted, provided that changes have not been made to the equipment since the existing validation.

9.2 Installation qualification (IQ)

9.2.1 Installation qualification shall demonstrate that the equipment and ancillary items have been installed in accordance with their specification.

NOTE Additional regional, national and local regulations can also apply.

9.2.2 It shall be verified that the installation of the equipment, ancillary items and the supply of the services conform with their specifications.

9.3 Operational qualification (OQ)

9.3.1 Operational qualification shall demonstrate that the equipment will deliver the specified sterilization process(es).

9.3.2 The rationale for the number and locations of the temperature sensors used to demonstrate that requirements are met for temperature distribution in the chamber and, if used, the test load in place in the chamber shall be documented. The OQ may be performed with a test load.

NOTE If the guidance in Annex C is followed, this can include a test load.

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9.3.3 Prior to OQ, the calibration of all instrumentation (including any test instruments) used for monitoring, controlling, indicating or recording of the sterilization process shall be verified.

9.4 Performance qualification (PQ)

9.4.1 Performance qualification shall demonstrate that product has been exposed to the specified sterilization process, including the specified sterilizing agent, by the equipment to be used for routine sterilization.

9.4.2 Performance qualification shall verify that the conditions required to achieve the specified SAL have been met.

9.4.3 Rationale shall be documented for the number and locations of temperature sensors, biological indicators and/or chemical indicators used to demonstrate that requirements are met throughout the load.

9.4.4 Checks shall include and verify that:

a) the IQ and OQ were successful;

b) the SBS or packaging system is the same as, or is a greater challenge to that intended for routine production;

c) the load configuration conforms with 6.2.2 f) and g) and is considered to be representative or more challenging to the sterilization process than the routine load;

d) the test load, if used, represents product that will be routinely processed and that is assigned to a product family(ies) compatible with the one(s) assigned to the sterilization cycle or that represents the product families considered to be a greater challenge to the sterilization process;

e) the load configuration and any required preconditioning conforms with 6.2.2 f), g) and h) and 7.13;

f) if varying load configurations will be used, the extent to which the variation affects the sterilization process shall be evaluated to ensure that all product exposed to the sterilization process achieves the required SAL.

9.4.5 For each of the following, studies shall establish:

a) conformity to the sterilization process identified during process definition and the limiting process parameters of the process variables identified for the product, SBS or packaging system;

b) data as required for the condition of the product and SBS (as applicable) as presented to the sterilization process;

c) the temperature profile(s) on and throughout product located in representative positions in the load;

d) the temperatures measured during the plateau period;

e) the equilibration time;

f) the minimum and maximum temperatures during the holding time and their locations including:

   — at the reference measurement point;

   — on the surface of/ in the load;

   — calculated from the measured chamber pressure according to steam table values, if applicable (see Annex E).

   For saturated steam sterilization processes, national or regional requirements should be taken into consideration when defining the maximum permissible difference between the measured temperature

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and the temperature determined from measured chamber pressure according to steam tables. See Annex E and, for example, EN 285.

NOTE 1 If a difference between the measured temperature and the temperature determined from measured chamber pressure exists, this can indicate a process failure. If there is no difference between the measured temperature and the temperature determined from measured chamber pressure this cannot be regarded as an indication of an acceptable process. Other information is required to confirm process acceptability.

g) the holding time;

h) the response of chemical indicators according to their instructions for use, when used;

i) that the response of the chemical indicator or biological indicator or sensor contained in the PCD according to its instructions for use (if used) is acceptable;

NOTE 2 PCDs are discussed in greater detail in Annex A (air removal indicator) and in Annex B (microbiological indicator).

j) the integrity of the SBS when used.

NOTE 3 Product is normally wrapped in an SBS or packaging system. However, medical devices can be sterilized unwrapped if they are immediately and aseptically transferred to the point of use (e.g. the sterile field in an operating room) after removal from the sterilizer.

9.4.6 If, in addition to the measurement of physical parameters, the sterilization process is to be verified by microbiological methods, then it shall be qualified and one of the following methods shall be used:

a) bioburden method;

b) combined bioburden/biological indicator method; or

c) overkill method.

NOTE 1 See Annex B.

NOTE 2 The bioburden and bioburden/biological indicator methods are also known as product specific approaches.

When the bioburden is not known or measurable, a process based on an overkill approach shall be used provided that the product is stable when exposed to the specified process conditions.

9.4.7 The reproducibility of the sterilization process shall be demonstrated to ensure the required SAL is consistently delivered to the load. Either a defined load (e.g. a contained product load) or load configuration(s) considered to be the most challenging to the sterilization process (e.g. a load configuration containing defined product families for saturated steam sterilization) shall be exposed to at least three consecutive sterilization processes to demonstrate that the sterilization process is reproducible within its specification and specified tolerances.

NOTE Three consecutive sterilization processes does not necessarily mean one after the other. See Annexes F and H for additional information on the interpretation of this subclause.

9.4.8 If, during the sequence of three consecutive cycles specified in 9.4.7, a failure occurs and this can be attributed to factors not relevant to the effectiveness of the sterilization process being validated (see example below), the failure shall be documented as unrelated to the performance of the sterilization process and the cycle omitted from the sequence.

EXAMPLE Failure of external services, e.g. electricity, steam, water, compressed air or a failure of external monitoring equipment.

9.4.9 Non-conformance with the sterilization process specification during PQ shall be reviewed and corrected.

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9.5 Review and approval of validation

9.5.1 Information gathered or produced during IQ, OQ and PQ shall be reviewed for conformity to the acceptance criteria specified for each stage of the validation process. The outcome of this review shall be documented and approved.

9.5.2 The sterilization process specification shall be confirmed. This specification shall include the criteria for designating the sterilization process used for a particular product or load as conforming, and shall document at least the following:

a) the sterilizer including the associated services;

b) the cycle parameters of the cycle to be used;

c) the product family(ies) that can be processed;

d) the load configuration(s) (including orientation, size and mass);

e) the procedures for any preconditioning of product, if used;

f) a description of the SBS or packaging system and methods of packaging;

g) the distribution and orientation of medical devices within a package containing multiple medical devices, if applicable;

h) the periodic tests and equipment maintenance activities necessary to indicate delivery of a reliable process;

i) the PCD and the product family(ies) for which it is relevant;

j) the bioburden, if applicable.

10 Routine monitoring and control

10.1 Routine monitoring

10.1.1 The purpose of this activity is to demonstrate that the validated and specified sterilization process has been delivered to the product for each sterilization process that is carried out.

10.1.2 Routine monitoring and control shall be performed on each operating cycle in order to demonstrate that the process variables for moist heat sterilization are attained.

10.1.3 Delivery of an effective sterilization process shall be verified by confirming that recorded data from routine monitoring are within specified tolerances measured by physical sensors together with the results from chemical indicators and/or biological indicators and/or PCDs, if used.

10.2 Operational status

The operational status of the equipment shall be verified by evidence from the following periodic tests:

a) air leakage into the chamber;

b) quality of steam or heat transfer media admitted to the chamber (which can include checks for, e.g. NCG, conductivity of feed water, contaminant(s), moisture content);

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

EXAMPLE A record of the timings of each stage along with pressure maximum and minimum values for each air removal and steam admission pulse.

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d) a steam penetration test using a defined test load which shall be conducted using devices independent of the sterilizer and the sterilizer control;

NOTE 1 The steam penetration test comes in many forms including Bowie and Dick tests and hollow PCDs both of which can contain an indicator.

NOTE 2 For equipment or processes not intended for hollow or porous items (i.e. those which do not entrain air) a steam penetration test cannot be required.

10.3 Process verification

For verification of a successful process, any fault indication, defined failure message and further relevant information provided by the monitoring system (e.g. fault indication system, process evaluation system) shall be documented and evaluated with respect to possible detrimental impact on the reliability of the process outcome.

10.4 Evaluation of additional data for saturated steam sterilization processes

For saturated steam sterilization processes, evaluation of additional data and information shall include:

NOTE 1 Evaluation can be carried out automatically by a validated software system or by visual examination of recorded data.

a) the duration when the temperature at the reference measurement point is at or above the sterilization temperature;

NOTE 2 If the data recording system reports that the validated duration has been achieved this can be regarded as meeting the requirement.

b) temperature at the reference measurement point and chamber pressure during the plateau period and, when available, the temperature determined from measured chamber pressure according to steam table values (see Annex E) during the holding time;

c) for all stages of the operating cycle:

— the chamber pressure;

— the temperature measured at the reference measurement point;

— the chamber temperature if provided;

NOTE 3 Printed records can provide a summary of the information above, assisting conformity assessment.

d) the results obtained from a PCD containing an indicator sensor designed to assess a specific characteristic of the sterilization process, such as adequacy of air removal and steam penetration, if used [see 6.3 c) and d)];

e) the results obtained from a process monitoring system (e.g. an air detector) fitted to the sterilizer as part of process control, if used, [see 6.3 c) and e)];

f) results of inspection procedures employed to confirm the dryness and integrity of the SBS or packaging systems of the load.

NOTE 4 This can involve direct inspection of every package as can happen, for example, in a health care facility or can involve a risk assessment and qualification exercise (which can involve a sampling and inspection plan) as can, for example, be used in an industrial setting.

10.5 Evaluation of additional data for contained product sterilization processes.

For sterilization processes for contained product, evaluation of the data shall include:

a) the temperature(s) measured in the PCD that represents the product in the load, having a known thermal relationship to the contained product or load, if used as part of process control;

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b) the temperature at the reference measurement point and the chamber pressure for all stages of the operating cycle;

c) the temperature measured in the product during the heating stage, plateau period and cooling stage if used as part of process control and monitoring;

d) the time of the plateau period;

e) the holding time;

f) the integrated lethality, F_0, if used;

g) the value(s) for the process parameter(s) for homogeneity of the heating media in the chamber.

10.6 Record retention

All records shall be retained in accordance with specified procedures (see A.10.10).

11 Product release from sterilization

11.1 The purpose of this activity is to specify procedures for establishing if product exposed to a sterilization process can be released into use.

11.2 Procedures (e.g. standard operating procedures, also known as SOPs) for the review of records and product release from the sterilization process shall be specified and documented. The procedure(s) shall define the requirements for designating a sterilization process as conforming. If a requirement is not met, product shall be designated as non-conforming and handled in accordance with standard operating procedures.

NOTE 1 Suitably trained and qualified individuals can perform product release (see 4.1, A.10.2 and Annexes F and H).

NOTE 2 Examples of nonconformance include a process or cycle parameter being out of specification, a growth positive biological indicator or a chemical indicator failing to meet its endpoint. An acceptable test for sterility cannot be used as confirmatory evidence of process success. See also Annex F and H for further guidance.

11.3 A system shall be specified to ensure that processed and non-processed items are clearly differentiated.

12 Maintaining process effectiveness

12.1 Purpose

The purpose of this activity is to ensure that the products to be sterilized are presented for sterilization in accordance with its specifications, configurations and pre-conditioning requirements as stated in the validation documentation. In addition, it shall be confirmed, that appropriate periodic tests calibration of measuring chains, equipment maintenance, any required requalification and an assessment of any changes, has been carried out.

12.2 Demonstration of continued effectiveness

12.2.1 Product presented for sterilization shall conform with:

a) the product identified during product definition;

b) the load configuration as defined during PQ;

c) if specified during PQ, any pre-conditioning of the load.

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12.2.2 Successful completion of periodic tests, calibrations, equipment maintenance tasks and requalification carried out at specified intervals shall be verified.

12.2.3 If the sterilization process makes use of a vacuum, an air leakage test shall be defined and carried out at specified intervals.

12.2.4 If the sterilization process relies on the removal of air from the chamber and load to achieve rapid and even penetration of steam into the load, an air removal and steam penetration test shall be carried out each day before the sterilizer is used [see 10.2 d].

NOTE 1 The steam penetration test is carried out using a device having a defined challenge to air removal and steam penetration for the process.

NOTE 2 If the sterilizer is used continuously for production of product, the test can be done at least every 24 h.

12.2.5 For applications using saturated steam sterilization in which defined loads known not to inhibit the penetration of steam, are being processed, alternative methods may be used to confirm steam penetration based on specified physical measurements and a risk assessment of the likelihood of process failure.

12.2.6 Product shall conform to bioburden requirements if the sterilization process was established by the bioburden microbiological method (see B.2) or bioburden/biological indicator microbiological method (see B.3).

12.3 Recalibration

The accuracy and reliability of each measuring chain used to control, monitor, indicate, or record the sterilization process shall be verified periodically in accordance with standard operating procedures.

12.4 Equipment maintenance

12.4.1 Preventative equipment maintenance shall be planned and performed in accordance with documented procedures.

Calibration, equipment maintenance, performance test(s) and acceptance criteria (where applicable) intended to ensure that the sterilization process remains reproducible shall be specified as part of the process (see 8.13).

12.4.2 Equipment shall not be used to process product until all specified equipment maintenance tasks have been satisfactorily completed and recorded.

12.4.3 The equipment maintenance plan, procedures and records shall be retained and reviewed at specified intervals by a responsible person. The results of the review shall be documented.

12.5 Requalification

12.5.1 Requalification of a sterilization process shall be carried out for defined product and specified equipment, at defined intervals and after the assessment of any change determined to require requalification. The extent to which requalification is carried out shall be justified.

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

12.5.3 Requalification data shall be reviewed against specified acceptance criteria in accordance with documented procedures.

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12.5.4 Requalification records shall be retained and reviews of requalification data together with corrections made and corrective actions taken shall be documented.

12.6 Assessment of change

12.6.1 Any change shall be assessed for its impact on the safety of the equipment (hardware and software), specified process and cycle parameters, and the effectiveness of the sterilization process. Changes to be considered shall include:

a) replacement of a part which can cause a process parameter to change;

b) replacement of a part which can cause an increase in leakage into the chamber;

c) variation of homogeneity of the process variables in the usable chamber space of the sterilizer;

d) new or modified software for process or cycle control and monitoring and/or hardware replacement or modification of the automatic controller or its software;

e) any change to a process or cycle parameter;

f) any change to services and the outcome of equipment maintenance on a service;

g) any change of the SBS or packaging system or packaging procedures used;

h) any change of load configuration;

i) any change of product manufacturing processes, product materials or source of materials or design of product;

j) any change of equipment maintenance procedures.

12.6.2 The outcome of the assessment, including the rationale for the decisions reached and the extent of changes made to the sterilization process, product or requalification requirements, if any, shall be documented.

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Annex A
(informative)

Guidance on the principles of moist heat sterilization and rationales for requirements

A.1 General

A.1.1 The purpose of this Annex is to provide general guidance on the principles of moist heat sterilization and rationales for the requirements. The clause numbering in Annex A does not, and is not intended, to align with the normative text. Specific guidance for health care facilities is given in Annex F and for industrial settings in Annex H where guidance clause numbers align with normative clause numbers.

A.1.2 The development, validation and routine control of a sterilization process comprise a number of discrete but interrelated activities, e.g. calibration, equipment maintenance, product definition, process definition, IQ, OQ and PQ. Table A.1 summarises the various sections comprising this document, its component parts and purpose and an indication of the personnel or operational functions within an organisation who can be responsible for ensuring implementation. The subsequent sections discuss, in more detail, those elements.

A.1.3 The guidance given in this Annex is not intended as a checklist for assessing conformance with the requirements of this document. This guidance considers the principles of moist heat sterilization and is intended to assist in obtaining a uniform understanding by providing explanations and acceptable methods for achieving conformance with requirements. Methods other than those given in the guidance can be used.

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

Elements	Purpose	Components	Responsible party
Quality system	To provide a structure to control all stages of the sterilization process	Management responsibility, design control, product realization, measurement, analysis and improvement	All parties with respect to the elements undertaken
Sterilizing agent characterization	To specify the sterilizing agent and to establish its microbicidal effectiveness considering relevant parameters impacting efficacy.	Sterilizing agent definition, microbicidal effectiveness studies, material compatibility and biological safety	Developer of the sterilization process
Sterilization process/equipment characterization	To provide a specification of the whole of the sterilization process and the equipment necessary to carry it out	Sterilization process cycles and parameter specification, equipment specification, ancillary equipment, and services, safety and environment	Sterilizer manufacturer, in collaboration with the developer of the sterilization process, if appropriate
Product definition	To define the product to be sterilized	Product definition / identification, packaging materials and configuration, product quality prior to sterilization	Manufacturer of the product to be sterilized (and sterilizer manufacturer, depending on claims made for sterilizing equipment)
Sterilization process definition	To define the sterilization process in order to achieve sterility for identified product whilst maintaining safety and performance of the product	Cycle definition / specific adaptations, biological safety, process residuals, product compatibility and restrictions on re-sterilization	Manufacturer of the product to be sterilized, in collaboration with the sterilizer manufacturer and, if appropriate, the health care facility

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Table A.1 *(continued)*

Elements	Purpose	Components	Responsible party
Validation	To demonstrate that the defined sterilization process can be delivered effectively and reproducibly to the load	Installation qualification, operational qualification, performance qualification, review, and approval of validation	Organization with responsibility for sterilizing the product which can be either: — the manufacturer of the product to be sterilized; — or the processing facility, in collaboration with the sterilizer manufacturer, if appropriate.
Routine monitoring and control	To demonstrate that the validated sterilization process has been delivered within defined tolerances to all products within a load	Load, load configuration, sterilization process monitoring, record generation, periodic testing, record retention	Organization with responsibility for sterilizing the product which can be either: — the manufacturer of the product to be sterilized; — or the processing facility, in collaboration with the sterilizer manufacturer, if appropriate.
Product release from sterilization	To review records of routine control procedures and determine the disposition of a particular load	Record review, indicator testing (if any), product disposition, corrective action (if any)	Organization with responsibility for sterilizing the product which can be either: — the manufacturer of the product to be sterilized; — or the processing facility, in collaboration with the sterilizer manufacturer, if appropriate.
Maintaining sterilization process effectiveness	To ensure the continued acceptability of the validated sterilization process	Equipment maintenance and calibration. Assessment of change.	Sterilizer manufacturer and the organization with responsibility for sterilizing the product which can be either — the manufacturer of the product to be sterilized; — or the processing facility.

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A.2 Normative references

No additional guidance.

A.3 Terms and definitions

Users of this document should familiarise themselves with the terms and definitions defined in Clause 3 and subsequently used throughout this document to ensure a complete understanding of the context in which they are used. ISO/TC 198 has made a concerted effort to harmonise definitions across the series of standards for which it is responsible. These agreed harmonised definitions are found in ISO 11139. Working groups are encouraged to utilise a harmonised definition should one exist and, if necessary, add additional clarification in the form of notes to entry where contextualisation is required for individual standards.

A.4 General

A.4.1 This subclause describes the need to have a documented approach to specific processes in order to ensure consistent implementation of the requirements of this document. This document cannot require a formal quality management system (e.g. as described in ISO 13485), however there are significant benefits of combining the individual documentation processes required in this document into a formal quality management system.

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A.4.2 This document does not require that a complete quality management system conforming with ISO 13485 be implemented, nor does it require that those quality management system elements that are specified be subject to third party assessment. However, it is advisable to consider implementation of documented procedures in order to reduce the risk of non-sterile products entering into use.

A.4.3 The effective implementation of defined and documented procedures is necessary for the development, validation and routine control of a sterilization process for medical devices. Such procedures are commonly considered to be elements of a quality management system and can include (but are not limited to):

a) control of documentation, including records;

b) assignment of management responsibility relating to;

   1) management commitment,

   2) customer focus,

   3) quality policy,

   4) planning,

   5) responsibility,

   6) authority and communication, and

   7) management review;

c) provision of adequate resources, including competent human resources and infrastructure;

d) control and verification of product and services provided by external parties;

e) identification and traceability of product throughout the process;

f) control of non-conforming product;

g) maintenance and repair of equipment;

h) calibration of monitoring and recording systems;

i) measurement and analysis systems designed to monitor and improve performance including corrective and preventive actions.

A.4.4 The processes involved in the development, validation and routine control of a sterilization process can involve a number of separate parties, each of whom has responsibility for certain elements. The parties accepting responsibility for defined elements are required to ensure competent personnel, with competence demonstrated and documented through appropriate training and qualification, carry out the necessary steps to implement those elements.

A.4.5 National and regional regulatory requirements can exist for quality management systems in the manufacture of medical devices and for third party assessment of such systems whether in an industrial setting or health care facility.

A.5 Sterilizing agent characterisation

A.5.1 Sterilizing agent characterisation

This activity can be undertaken in a test or prototype system. The final equipment specification should be relatable to the experimental studies undertaken using any such test or prototype system.

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A.5.2 Sterilizing agent

Moist heat is water in a vaporous or liquid state at elevated temperatures sufficient to cause microbial inactivation. Temperatures usually at, or higher than 115 °C, are employed for sterilization. Moist heat can be provided as saturated steam or can be generated in situ by applying thermal energy to water already present in the product. Moisture acts as the medium for transferring thermal energy to microorganisms. Water molecules also act as a catalyst for the destruction of macromolecules within microbial cells.

A.5.3 Microbicidal effectiveness

A.5.3.1 The microbicidal efficacy of moist heat is reliant upon the temperature and the duration of contact between water molecules (moisture) and microorganisms. Therefore, the process variables for a moist heat sterilization process are the duration of exposure to a specified temperature in the presence of moisture sufficient to bring about microbial inactivation.

A.5.3.2 There are a number of recommended time and temperature combinations which are recognised by some regulatory authorities and pharmacopoeias as acceptable processing conditions. It is common for one or more of these time temperature combinations to be available on commercially available sterilizers. The time and temperature combinations only describe the holding times, not the air removal or drying stages which make up the whole of a saturated steam sterilization cycle. Some examples of these combinations are listed in Table A.2. The tolerances (often termed the sterilization temperature band) associated with a particular sterilization temperature is determined by a minimum temperature and a maximum temperature at which product qualification can be maintained. For example, a sterilization temperature band would be plus 3K minus zero K. All combinations listed in Table A.2 are based on the concept of an overkill approach in which the microbial inactivation brought about by exposure to the moist heat process ensures a SAL which provides a greater assurance of sterility. If other less widely recognised combinations of time and temperature in the presence of moisture are used, then microbicidal capability could need to be established. Generally, the lethality of moist heat processes is predictable using the mathematical methods described in the literature (e.g. F_0 estimation of equivalent time of exposure at 121,1 °C). However, care should be taken when applying this approach since such mathematical approaches will only apply across a limited range of time and temperature combinations.

Table A.2 — Examples of typical combinations of minimum temperature and time for moist heat sterilization

Temperature °C	Holding time[b] min	F_0 value[a] min
121	15	15
126	10	30
132	4	50
134	3	60

[a] F_0 value is only known to be applicable to contained product sterilization processes. Its application in saturated steam sterilization processes is possible but the presence of significant quantities of residual air in the chamber or other NCGs introduced with the steam can reduce the microbicidal lethality to a point when the equation used to calculate F_0 values is no longer valid.

[b] The time when all measured temperatures in the load and at the reference measurement point are at the specified temperature (holding time).

A.5.3.3 Saturated steam is water vapour in a state of equilibrium with its liquid state. If dry saturated steam (i.e. no liquid water present) at a defined pressure and temperature is heated whilst maintaining a constant pressure, the steam will become superheated (this is discussed further in Annex E). Superheated steam behaves like a dry gas; it is unable to condense and release the latent heat that saturated steam has, until the superheated steam is cooled to its saturation temperature. This results in extremely slow heating of loads, when compared to saturated steam. Superheated steam also has a low microbicidal effectiveness when compared to saturated steam. Superheated steam can be created by rapid pressure reduction in which the pressure/ temperature energy relationship of saturated steam is disrupted. The adiabatic expansion of saturated steam results in the excess thermal energy present being converted to superheat. It can also

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occur from the exothermic rehydration of parts of the load containing natural fibres such as cellulose (e.g. paper and linen). The formation of superheated steam can be minimized by careful engineering of the steam supply system and correct conditioning of loads prior to sterilization, for example:

a) having a series of pressure reduction stages from the supply pipe to the chamber and ensuring the pressure reduction ratio for each stage does not exceed 2:1;

b) ensuring steam velocity does not exceed a value which would cause superheating of the steam (e.g. 25 m/s);

c) ensuring materials made from natural fibres are preconditioned to a humidity greater than 40 % RH prior to sterilization.

A.5.4 The effect of contaminants

A.5.4.1 For a saturated steam sterilization process, contaminants can include NCGs arising from an inadequate air removal stage, air leakages into the chamber, or carried within the steam supply to the sterilizer and which can affect the microbial lethality of moist heat at the surfaces to be sterilized, or corrosive agents similarly carried in droplets of liquid mixed with the steam supply. Liquid water, expressed as a dryness fraction (see C.10), can also be considered a contaminant since this will affect steam penetration and heat transfer rates to product and the ability of the process to dry the product (see D.2) at the end of the plateau period of the process. The level of risk to the process and load associated with the presence of contaminants can depend upon the point in the process when maximum quantities occur.

A.5.4.2 Inorganic (e.g. salts used in water purification systems) or organic (e.g. filming amines, endotoxins) contaminants suspended in the sterilizing agent can be both toxic and corrosive and can generate a barrier between the microorganism and the sterilizing agent on load surfaces. The contaminants can originate from feed water, that is heated or evaporated into steam. They can also originate from contact between the materials of the steam generation system (e.g. shell boilers) and the generated steam. The contaminants can also arise from the pipework and engineering devices employed to condition the steam (e.g. condensate traps) as it is transported to the chamber and finally condenses on the product. Consideration should be given to the impact from raw water, water treatment plant, boiler and steam distribution which can carry over unwanted substances such as anti-foaming agents, and corrosion inhibitors. The presence of waterborne microorganisms in boiler feedwater can give rise to the creation of organic bacterial endotoxins, which, if present in fine droplets of water carried within the steam, can contaminate the load and therefore present a risk of adverse reaction (pyrogenesis) in patients, e.g. toxic anterior segment syndrome (TASS) in ophthalmic surgery. If the level of contaminants in the sterilizing agent can be affected by the quality of the feed water to the steam generation system, the feed water quality should be specified. The use of stainless steel for the fabrication of steam generation equipment and pipework can help reduce the need for corrosion inhibitor chemicals and therefore contamination from inorganic and organic substances. Similarly, use of dedicated steam generation equipment enables greater control over the quality of the steam produced.

A.5.5 Non-condensable gases in the steam supply

Non-condensable gases (NCG) will inevitably be present in steam from dissolved gases in the feedwater of the steam generation equipment. Hence, steam supplied to a sterilizer will inevitably have small quantities of NCG entrained within it. The acceptable content of NCG in the steam supply is given by the method in EN 285 and Annex C, where a maximum value of 3,5 ml of NCG is collected from 100 ml of condensed steam. Due to steam having a much greater volume than its condensate, the value of NCG in steam is hundreds of times lower than when expressed as a percentage of condensed steam. The presence of NCG in steam supplied to the chamber can be detected using air removal and steam penetration tests (C.4 and C.5 describe examples of such tests). Whilst it is accepted that small levels of NCG in steam are unlikely to influence microbial inactivation, larger quantities can begin to have a deleterious effect on process lethality. NCG will be concentrated at sites of steam condensation, due to steam condensing and reducing in volume to liquid water that will run away by gravity, whereas NCG will not condense and can accumulate in large quantities, where moist heat conditions can no longer be present, affecting heat transfer to the load and microbial inactivation. NCG and residual air mixed with steam pose other processing problems due to the possibility of stratification within the chamber because cold air is denser than steam.

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A.5.6 Residual air in the chamber

A.5.6.1 Many moist heat sterilization cycles employ an air-removal (conditioning) stage designed to remove the residual air within the chamber to a very low level (saturated steam sterilization processes). This ensures that air pockets or stratified layers of air cannot form in the chamber or load which can inhibit the formation of moist heat conditions on the surfaces which need to be sterilized. Air removal can be achieved by dynamic means, typically by the use of a vacuum pump to give alternate steam and vacuum pulses, sometimes termed a pre-vacuum or fractionated vacuum process. Air removal can also be achieved by passive means, where gravity forces the heavier (denser) air to be displaced by the lighter (less dense) steam, termed a downward displacement or gravity process. Some other moist heat sterilization processes deliberately employ mixtures of steam and air; if such mixtures are used as the sterilizing agent, then the methods described in ISO 14937:2009, 5.3, can be used to establish microbicidal capability. Furthermore, some sterilization processes (contained product sterilization processes) can deliberately employ an overpressure of air (air ballasting) within the chamber in order to prevent distortion and fracture of product containers. When these processes are used, engineering measures are implemented to ensure mixing of the steam and air in order to create a homogenous heat transfer medium within the chamber.

A.5.6.2 In saturated steam sterilization processes thermal measurements are often used to assess air removal from and steam penetration into loads. Thus, throughout the air removal and equilibration part of the operating cycle, the difference in temperature between the temperature measured at the reference measuring point in the sterilizer and a measurement point on a medical device or in a reference load can sometimes be considered an indicator of the presence of moist heat at the measurement location. This approach should be used with care as thermometric methods cannot differentiate hot air from saturated steam at the same temperature. Additional evidence in the form of supplementary tests using different measurement methods responsive to the presence or absence of moisture (for example biological indicators or chemical indicators) can be needed to confirm the presence of moist heat and sterilizing conditions.

A.5.7 Water droplets entrained within the steam supply

A.5.7.1 Water droplets can be entrained within the steam supplied to a sterilizer. This water can arise from the steam generation system. The water can contain inorganic and organic contaminants present in the steam generator as discussed above. Steam containing large quantities of liquid water carries less energy and as a result does not facilitate rapid heating of load items. Water entrained within steam can remain with the load after the drying stage (also known as reconditioning) resulting in loads which are wet when removed from the sterilizer. This can compromise the efficacy of the SBS or the packaging system and the quality of the product if using a saturated steam sterilization process, resulting in microbial recontamination and a non-sterile load. Methods for determining the water content of steam supplied to the sterilizer are described in Annex C.

A.5.8 Effects on materials

Material effects are generally limited to corrosion, deformation and fracture caused by the temperatures and pressures of the sterilizing agent, water content (dryness fraction low) and contaminants in the sterilizing agent.

A.5.9 Environmental considerations

A.5.9.1 The presence of noxious substances in the exhausts and effluents from the sterilizer should be considered. For moist heat sterilization, hot water condensed from the steam can be a major effluent. Many authorities have limits on the temperature of discharges into public waste systems and these should be observed. Further guidance is given in ISO 14937:2009, Annex E.

A.5.9.2 Principles of an environmental management system can be applied to a moist heat sterilization process. ISO 14001 specifies the requirements for an environmental management system. ISO 14040 provides guidance on designing a life cycle assessment study.

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A.6 Process and equipment characterisation

A.6.1 Process

A.6.1.1 General considerations

A.6.1.1.1 The purpose of this activity is to specify the entire sterilization process and the equipment necessary to deliver the sterilization process safely and reproducibly.

A.6.1.1.2 The process variables for moist heat sterilization processes are exposure for a specific time at a specified temperature in the presence of moist heat sufficient to bring about microbial inactivation. A cycle variable for moist heat sterilization would be pressure which plays no part in microbial inactivation. The sterilization process specification should include all the process and cycle parameters that define the exposure profile throughout the operating cycle, e.g. pressure transition points and the time between them during the air removal stage (conditioning) and the temperature during the holding time. It should also include the ones used to verify reproducibility. Annex D provides examples of moist heat sterilization processes and the associated operating cycles.

A.6.1.1.3 A sterilization process is established for a specified product family(ies) and loading configuration(s). The portion of the operating cycle over which microbial inactivation is claimed or established should be identified (e.g. the holding stage in a saturated steam sterilization process or the time when the contents of containers are above 115 °C and fall below that value at the end of exposure for an F_0 estimation of process lethality). The upper and lower limits of each process variable that can affect both this lethality and the performance of the medical device, should also be defined. The specification for the sterilization process and the equipment that delivers the process should contain sufficient detail for them to be considered in the subclause that covers process definition (see Clause 8) when a new product or loading configuration is proposed.

A.6.1.1.4 The performance of a medical device can be affected by contaminants on its surface. The contaminants and maximum acceptable concentration(s) contained in each fluid coming into contact with the medical device should be specified and included in the sterilization process specification (e.g. the quality of steam entering the chamber in a saturated steam sterilization process or of a ballasting overpressure of air in a contained product sterilization process). Some of the contaminants which can be considered are discussed in Clause 5 and in C.10

A.6.1.1.5 Provision should be made to monitor and record data for assessing the effectiveness and suitability of a routine sterilization process using calibrated instruments. The accuracy of measurement should be related to the tolerances of the process and cycle parameters.

A.6.1.1.6 The relationship between the temperature measured at the reference measurement point and the temperature measured in the load should be known for each product family.

A.6.1.2 Specific considerations for saturated steam sterilization processes

A.6.1.2.1 Saturated steam sterilization processes are those in which the steam within the chamber is the sterilizing agent, i.e. provides the moist heat on the surfaces which require sterilization.

A.6.1.2.2 Steam can be generated within the chamber or can be admitted to the chamber from an external source (e.g. a steam generator or boiler). Air in the chamber will be gradually reduced in quantity by gravity displacement, active flow or by forced evacuation. Annex D describes such processes in greater detail. It is assumed that if residual air is reduced to a level so that standardised test procedures reach their acceptance criteria then moist heat conditions will be present on the surfaces requiring sterilization. Annexes B and C describe some of these standardised test procedures.

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A.6.1.2.3 Variations in process and cycle parameters can result in an amount of air remaining in the chamber at the end of air removal which result in an ineffective process. The sterilizer technical documentation or a responsible person should provide adequate information to the user so that this can be guarded against. The information should include:

a) the upper and lower limits for each process and cycle parameter;

b) the method used for air removal;

c) sources of residual air including:

   1) leaks into the chamber (e.g. from a faulty door gasket),

   2) inadequate air removal (e.g. due to an insufficient vacuum level being achieved),

   3) NCG present in the steam supply;

d) the test methods, monitoring procedures, test frequency and acceptance criteria for sterilization process evaluation (e.g. the maximum leak rate permitted into the chamber).

A.6.1.2.4 Consequences of residual air

A.6.1.2.4.1 Residual air can reduce the efficacy of the sterilization process so that the defined SAL is not achieved. The removal of air from the chamber and surface of the load by either gravity displacement or active flow is more predictable when simple solid medical devices are processed. Care should be taken when using these processes for other types of products so that residual air does not affect the microbial inactivation achieved by the sterilization process.

A.6.1.2.4.2 Air removal is more challenging from complex medical devices such as instruments containing lumens, heavy solid masses and instruments and textiles contained within their SBSs. The physical conditions required for effective air removal are influenced by length, width and shape of lumen, wall thickness, material of the product, mass, density, the SBS used and other items contained in the same package of medical devices (see also Annex G). For such medical devices, an operating cycle that employs active air removal should be used to attain a predictably low residual air level. An example is one that employs several vacuum and/or steam pulses (sometimes known as dynamic or fractionated air removal) to serially dilute the air from the chamber and medical device(s) (see D.2 for example). During each pulse, steam will move into and out of the medical device and the condensing steam will re-evaporate and cause a dynamic 'scouring' of the residual air contained in, crevices, lumens and SBSs. The number of pulses, the upper and lower pressures associated with each pulse, the rate of change of pressure and temperature, and the interval of time between each change are cycle variables and these will play a part in effecting air removal and steam penetration thereby assuring moist heat is attained at surfaces which require sterilization. When assigning the suitability of a product family to a sterilization process, the combination of these pressure and temperature changes, the rates of change, and the duration of each change should be taken into account.

A.6.1.2.5 Measuring air removal by temperature and pressure correlation according to steam tables

A.6.1.2.5.1 A sterilization process that removes air from the chamber to a low level can fail to remove sufficient air from a lumen or cavity within a medical device so as to allow steam penetration and formation of moist heat at the internal surfaces which need to be sterilized. Dalton's law states that the total pressure in an enclosed space is equal to the sum of the partial pressures of the individual gases present. In theory the temperature in a chamber containing a mixture of steam and residual air will be lower than the calculated temperature derived from the measured pressure in accordance with steam table values (see Annex E for further information). However, there is evidence to show (see E.2.3) that an amount of residual air sufficient to cause a process failure in a load can only reduce steam temperature by less than 0,001 K. A temperature difference of this magnitude is smaller than the tolerances applied to the temperature and pressure measuring chains fitted to modern sterilizers and therefore cannot be detected. As a consequence, using the differences between the temperature at the reference measurement point and the temperature calculated

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from the measured chamber pressure using the steam table values will not be an acceptable approach for detecting the small volumes of air which can cause a process failure.

A.6.1.2.5.2 However, whenever the measured temperature exceeds the theoretical temperature calculated from measured pressure, superheated steam can be present. The presence of superheated steam can be detrimental to the medical device or its SBS and can compromise the sterilization process (see Clause 5 and Annex E for more information). In addition, a difference between measured and theoretical temperature can also be due to inadvertent calibration offsets or defective sensors. Any differences between the measured temperature and that calculated from pressure which exceed specified tolerances can be indicative of a fault and therefore require investigation into the source of error and application of corrective actions.

A.6.1.2.5.3 Ideally the limit assigned to the difference should allow for the measured temperature to be higher than that calculated from pressure, but should not be lower, to take into account and limit the possibility of superheated steam being present. However, the measurement tolerances for the temperature and pressure measurement chains are taken into account when setting this limit (typically 1 K or less, see Annex C and E for more information).

A.6.1.2.5.4 For these reasons the efficacy of air removal and steam penetration should be predicted from data obtained from a steam penetration test or a PCD or monitoring device, not by the correlation of measured temperature with that calculated from measured pressure according to steam tables.

A.6.1.2.6 Measuring air removal using steam penetration tests

A.6.1.2.6.1 The term steam penetration test is generic and can include those devices which are used in periodic specific tests to establish equipment performance, e.g. the daily Bowie and Dick Test (for more information see A.12 and Annex C) or in combination with loads to assess a particular characteristic of the process.

A.6.1.2.6.2 A steam penetration test is designed for use with a specified product family(ies) and is used to check that the amount of residual NCG remaining in the chamber at the commencement of the holding time will not prevent the formation of moist heat on the surfaces of the medical device for the duration of the holding time. The efficiency of the air removal system, air leakage into the chamber and NCG carried by the steam contribute to this amount. Air leakage into the chamber and NCGs carried by the steam supply can be measured by standardised tests (see for example, Annex C and EN 285) or using in-line monitoring systems the results from which have a known relationship to those given by the standard method. The presence of all gases present in the chamber is monitored by the steam penetration test.

A.6.1.2.6.3 A steam penetration test can be based upon a physical measurement, biological indicators or chemical indicators. The test system should be equivalent to the most challenging example of the product family(ies) it represents. A number of steam penetration and air removal test devices are available. Performance requirements for chemical indicator-based tests can be found in ISO 11140-3, ISO 11140-4, ISO 11140-5 and ISO 11140-6, for physical measurement-based tests in EN 285 for large steam sterilizers and EN 13060 for small steam sterilizers. Requirements for biological indicators are found in ISO 11138-1 and ISO 11138-3. Guidance on the selection and use of biological indicators is found in ISO 11138-7. Guidance on the selection and use of chemical indicators is given in ISO 15882.

A.6.1.2.6.4 Master product, which is a health care product or procedure set used to represent the most difficult to sterilize item in a product family or processing category and reference loads can consist of a single medical device type, medical devices from different product families or medical devices assigned to different product families but assembled into a single package. For any reference product or medical device, difficulty in air removal and the challenge to the sterilization process should not be less than that for any medical device in the product family(ies) assigned to the sterilization process. Annex G discusses assignment of medical devices to product families.

A.6.1.2.6.5 If it is proposed to use a PCD, i.e. an independent monitoring device such as one which is made to a specific design by the user or of commercial origin, to represent specific characteristics of a product

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family(ies), then the validity of the PCD when used in the sterilization process should be established and documented in the information supplied with the PCD and this should include information related to the conditions which give rise to a failure indication.

A.6.1.2.6.6 An air detector is an example of a monitoring device that can be permanently fitted to a sterilizer which uses vacuum and steam pulsing to remove air during the air removal stage of a saturated steam sterilization process. It can be used to predict whether NCG remaining in or leaking into the chamber or being carried in the steam, could, at the commencement of the plateau period, accumulate in parts of the load (e.g. lumens) and cause a failure of the sterilization process in these parts. The presence of NCG identified by an air detector can also be caused by the release of NCG when a product or its SBS or packaging system are heated. The setting of the air detector is based on the defined process parameters and the product family(ies) that the sterilization process is designed to process. The performance of an air detector can be established using specified reference loads and procedures as discussed in Annex C and EN 285. The air detector performance can also be established using specified reference loads which have a direct relationship to product which will be routinely processed. In such circumstances the user will specify the method and acceptance criteria by which air detector performance is established.

A.6.1.3 Specific considerations for contained product sterilization processes

A.6.1.3.1 A contained product can be processed in a water immersion cycle, a water spray cycle, a cycle with a steam-air mixture, a cycle with steam and gravity displacement, or a cycle with forced air removal (see Annex D for more information). The requirements for air removal and steam penetration are very different to those for saturated steam sterilization of surfaces. Steam and air mixtures are often deliberately used to provide an overpressure which prevents distortion or fracture of the sterilized container. Such distortion or fracture is caused by the high internal pressure generated when water-based solutions and air are heated in a sealed container. Flexible containers can soften during processing, losing mechanical strength and can rupture.

A.6.1.3.2 The energy required to heat up a load to the defined sterilization temperature depends on the product family, the mass (thermal capacity) of the load and its initial temperature. Heat transfer depends on the heating medium, its contact with the product container, the material of the container and container support system, and the temperature difference at the heat transfer site. The type of product family and the load configuration has a major influence on temperature differences between containers. These differences can be minimized by increasing the flow and distribution of the heating medium by forced circulation. Mass flow and homogeneity of the heat transfer medium throughout the chamber can be verified by cycle variables such as fan speed, circulation pressure and flow. Temperature of the heat transfer medium at the outlet should be identified as a cycle variable. If steam is used, the temperature of the steam environment should also be considered a cycle variable. Consideration can need to be given to ensure the heat transfer medium is free of pyrogens and chemical impurities that can cause spotting on the container. In addition, the heat transfer fluid can need to be sterile by the end of the period of the operating cycle for which lethality is claimed and during the cooling stage.

A.6.1.3.3 The temperature distribution within the product container depends on the shape of the container, viscosity of the product, conduction through the container wall and product, and convection within the product. Large product containers need longer times to heat up and cool down, which can restrict the size of container that can be used for products sensitive to prolonged exposure. Integration of process lethality can be considered as a means of reducing the thermal energy applied to the product in order to minimise product degradation whilst still achieving a specified SAL. During the sterilization process, the locations of the product containers exhibiting the highest and lowest temperatures during the heating stage and the highest and lowest temperatures during the cooling stage in the load should be identified. The temperatures measured in these locations should be treated as cycle variables; however, if either location cannot be reproduced, a statistical approach can need to be used to ensure the specified microbial inactivation is consistently attained while maintaining product integrity.

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A.6.2 Equipment

A.6.2.1 Specification

Equipment used to deliver the sterilization process should be specified. The specification for the equipment should include sufficient information to perform a process definition for a new product or loading configuration (see Clause 8 for more information). The specification can be developed by the organisation which will use the sterilizer, as can be the case for industrial users or a published standard can be referred to. European, regional and national standards for sterilizing equipment have been published (e.g. EN 285). These standards contain such information as materials which can be used in construction, performance requirements and methods of conformity assessment. Materials used for the construction of a sterilizer should minimize corrosion and any contaminant that can be released during routine operation. Steam, heat transfer fluids or air used to pressurize the chamber can carry corrosive and toxic agents. These should be identified, and maximum permissible levels specified (see C.10 for some examples of contaminants which can be considered). The correct choice for the material of construction and the control of corrosive contaminants will eliminate the need for protective agents such as filming amines (e.g. hydrazine) to be used.

A.6.2.2 Services required

A sterilization process delivered in accordance with its specification is dependent upon the quality of the services provided. The services required should be identified in the specification (e.g. steam, water, compressed air, electrical power), along with the values and tolerances for each. During maximum demand, pressure measured at the connection to the sterilizer for each service should not fall below the minimum specified. If services are provided by another party, recommendations from the sterilizer manufacturer should be followed and conformity confirmed. For example, in some health care facilities the steam generation equipment can be operated by an engineering utility company whereas the user is part of the health care facility organisation. This is established during IQ. For example, the efficiency of a water ring vacuum pump and a heat exchanger deteriorates with falling water pressure and rising water temperature. For this reason the minimum water pressure and maximum temperature should be specified and then established during IQ.

A.6.2.3 Filters

The requirements for filters should be specified, e.g. water strainers or air filters. The air entering the chamber to allow pressure equalisation at the end of the sterilization process should be passed through a microbially retentive filter in order to prevent re-contamination of the load. The equipment specification should include such a requirement and consider means to protect the filter from inadvertent exposure to a backflow of a chamber fluid which could impede performance.

A.6.2.4 Measuring chains

A.6.2.4.1 The measuring chains including sensors, e.g. temperature probes, used to monitor the process and cycles variables, interconnections and signal processing equipment, e.g. a programmable logic controller (PLC) or microcomputer, should be specified.

A.6.2.4.2 The measuring chain providing the records of the sterilization process is independent from those used by the automatic controller and indicating instruments. In practice this means the use of duplicate or duplex sensors and signal processing systems which are independent of the system used to control the process. A system that combines recording, control and indication can lead to an ineffective sterilization process being interpreted as effective. Independent recorders are characterized by separate measurement chains, data processing and printing and recording systems that are independent from those used by the automatic controller. Interchange of informative data between the recorder and the controller for other purposes is not excluded. It should not be assumed that an independent system implies a completely separately hardwired measurement chain. An independent measuring chain can co-exist within the same electronic device or even within the same electrical circuitry. The implementation of a monitoring and

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recording system, which is independent from the control system in its various guises, is considered in ISO/TS 22421:2021, Annex B.

A.6.2.5 Environmental and safety considerations

A.6.2.5.1 Local regulations for environmental considerations can govern the discharge of emissions and effluents from the sterilizer and these can vary from one jurisdiction to another. For example, the temperature of hot water discharged from the sterilizer vacuum pump or condensate traps (if not recovered) into the public sewer system, the particulates released from either the product or packaging, or both, during sterilization, and the volume of water used during the process, can need to be controlled.

A.6.2.5.2 Safety considerations are part of equipment design, installation and operation. Pressure systems regulations govern pressurised fluids used in a moist heat sterilizer and can be specific to a particular jurisdiction. This document does not provide guidance in this area. Reference should be made to IEC 61010-2-040 and national regulations.

A.6.2.5.3 Failures of items critical to process performance or safety, including the operating equipment and services, should be detected by the monitoring system of the equipment (e.g. fault indication system, process evaluation system, air detector). A failure can require different types of indications depending upon its potential effects and urgency, e.g. audible and visual alarms, warnings, error indications, messages, displays, as well as subsequent automated responses of equipment or corrective actions by the operator.

A.6.2.5.4 The consequences of a failure can depend on the current operation mode of the equipment. Different levels for alarms and indications depending on the related criticality can be provided.

A.6.2.6 Accessories

Accessory systems, such as containers, shelving, racks and carriers designed to support, transport or contain the medical device, should not unduly restrict uniform steam distribution, circulation of heat transfer fluid (e.g. a steam-air mixture in a contained product sterilization process), removal of residual air, drainage of condensate or drainage of water. The system should also prevent damage to either the medical device or its packaging, or both, and retain the integrity of the load.

A.6.2.7 Software

Local regulatory requirements should be taken into consideration regarding software design, verification and validation. Additional guidance is given in Good Automated Manufacturing Practice 5 (GAMP 5).[49] ISO/TS 22421 also considers various aspects of software systems used in sterilizers.

A.7 Product definition

A.7.1 General

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

A.7.2 Product design

A.7.2.1 Product design normally follows a structured approach. Early in the product design stages consideration should be given to the sterilization process which will be used. Exposure of a medical device to the sterilizing agent should not cause the design parameters for each material used in the construction of the medical device to exceed the maximum or minimum permissible values. As temperature rises, some materials soften and are more susceptible to physical stresses or mechanical forces. Differential expansion through low heat-conductive materials, or the expansion and contraction of dissimilar materials in contact with each other, can cause an increase in material and joint stresses.

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A.7.2.2 Limiting values can be identified for all materials and combination of materials used including the proposed SBS. The effects of exposure or repeated exposure (when applicable) to the sterilizing agent under any combination of process parameters on the physical and chemical characteristics and biocompatibility of the product should be identified. Limiting values for these process and cycle parameters are specified, because exceeding the specified values could have an adverse effect on the performance of the product or its SBS.

A.7.2.3 Examples of some process and cycle variables which should be considered include:

a) temperature;

b) holding time (dwell time) at the limiting values;

c) pressure;

d) rate of change of pressure;

e) rate of change of temperature.

A.7.2.4 Any special requirements for preconditioning of the medical device prior to sterilization should be specified. Natural fibres can contain up to 5 % moisture. When natural fibres are dried or conditioned in an environment of less than 35 % RH they can become dehydrated so that when they are sterilized, they exothermically rehydrate. The process of exothermic rehydration can cause localised superheated steam conditions which can in turn reduce the level of moist heat to one that no longer achieves microbial inactivation.

A.7.2.5 Medical devices that are to be processed repeatedly can suffer accumulative changes such as surface cracking caused by differential expansion through a thick material, brittleness or delamination. Crevices and lumens can retain organic, chemical and biological contaminants that can cause material reactions or be unpredictably released during use. Many materials that are subject to repeated moist heat sterilization have a long history of safe use, are known to be suitable and have longevity (e.g. stainless steel). Other materials, however, can have limited lifespans and require further study. Reference should be made to ISO 10993-1, ISO 10993-17, ISO 17664-1 and ISO 14971. During product design, consideration should be given to the procedures for disassembly (if appropriate), cleaning, disinfection, inspection and sterilization. Guidance and methods for the cleaning and disinfection of medical devices prior to sterilization are addressed in the ISO 15883 series of standards. Information to be provided by a medical device manufacturer for the processing of a medical device is given in ISO 17664-1. The efficacy of the sterilization process can be affected by contaminants present on the surface of the medical device prior to sterilization. A system should be defined, documented and maintained to ensure that the condition of the product presented for sterilization, including microbiological, organic and inorganic contamination levels, is controlled and does not compromise the effectiveness of the sterilization process. The means by which this can be achieved depend upon the area of application. In a health care facility multiple factors are considered, including the cleaning method and procedures recommended in the medical device instructions for use, the typical level of soil on the device based on the type of procedure in which it was used, the cleaning solutions, the efficiency of the manual or automated washer-disinfector process, the control of the environment under which further handling occurs and the efficacy achieved in the saturated steam sterilization process. Further guidance for a healthcare facility is provided in Annex F.

A.7.2.6 An evaluation should establish that, after processing, a medical device will perform as intended and will be safe for use. The evaluation should consider mechanical, chemical, electrical, toxicological, physical, biological and morphological properties. Intended additives, process contaminants, process residues, leachable substances and degradation products should be considered for their relevance to the safety of the device and its SBS. Corrosion on some materials can occur if steam is generated from water of low pH or if the water contains a contaminant such as chlorides and silicates. For example, rubber can become oxidised in the presence of residual air at elevated steam temperatures. In health care facilities, this evaluation is completed by the medical device manufacturer and data should be obtained by the health care facility.

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A.7.2.7 In a contained product sterilization process, the heat sensitivity and thermal expansion coefficient of a liquid product can dictate the maximum fill volume, material and size of the container that can be used. The stability and sterility of the liquid should be assessed from temperature mapping studies carried out in the proposed container when the liquid is exposed to at least the upper limits of the proposed sterilization process profile.

A.7.3 Sterile barrier system

A.7.3.1 The major function of an SBS is to ensure that the medical device remains sterile until opened for use. Sterile barrier systems should allow penetration of the sterilizing agent and withstand the stresses that occur during a sterilization process, remain secure, and should not have a negative effect on the quality of the medical device (e.g. by generating particles). Sterile barrier systems for a medical device sterilized in a saturated steam sterilization process should meet the requirements of the ISO 11607 series of standards. The combination of materials used to construct an SBS for the product, for example an injection moulded polymeric container, should withstand the process parameters that are typical in moist heat processes. Any restrictions resulting from the design of the product and the materials used should be defined.

A.7.3.2 For contained product non-permeable packaging (e.g. vials, ampoules, non-permeable flexible pouches), the material and design should permit heat transfer to the product and, if a closure is fitted, it should remain secure and sealed. Non-permeable packaging should only be employed if the product is aqueous-based and can create moist heat within the container. If flexible it can be necessary to employ a steam-air mixture in order to provide an external overpressure which will prevent the container distorting or breaking as a result of the pressure which can build up inside the container during processing.

A.7.3.3 Protective packaging (see ISO 11607-1) should protect the product during customary handling, storage and distribution. If protective packaging is exposed to the sterilization process it should retain its ability to protect the product and should not be adversely affected by the sterilization process (e.g. cardboard boxes can be unsuitable). Similarly, if product is sterilized in secondary packaging, then product used for PQ of the sterilization process should include the protective packaging to ensure it does not adversely affect the effectiveness of the sterilization process (e.g. impeding air removal and steam penetration, attainment of process parameters, the dryness of product after removal from the sterilizer).

A.7.3.4 If, at the end of a sterilization process, controlled conditions are required for the equilibration of a medical device and its SBS to atmospheric conditions, the method by which this is to be achieved (e.g. in an environmentally controlled chamber or room) should be defined.

A.7.4 Product families

A.7.4.1 A medical device that is to be sterilized can be characterized by its shape, mass, materials of construction, moving parts and SBS. A contained product will be characterized by formulation, volume and viscosity. Its container can be characterized by size, material and closure.

A.7.4.2 A study should be carried out to assign a product to a product family. Annex G provides guidance on assigning medical devices to product families and Annex F describes how this study can be carried out.

A.7.5 Pre-treatments and preconditioning

A.7.5.1 Pre-treatment can be advised in processing instructions to include use of lubricants, protection sheets or covers. These actions or accessories can hinder the penetration and development of moist heat on the device surfaces and adversely influence the sterilization efficacy. Storage of paper-based SBSs and packaging systems in low humidity can lead to dehydration of the cellulose fibres resulting in the risk of localised superheating unless re-humidified. See 7.13 d).

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A.8 Process definition

A.8.1 General

The purpose of this activity is to establish a sterilization process, including the cycle parameters by which it will be controlled and the process parameters to be applied to product to achieve sterility without compromising the safety, quality and performance of that product.

A.8.2 Process

A.8.2.1 The process variables for moist heat sterilization are exposure for a specific time at a specified temperature in the presence of moist heat sufficient to bring about microbial inactivation. See Clauses 5 and 6 for further information. The established process parameters should ensure that the conditions in all parts of the product achieve the required SAL without causing any part to exceed its design limit.

A.8.2.2 There are a number of time and temperature combinations which are recognised by some regulatory authorities and pharmacopoeias as acceptable processing conditions. Some examples of these combinations are listed in Table A.2. A sterilization process based on these recommendations will provide a very large safety margin in terms of delivered SAL. This is termed an overkill approach. In other cases, a sterilization process is established and validated to predict achievement of a SAL equal to or less than a specified value. This includes, but is not limited to, achievement of the maximal SAL, generally specified by regulatory bodies. A SAL has a quantitative value and mathematically, a SAL of 10^{-6} takes a lesser value than a SAL 10^{-4}. When all other factors influencing assurance of sterility are equal, there is a greater assurance of sterility associated with a lesser SAL.

A.8.2.3 The sterilization process can be developed in the production sterilizer or in a research sterilizer. During qualification the cycle parameters for the defined sterilization process should be set at their least favourable but nevertheless delivering acceptable values for the process parameters for effective sterilization. For example, by using the lower tolerance limit for exposure stage or by using the lowest allowable recirculation rate for a water immersion process.

A.8.2.4 A sterilization process should be established for each product family or load configuration presented for sterilization. The sterilization process can be:

a) identified from equipment that has been validated and known to process product assigned to the same product family;

b) developed by the user for the product family assigned to the product;

c) specified in the medical device instructions for use;

d) specified in the sterilizer's instructions for use.

The approach taken in a health care facility is more likely to rely on c) and d).

A.8.2.5 In all cases the limits on process parameters and restrictions on exposure identified in product definition should be observed. Process parameters should apply to the equipment used. They should be optimised to ensure that for defined product families specified exposure conditions will be routinely obtained throughout the chamber, and the maximum temperatures and rates of change of temperature and pressure will not cause damage or degradation to the product. Any restrictions on the size and mass of the load and its configuration should be identified and included in the process specification. In saturated steam sterilization processes, some loads (e.g. those containing heavy metal medical devices) can require an extended drying stage of the operating cycle to ensure that residual moisture is reduced to a level which will not compromise the SBS or product characteristics upon removal from the sterilizer.

A.8.2.6 Compatibility of a new medical device to the least favourable sterilization process conditions should be assessed. Such assessment should include measurement uncertainties associated with cycle and process parameters and the quality of the services supplied (see Annex C). The challenge identified for the

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new medical device or loading condition should be less than or equal to the challenge from the existing load(s). For some product families, assurance that defined exposure conditions will be reproduced might only be possible if the size of the load and the load configuration have been clearly defined. Examples of some moist heat sterilization operating cycles are illustrated in Annex D. Assignment of medical devices to product families is discussed in Annex G.

A.8.3 Role of physical measurements in process definition

A.8.3.1 Effectiveness and reproducibility of a sterilization process can be defined by conditions that can be controlled and confirmed by physical measurement (e.g. time, temperature, pressure) and the employment of additional monitoring systems where suitable physical sensors are not available. If a condition changes and this can affect the SAL, this condition can be identified as a process variable and the value at which the change occurs, a process parameter.

A.8.3.2 For some medical devices the measurement of physical conditions (e.g. temperature) might not be possible inside SBSs. For such medical devices the reproducible attainment of the defined SAL should be verified at a reference measurement point(s) (e.g. the chamber drain or active discharge line) for the measurement of sterilization temperature. In the case of a saturated steam sterilization process, evidence that establishes reproducibility of the sterilization process can be generated from:

— the verification of estimated equilibration time based on known product families and loading configurations;

— temperature and pressure at least at the turning points of pressure;

— number of steam pulses;

— pressure and/or temperature change rates;

— holding time;

— air leakage into the chamber;

— steam quality.

A.8.4 Role of chemical indicators in process definition

A.8.4.1 A chemical indicator can be used as an element in sterilization process definition. It is used to demonstrate the attainment of process parameters in the location in which it is placed. For chemical indicators of type 1, 3, 4, 5 and 6 see ISO 11140-1. For chemical indicators of type 2, special test indicators such as air removal and steam penetration tests (e.g. the Bowie and Dick type tests) see ISO 11140-3, ISO 11140-4, ISO 11140-5 and ISO 11140-6.

A.8.4.2 Chemical indicators show exposure by means of either physical or chemical changes, or both, and are designed to react to one or more variables of the sterilization process such as time of exposure, temperature and presence of moisture. The instructions for use accompanying the chemical indicator should be consulted with regard to interpretation of the results and to verify that the exposure conditions (stated values) that cause the chemical indicator to reach its endpoint (a satisfactory result) are appropriate for the sterilization process which is to be monitored. Attainment of the chemical indicator's endpoint should not be regarded as an indication of attainment of an acceptable SAL, but rather one of many factors which should be taken into consideration when judging the acceptability of a sterilization process. Failure of a chemical indicator to reach its endpoint should be regarded as evidence of a sterilization process failure and be investigated. Guidance on the use of chemical indicators is found in ISO 15882.

A.8.5 Role of biological indicators in process definition

A.8.5.1 A biological indicator is a viable microbiological challenge of known resistance that is used to confirm sterilization process lethality at locations on or in the product where it is placed. The requirements

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for biological indicators and guidance on their use can be found in the ISO 11138 series of standards. Microbiological process definition and development is discussed in Annex B. When using biological indicators, consideration should be given to the entrapment of microorganisms in the product, contaminants in and/or on product, adverse reactions from the materials of construction and the difficulty in locating biological indicators in hollow devices and lumens.

A.8.5.2 Whenever biological indicators are used to confirm microbial inactivation in prescribed locations, the physical parameters measured during the sterilization process should always be used to verify that the defined sterilization process has been carried out according to its specification.

A.8.5.3 A sterilization process based on a defined microbiological challenge represented by biological indicators is used during process development by the pharmaceutical industry, medical device industry and in health care facilities. This method is known as the overkill approach (see B.4).

A.8.5.4 A sterilization process based on bioburden in its natural state or combined with the use of biological indicators requires extensive microbiological studies (see Annex B) followed by frequent microbiological screening of product and the environment in order to control bioburden within defined limits. This method is generally used in the pharmaceutical and medical device industries but rarely in health care facilities. It is chosen if some attribute of the product or equipment has been demonstrated during product definition to be sensitive to moist heat sterilization processing. In this case, a minimum process is used to attain the conditions that will allow the product to be designated "sterile" without compromising product quality or function (see Annex B).

A.8.5.5 If a product has been assigned to a product family for which a sterilization process has been defined and this sterilization process is based on an established time/temperature relationship, additional microbiological assessment is generally unnecessary.

A.8.6 Role of reference devices or process challenge devices (PCDs) in process definition

A.8.6.1 Data generated from a PCD, and/or a reference device designed to mimic specific attributes of the product or product family, can be used in the development of the process. For saturated steam sterilization processes, factors that can require consideration are (see also Annex G):

a) materials of construction;

b) mass;

c) length and diameter of hollow devices and tubing;

d) absorbency to moisture;

e) thermal conductivity;

f) specific heat capacity;

g) safety margins associated with the challenge;

h) the means by which air dilution and steam penetration can be evaluated.

A.8.6.2 Air dilution and steam penetration can usually be assessed by the measurement of temperature in combination with the use of either chemical indicators or biological indicators, or both, but it should be noted that temperature measurement alone cannot differentiate hot air at the same temperature as saturated steam, and so the presence of moisture.

A.8.6.3 For contained products, the reference device should mimic the temperature profile in the least favourable location within the product.

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A.9 Validation

A.9.1 General

A.9.1.1 All sterilization processes for medical devices should be validated. The means by which this is achieved can depend upon the area of application. Readers should refer to Annex F for health care facilities and Annex H for industrial settings for more information. The purpose of validation is to establish that the sterilization process developed in process definition can be delivered effectively and reproducibly to the load. Validation also provides evidence that the load is not compromised in terms of its safety, quality and performance during sterilization. Validation consists of several identified stages, IQ, OQ and PQ:

— Conformity to the equipment, services and installation specifications is established during IQ.

— Delivery of the prescribed sterilization process is established during OQ.

— The attainment of the required SAL in and/or on product is established during PQ.

A.9.1.2 It can be acceptable to move elements of validation between IQ, OQ and PQ if, during planning of a specific validation exercise, it is found to be more practical to do so. The processes used during validation can be considered in whole or in part for periodic requalification throughout the life cycle of the equipment. It should be noted that where the bioburden is unknown, the certainty and reproducibility of the delivered SAL to product will be decreased. Under such circumstances an overkill approach should be considered. Validation cannot be regarded as a substitute for the routine monitoring and load release practices discussed in Clauses 10, 11 and 12.

A.9.2 Validation plan

A documented validation plan should be prepared and agreed upon and approved by the responsible parties before the validation study begins. The validation documents should be subjected to document history and change control procedures (see Clause 4). A new product family can require additional OQ on an existing sterilizer and operating cycle and/or PQ as determined by the product adoption assessment.

A.9.3 Calibration of measurement chains

A.9.3.1 Before validation studies are performed all measuring chains should be subject to calibration checks and where necessary adjustment under carefully controlled conditions using approved procedures. Use of uncalibrated instruments can lead to a process operating outside of its specification being regarded as acceptable.

A.9.3.2 A temperature or pressure measurement chain should be verified using a calibration reference and a working standard. One example for temperature calibration is use of an oil bath or dry heat calibrator of known stable temperature traceable to a temperature reference standard. Whenever a number of sensors are immersed together in the calibrator, differences in measured temperature between sensors can be identified. Attention should be paid to ensure good heat contact is made between the heat source and the temperature measuring element otherwise systematic errors can be introduced into the measurement chain.

A.9.3.3 Whenever differences between measured temperatures are used to judge the results of a sterilization process, the error in each measurement should be known at the temperature at which comparison is to be made. For example, the differences in temperature between the centre of a standard test pack (see Annex C) and the chamber reference point measured during the holding period of a saturated steam sterilization process. Similarly, the temperatures measured at different locations within a contained product load.

A.9.3.4 The calibration of an instrument(s) fitted to the sterilizer and the calibration of a measuring chain(s) used for control can often be verified at critical parts of the operating cycle by reference to measurements registered by test instrumentation used during a performance test. For example, temperature and pressure

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checks can be carried out during the sterilization hold period where a relatively stable high temperature and pressure is maintained and during the drying stage when a relatively low, very gradually falling pressure and temperature will be observed. Caution should be exercised if using the rapidly increasing and decreasing pressure and temperature gradients occurring during, for example, a saturated steam sterilization process employing active air removal since the hysteresis and time constant of the measuring chains can introduce offset or phase shifts in the measured signals.

A.9.4 Installation qualification (IQ)

A.9.4.1 Installation qualification will be necessary whenever a new sterilizer is to be commissioned or when an existing sterilizer is replaced or relocated. A new sterilizer should be provided and installed in accordance with its drawings and specifications. An IQ plan, which can form part of a validation master plan, should include procedures that will provide documented evidence that:

— the sterilizer and documentation conform with the specification;

— the services connected to the sterilizer conform with the specification;

— the operating cycles are functioning safely as intended;

— during an operating cycle there is no evidence of a malfunction or leakage;

— during maximum demand, the supply pressure for each service is between the minimum and maximum pressures specified for the sterilizer.

A.9.4.2 The provision and function of safety systems as required by IEC 61010-2-040 should be established after installation but can be carried out during works testing if deemed acceptable by the purchaser. The method by which fault recognition systems are tested should be planned and documented. The performance of fault recognition systems fitted to the sterilizer should be verified to function as intended. The instructions for use or accompanying documentation for the sterilizer should provide guidance for tests and routine monitoring of each fault recognition system, for example, for a service fault or, if used, a method by which an air detector alarm can be created.

Failures of items critical to process performance or safety including the operating equipment and services should be detected by the monitoring system of the equipment (e.g. fault indication system, process evaluation system, air detector). A failure can require different types of indications depending upon its potential effects and urgency, e.g. audible/visual alarms, warnings, error indications, messages, displays, as well as subsequent automated responses of equipment or corrective actions by the operator.

A.9.5 Operational qualification (OQ)

A.9.5.1 An OQ plan, which can form part of a validation master plan, should include procedures that will provide documented evidence that:

a) the installed equipment operates within pre-determined limits;

b) the quality of each service conforms with its specification;

c) the operating cycle is delivered as specified;

d) during an operating cycle there is no evidence of interference from, or to, other equipment;

e) the sound pressure at the site of installation does not exceed regional or national requirements;

f) when operated with specified, preferably standardised, tests loads (e.g. small and full load), the temperature and pressure recorded and indicated throughout the sterilization cycle on instruments fitted permanently to the sterilizer are within specified limits of the sterilization process;

NOTE The specified test load can comprise the chamber furniture which then becomes an empty chamber test.

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g) there are no obvious leaks of steam, compressed air, water or effluent at any temperature or pressure within the working range of the sterilization cycle;

h) the maximum and minimum value for any process or cycle parameters do not exceed the permissible value specified by the medical device manufacturer(s).

A.9.5.2 Sterilizer performance tests

A.9.5.2.1 If performance tests are recommended for the sterilizer, they should be done during OQ and conformity with defined acceptance criteria should be verified. If conformity to an equipment standard is claimed, tests performed during OQ should conform with the tests specified by the equipment standard. Additional tests can become applicable for verification of claims which are in addition to the requirements of the equipment standard. When specific cycle types are specified for a sterilizer, the corresponding test procedures should consider these specific performances and modified procedures and test loads for verification (see for example EN 13060).

A.9.5.2.2 If an existing sterilization process is to be used, its current performance status should be verified by demonstrating conformity with the results from previous performance tests carried out during IQ and OQ.

A.9.5.2.3 Annex C identifies the tests that should be done during OQ for a sterilization process established primarily based on measurement of physical parameters. Annex B identifies the tests that are usually done during PQ but can be done during OQ for a sterilization process established by microbiological inactivation. The tests described in Annex B and Annex C are not mutually exclusive and some described in one Annex can be used to supplement the information provided by the methods described in the other.

A.9.5.3 Additional information and OQ tests for saturated steam sterilization processes

A.9.5.3.1 A challenging loading configuration can depend upon the element of the operating cycle to be tested. Thus, a single challenge device in an otherwise empty chamber can be the most challenging to the air removal stages whereas a full load in which the usable chamber space is filled to the maximum weight and density recommended will challenge other elements of the operating cycle, e.g. steam capacity, load drying capability. Therefore, tests on multiple loading configurations can be required. Commonly a small load consisting of a standard textile pack and a large load with a full chamber are used to establish the range of operating conditions allowed. Annex C provides more information.

A.9.5.3.2 Many of the tests described in Annex C are based on thermometric measurement from within a standardised test load and comparison with measurements taken at a chamber reference point. For the test loads identified in Annex C an extended equilibration time can indicate the presence of residual NCGs within the test load at the commencement of the holding time. Increases in NCGs can decrease the holding time and reduce the delivered lethality. The rate of pressure rise from vacuum to the commencement of the plateau period can affect the sensitivity of the determination of residual air. A lower rate of pressure rise can result in heating of residual air, which would cause a smaller temperature difference and result in the misinterpretation of the recorded data relating to steam penetration.

A.9.5.3.3 The following tests are useful in establishing the operational performance of a saturated steam sterilization process.

a) Steam quality and air leakage into the chamber can affect the efficacy of the sterilization process (see Clause 5 for more information). The quality of the steam and the chamber air leak rate should be established on the installed sterilizer. Examples of methods for carrying out these determinations are described in Annex C.

b) If a steam penetration test is required (see Clause 6), conformity of the test procedures and acceptance criteria for the test should be demonstrated. If a steam penetration test is intended to be used routinely to check air removal and steam penetration, the validity of the test should be known, for example,

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conformance to recognised standards describing steam penetration tests such as ISO 11140-3, ISO 11140-4, ISO 11140-5, ISO 11140-6.

c) If an independent, free-standing PCD is intended to be used for routine monitoring, to represent specific characteristics of a product, the sterilization process should be challenged with this device. The device can contain physical sensors, biological indicators or chemical indicators. The instructions provided with the PCD should be followed.

d) If an air detector fitted to the sterilizer is intended to be used for routine monitoring and control, its sensitivity (failure point) should be set during OQ testing using a reference load. The air detector should cause a fault to be indicated if the process parameters for the reference load during air removal are not attained. The reference load should be representative of a particular challenge of a medical device and loading configuration (see Annex C for more information).

e) If the level of residual moisture within the product can affect its performance at the point of use (e.g. by facilitating microbial recontamination), a load dryness test should be carried out.

A.9.5.4 Additional information and OQ tests for contained product sterilization processes

The following tests are useful in establishing the operational performance of a contained product sterilization process.

a) The heating, exposure and cooling profiles should be checked in an empty chamber.

b) Cold spots and hot spots should be identified.

c) Conformity with the requirements for process parameters such as pump pressure, circulation and temperature should be verified.

A.9.6 Performance qualification (PQ)

A.9.6.1.1 A PQ plan, which can form part of a validation master plan, should be provided. Procedures should be included to provide documented evidence that the sterilization process will sterilize the product(s) assigned to the product family the sterilization process is designed to process.

A.9.6.1.2 The load and load configuration should be as proposed for routine production. If repeated processing is intended, a load configuration and the least favourable combination of products from the product families assigned to the sterilization process should be used. The SBS should be that which will be used routinely. If preheating of the sterilizer directly before use is recommended by the sterilizer manufacturer this should be stated and carried out before PQ is carried out.

A.9.6.1.3 Performance qualification will obtain, along with other factors, information about thermal penetration into loads. This will require the introduction of a number of temperature sensors into the chamber. The numbers of sensors required will depend upon a number of factors such as the size of the chamber and the area of application. Annex F provides guidance on the number of sensors used in a health care facility application and Annex H on the number of sensors used in an industrial setting.

A.9.6.2 Additional information and PQ tests for saturated steam sterilization processes

a) Steam quality and air leakage into the chamber can both have an impact on predefined process variables and should be known before commencing PQ (see OQ). If a steam penetration test such as a Bowie and Dick test is to be used, the results of the test should be known before commencing tests on load configurations.

b) During OQ a number of standardised test loads can be used to establish the efficiency of air removal and steam penetration of the proposed operating cycle. These are basic performance tests establishing process capability under defined test conditions. An evaluation of their validity as predictors of air removal and steam penetration for a load, loading configuration or medical device considered to represent the most difficult challenge for the sterilization process should be carried out. Data from

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which these judgements can be made should include temperature measurements supplemented by either chemical indicators or biological indicators, or both, positioned in difficult to sterilize locations.

c) If a reference or model load is used instead of a production load its validity as an equivalent or greater challenge to the sterilization process should be established. If a PCD is used to provide a defined resistance for specific aspects of the load its validity as an equivalent or greater challenge than the load, including its SBS, should be established. If the SBS of the load is subsequently changed this can change the relationship between the challenge represented by the PCD and that of the newly packaged load and can represent a different product family.

d) The plateau period is a combination of the equilibration time and the holding time. In most cases the holding time is the part of the operating cycle used to establish lethality.

e) Heat penetration into each type of load should be determined either from the temperature measured within a number of medical device packages or in a reference load. At least one temperature sensor should be situated adjacent to the temperature sensors connected to the measurement chain used for process control. If a sensor or indicator cannot be located at a position on a medical device known to be difficult to sterilize, the medical device can be substituted by a different type of medical device or PCD, provided that the challenge to the process from the alternative has been demonstrated to be equal to or greater than the medical device it is to represent. The sensors placed within the load should be located on or within those parts from which air is difficult to remove. Caution should be exercised when interpreting thermometric data from within hollow or porous medical devices capable of entrapping air. Temperature measurement alone cannot differentiate between hot air and saturated steam. The presence of moist heat can be judged from the exposure of chemical indicators or biological indicators.

f) Reproducibility within acceptable limits should be checked using a minimum of three replicate cycles.

A.9.6.3 Additional information and PQ tests for contained product sterilization processes

For contained product processes, the test load and its location in the chamber should be as proposed for routine production. Heating, exposure and cooling profiles within the chamber should be checked at least in positions adjacent to the containers as identified in OQ to attain the shortest and longest exposure. The profiles should then be checked within the reference product placed in these locations in a test load and loading configuration according to the proposed production load. Conformance with the critical parameters identified in Clause 8 should be verified. If an existing sterilization process is to be used for either a new product family or loading configuration, or both, the limits on exposure identified in Clause 7 should be observed and the attainment of microbiological effectiveness identified in Clause 8 should be verified. If process parameters change during subsequent development, microbiological effectiveness and the limits on exposure for the existing product family(ies) should be verified.

A.9.7 Review and approval of the validation

A.9.7.1 Data collected during validation should be reviewed and approved by a responsible person organizationally independent of those conducting the tests, those preparing the validation report and those responsible for production.

A.9.7.2 Data, which can be in the form of a validation report, used to confirm the sterilization process should include, where applicable:

a) reference to the sterilizer specification and any subsequent changes to it;

b) the location and unique identification for the sterilizer, e.g. serial number together with name and address of the manufacturer, type of sterilizer and model reference;

c) documentation to demonstrate conformance with the safety specifications;

d) the pressure vessel certificate(s);

e) reference to an equipment maintenance manual and a planned equipment maintenance schedule for the sterilizer;

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f) the installation instructions;

g) the operating instructions;

h) documents suitable to support users' obligations to demonstrate compliance with applicable regulations;

i) operational procedures for all equipment maintenance, checks and tests;

j) details of any modification to the sterilizer, instrumentation or controls;

k) evidence of calibration of the test instrumentation;

l) details of any faults found on the sterilizer and how they have been corrected;

m) for contained product and, if applicable, packaged product (e.g. containerized product) heat penetration studies for each type of load/product family;

n) the parameters used to control the sterilization cycle and a copy of the specification for the sterilization process;

o) the identity of all personnel together with their professional qualifications (in terms of their competence to do the work) involved in validation.

A.9.8 Tests of sterility and tests for sterility

A.9.8.1 Tests of sterility and tests for sterility are tests used in this document for the qualitative detection and/or quantitative determination of viable microorganisms. Either or both of these tests can be used during process development, validation and routine control.

A.9.8.2 Tests for sterility (often termed "sterility tests") are carried out on product which has been subjected to a sterilization process. They are a formalised test described in pharmacopoeias and involve sampling a defined number of product units from the processed load and testing for the presence of microbial contamination. Such tests have little statistical relevance and will only be capable of determining high levels of microbial contamination, indicative of a major process failure. Such tests should not be accepted as sole proof that a sterilization process is valid.

A.9.8.3 Tests of sterility are an essential part of a means of determining absence or presence of residual bioburden on product, components of product or in challenge devices to be used routinely. They are usually used in microbiological approaches during process development and are critical during PQ for processes established using the approach discussed in B.2 and to establish the appropriateness of a microbiological PCD.

A.10 Routine monitoring and control

A.10.1 The purpose of routine monitoring and control is to ensure that the validated sterilizing process has been delivered to the product each time that it is used. This is evidenced from the results of periodic tests and data obtained during the sterilization process. Validation tests cannot be considered a substitute for the routine monitoring and control measures described in Clause 10 and explained below.

A.10.2 The outcome of all monitoring and control should be documented, reviewed, approved by suitably qualified and trained personnel and retained.

A.10.3 The consequences of a failure can depend on the current operation mode of the equipment. Different levels for alarms and indications depending on the related criticality can be provided. Besides the documentation of the physical parameters of the cycle, and biological or chemical indicators, if used, any indication of a failure should be considered as well for evaluation of the cycle prior to product release for further use.

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A.10.4 Persons responsible for sterilization should ensure that before the sterilizer is used for production, they have evidence to show that:

a) scheduled equipment maintenance has been satisfactorily completed;

b) PQ and periodic re-qualification reports are up to date and include the types of load and product families that can be sterilized;

c) the results of regular periodic tests such as the chamber integrity (leak rate) test and the daily Bowie and Dick Test are satisfactory.

A.10.5 In order to assist the periodic review of this information a procedure can be considered in which each sterilizer has a "permit to operate" system in place which is agreed between the persons responsible for sterilization and the engineering support functions which certify that equipment maintenance has been carried out.

A.10.6 A recording of both chamber temperature and chamber pressure is normally generated automatically during the operating cycle. The recording, sometimes known as a batch process record (BPR) can then be used for comparison with the profiles, often described as master temperature / pressure recordings or master process records (MPR), obtained during validation. These profiles can also indicate the parameter tolerances. Traditionally, this would have been carried out using an acetate overlay, however with modern data processing software, such comparisons can be carried out electronically.

A.10.7 Along with the records of the physical parameters of the sterilization cycle and the biological and/or chemical indicator results, if used, any indication of a failure should be considered as part of the evaluation of the cycle in order to determine if the product can be released.

A.10.8 If a medical device is packaged, or if NCGs or residual air can be trapped within the load or load item (e.g. a lumen, tube or crevice), a daily steam penetration test is used to confirm the air removal and steam penetration performance of the operating cycle is performing effectively before the process is used for sterilizing loads. A comparison of the temperature measured at the reference measurement point and the temperature determined from the measured pressure using steam table values [see Annex E and Formula (E.1)] can be used to demonstrate the presence of superheated steam conditions within the usable chamber space during the sterilization process, but this approach cannot be used to demonstrate adequate air removal, steam penetration and presence of moist heat on surfaces. If a medical device is wrapped and/or NCG can be trapped in a part, such as a lumen, tubing or crevice, F_0 calculated from temperatures measured at the reference measurement point will not represent the lethality delivered to the medical device and should not be used to judge the results of a sterilization process for this type of medical device. In addition to the measurement of process parameters, air removal and steam penetration should be assured for each operating cycle using a PCD. Examples of how air removal can be assured for every cycle would include the use of an air detector fitted to the sterilizer or use of a PCD that is not fitted to the sterilizer [see 6.3 d)]. Other approaches can be employed but need to be specified, established and validated. The means by which air removal and steam penetration is established for production cycles should have been verified as valid for the product in the load.

A.10.9 The temperature of fluid in reference containers in locations shown from a number of exploratory cycles to represent the coolest and hottest parts of the load can be used to predict the highest and lowest temperatures throughout a load of fluids. Temperature profiles generated for the chamber and the circulating heat transfer fluid can sometimes be used to predict a reproducible temperature profile for the coolest product. Whenever temperatures are to be measured in reference containers located in a production load, wireless systems can be considered.

A.10.10 The requirements for the duration that records are kept can be specified in local policies and procedures or in law.

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A.11 Product release from sterilization

A.11.1 The purpose of product release from sterilization is to confirm that the product has been successfully exposed to the specified sterilization process.

A.11.2 All results of periodic tests should be referenced on release documentation, for example a cross reference to the air leakage and Bowie and Dick type test results.

A.11.3 Product release can be based on the comparison of the temperature profile for the chamber with the temperature profile measured in either a reference product(s) or in a reference location from which the temperature profile within the product can be predicted which is based on the PQ study. Attainment of the specified values for sterilization temperature, plateau period, and sterilization temperature band in a location from which the holding time can be predicted can also be used for product release.

A.11.4 For medical devices sterilized by saturated steam in gravity displacement or pulsed steam cycles in small steam sterilizers, release based solely on sterilization temperature and holding time should be restricted to unwrapped medical devices of relatively low thermal mass and simple design. These are typical of sterilizers used in a small health care facility, e.g. a dental surgery.

A.11.5 If either chemical indicators or biological indicators, or both, are used routinely, they should be treated as part of the release criteria and should be additional to the measurement of process parameters.

A.11.6 The integrity of SBSs and containers should be visually checked after removal from the sterilizer. Damaged packaging and containers should be treated as non-conforming product.

A.11.7 Similarly, a system should be in place to ensure wet packs are appropriately addressed in order to avoid recontaminated products entering the supply chain (see [47]). Drying should be carried out in an environment in which particles and microbial contamination are controlled.

A.11.8 The identification of non-processed and processed loads can be achieved by one or all of the following:

a) physical barriers;

b) double-ended pass through sterilizers;

c) use of type 1 process indicators on the SBS;

d) validated track and trace systems.

A.12 Maintaining process effectiveness

A.12.1 General

A.12.1.1 The purpose of this activity is to identify and implement the periodic checks and tests necessary to predict the specified sterilization process will continue to be delivered to product during routine processing.

A.12.1.2 Any change that raises doubt about the lethality that will be delivered to the load or that will affect the quality of the product should initiate a review.

A.12.2 Demonstration of continued effectiveness

A.12.2.1 Whenever records of routine monitoring, periodic testing and performance requalification indicate unacceptable deviations from data determined during validation, the cause should be identified and

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corrected, and the sterilizer requalified. Product sterilized in processes exhibiting such deviations should be placed into quarantine until investigations are complete.

A.12.2.2 When a sterilizer is operated infrequently, the periods of inactivity can result in changes to the performance of the sterilizer or its associated services. This can result in the delivery of a process that does not conform with the specified process. If the sterilizer undergoes periods of inactivity, a review should be carried out to ascertain the consequences for process effectiveness, and the measures to be taken to redefine routine monitoring, testing or requalification to confirm process effectiveness. For example, the consequences of a weekend shut down or the effect of an energy conservation system should be considered. Similarly, even periods of inactivity during a production shift can give rise to changes which will result in not conforming process until, for example, a warm up operating cycle has been carried out.

A.12.3 Daily air removal and steam penetration test

A.12.3.1 The test cycle for carrying out the daily steam penetration test (e.g. the Bowie and Dick Test) should use the same operating cycle as that used for sterile product production. The steam penetration test is designed to assess the ability of the production process to effect air removal and rapid and even steam penetration into the PCD. If using a test cycle that is modified from the operating cycle, the air removal stage is identical rather than being a specially designed test cycle. If such a test cycle is used, it is only acceptable to adjust the holding time of the test cycle in order to match the specified exposure time and temperature indicated in the instructions for use accompanying the challenge device (e.g. some commercially produced test devices specify a holding time of 3,5 min), or reduce the drying time of the test cycle. Reference can be made to ISO 11140-4 and ISO 11140-6 which describes the performance requirements for steam penetration test devices used for carrying out a daily steam penetration test in an empty chamber.

A.12.4 Process challenge device (PCD) for monitoring every process

The success of a steam sterilization process depends on the combination of the sterilizer, process, load, loading pattern and SBS. If the sterilization process relies on the removal of air from the chamber in order to achieve rapid and even penetration of steam into the load, a PCD should be used in every production cycle of the sterilizer to establish the adequacy of air removal and steam penetration. The PCD should be proven to have a known relationship to the load with regard to air removal and steam penetration. This relationship can be established during process development where the sensitivity of the PCD towards process failures can be established and confirmed during validation, e.g. how the PCD responds when a chamber leak is present sufficient to cause a process failure. There are no international standards describing the design and requirements for PCDs employed to establish adequacy of air removal and steam penetration in a sterilizer in which a load is being processed.

A.12.5 Recalibration

A specification for the interval between recalibration of each measuring chain should consider the recommendations given in the user instructions or the service manual. The intervals should be reduced if there is unscheduled equipment maintenance or evidence of inaccuracy.

A.12.6 Equipment maintenance

A.12.6.1 Periodically, the sterilizer should be examined to confirm that the installation is still in accordance with the specification and that there is no evidence of malfunction. Checks and tests should also be carried out to demonstrate that the equipment remains safe (see IEC 61010-2-040) and that the services are satisfactory. It is essential to have an effective change control process which documents any changes made to equipment or process and the requalification carried out to ensure process effectiveness.

A.12.6.2 An equipment maintenance scheme should be developed from the schedules provided for the sterilizer, instrument(s) and associated equipment, from the routine tasks and tests carried out in the plant and as a result of experience. A set of procedures should be developed for each sterilizer containing full instructions for each equipment maintenance task. The equipment maintenance scheme and frequency with which each task is performed should be based on the recommendations given for the sterilizer, its usage and

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safety considerations. National directives concerning periodic inspection and tests in order to comply with pressure equipment regulations should also be included in the scheme.

A.12.6.3 Safety and functional checks should be done after each equipment maintenance sequence is completed in order to evaluate the effect, if any, on the process.

A.12.7 Requalification

A.12.7.1 Requalification is performed to confirm that process changes have not compromised the effectiveness of the sterilization process and that the data acquired during validation remains valid. To guard against unreported changes, the extent of, and the interval between each part of requalification should be determined from the type of sterilization process data obtained through periodic tests and from data that verifies that established process parameters are routinely reproduced. Typically, requalification is performed annually. The following should be reviewed and evaluated to confirm the continued valid state of the IQ, OQ and PQ:

a) non-scheduled maintenance including calibration;

b) deviations on the sterilizer or with the process;

c) changes to the sterilizer, supplies or product including load configuration.

A.12.7.2 The outcome of the review, including any need for requalification, should be documented taking into account manufacturers' instructions. This can include an assessment of the need to reconfirm achievement of the specified SAL, if necessary, through microbiological studies. The extent to which requalification is carried out should be justified by the designated responsible person based on the result of annual review and the assessment of the change. The outcome of this review, including the rationale for decisions reached, should be documented.

A.12.7.3 The extent of requalification will depend on the reasons for the inconsistency in performance; if a component is changed, or the control system is modified, it could only be necessary to show repeatability of the qualified sterilization cycle. If, in the case of a wrapped goods and porous load process, the cause is shown to be a leak into the chamber, it might only be necessary to repeat a leak test on the chamber and then carry out a steam penetration test.

A.12.7.4 Performance requalification might also need to be performed after a change of product, product SBS or loading pattern, or when the data for the load are not within specified limits.

A.12.7.5 If biological indicators are used during requalification, their performance should be compared to those used during previous validations. Use of biological indicators which have a significantly different microbial population or D value can result in a challenge which is greater or less than that used during validation. If a biological indicator is used during requalification which has significantly different characteristics, then this should be justified and documented. ISO 11138-3 identifies minimum requirements for population count and D value but does not specify maxima, however the information accompanying the biological indicator will specify these values.

A.12.7.6 Any change that raises doubt about the effectiveness of the sterilization process should initiate a review.

A.12.7.7 To facilitate comparison of PQ and performance requalification data, it can be helpful for the same report format to be used.

A.12.7.8 Some common changes, which can cause a change in performance and therefore require some testing in order to establish performance, can include but are not limited to:

a) new pressure and or temperature sensor;

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b) new chamber door seal requiring a chamber leak rate test;

c) new controller circuit or PLC;

d) adjustment of steam supply pressure;

e) new steam boiler/boiler maintenance;

f) new SBS supplier;

g) adoption of rigid sterilization containers where flexible sterile barrier material was used previously;

h) adoption of a new instrument with complex design features.

A.12.7.9 Some elements of IQ can be necessary to be performed during requalification when there are changes to an existing sterilizer which can affect the sterilization process effectiveness, e.g. changing a door seal, steam supply modifications, vacuum pump replacement or refurbishment.

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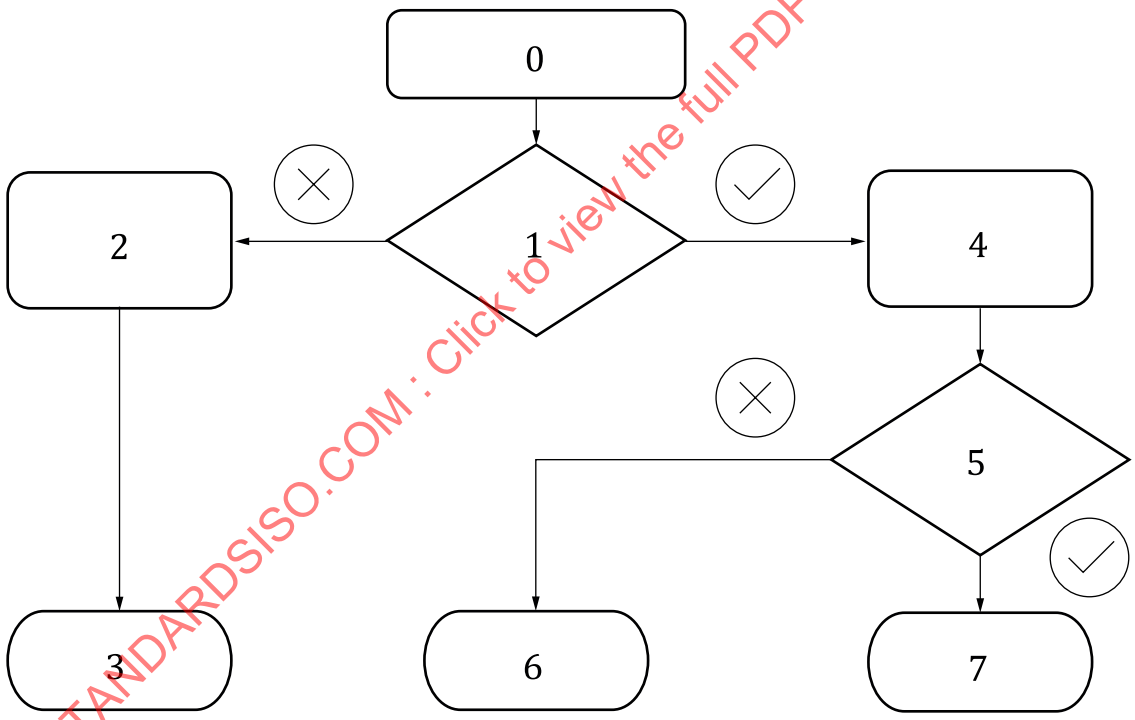
Annex B
(informative)

Establishment and evaluation of a sterilization process primarily based on microbiological inactivation

B.1 General

When the product SAL of the moist heat sterilization process is based on microbial inactivation there are three methods that can be used. The first two methods, bioburden-based (see B.2) and combined bioburden/ biological indicator (see B.3), are based on a knowledge of the product bioburden and the third, overkill (see B.4), does not take bioburden into consideration but is considered a conservative approach. Figure B.1 shows a decision tree that can be used to assist in determining which method is appropriate. The questions posed in Figure B.1 direct the method selection to either a conservative process using reference microorganisms (Boxes 2 and 3) or methods that use product bioburden (Box 4). For these bioburden-related methods the key question in Box 5 determines if the combined bioburden/biological indicator method (Box 6) or a solely bioburden-based method (Box 7) would be most appropriate.



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Key

0	selection of microbiological qualification method
1	can the product be adversely affected by the thermal conditions of the moist heat sterilization process or is process optimization desired or required?
2	conservative process based on inactivation of reference microorganisms
3	overkill method (see B.4)
4	knowledge of product bioburden
5	is the least amount of product thermal exposure desired or required?
6	combined bioburden/ biological indicator method (see B.3)

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7 bioburden based method (see B.2)

Yes

No

Figure B.1 — Selection of method based on microbial inactivation

There can be acceptable microbiological approaches other than those described in this Annex (see Reference [68] for an example in which a bioburden / overkill approach is used). Aspects of the microbiological approaches taken can be influenced by national or regional regulatory requirements or standards.

B.2 Process definition based on inactivation of the microbial population in its natural state (bioburden-based method)

B.2.1 General

Guidance and discussion on this method are given in the literature, e.g. References [52],[59],[61] and [62].

The method requires knowledge of the resistance and population of the naturally occurring product bioburden and potential manufacturing environmental contaminants. Bioburdens representative of production should be determined in accordance with ISO 11737-1 and routinely evaluated for resistance to the sterilization process. A thermophilic microorganism screening procedure should be used exposing either the liquid product or an extract of the product, e.g. in buffered surfactant solution, or other eluant used to remove microorganisms from the surface of representative product samples to heating at 80 °C to 100 °C for 10 min to 15 min (see References [59, 64]). After exposure the liquid product or extract of the product are tested for surviving microorganisms, followed by identification of any isolates. In general, a *D* value of ≤0,5 min can be assumed for bioburden (see References [61, 62]), therefore the thermophilic microorganism screening will confirm that the *D* value does not exceed this value.

Isolates are generally characterized and identified to the genus or species level.

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. While most purified water systems do not contain the nutrients required for growth of thermophilic and or hyperthermophilic microorganisms (e.g. *Geobacillus stearothermophilus*), consideration of the makeup of final product and or potential environmental isolates should be considered. If the product or eluant supports microbial growth a maximum hold time of both test samples and product prior to testing and or sterilization should be established considering other product requirements (e.g. endotoxin, pH, chemical makeup.).

The bioburden approach is often used where delivery of thermal stress to the product needs to be minimized or when process optimization is desired. This can include alternate process temperatures (e.g. lower or higher than the standard 121,1 °C moist heat process) with low process *F*-values (110 °C). Where products are degraded from longer periods of thermal stress, a process of High Temperature Short Time (HTST) using near square wave temperature conditions might be less detrimental.

B.2.2 Use of a bioburden-based method.

Use of a bioburden-based method for process definition requires that product bioburden levels are relatively consistent over time. Implementation of an ongoing bioburden monitoring program is required to use this method (see ISO 11737-1).

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

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B.2.3 Procedure to establish the sterilization process

B.2.3.1 If thermophilic microorganisms are recovered in the thermophilic microorganism screening procedure, product should be exposed to the sterilizing agent in predetermined increment(s) of the anticipated sterilization process to establish the lethal rate of inactivation and *D* value of organism(s) present. However, if microorganisms of low resistance are present it might not be possible to establish an accurate *D* value in either a production sterilizer or a resistometer vessel.

B.2.3.2 The required accuracy and precision of increments should be established, and the delivery of the sterilizing agent should be controlled and monitored to meet defined limits. It is important to consider the impact of initial heating / conditioning, dwell and cooling stages of the process on delivered lethality. The variation of these process stages should be defined and considered when establishing the exposure time.

B.2.3.3 Following exposure to the sterilizing agent, the product, selected from locations in the load most difficult to achieve sterilizing conditions, should be subjected individually to tests of sterility (see ISO 11737-2) and or enumeration.

B.2.3.4 The extent of thermal exposure, considering all stages of the process, to the sterilizing agent, should be used to define the sterilization process along with either a knowledge of the relationship between the proportion of product exhibiting no growth in tests of sterility or the reduction in the numbers of thermophilic microorganisms present (see ISO 11138-7).

B.2.3.5 Based on the known population and organisms present, the level of treatment identified to provide no growth in representative or inoculated products samples is carried out in triplicate to demonstrate reproducibility.

B.2.4 Follow up

The continued appropriateness of the sterilization process is confirmed at defined intervals using product representative of routine production (see Clause 12).

The method requires on-going monitoring of and control over the bioburden. It is common practice to conduct bioburden 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.

B.3 Process definition based on inactivation of a reference microorganism and knowledge of bioburden on product items to be sterilized (combined bioburden/ biological indicator-based method)

B.3.1 General

Guidance and discussion on this method can be found in ISO 11138-7 and in the literature, e.g. References [52],[59],[62] and[63].

The use of a biological indicator that conforms with ISO 11138-3 (D_{121} value of at least 1,5 min) can reduce the amount of bioburden characterization that is needed (see Reference [59]). For example, it might only be necessary to perform the thermophile screening procedure (see B.2.1) without further characterization or identification of the isolates; or identification of the isolates can be performed to show that the microorganisms are not more resistant to moist heat sterilization compared with selected biological indicator based on the literature.

Examples of microorganisms that demonstrate resistance to moist heat and which are suitable for use in this approach are *Geobacillus stearothermophilus, Bacillus coagulans, Clostridium sporogenes, and Bacillus atrophaeus.*

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B.3.2 Procedure

B.3.2.1 The location within the product at which sterility is most difficult to achieve should be established.

B.3.2.1.1 Place the biological indicator into the most difficult to sterilize location/s of the product. If the location of the microbiological challenge is other than the location within the product at which sterility is most difficult to achieve, its relationship to the most difficult location should be established. PCDs can be used for test cycle monitoring if their relationship to the location within the product at which sterility is most difficult to achieve and/or load locations are known and provides an equivalent or greater challenge to sterilization.

B.3.2.1.2 The biological indicators/PCDs should be packaged in a manner that represents the packaging to be used for routine moist heat sterilization processing. If the validation packaging differs from that which will be used for routine sterilization, its relationship to the routine packaging should be documented. Validation packaging that differs from the routine sterilization packaging should represent an equivalent or greater challenge when compared to routine sterilization packaging.

B.3.2.1.3 The packaged, biological indicators/PCDs should be placed into the most difficult-to-sterilize locations of the load. The validation load should be configured in a manner to represent an equivalent or greater challenge than the routine sterilizer loading. Depending on the contents of the load and the cycle set points, this can be a fully loaded chamber or another load configuration. If the placement of the biological indicator/PCD is such that it differs from the most difficult-to-sterilize locations within the load, its relationship to the most difficult-to-sterilize locations within the load should be established and should represent an equivalent or greater challenge to sterilization.

B.3.2.2 From a knowledge of the resistance and population of the naturally occurring product bioburden (see B.2.1 for information on thermophilic microorganism screening) and the resistance of the reference microorganisms, the extent of treatment required to achieve the specified requirements for sterility should be determined. The method requires on going periodic monitoring of and control over the bioburden; see ISO 11737-1.

B.3.2.3 A challenge to the sterilization process comprising a known number of microorganisms with known resistance to the sterilizing agent should be created by either:

a) placing biological indicators within the product at position(s) or representative of positions where sterilizing conditions are most difficult to achieve; or

b) inoculating the product with reference microorganisms at position(s) within the product where sterilizing conditions are most difficult to achieve.

NOTE 1 An inoculated product can be a biological indicator (see ISO 11138-1).

NOTE 2 Direct inoculation with a spore suspension onto a product surface can result in variable resistance of the inoculated product because of surface phenomena, other environmental factors, and the occlusion of the spores on or in the product. See References [50], [76] and ISO 11737-1 for additional information.

B.3.2.4 The challenge should be packaged the same as routinely produced product and should be included within the load in the location where it is most difficult to achieve sterilizing conditions.

B.3.2.5 The load should be exposed to the sterilizing agent under conditions selected to deliver less lethality than is delivered during routine sterilization, so that not all reference microorganisms will be inactivated.

B.3.2.6 The level of treatment identified should be carried out in triplicate to demonstrate reproducibility.

B.3.2.7 The number of microorganisms surviving should either be determined by direct enumeration or estimated by the most probable number technique (see ISO 11138-1).

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B.3.2.8 The rate of inactivation of the reference microorganisms should be calculated.

B.3.3 Quantity of biological indicators

The minimum recommended number of biological indicators can be based on product load volume and is as follows:

a) For product load volumes of up to 10 m^3, use three biological indicators per m^3 of product volume, with a minimum of 5 BIs.

b) For product load volumes above 10 m^3, use one additional biological indicator per additional m^3 beyond 10 m^3.

For some sterilization processes, the above recommendations might not be appropriate. A rationale should be documented for the number of biological indicators used.

B.3.4 Examples

B.3.4.1 Example 1 — Direct enumeration

This example assumes a bioburden D_{121} value of 0,5 min.

With a D_{121} value of 0,5 min, first calculate the ***F*** value required for the process:

F value = 0,5 min x (log N_0 – log N)

where

N_0 is the bioburden action level (100 Colony Forming Units, CFU);

N is the selected SAL for the product (in this case, 10^{-6}).

F value = 0,5 min x (log 100 – log 10^{-6}) = 4,0 min

To determine the required log reduction for the reference microorganism with a D_{121} of 1,0 min, substitute the log reduction (L_R) for (log N_0 – log N):

F value = 1,0 min × L_R

if solving for L_R:

L_R = ***F*** value / 1,0 min

F value = 4,0 min

L_R = 4,0 min / 1,0 min = 4,0 logs

For this example, the reference microorganism population is 1,0 × 10^6 CFU (N_0) and a holding time of 5 min gives the results shown in Table B.1.

Table B.1 — 5-min exposure example results

Biological indicator ID	Count (CFU)
1	23
2	22
3	24
4	19
5	17

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NOTE The numbers shown in Table B.1 are theoretical examples. The variability in real test data can be higher.

Using the highest result of 24 CFU, the L_R for the process can be determined.

$L_R = \log N_0 - \log N = \log (1 \times 10^6) - \log 24 = 6 - 1,4 = 4,6$ logs

Since 4,6 logs is greater than the required 4,0 logs, the process demonstrates the product SAL will be achieved as shown below. This study would be completed two more times to demonstrate reproducibility.

To determine the SAL the following calculation can be performed:

$S_{AL} = 10^{[\log(N_0) - L_R]}$

where

D value = F value / L_R and L_R = F value/D value therefore for the above example:

N_0 = 100

L_R = 4,6 min /0,5 min = 9,2

S_{AL} = $10^{(2-9,2)} = 10^{-7,2}$

B.3.4.2 Example 2 — Fraction negative

This example assumes a bioburden D_{121} value of 0,8 min.

With a D_{121} value of 0,8 min, first calculate the ***F*** value required for the process:

F value = 0,8 min × ($\log N_0 - \log N$)

where

N_0 is the bioburden action level (5 000 CFU);

N is the defined SAL for the product (in this case, 10^{-6}).

F value = 0,8 min × ($\log 5\,000 - \log 10^{-6}$) = 7,8 min

To determine the required log reduction for the biological indicator with a D_{121} of 2,0 min substitute the log reduction (L_R) for ($\log N_0 - \log N$):

F value = 2,0 min x L_R

if solving for L_R:

L_R = ***F*** value / 2,0 min

F value = 7,8 min

L_R = 7,8 min / 2,0 min = 3,9 logs

For this example, the biological indicator population is 6,2 × 10^5 CFU (N_0) and a sterilization holding time of 10 min gives the results shown in Table B.2.

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Table B.2 — 10-min exposure example results

Biological indicator ID	Growth
1	No
2	Yes
3	No
4	Yes
5	Yes
6	Yes

Using the result of 2 negatives out of the 6 tested, the L_R for the process can be determined:

$L_R = \log N_0 - \log (\text{Ln } r/n) = \log (6{,}2 \times 10^5) - \log (\text{Ln } 6/2) = 5{,}79 - 0{,}04 = 5{,}75$ logs

where

n is the total number of biological indicator replicates, in this case, 6;

r is the number of replicates showing no growth, in this case we are assuming 2.

Since 5,75 logs is greater than the required 3,9 logs the process demonstrates the product SAL will be achieved as shown below. This study would be completed two more times to demonstrate reproducibility.

To determine the SAL the following calculation can be performed.

$S_{AL} = 10^{[\log(N_0) - LR]}$

where

D value = F value / LR and LR = F value/D value therefore for the above example:

N_0 = 5 000

L_R = 11,5 min/0,8 min = 14,375

S_{AL} = $10^{(3,7\text{-}14,375)} = 10^{-10,7}$

B.3.5 Follow up

The continued appropriateness of the sterilization process is confirmed at defined intervals by repeating a single qualification cycle (see 12.4).

The method requires ongoing monitoring of and control over the bioburden 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 bioburden is within defined limits.

B.4 Conservative process definition based on inactivation of reference microorganisms (overkill method)

B.4.1 General

B.4.1.1 This subclause describes the overkill method which is based on the inactivation of reference microorganisms. The overkill approach is often selected for items that are heat-stable due to its simplicity, robustness, and ease of validation relative to other approaches. It is also the typical method to sterilize re-usable items. Qualifying a sterilization process for such products requires an approach different from that often used for new and unused product, because the challenge to the sterilization process is difficult to

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define and pre-sterilization treatments (e.g. cleaning) can be difficult to validate and control. A sterilization process in this situation is usually conservative and designed to deliver a treatment exceeding that required to achieve the specified requirements for sterility.

When using the overkill approach, product bioburden monitoring is recommended. It should be noted that health care facilities and industrial settings have different approaches to monitoring and controlling bioburden.

B.4.1.2 One example of a microorganism that demonstrates resistance to moist heat and which is suitable for use in this approach are spores of *G. stearothermophilus*. The microorganisms *Bacillus coagulans, Clostridium sporogenes,* and *Bacillus atrophaeus* can be used as well if the resistance properties have been demonstrated (see ISO 11138-3).

B.4.1.3 The overkill method is based on a cycle designed to provide greater than or equal to a 12-log reduction of a microorganism population, on or in a product with an assumed D_{121} value of 1 min. The overkill approach requires:

a) achievement of a maximal SAL of 10^{-6} after sterilization;

b) achievement of an $F_{\mathrm{BIOLOGICAL}}$ of at least 12 min using an appropriate biological indicator.

NOTE 1 The BI microbiological challenge is calculated as the product of the logarithm to the base ten of the initial population of microorganisms and the D value (= log $N_0 \times D_{121}$ value). $F_{\mathrm{BIOLOGICAL}}$ value describes the achieved lethality during a sterilization cycle based on the achieved inactivation of a biological indicator ($F_{\mathrm{BIOLOGICAL}} = D_{121}$ value × (log N_0-logN_f)).

NOTE 2 The rationale for using a D_{121} of 1,0 min as a worst-case assumption for naturally occurring bioburden was based on a review of experimental laboratory data and reasonable judgement for naturally occurring mesophilic spores in a medical device plant operating under good manufacturing practice (see References [59] and [63]).

B.4.1.4 By adjusting the population of the biological indicator in relation to the D_{121} value of the biological indicator, an appropriate partial cycle BI microbiological challenge or an appropriate full cycle BI microbiological challenge can be obtained, as is outlined in the following examples with D_{121} values that are more reflective of actual resistances available from commercially sourced biological indicators:

— Partial cycle approach biological indicator: Assuming a biological indicator with a D_{121} value of 1,5 min, using a population of $1,0 \times 10^4$ CFU then the BI microbiological challenge will be 6 min and if complete kill is obtained it will result in an $F_{\mathrm{BIOLOGICAL}}$ of 6 min.

  — BI microbiological challenge =1,5 min × $\log_{10}(1,0 \times 10^4$ CFU) = 6 min

  — $F_{\mathrm{BIOLOGICAL}}$ = 1,5 min × ($\log_{10}(1,0 \times 10^4$ CFU) – $\log_{10}$ $(1,0 \times 10^0$ CFU*)) = 6 min

  *Assumes one (1) survivor for purposes of the calculation

— Full cycle approach biological indicator: Assuming a biological indicator with a D_{121} value of 2,0 min, using a biological indicator population of 1,0 x 10^6 CFU then the BI microbiological challenge will be 12 min and if complete kill is obtained it will result in an $F_{\mathrm{BIOLOGICAL}}$ of 12 min.

  — BI microbiological challenge = 2,0 min × $\log_{10}(1,0 \times 10^6$ CFU) = 12 min

  — $F_{\mathrm{BIOLOGICAL}}$ = 2,0 min × ($\log_{10}(1,0 \times 10^6$ CFU) – $\log_{10}$ $(1,0 \times 10^0$ CFU*)) = 12 min

  *Assumes one (1) survivor for purposes of the calculation

B.4.1.5 When the BI microbiological challenge is known, the user can compare the challenge presented by biological indicators with varying populations and resistances. An example of this is shown below;

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each biological indicator outlined in the example has the same BI microbiological challenge and would be appropriate for use with the partial cycle approach:

— biological indicator 1:

  — Population = $1{,}0 \times 10^4$ CFU

  — D_{121} value = 1,5 min

  — BI microbiological challenge =1,5 min × $\log_{10}(1{,}0 \times 10^4)$ = 6 min

— biological indicator 2:

  — Population = $1{,}0 \times 10^5$ CFU

  — D_{121} value = 1,2 min

  — BI microbiological challenge = 1,2 min × $\log_{10}(1{,}0 \times 10^5)$ = 6 min

— biological indicator 3:

  — Population = $1{,}0 \times 10^6$ CFU

  — D_{121} value = 1,0 min

  — BI microbiological challenge = 1,0 min × $\log_{10}(1{,}0 \times 10^6)$ = 6 min

Guidance and discussion on the overkill method are given in ISO 11138-7 and in literature, e.g. References [52], [59] and [62].

B.4.2 Procedure

B.4.2.1 The location within the product at which sterility is considered the most difficult to achieve should be determined. For the placement of biological indicators/PCDs, refer to B.3.2.1.1 through B.3.2.1.3.

B.4.2.2 A challenge to the sterilization process should be created by either:

a) placing biological indicators within the product at position(s) or representative of positions where sterilizing conditions are considered the most difficult to achieve; or

b) inoculating the product with reference microorganisms at position(s) within the product where sterilizing conditions are considered the most difficult to achieve.

NOTE 1 An inoculated product can be considered a biological indicator (see ISO 11138-1).

NOTE 2 Direct inoculation with a spore suspension onto a product surface can result in variable resistance of the inoculated product because of surface phenomena, other environmental factors, and the occlusion of the spores on or in the product. See References [51], [76] and ISO 11737-1 for additional information.

B.4.2.3 The challenge should be packaged the same as routinely produced product and included within the load in the location where it is most difficult to achieve sterilizing conditions.

B.4.3 Quantity of biological indicators

B.4.3.1 For the number of biological indicators to be used refer to B.3.3.

B.4.3.2 For validation of items intended to be processed in health care facilities, biological indicator numbers of 5 to 12 biological indicators per load are often appropriate. biological indicator placement should account for all potential challenge areas in the product regardless of biological indicator number recommendations provided in B.3.3. For multi-device trays and complete device sets, biological indicator

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numbers exceeding the recommended biological indicator numbers can be necessary to provide adequate microbiological challenge to the process.

B.4.4 Partial cycle approach

B.4.4.1 General

The load should be exposed to the sterilizing agent under conditions designed to deliver a reduced level of treatment compared with the routine sterilization process. This can be half the holding time or any fraction of the holding time that will allow calculation of the log reduction of the process. There are two approaches:

a) Half-cycle approach: Performed using a biological indicator with a BI microbiological challenge greater than or equal to 6 min resulting in no survivors.

b) Cycle calculation approach: The routine holding time delivers minimally a calculated 12 spore log reduction (SLR) to a microorganism with a D_{121} value of 1,0 min using a biological indicator that conforms with ISO 11138-3.

NOTE 1 The calculated SLR is based on a D_{121} value of 1 min not the minimum of 1,5 min specified in ISO 11138-3 for a moist heat biological indicator.

NOTE 2 It is recognized that the validation and monitoring of some sterilization processes can use biological indicators that do not meet the minimum population and/or resistance criteria specified in ISO 11138. These biological indicators are acceptable provided that:

— all other requirements of ISO 11138 (including the method of test for population and resistance) are met;

— the product information includes a clear statement of the population and resistance;

— the product label carries a clear warning that the population and/or resistance (as appropriate) is below the value specified in the relevant part of ISO 11138.

B.4.4.2 Half-cycle approach

If the inactivation of the biological indicator is confirmed, the exposure time can be defined conservatively as twice the exposure time in the half cycle.

B.4.4.3 Cycle calculation approach

The exposure time for the sterilization process is established by extrapolation to a predicted probability of survival of 10^{-6} or less. When using this calculation, consider the number and resistance of the microorganisms on the biological indicator.

B.4.4.4 Partial cycle approach qualification testing

B.4.4.4.1 The sterilizer should be programmed to reflect a processing time that conforms with B.4.4.1.

B.4.4.4.2 Upon completion of the qualification cycle, the biological indicators/PCDs will be removed from the load and the biological indicators from the inoculated products or from the PCDs will be tested for inactivation of the indicator organism.

B.4.4.4.3 As indicated in B.4.4.1 a), a successful qualification cycle should demonstrate that a 12 SLR or greater for a biological indicator with a D_{121} of 1,0 min will be achieved in the routine holding time, which is verified by inactivation of a sufficient number of biological indicators.

B.4.4.4.4 The qualification cycles should be carried out in triplicate to demonstrate reproducibility.

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B.4.5 Examples partial cycle approach

B.4.5.1 Example 3 — Half-cycle approach

This example assumes a routine production cycle with an exposure time of 40 min at a minimum of 121 °C. Then a biological indicator conforming with B.4.4.1 a) that can be inactivated by 20 min at 121 °C would be chosen.

For this example, the following biological indicator is chosen:

D_{121} = 1,6 min and $N_0 = 1{,}2 \times 10^6$

To check if the biological indicator can demonstrate the $F_{BIOLOGICAL}$, the BI microbiological challenge is calculated as follows:

BI microbiological challenge = $D_{121} \times \log N_0 = 1{,}6 \times \log (1{,}2 \times 10^6) = 9{,}7$ min

The biological indicator in this example can demonstrate an $F_{BIOLOGICAL} \geq 6$ min in the half cycle.

All the biological indicators are inactivated by the reduced cycle and when done in triplicate it is proven that the full cycle of 40 min has a SAL of 10^{-6} or less and that a log reduction of greater than 12 for a microorganism with a D_{121} value of 1 min is achieved by the full cycle.

For the full cycle, the log reduction of microorganisms with a D_{121} value of 1 min can be calculated by extrapolation from the half cycle. The half cycle has proven an $F_{BIOLOGICAL}$ greater than or equal to 9,7 min. Then the $F_{BIOLOGICAL}$ of the full cycle is at least twice that of the half cycle, i.e. 19,4 min which equates to a SLR of 19,4.

It can also be concluded that the SAL of the full cycle is $10^{-13,4}$ or less. It is calculated as follows:

$S_{AL,\ full\ cycle} = 10^{(6\text{-}SLR)} = 10^{(6-19,4)} = 10^{-13,4}$

For this formula SLR is understood as the log reduction of a microorganism with a D_{121} value of 1 min and the value 6 comes from the understanding, that the starting population of the product bioburden is not more than 10^6 microorganisms with a D_{121} value of 1 min.

B.4.5.2 Example 4 — Cycle calculation approach

This example assumes a routine production cycle with an exposure time of 15 min at minimum 121 °C. Then a biological indicator conforming with B.4.4.1 b) is used.

For this example, the following biological indicator is chosen:

D_{121} = 1,8 min and $N_0 = 1{,}3 \times 10^6$

A holding time of 7 min is used. The number of biological indicators with growth are 4, 3, and 5 from each of the qualification runs; a total of 10 per run is tested. To determine the minimum log reduction, the cycle with the most growth (5 positives) is used.

To calculate the log reduction the following is used:

Log reduction = $\log N_0$ – log (ln (Number Tested/Number Sterile)) = $\log (1{,}3 \times 10^6)$ – log (ln (10/5)) = 6,11 – (-0,16) = 6,27

Then, the log reduction of the full cycle can be calculated as this:

$L_{R,\ full\ cycle}$ = (Partial Cycle Log Reduction × Full holding time)/Partial Cycle Time = (6,27 × 15)/ 7 = 13,4

Thus, the 15-min holding time for the full cycle is acceptable, i.e. log reduction is greater than 12. It can also be concluded that the SAL of the full cycle is $10^{-7,4}$ or less based on the following calculation:

$S_{AL,\ full\ cycle} = 10^{(6\text{-}SLR)} = 10^{(6-13,4)} = 10^{-7,4}$

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For this and the above equation, SLR is to be understood as the log reduction of a microorganism with a D_{121} value of 1 min and the value 6 comes from the understanding, that the starting population of the product bioburden is not more than 10^6 microorganisms with a D_{121} value of 1 min.

B.4.6 Full cycle approach

B.4.6.1 The load should be exposed to the sterilizing agent under conditions designed to deliver a level of treatment that will inactivate a biological indicator which conforms with ISO 11138-3 and which provides a BI microbiological challenge of at least 12 min.

B.4.6.2 For the full cycle approach, a biological indicator that conforms with ISO 11138-3 and has at least a microbiological challenge of 12 min should be used. Table B.3 documents the minimum population required based on the D_{121} value.

Table B.3 — Minimum population (N_0) and BI microbiological challenge based on D_{121} value

D_{121} value (min)	Minimum population to demonstrate an $F_{BIOLOGICAL} \geq 12$ min (spores/biological indicator)
1,5	$1,0 \times 10^8$
1,6	$3,2 \times 10^7$
1,7	$1,1 \times 10^7$
1,8	$4,6 \times 10^6$
1,9	$2,1 \times 10^6$
2,0	$1,0 \times 10^6$
2,1	$5,2 \times 10^5$
2,2	$2,8 \times 10^5$
2,3	$1,6 \times 10^5$
2,4	$1,0 \times 10^5$

When a biological indicator with a D_{121} value of 2,4 min and the minimum population of $1,0 \times 10^5$ is completely killed after the full cycle, a 12,0 SLR results when related to a D_{121} value of 1.

The effective/actual SLR with the above-mentioned cycle and biological indicators is: SLR = 5,0 × 2,4 = 12,0.

This results in a SAL based on a D121 value of 1 as shown below and this is equivalent to specified SAL of 10-6:

$S_{AL,\ full\ cycle} = 10^{(6\text{-}SLR)} = 10^{(6\text{-}12,0)} = 10^{-6}$

B.4.6.3 Variations in the delivered lethality can occur within the chamber. Similarly, variations occur in the characteristics of the biological indicator. These variations can result in a positive biological indicator and therefore should be considered in the determination of the full cycle. If F_0 is to be used as part of the criteria for product release, its relationship to the $F_{BIOLOGICAL}$ value should be established.

EXAMPLE This relationship can be established in process definition or during PQ. There are several ways this relationship can be established; this is one example that assumes biological indicators with the following characteristics:

— BI population (N_0) = 1,0 x 10^6 CFU/BI

— BI D_{121} Value = 2,0 min

— BI z-value = 10 °C

— BI microbiological challenge = $D_{121} \times \log_{10}(N_0)$ = 2,0 min × $\log_{10}(1,0 \times 10^6)$ = 12 min

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A cycle is planned to demonstrate complete biological indicator inactivation using the ending population from the kill time description outlined in ISO 11138-1:2017, E.3.5 (i.e. $N = 1{,}0 \times 10^{-4}$ CFU). To determine the $F_{BIOLOGICAL}$ for exposure, the following formula is used:

— $F_{BIOLOGICAL} = D_{121}$ value × ($\log_{10} N_0 - \log_{10} N_f$)

— $F_{BIOLOGICAL}$ = 2,0 min × [6 – (–4)]

— $F_{BIOLOGICAL}$ = 2,0 min × 10

— $F_{BIOLOGICAL}$ = 20 min

Performing a cycle with a 20-min exposure should have no surviving biological indicators. When performing this testing, the z value of the biological indicators needs to be considered when the relationship to F_0 is established (refer to ISO 11138-7:2019, 7.2.4). F_0 values assume a reference temperature of 121,1 °C and a z value of 10 °C.

See also ISO 11138-7 and Reference [61] for more information.

B.4.6.4 The load should be exposed to the sterilizing agent for the target F_0 or the selected full cycle exposure time to confirm that there are no survivors. If the results of the test establish that this level of treatment is acceptable, then two further repeats should be done to demonstrate reproducibility and to confirm the defined treatment to be delivered by the sterilization process.

B.4.6.5 Full cycle approach qualification testing

B.4.6.5.1 A BI microbiological challenge should be selected that conforms with B.4.6.2. A biological indicator is an appropriate BI microbiological challenge and should be placed as defined in B.3.2.1.1 through B.3.2.1.3.

B.4.6.5.2 The sterilizer should be programmed to expose the load to the target F_0 value or selected time and temperature combination.

B.4.6.5.3 Upon completion of the qualification cycle, the biological indicators/PCDs will be removed from the load and tested for inactivation of the indicator organism.

B.4.6.5.4 A successful qualification cycle will demonstrate complete inactivation of the microbiological challenge from all biological indicators/PCDs placed into the qualification load.

B.4.6.5.5 Complete BI microbiological challenge inactivation from three separate, consecutive qualification cycles should be obtained to demonstrate reproducibility and to confirm the defined moist heat treatment delivered by the routine sterilization process.

B.4.7 Example 6 — Full cycle approach

This example assumes a routine production cycle with a holding time of 30 min at minimum 121 °C. A biological indicator conforming with B.4.6.2 that can be inactivated by 30 min at 121 °C can be chosen.

For this example, the following biological indicator is chosen:

D_{121} = 2,1 min and $N_0 = 3{,}0 \times 10^6$

To check if the biological indicator can demonstrate the $F_{BIOLOGICAL}$ the BI microbiological challenge is calculated as follows:

BI microbiological challenge = $D_{121} \times \log N_0 = 2{,}1 \times \log (3{,}0 \times 10^6) = 13{,}6$ min

The biological indicator can demonstrate an $F_{BIOLOGICAL} \geq 12$ min.

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All the biological indicators are inactivated by the full cycle and when done in triplicate it is proven that the full cycle of 30 min has a maximal SAL of 10^{-6} and that a minimum 12-log reduction of a microorganism with a D_{121} value of 1 min is achieved with the full cycle.

The actual minimum log reduction of a microorganism with a D_{121} value of 1 min that is shown by the full cycle is the same as the $F_{\text{BIOLOGICAL}}$, i.e. 13,6 logs.

The SAL for the full cycle can be calculated as for the partial cycle:

$S_{\text{AL, full cycle}} = 10^{(6\text{-SLR})} = 10^{(6\text{-}13,6)} = 10^{-7,6}$

B.4.8 Follow-up

The continued appropriateness of the sterilization process is confirmed at defined intervals by repeating a single qualification cycle (see 12.4).

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Annex C
(informative)

Establishment and evaluation of a sterilization process primarily based on the measurement of physical parameters

C.1 General

C.1.1 Establishment of a sterilization process primarily based on the measurement of physical parameters will normally be from data generated from a series of performance tests. Each test should be designed to identify whether one or more of the performance requirements specified for the sterilization process has been attained.

The performance requirements, tests and acceptance criteria outlined in this annex are examples and relate to a sterilizer conforming to EN 285 and apply when test equipment and procedures meeting the requirements of EN 285 are used (see also Clause 9). Similar tests and performance requirements for small sterilizers are given in EN 13060. The requirements for the differences between measured and calculated temperature from pressure is discussed in Annex E.

The frequency of tests for a large steam sterilizer conforming to EN 285 is identified in Table C.1 and for small sterilizers in Table C.2. The requirements stated in equipment standards can differ due to technical differences and results of risk evaluations between large and small steam sterilizers, as well as the implications for their use. Test scenarios should be adapted to corresponding load configurations. Tests of IQ, OQ and PQ are limited by the specification of a corresponding type test, since type tests provide reference data for subsequent testing.

EN 285 and EN 13060 are European documents intended for sterilizer manufacturers for design specifications, test methods, materials and other pertinent information for saturated steam sterilization processes. Sterilizers conforming to these standards can be used in industrial or health care applications.

NOTE ISO 19253[1)] is under preparation and is intended to apply to contained aqueous fluid sterilizers and contain appropriate standard tests for such sterilizers.

C.1.2 For sterilizers not conforming to EN 285 or EN 13060, it might not be possible to attain all the acceptance criteria given in this annex but attention should be paid to ensuring the attainment of moist heat on the surfaces which require sterilization which can be impeded by, for example, the quantities of residual air and NCGs in the chamber during the sterilization cycle. For such sterilizers, documented validation procedures can include tests and procedures from both this Annex and Annex B. The data from the tests can then be used to verify the efficiency of the proposed sterilization process for treating the defined medical device(s). This approach can also be appropriate for demonstrating conformity with the requirements of medical device legislation (if required).

C.1.3 When selecting a test instrument for validation studies and routine testing, attention should be paid to the number and type of signal inputs required. Both temperature and pressure will need to be recorded. Other input signals can also be needed. For example, the small load test (see C.4) requires at least seven temperature signal inputs and one pressure signal input. Typically, thermocouple or platinum resistance temperature sensors can be used and a pressure sensor giving an electrical voltage or current signal.

1) Under preparation. Stage at time of publication: ISO/AWI 19253.

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C.2 Hollow load test

C.2.1 This is a test for establishing the capability of the sterilization process to remove air and effect steam penetration into a PCD containing a lumen. The challenge device is not meant to represent any particular medical device but will present a challenge to air removal and steam penetration analogous to medical devices having lumens. The test is based on a hollow load test piece described in ISO 11140-6. This test complements the tests in which the standard test pack is specified (see C.3). It should be noted that medical devices containing narrow channels can require a higher level of air removal leading to improved steam penetration performance than that required in order to fulfil the hollow load test.

C.2.2 The result of the hollow load test is judged from exposure to a chemical indicator inserted into the test piece.

C.3 Standard test pack

C.3.1 The standard test pack is used for the small load test, the full load test, the Bowie and Dick test, air detector tests, load dryness tests for textiles and can be used with other materials to form a full load. The standard test pack is a reusable item that can be used for testing a number of times if the requirements in C.3.3, C.3.6 and C.3.7 are met.

C.3.2 The standard test pack should be composed of plain cotton sheets, each bleached to a good white and having an approximate size of 900 mm × 1 200 mm. The number of threads per centimetre in the warp should be (30 ± 6) and the number of threads per centimetre in the weft (27 ± 5). The weight should be (185 ± 5) g/m^2 and the edges, other than selvages, should be hemmed.

C.3.3 The sheets should be washed when new or soiled and should not be subjected to any fabric conditioning agent during laundering. The sheets should be dried and then allowed to equilibrate in an environment of between 20 °C to 30 °C and 40 % RH to 60 % RH.

NOTE Fabric conditioning agents can affect the characteristics of the fabric and can contain volatiles that will contribute to the NCGs in the sterilizer.

C.3.4 After equilibration the sheets should be folded to approximately 220 mm × 300 mm as illustrated in Figure C.1.

C.3.5 The sheets should be stacked to a height of approximately 250 mm after moderate compression by hand. The pack should then be wrapped in a similar fabric and secured with tape not exceeding 25 mm in width. For sterilizers unable to accommodate more than one sterilization module (rectangular parallelepiped of dimensions 300 mm height, 600 mm length and 300 mm width) the height of the stack should be approximately 150 mm.

C.3.6 The total weight of the standard test pack should be 7,0 kg ± 0,14 kg (approximately 30 sheets) and for the small pack 4,0 kg ± 0,16 kg (approximately 17 sheets).

After use, the sheets will become compressed. When the weight of sheets used to form a stack 250 mm high exceeds 7,14 kg, the sheets should be discarded. Similarly, for the smaller pack, when the weight of the sheets used to form a stack 150 mm high exceeds 4,16 kg the sheets should also be discarded.

C.3.7 Immediately before use, the temperature and humidity at the centre of the test pack should be between 20 °C and 30 °C and 40 % RH to 60 % RH. After use the pack should be removed from the sterilizer and aired in a similar environment.

C.3.8 Test packs comprising different materials and of different sizes and weights can be used provided equivalence with the requirements for the test in which the standard test pack is used is demonstrated (see ISO 11140-4).

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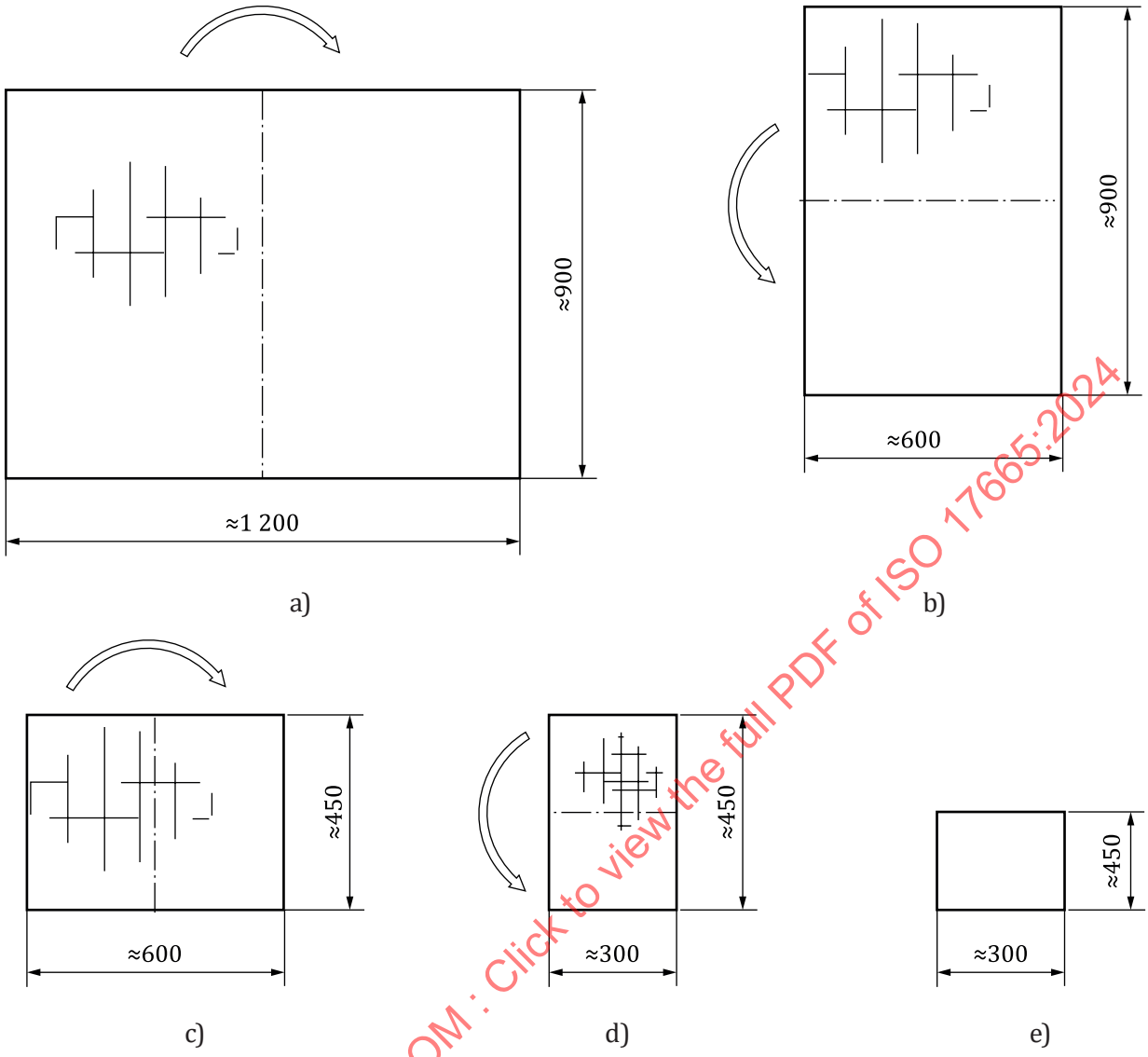
Dimensions in millimetres



Key

a 1 layer unfolded
b 2 layers folded once
c 4 layers folded twice
d 8 layers folded thrice
e 16 layers folded four times

Figure C.1 — Folding each sheet

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C.4 Thermometric tests

C.4.1 Small load thermometric test

C.4.1.1 This is a test for steam penetration into a standard test pack (see C.3). This test pack is used to identify a level of air removal or reduction in the level of NCGs in the steam within the chamber sufficient to qualify the sterilization process for a wide range of cannula, metal and textile products. For this test a number of temperature sensors (typically 5 sensors) are located at different levels within the standard test

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pack around the vertical axis. EN 285:2015+A1:2021, Figure 6 provides an illustration of the temperature sensor locations.

C.4.1.2 Acceptance criteria for the test are as follows.

a) All measurements should fall within the sterilization temperature band which should have a lower limit defined by the sterilization temperature and an upper limit of +3 °C.

b) The equilibration time should not exceed 15 s for chambers up to 800 l usable space and 30 s for larger chambers.

c) During the plateau period the temperature measured above the test pack should not exceed the temperature measured at the reference measurement point of the chamber by more than 5 °C for the first 60 s and 2 °C for the remaining period.

d) Throughout the holding time the temperature measured at the reference measurement point of the chamber, and any temperature measured at the same instant within the test pack should be within the sterilization temperature band and not differ from each other by more than 2 °C [see 6.3 a)].

e) Throughout the holding time the temperature measured at the reference measurement point of the sterilizer should be not more than 2 °C higher than the respective saturated steam temperature calculated from the chamber pressure (maximum allowed level of superheating, see Annex E).

f) Throughout the holding time the temperature measured at the reference measurement point of the sterilizer should be approximately the same as and have a known correlation to, the saturated steam temperature calculated from the measured chamber pressure allowing for the measurement tolerances of both the temperature and pressure measurements (see Annex E).

g) The holding time should be not less than that specified for the sterilization stage of the cycle.

NOTE See Table A.2 for examples.

C.4.2 Full load thermometric test

C.4.2.1.1 This is a test for steam penetration into the maximum size of load intended to be processed in the sterilizer and complements the small load test. The textile test pack is located in the centre of a full load of textiles. The test load is designed to represent the maximum mass of textiles which can be processed in the sterilizer and is used to demonstrate that, at the levels at which cycle parameters are set, rapid and even penetration of steam into the centre of a load occurs and the sterilizing condition is achieved.

C.4.2.1.2 The full load of textiles comprises folded sheets and a standard test pack as described in C.3. The sheets are dried and conditioned as described in C.3.3, and then folded and laid one on top of the other to form a stack with a mass of (7,5 ± 0,6) kg.

C.4.2.1.3 A standard test pack as described in C.3 is located within the chamber in a position previously identified and noted in the instructions for use. In the absence of this information the test pack should be located within the usable space and where possible approximately 100 mm above the geometric centre of the base of the chamber. The remainder of the usable space is then loaded with stacks of sheets as described in C.4.2.1.2 each with the layers of fabric in baskets dimensionally similar to one sterilization module or loosely wrapped in a textile sheet.

The mass of fabric in the test load should be equivalent to (7,5 ± 0,6) kg per sterilization module.

C.4.2.1.4 The standard test pack is equipped with thermometric monitoring sensors as described in C.4.1.1 and then an operating cycle is carried out and temperature and pressure data monitored and recorded.

C.4.2.2 Acceptance criteria for the full load test are the same as for the small load test, except that the temperature measurement above the test pack is omitted.

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C.5 Bowie and Dick test

C.5.1 This test is a steam penetration test, similar to the small load test and intended for daily use. This test is also used to identify a level of air removal or reduction in the level of NCGs in the steam within the chamber sufficient to qualify the sterilization process for a wide range of cannula, metal and textile products. A chemical indicator meeting the requirements of ISO 11140-3 is placed in the centre of a standard test pack and a pass is identified from a uniform colour change to the indicator.

NOTE For the original work on which the Bowie and Dick test is based, see Reference [44].

C.5.2 The standard test pack described in C.3 offers a challenge to the sterilization process nominally the same as the challenge from the textile test pack described by Bowie.[44] Indicators conforming with ISO 11140-4 can be used as an alternative to the standard test pack for conducting the Bowie and Dick steam penetration test.

NOTE The rate of steam admission to the chamber during pressurisation to the sterilization stage can have an influence on the measured thermometric values or the visible change taking place in the chemical indicator. Thus, if the rate of pressurisation is slow then any residual air pocket can be heated close to steam temperature leading to an inaccurate determination of temperature difference between the drain and the centre of the test pack. Similarly, any residual air present can be sufficiently heated and humidified during a slow rate of pressurisation to allow a visible change in a chemical indicator placed within the test pack.

C.6 Air leakage flow rate test

The performance specification identified in C.2, C.4 and C.5 are based on achieving a low level of residual air. Air leakage into the chamber will affect this level. In steam sterilizers (see EN 285, EN 13060) leakage into the chamber should not cause the pressure to rise by more than 0,13 kPa/min (1,3 mB/min) when measured at a defined chamber pressure.

C.7 Air detector tests (if fitted), small load, full load and function

C.7.1 These tests are used to set the air detector to register a fault whenever residual air is sufficient to cause a failure of the small load test (see C.4.1) and the full load test (see C.4.2).

C.7.2 The air detector should register a fault when, at the commencement of the equilibration time, residual air causes a difference of more than 2 °C between the lowest temperature measured in the standard test pack (used in the tests given in C.4.1 and C.4.2) and the temperature measured at the reference measurement point of the chamber. For a chamber too small to accommodate this test pack, a smaller version is used (see C.3).

C.7.3 In certain applications and settings (e.g. industrial settings) the performance of the air detector can be based on the defined process parameters and the product or product family(ies) that the sterilization process is designed to process.

C.8 Load dryness — Small and full load with textiles, full load with metal

These tests are used to verify that the design of the operating cycle, selection of the process parameters and the moisture contained in the steam are such that the level of moisture remaining in the load at the end of a sterilization process has not increased by more than 1 % for textiles and 0,2 % for metal. See EN 285 for the test method.

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C.9 Dynamic pressure test

This test is used to verify that the maximum rate of pressure change in the chamber will not cause damage to packaging. The average pressure change for any 3 s interval during the sterilization process should not exceed 1 000 kPa/min (10 bar/min).

C.10 Steam quality tests

C.10.1 Non-condensable gas in the steam affects air dilution in the chamber. Water in the steam affects residual moisture in the load. Superheated steam can prevent or delay the formation of moist heat on the surfaces which need to be sterilized. Wide variations in delivery pressure to the sterilizer is indicative of inadequate steam capacity and this can affect the validity of thermometric measurements for assessing the presence of saturated steam (see C.4 but also Annex E). Contaminants can cause corrosion and deposit toxic substances on the product.

C.10.2 When tested by the methods given in EN 285 the following should apply to the quality of steam supplied to the sterilizer:

a) a maximum of 3,5 ml of gas collected from 100 ml of condensed steam;

b) a minimum dryness value of 0,95 (5 % moisture);

c) a maximum of 25 °C of superheat when expanded to atmospheric pressure;

d) contaminants (see ISO/TS 5111 and also EN 285 and EN 13060).

NOTE Contaminants which can be considered include but are not limited to iron, cadmium, lead, chloride, phosphate, ammonium, calcium, magnesium, nitrate sulphate and silicate ions and bacterial endotoxins. In addition, other physicochemical properties can also be considered including pH, conductivity, appearance, oxidisable substances, the residue on evaporation of a defined volume of condensate.

e) fluctuations in steam pressure not exceeding ±10 % of the nominal gauge pressure measured at the inlet to the final pressure reduction valve.

C.11 Automatic control test

The automatic control test compares the performance of an operating cycle with its specification, normally by visual observation. The user activates an operating cycle and then observes each stage, noting the pressure and temperatures attained at each of the cycle switching points. The observed values are then compared with the specified values to ensure they remain within the defined tolerances for the cycle. Modern sterilizers carry out this test automatically using a control and monitoring system (see ISO/ TS 22421:2021, Annex B)

C.12 Water

The water supply should be of potable quality and fitted with a backflow protection device. The hardness value of water, Σ (ions of alkaline earth), should be between 0,7 mmol/l and 2,0 mmol/l. Hardness values outside these limits can cause scaling and corrosion problems. The maximum temperature of water used with a vacuum pump and for cooling is specified in standards (e.g. see EN 285 and EN 13060). However, in some circumstances higher feed water temperatures can be used provided the effect on vacuum level attainment and pump efficiency and cooling is known and controlled and is part of the sterilizer specification.

C.13 Compressed air

The compressed air supply should be at a pressure of 600 kPa to 800 kPa (5 to 7 bar), free of liquid water, filtered to 25 µm and free from oil droplets greater than 2 µm.

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C.14 Test programmes

The example shown in Table C.1 and Table C.2 includes the tests needed to verify the attainment of defined process parameters for large and small steam sterilizers respectively and also to judge from the data whether NCG present in the chamber during the plateau period is sufficient to prevent steam penetration into medical devices used in health care.

Table C.1 — Example of a schedule of tests for validation and periodic testing for a large steam sterilizer conforming to EN 285

Test	Installation qualification	Operational qualification	Performance qualification	Periodic testing
Safety tests and checks	××[b]	—	—	×[b]
Steam quality (C.10)				
— Non-condensable gases [C.10 a)]		×	—	×[d]
— Dryness value [C.10 b)]		×	—	×[d]
— Superheat [C.10 c)]		×	—	×[d]
— Contaminants[a] [C.10 d)]		×	—	×[d]
Thermometric tests (C.4)				
— Small load (C.4.1)	—	××	—	×[c]
— Full load (C.4.2)	—	××	—	×[d]
Hollow load test (C.2)	—	××	—	-
Bowie and Dick test (C.5)	—	××	××	××[e]
Air leakage flow rate (C.6)	—	××	—	××[f]
Air detector (if fitted) (C.7)				
— Small load	—	××	—	×[d]
— Full load	—	××	—	×[d]
— Function	—	××	—	×[f]
Load dryness tests (C.8)				

Key

×× Tests that are suggested.

× Tests that may be considered.

— Tests that need not be performed.

[a] Conformance should be tested in accordance with acknowledged analytical methods.

[b] Specified for the sterilizer.

[c] At least three-monthly.

[d] At least annually.

[e] At least daily.

[f] At least weekly.

[g] This is a weekly test unless it is carried out automatically by the control and monitoring system.

[h] Required if exposure of specific load configuration to defined sterilizing conditions cannot be predicted from OQ tests (see Annex G).

NOTE In some sterilizers, the air leakage flow rate test may be performed automatically more frequently or as an automatic stage within the operating cycle and carried out on every cycle in which case a separate air leakage flow rate test can be carried out less frequently.

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Table C.1 *(continued)*

Test	Installation qualification	Operational qualification	Performance qualification	Periodic testing
— Small load textiles	—	×	—	—
— Full load textiles	—	×	—	—
— Metal	—	×	—	—
Dynamic pressure test (C.9)	—	—	—	×[b]
Automatic control test (C.11)	—	××[g]	××[g]	××[g]
Product test	—	—	×[h]	×[d]

Key

×× Tests that are suggested.

× Tests that may be considered.

— Tests that need not be performed.

[a] Conformance should be tested in accordance with acknowledged analytical methods.

[b] Specified for the sterilizer.

[c] At least three-monthly.

[d] At least annually.

[e] At least daily.

[f] At least weekly.

[g] This is a weekly test unless it is carried out automatically by the control and monitoring system.

[h] Required if exposure of specific load configuration to defined sterilizing conditions cannot be predicted from OQ tests (see Annex G).

NOTE In some sterilizers, the air leakage flow rate test may be performed automatically more frequently or as an automatic stage within the operating cycle and carried out on every cycle in which case a separate air leakage flow rate test can be carried out less frequently.

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Table C.2 — Example of a schedule of tests for validation and periodic testing for a small steam sterilizer conforming to EN 13060

Test	Installation qualification	Operational qualification	Performance qualification	Periodic testing
Safety tests and checks	×× [f]	—	—	× [f]
Steam quality [a] (external supply)				
— Non-condensable gases	×	—	—	× [f]
— Contaminants		×	—	× [f]
Thermometric tests [a]				
— Solid load	—	×× [b, i]	—	× [c, f, i]
— Porous load	—	× [b, i]	—	× [c, i]
Hollow load tests [a]				
— Narrow lumen	—	××	××	×[g, h]
— Simple hollow item	—	×× [b, i, j]	—	—
Air leakage flow rate	× [b]	××	—	×× [h]
Air detector (if fitted)				
— Load	—	××	—	× [f]
— Function	—	××	—	× [h]
Load dryness tests [a]				
— Solid load	—	×× [e]	—	× [c]
— Porous load	—	×× [e]	—	× [c]
Dynamic pressure test	—	—	—	—

Key

×× Tests that are suggested to be carried out before PQ.

× Tests that may be considered.

— Tests that need not be performed.

[a] According to the specification provided for the sterilization cycle such as load, wrapping.

[b] Valid results from works test may be used.

[c] In combination with requalification.

[d] Required if exposure of specific load configuration to defined sterilizing conditions cannot be predicted from OQ tests (see Annex G).

[e] May be performed as product test.

[f] Frequency as specified for the sterilizer.

[g] At least daily.

[h] At least weekly.

[i] Where specified, the theoretical temperature may be used (see Annex E) as reference.

[j] Not if narrow lumen.

[k] This can be a weekly test unless it is carried out automatically by the control and monitoring system.

[l] May be considered as a demonstration of basic functionality.

NOTE Details on tests are provided with reference to EN 13060.

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Table C.2 *(continued)*

Test		Installation qualification	Operational qualification	Performance qualification	Periodic testing
Automatic control test		—	×[k, l]	×[k, l]	×[k, l]
Product test[a] Microbiological, thermometric — Solid loads — Narrow lumen — Simple hollow item — Porous load		—	—	×[d, i]	×[f, i]

Key

×× Tests that are suggested to be carried out before PQ.

× Tests that may be considered.

— Tests that need not be performed.

[a] According to the specification provided for the sterilization cycle such as load, wrapping.

[b] Valid results from works test may be used.

[c] In combination with requalification.

[d] Required if exposure of specific load configuration to defined sterilizing conditions cannot be predicted from OQ tests (see Annex G).

[e] May be performed as product test.

[f] Frequency as specified for the sterilizer.

[g] At least daily.

[h] At least weekly.

[i] Where specified, the theoretical temperature may be used (see Annex E) as reference.

[j] Not if narrow lumen.

[k] This can be a weekly test unless it is carried out automatically by the control and monitoring system.

[l] May be considered as a demonstration of basic functionality.

NOTE Details on tests are provided with reference to EN 13060.

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Annex D
(informative)

Examples of moist heat sterilization cycles

NOTE This Annex describes examples of typical operating cycles used in moist heat sterilization. Figures are conceptual and give examples only.

D.1 Saturated steam sterilization — Vented systems

D.1.1 This sterilization cycle is primarily intended for surface contact steam sterilization, as air removal from fabrics and cavities is uncertain. It is also used as a process for the sterilization of contained fluids where the steam acts as a heating medium.

D.1.2 An example of a chamber temperature and pressure profile for a vented steam sterilization cycle is shown in Figure D.1.

D.1.3 The sterilization cycle consists of three major stages:

a) Heating (conditioning) stage: with the vent open, steam is admitted or generated in the chamber and displaces air until the desired conditions are met; this is normally determined by the measurement of temperature. The vent then closes and steam continues to be admitted or generated in the chamber until the sterilization temperature and corresponding saturated steam pressure are attained.

b) Plateau period: the sterilization temperature is maintained in the chamber by steam for the prescribed time.

c) Cooling (re-conditioning) stage: this stage can differ for various types of product. Air can be supplied to vent the chamber to atmosphere and to remove residual steam / condensate or, where solutions in sealed containers are cooled, filtered compressed air can be admitted into the chamber to prevent rapid de-pressurization. This stage is completed when the pressure in the chamber is at atmospheric pressure and also, in the case of sealed containers, when a safe temperature is reached in the containers.

D.2 Saturated steam sterilization — Active air removal

D.2.1 This sterilization cycle is primarily used for product where air is difficult to remove such as in porous materials, instruments with channels and/or cavities and packaged items. It can also be used for surface contact sterilization.

D.2.2 An example of a chamber temperature and pressure profile is shown in Figure D.2. This is only one example of the many implemented in modern sterilizers.

D.2.3 The sterilization cycle consists of six major stages:

a) Air removal (conditioning) stage: air is removed from the chamber and the load by either a deep vacuum or a combination of vacuum and steam pulses above and/or below atmospheric pressure.

b) Charge (conditioning) stage: steam enters the chamber until the sterilization temperature and pressure are attained in the chamber.

c) Plateau period: the sterilization temperature and pressure are maintained in the chamber by steam for the specified time.

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d) Exhaust stage: steam is exhausted from the chamber, and a pre-determined level of vacuum is obtained.

e) Drying (re-conditioning) stage: for items required to be dry, the temperature in the jacket surrounding the chamber and the vacuum in the chamber are both maintained for a pre-determined period.

f) Vacuum relief (re-conditioning) stage: air is admitted to the chamber until atmospheric pressure is reached.

D.3 Steam-air mixtures (to provide an overpressure) sterilization cycles

D.3.1 General

This sterilization cycle is primarily used for contained product where at certain stages in the cycle the pressure within the container exceeds the pressure within the chamber. This can result in fracture of the container or loss of integrity of the seal; to compensate for this an overpressure is used.

For such contained product, several sterilization processes are available to ensure that the pressure on the outside of a product balances the pressure on its inside.

D.3.2 Steam-air mixtures

D.3.2.1 An example of a chamber temperature and a pressure profile is shown in Figure D.3.

D.3.2.2 The sterilization cycle consists of three major stages:

a) Heating (conditioning) stage: the first part of this stage is the same as for the vented system except that where the product integrity can be affected by rising steam pressure, venting is precluded. Steam continues to enter the chamber until the prescribed sterilization temperature is attained. If product requires overpressure during this stage and where the partial pressure resulting from the entrapped air is insufficient to protect the product, compressed air is introduced. Circulation is normally required to maintain a uniform environment.

b) Plateau period: circulation and sterilization temperature are maintained for the prescribed time.

c) Cooling (re-conditioning) stage: cooling of the product is accomplished using cooled compressed air, heat exchangers or cooled water spray. During this stage, damage to the contained product from rapid de-pressurization of the chamber is prevented by compressed air. The required pressure is then maintained in the chamber until the contained product has been sufficiently cooled and it is then vented to atmosphere.

D.4 Water spray

D.4.1 An example of a chamber temperature and pressure profile is shown in Figure D.4.

D.4.2 The sterilization cycle consists of four major stages:

a) Fill (conditioning) stage: at the beginning of the sterilization cycle, a quantity of water is introduced into the sterilizer or produced as condensate from the steam. It is then sprayed over the product.

b) Heating (conditioning) stage: heating to the required sterilizing temperature is achieved, either by introducing air and steam into the circulating system or by heating the water through a heat exchanger and introducing compressed air into the chamber.

c) Plateau period: the circulation system is operated and the circulating water and contained product is maintained at the required sterilizing temperature for the desired time.

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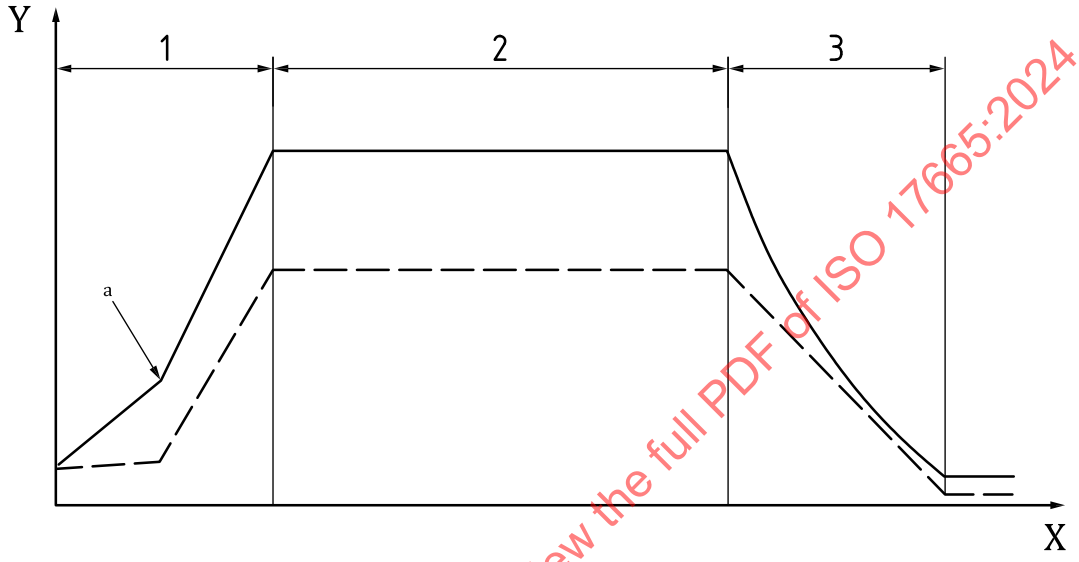
d) Cooling (re-conditioning) stage: the pressure in the chamber is maintained by compressed air and the contained product is cooled as the temperature of the circulating water is cooled at a controlled rate. The chamber is de-pressurized when the contained product has been reduced to a safe temperature.

D.5 Water immersion

D.5.1 An example of a chamber temperature and pressure profile is also shown in Figure D.4.

D.5.2 This is a similar sterilization cycle to the water spray system, except that the contained product is totally immersed in water in order to maintain its shape.



Key

X time

Y temperature (___); pressure (_ _ _ _)

1 conditioning stage (air removal by downward/gravity displacement)

2 plateau period

3 steam exhaust and cooling period

[a] Vent closure.

Figure D.1 — Example of a chamber temperature and pressure profile for a saturated steam sterilization — Vented cycle

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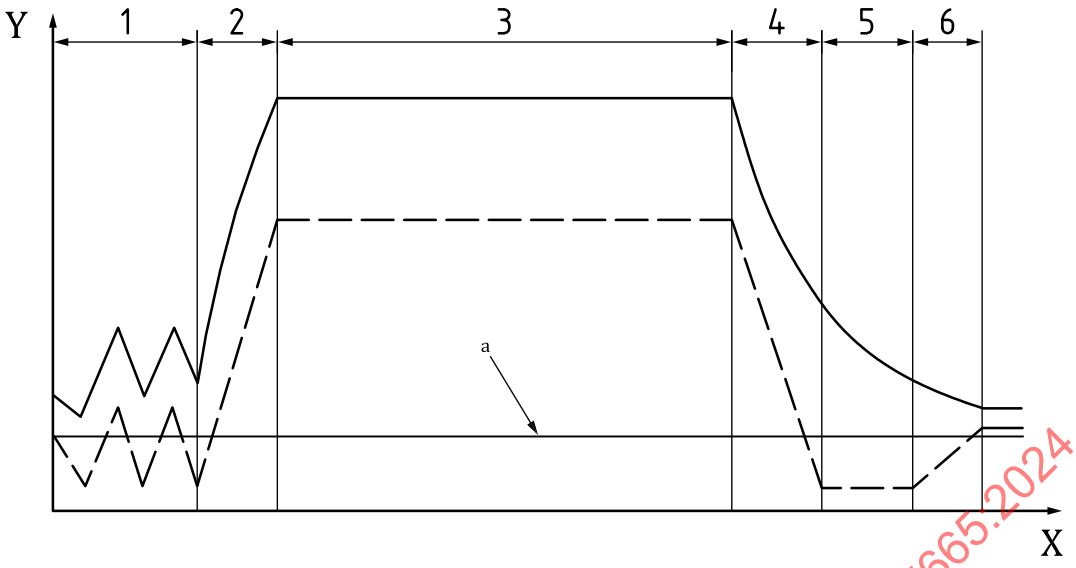

Key

X time
Y temperature (___); pressure (_ _ _ _)
1 conditioning stage (air removal by a sequence of evacuations and steam admissions/pressurizations)
2 conditioning stage (steam admission to sterilizing pressure)
3 plateau period
4 steam exhaust
5 drying stage
6 vacuum relief stage
[a] Atmospheric pressure.

Figure D.2 — Example of a chamber temperature and pressure profile for a saturated steam sterilization — Active air removal cycle

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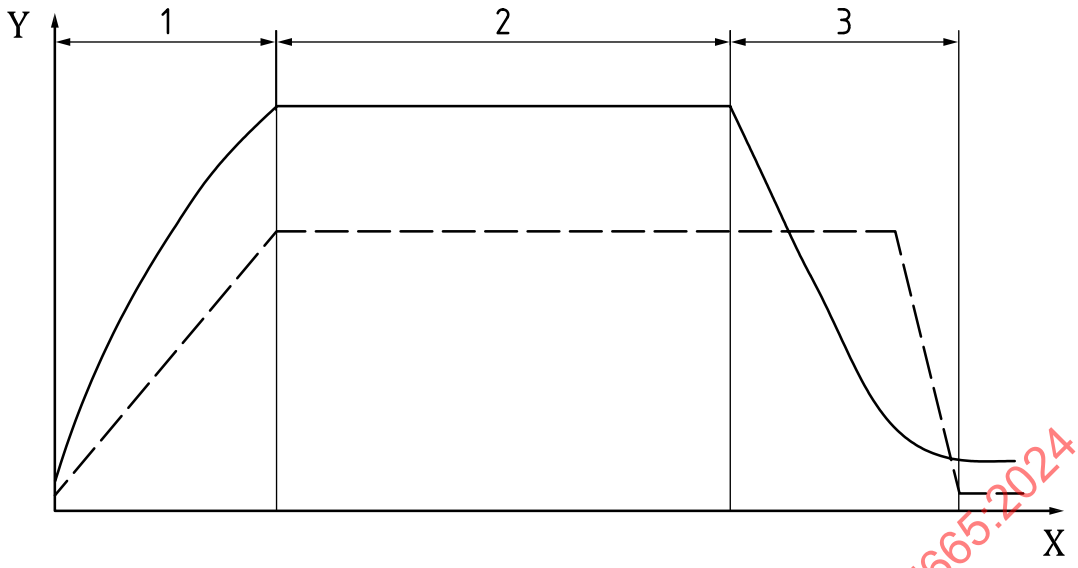

Key

X time

Y temperature (___); pressure including air overpressure (_ _ _ _)

1 conditioning stage (chamber pressurisation)

2 plateau period

3 reconditioning stage (steam exhaust and cooling period)

Figure D.3 — Example of a chamber temperature and pressure profile for a steam-air mixture cycle

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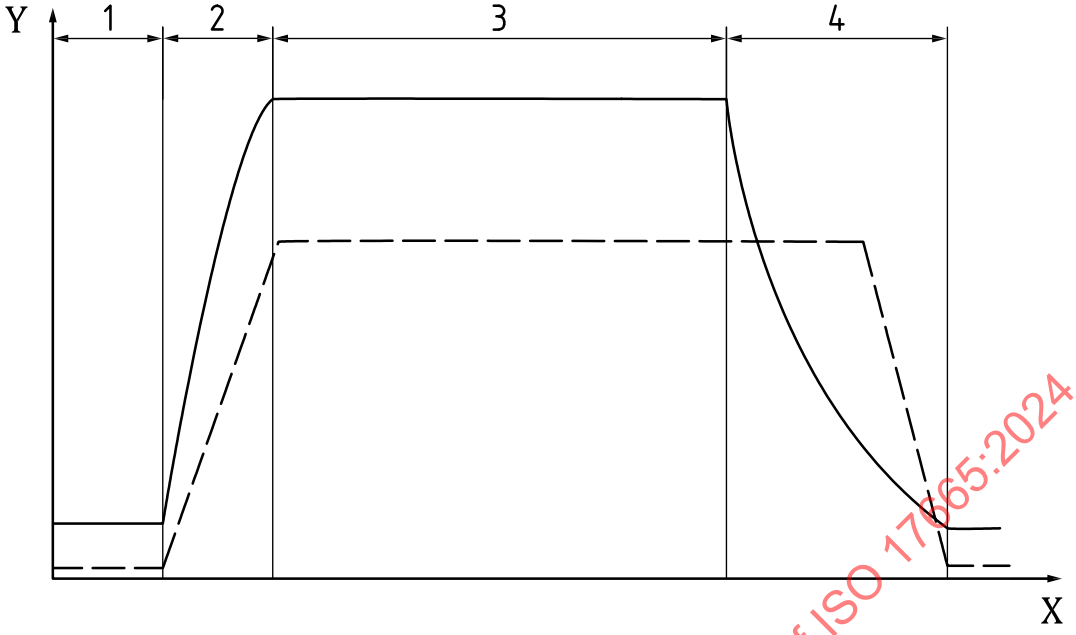

Key

X time

Y temperature (___); pressure including air overpressure (_ _ _ _)

1 conditioning (fill) stage

2 conditioning (heating) stage

3 plateau period

4 cooling stage

Figure D.4 — Example of a chamber temperature and pressure profile for a water immersion or water spray cycle

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Annex E
(informative)

Temperature and pressure of saturated steam for use in moist heat sterilization

E.1 Steam tables for use in moist heat sterilization

Theoretical steam temperature [see 6.3 b)] can be determined directly from the steam tables referenced below or calculated from Formulae (E.1).

$$T = [-3\,892{,}7/(\ln P - 9{,}486\,54)] - 230{,}602\,4 \quad \text{(E.1)}$$

where

T is the theoretical steam temperature in ° C;

P the measured chamber pressure in MPa.

Example calculation for:

P = 0,205 04 MPa

T= [–3 892,7/(ln (0,205 04) – 9,486 54)] –230,602 4

T= [–3 892,7/(–1,584 550 – 9,486 54)] –230,602 4

T= (–3 892,7/–11,071 09) – 230,602 4

T= 351,609 4 – 230,602 4

T= 121,007 0

At a pressure of 0,205 04 MPa the saturated steam temperature would be 121,000 °C. Using Formulae (E.1) the calculated value shown in the example is 121,007 °C. The difference is considered acceptable. The difference between calculated temperature using Formulae (E.1) and the values shown in Table E.1 have maximum deviations of +/– 0,01 °C over the range 100°C to 140 °C. The values shown in Table E.1 should not be used for the estimation of NCG in steam (see E.2).

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Table E.1 — Temperature and pressure of saturated steam for use in moist heat sterilization

Temperature °C	Pressure mbar	Pressure MPa	Temperature °C	Pressure mbar	Pressure MPa
100	1 014,2	0,101 42	120	1 986,7	0,198 67
101	1 050,9	0,105 09	121	2 050,4	0,205 04
102	1 088,7	0,108 87	122	2 115,8	0,211 58
103	1 127,7	0,112 77	123	2 182,9	0,218 29
104	1 167,8	0,116 78	124	2 251,7	0,225 17
NOTE 1 This table is extracted from ASME “International Steam Tables for Industrial Use” based on IAPWS “Industrial Formulation 1997 for the Thermodynamic Properties of Water and Steam (IAPWS)” (see Reference [64]). NOTE 2 1 014,2 mbar = 0,101 42 MPa = 101,42 kPa.					

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Table E.1 *(continued)*

Temperature °C	Pressure mbar	Pressure MPa	Temperature °C	Pressure mbar	Pressure MPa
105	1 209	0,120 9	125	2 322,2	0,232 22
106	1 251,5	0,125 15	126	2 394,6	0,239 46
107	1 295,1	0,129 51	127	2 468,8	0,246 88
108	1 340,1	0,134 01	128	2 544,8	0,254 48
109	1 386,3	0,138 63	129	2 622,7	0,262 27
110	1 433,8	0,143 38	130	2 702,6	0,270 26
111	1 482,6	0,148 26	131	2 784,4	0,278 44
112	1 532,8	0,153 28	132	2 868,2	0,286 82
113	1 584,3	0,158 43	133	2 954,1	0,295 41
114	1 637,3	0,163 73	134	3 042	0,304 2
115	1 691,8	0,169 18	135	3 132	0,313 2
116	1 747,7	0,174 77	136	3 224,2	0,322 42
117	1 805,1	0,180 51	137	3 318,5	0,331 85
118	1 864	0,186 4	138	3 415,1	0,341 51
119	1 924,5	0,192 45	139	3 513,9	0,351 39
			140	3 615	0,361 5

NOTE 1 This table is extracted from ASME "International Steam Tables for Industrial Use" based on IAPWS "Industrial Formulation 1997 for the Thermodynamic Properties of Water and Steam (IAPWS)" (see Reference [64]).

NOTE 2 1 014,2 mbar = 0,101 42 MPa = 101,42 kPa.

E.2 Guidance on the application of steam tables for determining the presence of saturated steam

E.2.1 Saturated steam and how steam tables are used to predict temperature from pressure and vice versa

Saturated steam is water vapour in a state of equilibrium between its liquid and gas phases.

Steam saturation is a term also used but should not be confused with the term saturated steam (see Reference [75] and definition 3.56).

Steam tables (see E.1) describe the physical relationship between the temperature and pressure of pure saturated steam. When saturated steam is used in saturated steam sterilization it normally has a temperature which correlates to a pressure shown in steam tables (Table E.1). If the pressure of saturated steam is known, the temperature, along with other properties, can be determined from steam tables (see E.1). Similarly, if the temperature is known the pressure can also be determined from the same tables. Subclause 6.3 b) requires that the chamber reference temperature should correlate with the temperature calculated from the measured chamber pressure. If the measured (T_m) and calculated (T_c) temperatures do not correlate, this can be due to:

a) the presence of superheated steam (T_m is greater than T_c: see E.2.2);

b) the presence of large quantities of residual air which have reduced the measured temperature below that calculated from measured pressure (T_m is less than T_c: see E.2.3);

c) discrepancies in the measuring chains for pressure and temperature (T_m can be greater or less than T_c);

   — A measuring chain outside of its specification can give rise to a difference between measured temperature and that calculated from measured pressure.

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— The specified tolerances for each measuring chain (temperature and pressure) can give rise to differences between measured temperature and that calculated from measured pressure.

E.2.2 Superheated steam and how steam tables can be used to identify its presence.

Superheated steam is steam which has been heated beyond its saturation point according to steam tables. The measured temperature of the steam will be higher than that calculated from the measured pressure. Superheated steam is considered less able to achieve microbial inactivation than saturated steam, but the relationship is complex (see References [66] and [67]).

E.2.3 Steam–air (NCG) mixtures and how steam tables can and cannot be used to identify their presence

The temperature and pressure of pure saturated steam has predictable properties. If air or other NCGs are mixed with steam then partial pressure laws apply (Dalton's Law of Partial Pressures) and the relationship between measured temperature and measured chamber pressure will no longer reflect steam table values. When a mixture of steam and air/NCGs exists, the only contributor to temperature is steam. However, the partial pressure of each gas will contribute to the total pressure in the mixture (i.e. $P_{\text{Total}} = P_{\text{NCG}} + P_{\text{steam}}$). The temperature will therefore be lower than that calculated from measured pressure according to steam table values Formula (E.1). If the measured temperature is lower than the temperature calculated from measured pressure, this is an indication that a steam-air mixture is present in the chamber (see the calculations given in References [74] and [77]). However, it is wrong to conclude that an equivalence between the measured temperature and that calculated from measured chamber pressure in accordance with steam table values indicates the presence of saturated steam. Large quantities of NCGs are required to create a measurable difference between the measured temperature and the temperature calculated from measured chamber pressure when taking into account the tolerances of the measurement chains used in moist heat sterilizers or the guidance given in C.4. Such quantities of residual air are several hundreds of times higher than the limiting values which would cause a steam penetration test failure [see 6.3 c) and d) and Annex C] and potentially cause a process failure (see 8.4) in a saturated steam sterilization process. It is, however, important to note that in some contained product sterilization processes employing steam-air mixtures (see A.7.3.2, D.3, F.6.4 and H.6.4) non condensable gases are deliberately left in or introduced into the chamber therefore higher values of NCGs in steam are applicable however measures are normally taken to ensure homogeneity of the steam-air mixture.

As an example, the acceptable content of NCG in the steam supply can be 3,5 ml of gas collected from 100 ml of condensed steam (see C.10 and a method in EN 285). This results in an NCG level in saturated steam at 121 °C to 124 °C or 134 °C to 137 °C hundreds of times lower (less than 100 parts per million NCG in steam) than the 3,5 ml limit. This level of NCG in steam will cause a difference between the measured temperature and temperature calculated from pressure of less than 0,001 °K which is well below the measurement tolerances for temperature and pressure suggested in this document. Thus, the comparison of measured and calculated temperature from chamber pressure would not detect a level of NCG in steam which can create a process failure (see also Reference [77]). An example of the calculation of these values is shown in Table E.2 and in the literature.

Table E.2 shows the effect of increasing quantities of non-condensable gases accumulating in the chamber on the correlation between the measured temperature and the temperature calculated from the measured pressure (the sum of the partial pressures of steam and non-condensable gases) using Formula (E.1). The table shows the effect on saturated steam sterilization cycles operating at 136 °C and 123 °C. Only when greater than approximately 6 % residual non-condensable gas is present in the chamber is the measured temperature below the acceptance criteria specified in C.4 for operating cycles with a temperature band of 134 °C to 137 °C and 121 °C to 124 °C (see Table A.2).

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Table E.2 — Effect of increasing quantities of non-condensable gases accumulating in the chamber on the correlation between the measured temperature and the temperature calculated from the measured chamber pressure

Measured chamber pressure (kPa)	Theoretical temperature from pressure (°C)	Measured chamber temperature (°C)	Theoretical pressure from temperature (kPa)	% Air in chamber by volume	Volume air in 1 000 L chamber (L)	% NCG found in 100 ml of condensed steam[a]
322,42	136	136	322,42	0,00	0,00	0,00
322,42	136	136	322,38	<0,01[b]	<0,1[b]	3,5[b]
322,42	136	135	313,20	2,86	28,60	94,10
322,42	136	134	304,20	5,65	56,51	97,09
322,42	136	133,8	302,50	6,18	61,80	97,36
218,29	123	123	218,29	0,00	0,00	0,00
218,29	123	123	218,00	<0,01[b]	<0,1[b]	3,5[b]
218,29	123	122	211,58	3,07	30,74	96,17
218,29	123	121	205,04	6,07	60,7	98,14
218,29	123	120,8	203,74	6,67	66,65	98,32

[a] This column is a theoretical calculation showing the percentage of NCG found in 100 ml of condensed steam using the method and calculation described in Annex C and EN 285 if a sample were taken from the pipe supplying steam to the chamber. It should be noted that the values are illustrative since at very high levels of NCG in steam certain anomalies will be introduced due to the method of calculation.

[b] These figures refer to the limiting values for NCGs in steam supplied to the sterilizer in EN 285 and EN 13060.

Example calculation: The temperature measured in the chamber is 133,8 °C. The measured chamber pressure is 322,42 kPa. At a temperature of 133,8 °C the chamber pressure should be 302,50 kPa. The difference in the measured pressure and pressure calculated from the measured temperature is 322,42 – 302,50 = 19,92 kPa. The proportion of NCG in the steam is 19,92 / 322,42 *100 = 6,18 %

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Annex F
(informative)

Guidance on the application of the normative requirements in health care facilities

F.0 General

This annex offers guidance to be considered for the use of moist heat sterilization processes in health care facilities. For application in industrial settings the reader should refer to Annex A in combination with Annex H. Reusable medical devices are used in health care settings and are processed in accordance with the manufacturer's instructions for use. Prior to sterilization, control of cleaning and disinfection processes are required. Due to the nature of use in a wide variety of settings and procedures, there is a significant range of possible contamination and devices. Policy and standard operating procedures should be in place to ensure that medical devices undergo safe processing.

NOTE For ease of reference, the numbering of clauses in this annex corresponds to that in the normative parts of this document as described. In some clauses, additional information is provided for which no normative clause number exists (e.g. bulleted text or additional numbered subclauses).

F.1 Scope

No additional guidance.

F.1.1 Inclusions

F.1.1.1 No additional guidance.

F.1.1.2 The most common moist heat sterilization process used in health care facilities is saturated steam sterilization.

F.1.2 Exclusions

F.1.2.1 No additional guidance.

F.1.2.2 No additional guidance.

F.1.2.3 No additional guidance.

F.1.2.4 No additional guidance.

F.2 Normative references

No additional guidance.

F.3 Terms and definitions

F.3.1 Users of this document in a health care facility should be familiar with the definitions given in Clause 3 since the terms used are carefully defined and will be used in the context of the definition, sometimes appearing obvious or counter intuitive. For example, the definition of establish requires both a theoretical and practical evaluation where data is created during testing.

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F.4 General

F.4.1 Development, validation and routine control of a sterilization process

F.4.1.1 Overview

The health care organization should understand the benefits of:

a) introducing a system focused on quality of the process, reviewed at regular intervals, and ensuring that the system is understood, implemented and maintained with current information;

b) defining roles and assigned responsibilities, tasks and processes to be undertaken;

c) defining organization levels of leadership with responsibilities that are clearly identified, assigned and documented;

d) creating procedures that ensure a change in a process is verified and documented (see 12.5, A.12.5 and F.12.5);

e) staff performance reviews that are established and implemented;

f) that resources are made available for trained personnel, supervision, work activities and quality audits.

NOTE Also see ANSI/AAMI ST90 and ISO 13485.

F.4.1.2 Quality systems considerations

The health care organization should understand the benefits to the facility of a quality focused system, including financial. The following are considerations for a quality focused process which the health care facility should address:

a) designating personnel trained in the performance of audits and the implementation of quality improvement initiatives;

b) defining staff and management responsibilities;

c) defining the qualifications, competency and responsibility of each person authorized (authorized person) and designated to carry out specific task(s);

d) establishing qualification, education and training of personnel;

e) introducing an infection prevention and control programme including procedures and protocols;

f) making provisions for worker occupational health and safety;

g) defining procedures for subcontractors, including whether they operate within or outside the health care facility, if applicable;

h) defining staff and training competency assessment procedures;

i) ensuring procedures are in place for control and monitoring of all phases of the operation and that there is documentation to ensure adherence to standards, guidelines and regulations (for example, procedures for sterile storage and transport conditions, manual and automated cleaning and disinfecting practices, safe handling of sterilization and disinfection agents and ensuring that they are being used according to instructions on their label);

j) purchased sterilizers conform to legal requirements and their specifications (see 6.2 and F.6.2);

k) sterilizers are installed correctly and safely with regard to proper functioning, safety of personnel and environmental protection;

l) the service and environment required for proper operation of the sterilization equipment meet the specifications of the sterilizer manufacturer;

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m) newly installed sterilizers are subject to IQ, OQ and PQ tests before they are put into service;

n) sterilizers are subject to a documented scheme of periodic tests at yearly, quarterly, weekly and daily intervals;

o) sterilizers have an equipment maintenance service contract or in-house inspection and equipment maintenance programme staffed by fully trained, qualified and competent personnel;

p) procedures for processing, quality control and safe work practices are documented and adhered to in accordance with statutory requirements and accepted best practice;

q) procedures for dealing with malfunctions, accidents and dangerous occurrences are documented and adhered to;

r) the sterilizer manufacturer recommendations for regular equipment maintenance and periodic inspections are followed and documented (see Clause 12 and 12.3);

s) each measuring chain (sensor to readout and recording) fitted to, or used with, the sterilization equipment is calibrated annually, inspected, checked and maintained;

t) the calibration of the equipment should be carried out using instruments calibrated and traceable to national standards;

u) the sterilizer technical documentation has information and schedules on any parts or components that require routine replacement and that this is made available to the user.

F.4.1.3 Operational considerations

The health care organization should address operational aspects such as:

a) work area design (decontamination, preparation, sterilization and sterile storage areas), transport, environmental controls, hand and eye washing facilities, disinfection/testing/equipment maintenance, work surfaces, traffic control, personal protective equipment and dress code;

b) collecting information about processing reusable medical devices;

c) disassembly, if needed, cleaning and disinfection;

d) inspection, reassembly and functional testing of complex devices;

e) SBS (packaging);

f) sterilizer loading, operation, unloading and load release;

g) storage, transport, and distribution;

h) need for a traceability system for each medical device;

i) purchase agreements;

j) equipment maintenance and sterilizer quality assurance; calibration of the measuring chain /sensors

k) management and reporting of incidents requiring attention or action;

l) the sterilization of a medical device(s) according to the validated manufacturer's instructions for use;

m) the sterilization of a medical device(s) that is (are) difficult to clean, disinfect, package, or sterilize.

F.4.1.4 Documentation

The health care organization should address requirements for sterilization process documentation and should ensure that this documentation includes:

a) regular quality audits of the documentation system;

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b) accessibility to the staff;

c) standardized policies and operating procedures and have pertinent information for all critical steps of the sterilization process;

d) operator manuals, diagrams and visual keys that should be available and readily accessible to staff;

e) all procedural and equipment audits and reports;

f) any changes to sterilizer equipment or processes, product or SBSs, which should be documented and communicated to the appropriate staff in a timely manner;

g) routine monitoring, load contents and load release results.

F.4.2 No additional guidance.

F.5 Sterilizing agent characterization

F.5.1 Sterilizing agent

F.5.1.1 No additional guidance.

F.5.1.2 The majority of health care facilities utilize moist heat processes with saturated steam in a commercially available steam sterilizer employing a well-recognized time and temperature combination during the holding time. (See Table A.2.)

F.5.1.3 See C.10 for additional guidance on the quality of steam supplied to the sterilizer.

F.5.2 Microbial effectiveness

The occurrence of superheated steam can impact the microbial effectiveness of the cycle. Whenever the measured temperature exceeds the theoretical temperature calculated from measured pressure as described in Annex E, superheated steam can be present. The presence of superheated steam can be detrimental to the medical device and or its packaging and can compromise the sterilization process. Superheated steam can occur and behaves more like a dry gas and has a low microbicidal effectiveness compared with saturated steam. Superheated steam can result from pressure reduction and/or adiabatic expansion of saturated steam. It can also occur from the rehydration of parts of the load, particularly those parts containing natural fibres. Superheated steam conditions can be minimized by engineering of the steam supply system, for example by:

a) having a series of pressure reduction stages from the supply pipe to the chamber and ensuring the pressure reduction ratio for each stage does not exceed 2:1;

b) ensuring steam velocity does not exceed 25 m/s;

c) ensuring materials made from natural fibres are pre-conditioned to a humidity greater than 40 % RH prior to sterilization.

NOTE See A.5.3 and A.7.5.

F.5.3 Effects on materials

Health care facilities should be aware of the information and material effects testing performed by manufacturer of the medical device and SBSs to be processed to ensure compatibility with the sterilization process.

F.5.4 Environmental consideration

No additional guidance.

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F.6 Process and equipment characterization

F.6.1 General

F.6.1.1 No additional guidance.

F.6.1.2 No additional guidance.

F.6.2 Process characterization

F.6.2.1.1 The process variables for moist heat sterilization are exposure for a specified time at a specified temperature in the presence of moist heat. It should be recognised that pressure is not a process variable in a moist heat sterilization process since it has no bearing on microbicidal lethality.

NOTE Process variables are those which contribute to microbial inactivation. Pressure is a cycle variable and is used by the control system to deliver the required operating cycle.

F.6.2.1.2 There are two common approaches to the development of sterilization processes typically used in health care facilities. One approach is described in B.4.4.2. When the inactivation of the biological indicator is confirmed, the exposure time can be defined conservatively as twice the exposure time in the half cycle. Alternatively, the approach described in Annex C is used. Evaluation of a sterilization process by this method will normally be from the data generated from a series of performance tests. Each test should be designed to identify whether one or more of the performance requirements specified for the sterilization process has been attained.

F.6.2.2 Process specification

a) The following is an example of an operating cycle specification (see Annex D, Figure D.2):

   1) Stage 1 - Conditioning:

      — Number of pulses: (e.g. 3)

      — Type of pulses: (e.g. trans-atmospheric)

      — Pressure value for all negative pulses: (e.g. 130 mbar)

      — Pressure value for all positive pulses: (e.g. 1 150 mbar)

   2) Stage 2 – holding time:

      — Sterilization temperature: (e.g. 134 °C)

      — the theoretical temperature calculated from the measured pressure according to steam tables can also be considered (see E.1). Theoretical temperature cannot be used to verify satisfactory steam conditions but can give an indication of rough deviations (e.g. large leakages, failure of pressure measurement/process control). In the temperature control for some sterilizers, theoretical temperature can be relevant.

      — Holding time: (e.g. 4 min)

   3) Stage 3 - Drying

      — Pressure value for vacuum point: (e.g. 90 mbar)

      — Drying time: (e.g. 15 min)

      — Drying pulses: (e.g. 1)

b) Tolerances can be included with the above items.

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c) See F.6.2.2 a) and b).

d) See F.6.2.2 a) and b).

e) See F.6.2.2 a) and b).

f) Health care sterilization loads commonly consist of different medical devices combined into sets with various sterilization barrier systems used to enclose them. For each type of load configuration the reusable medical device manufacturers instructions for use should be reviewed and supporting evidence established to ensure the items can be sterilized in the proposed sterilization cycle. It is important to establish product families that can be sterilized for each type of load configuration. The location where the electronic recording devices and PCDs are placed is specified for referenced load configurations. Information relating to the location can be available in the sterilizer's instructions for use.

NOTE Load configuration can include the types and number of items, loading pattern, orientation, location, and SBS in use.

g) No additional guidance.

h) Medical devices, SBSs and load configurations can impact the conditioning stage of the sterilization cycle, and it can be necessary to implement different conditioning phases according to the product family's characteristics.

i) To improve load drying during the drying phase, positive pressure pulses or air might be added during the phase to improve condensate evaporation. Any air introduced during this stage of the process is passed through a microbial retentive filter to ensure no recontamination of the sterile load can occur.

j) No additional guidance.

k) Monitoring can include physical parameters, biological and or chemical indicators. PCDs can contain either a biological or chemical indicator, or both.

l) Water and steam quality requirements are established to understand presence of contaminants that can have an adverse effect on the product or packaging. Excessive water in the steam supply is one of the causes of wet packs. The dryness fraction of the steam should be determined, monitored and where possible controlled (see Annex C).

The rate of pressure change can affect the medical device and SBS integrity and sterilization efficacy of some medical devices (e.g. with a lumen). This can warrant a controlled rate of pressure change to prevent damage to the SBSs and/or medical device and /or to allow steam penetration into the medical device.

F.6.2.3 No additional guidance.

F.6.3 Saturated steam sterilization processes

Steam can be generated in, or admitted to, a chamber from an external or internal source. Air in the chamber will be gradually removed by gravity displacement, active flow or by forced evacuation. It is assumed that if residual air is reduced to an acceptably low level such that standardised test procedures reach their acceptance criteria, then moist heat conditions will be present on the surfaces requiring sterilization.

Variations in process parameters and/or the amount of non-condensable gas remaining in the chamber at the end of the air removal stage can result in an ineffective process. Sources of non-condensable gases should be known.

The sterilizer technical specification documentation is often provided to the health care facility by the sterilizer manufacturer (see Table A.1).

The health care facility saturated steam sterilization process specification should include:

a) a description of cycles used, which should include the measured process variables and cycle variables and acceptable ranges, the upper and lower limits for each process parameter and cycle parameter, and

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the method used for air removal, test methods, monitoring procedures, test frequency and acceptance criteria for sterilization process evaluation;

b) no additional guidance;

c) identification of a steam penetration test to detect unacceptable levels of NCGs, air leakages into the chamber or other causes of inadequate air removal;

d) documentation on the type of monitoring and how often it is used;

NOTE A PCD can contain a biological indicator and/or chemical indicator. When used for qualification, the PCD can contain a temperature sensor.

e) the type of air removal test built into the sterilizer;

f) the load contents;

NOTE Reference loads can be specified from a consideration of items to be processed, product family designations, SBSs employed, and load configuration used, and should represent typical and the most challenging load to the process.

g) the instructions for use accompanying either the sterilizer or the medical device, or both, can provide information on drying times.

F.6.4 Contained product sterilization processes

Contained product sterilization processes are not commonly carried out in health care facilities. If used, they will often be associated with a pharmaceutical manufacturing department. The sterilizers employed will either be specifically designed for contained product sterilization or will have sterilization processes specifically designed for contained product sterilization (see A.6.1.3 and H.6.4). It is unlikely the saturated steam sterilization processes used for processing reusable medical devices would be suitable for processing contained product (see Annex D). Similarly, the SBSs used for medical devices (e.g. woven or non-woven wraps or rigid container systems) are unlikely to be used for contained products which will employ rigid (e.g. glass bottles or sealed ampoules), semi rigid (e.g. polypropylene bottles) or flexible (e.g. PVC IV pouches) containers. Annexes A, B, H and D describe in detail the processes typically used for contained product and the approaches taken for development, validation and routine monitoring.

F.6.5 Equipment

F.6.5.1 Sterilizers for use in health care facilities should be equipped with a sterilization process(es) designed to sterilize a range of medical devices routinely used in a health care facility. National and regional standards (e.g. EN 285, EN 13060, ANSI/AAMI ST8, ANSI/AAMI ST55, JIS T 7322, JIS T 7324) specify sterilizers which have such a capability. See also A.6.2.

a) The sterilizer make, model and serial number should be documented. The documentation accompanying the sterilizer usually provides this information along with an equipment specification. The installation and operator's manual should be obtained and retained.

b) Drawings and a description of the materials of construction for the steam delivery system(s) and any ancillary items should be obtained and retained.

c) Technical information, product codes and description of any accessories, replacement parts, frequencies of replacement, including filters (if used), should be obtained and retained.

d) A description of the measuring chains including sensors and recommended calibration and maintenance frequencies should be obtained and retained.

e) A description of equipment process capability including pressure ranges for each cycle stage should be obtained and retained.

f) A description of failure messages and audible alerts including recommended actions to take when they occur should be obtained and retained.

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g) Information on recommended safety features and safe work practices should be obtained and retained.

h) Certificates of conformity to local, national and regional regulations should be obtained and retained.

i) Information on the recommended routine monitoring procedures, including air leakage tests, should be obtained and retained.

j) Information on the type of air detector, if fitted and its accuracy, and recommended calibration and maintenance procedures and frequency, should be obtained and retained.

F.6.5.2 See F.7.12.

F.6.5.3 The IQ process should include an audit of the location of the sterilizer, the supplied services and their characteristics (e.g. the supply pressure and flow rates of the steam, water and compressed air supply). The characteristics of the electrical supply (e.g. voltage and amps) should be compared with the specification requirements. In a health care facility these activities can be undertaken by the sterilizer supplier or construction company, but the outcome should be documented. See Table A.1 for further information on roles and responsibilities.

F.6.5.4 The load support system refers to racks permanently fixed into the chamber or shelved trolleys which can be moved in and out of the sterilizer on guide rails.

F.6.5.5 The technical information provided with the sterilizer should be consulted.

F.6.5.6 Software validation/verification documentation for the specified equipment.

NOTE There can be national and regional regulations relating to software validation and security.

F.7 Product definition

F.7.1 It is not common for a health care facility to be involved in the design and development of a new or modified medical device or reprocessing a single use medical device, however it is more likely that the health care facility will be faced with the choice of purchasing commercialized products. In certain circumstances the health care facility can be involved in the design and development of a new or modified medical device, however the regulatory consequences of such activities should be carefully considered. If such circumstances arise the product family should be identified or established for the prototype instrument, and the requirements of this document followed.

Health care facilities are routinely involved in developing new instrument/device sets. This is usually done in conjunction with a surgeon or surgical department. Development of new sets involves determination of which and how many and where an instrument/device will be placed in the set, what type and size of containment device (tray will be used and the SBS that will be used.

F.7.2 The requirement in 7.2 can necessitate that appropriate information be provided by the manufacturer of the medical device and the manufacturer of the sterilization equipment to the organisation undertaking the sterilization process. This corresponds to the instructions for use provided for the sterilizer and medical device. It is important that the organisation responsible for reprocessing the medical device ensures that the product family into which the medical device has been allocated can be processed by the sterilization cycles implemented in the sterilizer. See Annex G on assigning products to product families and load configurations.

F.7.3 A health care facility will often combine several commercialized products into one pack. The product family for this combination should be identified. In most cases the product family identified should align with the product family for the medical device in the pack considered to be the most challenging to the sterilization process. See Annex G.

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F.7.4 Sterile barrier systems are designed to ensure that the medical device remains sterile until opened for use. Sterile barrier systems should allow penetration of the sterilizing agent and withstand the stresses that occur during the sterilization process, remain secure and should not have a negative effect on the quality of the medical device (e.g. generating particles). ISO/TS 16775 provides guidance on the ISO 11607 series for SBSs.

F.7.5 The instructions for cleaning and decontamination of the medical device prior to sterilization should be assessed and followed. Health care facility operating instructions should describe how the medical device can be cleaned and decontaminated following the instructions and the competency of staff following the instructions should be established.

F.7.6 This is not normally applicable to health care facilities as it applies to contained product.

F.7.7 PCDs in healthcare settings are typically facility assembled or commercial tests designed to create a challenge to a specific aspect(s) of the specific sterilization process (e.g. air removal and steam penetration). PCDs (e.g. an air detector or other independent monitoring device, biological indicator or chemical indicator), are intended to represent specific characteristics of the product family. The validity of the PCD when exposed to the sterilization process should be established and documented in the information supplied for the PCD.

F.7.8 Medical device and SBSs manufacturers establish compatibility with the recommended sterilization process. The medical device and/or SBS instructions for use should be consulted for any applicable limits on usability (e.g. maximum number of processing cycles for robotic instruments or rigid container systems prior to recommended maintenance).

F.7.9 The product should not be visibly wet and should also be maintained in the recommended environmental conditions as specified for the product. Sterile barrier systems should be maintained within recommended environmental conditions prior to use.

F.7.10 Medical devices (including rigid container systems) that are processed can suffer accumulative changes such as surface cracking caused by differential expansion through a thick material, brittleness or delamination. Crevices and lumens can retain organic, chemical and biological contaminants that can cause material reactions or be unpredictably released during use. Many materials that are subject to repeated moist heat sterilization have a long history of safe use, are known to be suitable and have longevity (e.g. stainless steel). Other materials, however, can have limited lifespans. Reference should be made to the device instructions.

F.7.11 In health care applications, any residual moisture remaining on the device or packaging after processing and cooling is unacceptable and considered a contaminated item. Corrosion of some materials can occur if steam generated from water of low pH or if the water contains contaminates.

F.7.12 Health care facilities should consider the development of operating policies and procedures based on local and national regulatory requirements, standards, equipment and product instructions for use and other relevant guidelines. Personnel should be trained and assessed on these procedures. The instructions for use accompanying a medical device can be in conformity with ISO 17664-1. Regional or national guidelines for cleaning, disinfection and sterilization of such medical devices can apply. The following can be considered:

a) The medical device and reusable SBSs instructions for use can be consulted for recommended methods for cleaning and disinfection. The recommendations should be incorporated into policy and procedures. Use of medical devices that are either difficult to clean or disassemble, or both, should be carefully considered prior to purchase because only a cleaned device can be successfully sterilized.

b) The medical device or SBS instructions for use can be consulted for any requirements for special pre-conditioning before exposure to the sterilization cycle. The recommendations should be incorporated into policy and procedures. See F.6.1.1 d).

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c) Load configurations can be established according to product family assignments (see Annex G) and validation results, particularly PQ test results (see F.9.4.3). The load configurations should be described in the policy and procedures.

d) The integrity of the SBS, both before and after processing, should be confirmed by visual inspection prior to releasing the item to use and again directly before opening the item for use.

e) Not normally applicable to health care facilities.

F.7.13 Processed, inventoried items should be maintained in controlled storage environments defined in the policy and procedures.

F.8 Process definition

F.8.1 No additional guidance.

F.8.2 A sterilization process used for processing in health care facilities is based on the recommendations for a sterilization temperature and holding time specified in national and regional guidance or developed from process parameters specified for the sterilizer and/or the medical device.

The holding time and temperature combinations used in different countries and regions varies therefore it is recommended but not prescribed that minimum time temperature combinations should be used. See Table A.2 for examples.

F.8.2.1 Standards have been developed for sterilizers suitable for processing a wide range of medical devices. A sterilization process that conforms to the performance requirements detailed in a relevant standard should be recommended for the medical device (see ISO 17664-1).

A dissimilar but existing sterilization process that has previously been defined by specified cycle parameters and validated to treat the product family to which the new medical device is assigned can be used providing that the size, design and construction material of the new medical device fits into the product family range.

F.8.2.2 A health care facility will often combine several instruments into one pack. Under these circumstances the facility should take into account the instructions for processing issued for each of the individual medical devices that make up the pack and the product families to which each medical device is assigned. The health care facility should consider the recommendations of individual suppliers of commercialized products for processing in relation to their existing sterilization process(es). It is typically possible to use an existing sterilization process; however it can be necessary to develop a new sterilization process based on the instructions accompanying the medical device. Any deviation for the proposed sterilization process should be agreed with the medical device manufacturer or validated by a responsible person.

If the intended sterilization process is neither recommended in the medical device instructions for use nor previously defined to treat the product family to which the new device fits, a detailed assessment of the new product in relation to a similar product already defined to the intended sterilization process should take place.

F.8.3 Physical parameters and exposure restrictions identified for the medical device and the sterile barrier should be observed for each medical device.

F.8.4 The SAL is generally an assumed value. The SAL of the process is either validated by the sterilizer manufacturer or the medical device manufacturer, or both. The resulting cycle to achieve that SAL is provided as a sterilization cycle.

F.8.5 Failure to follow the processing instructions can affect the performance of, and invalidate any warranties related to, the medical device. Adverse changes taking place in the medical device and/or SBS resulting from an inappropriate sterilization process can present a risk to patients and users.

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F.8.6 For many medical devices, air removal is a critical factor when predicting the presence of moist heat in locations that are difficult to sterilize. Relevant tests and acceptance criteria for factors that can affect steam penetration are identified in this document.

F.8.7 Biological indicators (see ISO 11138-1 and ISO 11138-3) can be used in health care facilities for process definition and equipment qualification (see F.9) to confirm the lethality of the cycle to the stated resistance of the biological indicator. The sterilizer and biological indicator instructions for use can be consulted for information on placement in the chamber and load, number of biological indicators to be used, incubation and interpretation of the biological indicator result. National and local compliance and regulatory guidelines related to process definition and qualification requirements should be taken into account.

F.8.7.1 Guidance on the use and application of biological indicators is found in ISO 11138-7.

F.8.7.2 The use of inoculated product or the placement of inoculated carriers within medical devices is not generally applicable to biological indicator use in health care setting.

Whenever biological indicators are used to confirm lethality in prescribed locations, the physical parameters measured during the sterilization cycle should always be used to verify that the defined sterilization process has been achieved.

F.8.8 Contained product is not commonly processed in health care facilities with the exception of pharmacy applications. See H.6.4.

F.8.9 A chemical indicator (see ISO 11140-1) can be used as an element in sterilization process definition to demonstrate the attainment of process parameters in the location in which it is placed.

Chemical indicators show exposure by means of either physical or chemical changes, or both, and are designed to react to one or more parameters of the sterilization process such as time of exposure, temperature, and presence of moisture. The instructions for use accompanying the chemical indicator should be consulted to verify the exposure conditions that can cause the chemical indicator to reach its endpoint. Attainment of the chemical indicator's endpoint should not be regarded as an indication of attainment of an acceptable SAL but rather one of many factors which should be taken into consideration when judging the acceptability of a sterilization process. Failure of a chemical indicator to reach its endpoint should be regarded as evidence of a sterilization process failure and be investigated. Guidance on the use of chemical indicators is found in ISO 15882.

F.8.10 PCDs can be either facility assembled or commercially provided and contain a biological indicator and/or a chemical indicator and are designed to mimic specific resistance attributes of the product or product family (e.g. a defined challenge representing the reference load to be processed).

F.8.11 The instructions for use for the sterilizer can be consulted for information on the sterilization cycles available. The instructions for use supplied with the sterilizer, medical device or SBS can be consulted to identify the sterilization process required for the medical device or product family. If a specific sterilization cycle is required, B.4 provides guidance on applying the half cycle method to develop or validate such a sterilization cycle.

F.8.12 Processed items should be dry and cool prior to handling. The medical device and SBS instructions for use can be consulted for recommended drying times. The effectiveness of the drying stage for the range of product families expected to be processed can be assessed and established as part of process definition. Different drying times can be necessary for different product families. In saturated steam sterilization processes, some loads (e.g. those containing heavy metal devices) can require an extended drying stage of the operating cycle to ensure that residual moisture is reduced to a level which will not affect the performance of the SBS upon removal from the sterilizer.

Policy should be established for sterile items to be maintained in controlled, sterile storage area(s) until use.

F.8.13 No additional guidance.

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F.9 Validation

F.9.1 General

F.9.1.1 Validation consists of IQ, in which the sterilizer and its installed services are checked against its specification, operational qualification (functional qualification), in which the sterilizer and sterilization process is tested for basic performance, often using predefined test loads (see Annex C for some examples) and performance qualification in which the sterilizer and sterilization process is tested for the ability to successfully process the medical devices and product families presented to it for sterilization. An established plan for the validation policy and procedures should include the scope of the validation and areas of responsibility for the key personnel involved. The purpose is to establish that the process developed in process definition (see Clause 8 and F.8) can be delivered effectively and reproducibly to the load. It provides evidence that the load is not compromised in terms of its safety, quality and performance.

Moist heat sterilization is a thermal process and the validation testing is primarily performed with physical methods. However, during routine monitoring and requalification it can be appropriate to also use biological indicators and integrating chemical indicators.

F.9.1.2 A complete master validation plan can be written and approved prior to installation of the sterilizer. Either the sterilizer manufacturer or authorized person, or both, can be consulted for the development of this plan. The plan can include IQ, OQ and PQ procedures and specifies the required documentation. The plan can include a formal review and approval of the validation results prior to release of the sterilizer for production. The plan can be reviewed annually and when changes are made that can trigger the need for requalification (see F.12.4).

F.9.1.3 No additional guidance.

F.9.1.4 A new product family can require either OQ or PQ, or both, as determined by the product adoption assessment.

F.9.1.5 Test instruments used to calibrate or verify each measurement chain should have documented evidence of calibration (e.g. a valid calibration certificate) to a known standard and be verified using a calibration reference to a working standard. One example is use of an oil bath or dry heat calibrator of known stable temperature traceable to a temperature reference standard.

F.9.1.6 No additional guidance.

F.9.1.7 No additional guidance.

F.9.1.8 Tests on each equipment fault recognition and alert system can verify that the equipment is working properly according to the original specification. Fault testing can be incorporated into any stage of validation procedures.

F.9.1.9 A new product family can require either OQ or PQ, or both, as determined by the product adoption assessment.

F.9.2 Installation qualification (IQ)

F.9.2.1 Installation qualification is necessary whenever a new sterilizing facility is to be commissioned or when an existing sterilizer is replaced or relocated. Installation qualification demonstrates that the sterilizer conforms with the agreed specification including conformity of the equipment, services and site requirements. The equipment specification provided with the sterilizer can contain the required information.

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F.9.2.2 All site conditions should correspond and be verified to the specifications including electricity, compressed air, steam quality, room air exchanges, temperature and relative humidity ranges as defined in the procedure**.** Site planning and installation requirements are commonly defined and established for the sterilizer and documentation provided to the health care facility (see also F.6.5.3).

IQ checks and documentation includes:

a) equipment manufacturer, model, serial number and installation location;

b) calibration certificates for controlling, and registering sensors including software version and software validation certificates if indicating sensors are used to verify processes effectiveness, their calibration certificates should also be documented;

NOTE The term sensors can include parts of the measuring chain.

c) operator manual including failure code identifications; local language versions can be available.

d) leak test results;

e) verification of electrical service requirements include frequency, phase, current and power cord (if applicable);

f) verification that any filters are within use life;

g) number of room air exchanges, room temperature and relative humidity and acceptable ranges;

h) factory acceptance test documentation;

i) documentation that all local code requirements are met;

j) documentation of any non-conformance.

NOTE See also F.6.5.3.

F.9.3 Operational qualification (OQ)

F.9.3.1 Operational qualification plan

F.9.3.1.1 The OQ plan includes procedures and documentation to demonstrate that the sterilizer operates according to equipment predetermined limits to deliver the specified process / operating cycle(s) within the define tolerances. This includes proof that the quality of each utility service conforms with the specification, there is no evidence of interference from or to other equipment, the sound or noise generated does not exceed regional or national safety requirements, the safety features and warning schemes function as designed and there is no leakage in the system (see A.9.3).

If an existing sterilization process is to be used to treat either a new medical device or loading configuration, or both, conformity to the performance requirements established during the original or subsequent OQ should be verified before PQ is conducted. This may be done by analysing data obtained during routine processing and/or periodic tests or by a repeat of OQ.

Whenever new equipment is installed, existing equipment is modified to deliver a new sterilization process, or a service is changed, the sterilizer manufacturer, or the party having responsibility for the sterilization process, establishes the operational performance requirements and tests that are to be used to verify the efficiency of the sterilization process are valid. Modifications to the sterilization process that can affect this efficiency include, for example, changes to process parameters.

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F.9.3.1.2 Operational qualification tests

Operational performance requirements and tests can be needed to establish that the following conditions are met (these can be predicted from the characteristics of the operating cycle but should also be established):

a) That effective air dilution is obtained during the sterilization cycle. This can be predicted from the operating cycle; reproducibility will be affected by air leakage into the chamber, NCG in the steam, the rate of change of temperature in the chamber and load and the mass of the load (see Reference [56]).

b) That contaminants are not deposited on the medical device. This can be predicted from the contaminants suspended in the steam (and the characteristics of the SBS in use).

c) That steam penetration occurs into those parts of the medical device from which air is difficult to remove. This can be predicted by comparing the temperature measured in a reference device to the temperature measured at the reference measurement point; the reference device should offer a similar challenge to the medical device(s) it represents, and the method should be verified by chemical indicators or biological indicators positioned in the reference device and/or medical device.

d) That the process dries the load of wrapped goods. This can be determined by both visual inspection and mass increase. Failure to adequately dry a load after the sterilization phase can lead to recontamination once removed from the sterilizer. Any evidence of wetness or staining should be considered a non-conformance and an investigation initiated. The load should be reprocessed.

F.9.3.1.3 Documentation checks and assessment of test results

After installation and prior to OQ the sterilizer-related documentation such as specifications, service and routine / scheduled equipment maintenance documentation, calibrations, certificates and others should be checked for being complete, valid, up to date if not performed immediately after IQ procedure.

Documented OQ test results and supporting documentation include:

a) results of tests in a chamber loaded with the type of specified loads including temperature profiles;

NOTE 1 Empty chamber studies can also be considered.

b) results of heating exposure and cooling profiles in an empty chamber;

c) identification of any cold spots in the chamber from thermometric test results;

d) results of alarm tests including verification that they are functional and working according to the sterilizer specification;

e) result of air leakage tests;

f) results of any steam quality tests;

g) results of steam penetration tests;

h) results from PCDs which can contain physical sensors, biological indicators or chemical indicators, when used;

i) results from air detectors, if used;

j) results of load dryness tests, if used.

NOTE 2 The documentation of b) and c) can be omitted if the sterilizer has been type tested according to an appropriate standard(s), e.g. EN 285.

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F.9.3.2 The number of sensors used should ensure that sufficient data are recorded to demonstrate the effectiveness of the process during OQ. Experience has shown that for a typical health care facility load and chamber volume (~ 400 l), 5 to 12 temperature sensors may be sufficient. See Table F.1

Table F.1 — Suggested minimum number of temperature sensors required

Chamber volume (L)	OQ	PQ
≤60	5	5
≥61	Not less than 5	Not less than 5

For sterilization in health care facilities other rationale may be used to establish the number of sensors required.

F.9.4 Performance qualification (PQ)

F.9.4.1 The purpose of PQ is to demonstrate that the sterilization process is capable of achieving a predetermined SAL for the subject load on a repeatable basis for routine operation. The efficiency and reproducibility of the sterilization process and process parameters should be known for the whole range of product family(ies) and load configuration(s) that the sterilization process is intended to process. The load most difficult to sterilize should be identified from the range of medical devices, product families and loading configurations that the sterilizing process may process and is established during PQ. When successful, the validation may then be deemed to be valid for other combinations from the whole range of product family(ies) and load configuration(s) that represent a lesser challenge to process.

Advice on characterizing product for difficulty to sterilize should be available in either the medical device(s) or sterilizer manufacturer instructions for use, or both.

PQ is performed as part of new installation, modification of existing equipment to deliver a new sterilization process, when a service is changed, when new or modified products or product families are established to process and a change is proposed to SBS(s), load configurations or process parameters. PQ demonstrates that repeatability is obtained, by means of at least three replicate cycles and establishes that the defined product family(ies) can be processed, the performance requirements are met and that the tests that are to be used to verify the efficiency of the sterilization process remain valid.

The PQ plan and tests are part of the master validation protocol and is approved and signed by a responsible person knowledgeable in sterilization science and practices and appointed by the health care facility management.

Process control through PQ is established with reference loads that are representative of product families and loading configuration routinely sterilized. For each reference load, acceptable tolerances are specified and documented. For composition of product families, see Annex G. The physical parameters can also be affected by the types and amount of product in the sterilization cycle.

PQ should also include a risk analysis for the handling of the sterilized product. Consideration for risk includes the transport and handling of the sterilized product from point of processing to the patient. The risk analysis is initiated and approved by a responsible person.

The PQ is completed with traceable calibrated equipment. It is advisable to seek assistance of internal or external technical expertise with knowledge and experience with moist heat sterilization. The person responsible for the validation processes provides the end user with a basis for ensuring that the products are suitable for their purpose when used on a patient.

PQ procedures include establishing packaging materials, packaging techniques, labelling, traceability, transport, storage and handling. Performance qualification by itself does not ensure a consistent process. Routine monitoring is used to verify the process is used within the validation specification. Results of PQ can also provide additional valuable criteria for product release (see F.11).

F.9.4.2 See F.8.4.

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F.9.4.3 See F.9.3.2 for information on sensors.

When biological indicators are used, they can establish evidence of lethality and satisfactory steam quality to achieve lethality at specific positions in the chamber or load. When chemical indicators are used, they establish evidence that conditions for sterilization were met at specific positions within the load. The sterilizer, chemical indicator and biological indicator instructions for use can be consulted for information on how to correctly use the indicators.

When biological indicators or chemical indicators are used, either with or without a PCD, the results should be documented and retained.

F.9.4.4 Checks on the results of PQ and associated documentation includes:

a) a review of the results of IQ and OQ, which along with PQ results will be included in the final validation report;

b) a specification for all SBSs used and alignment to product family and load configurations;

c) documented identification of representative and product, product family(ies), loads and load configurations presenting the greatest challenge intended to be used during routine production;

NOTE 1 Load configuration can include the types and number of items, loading pattern, orientation, location, SBSs in use.

d) no additional guidance;

e) specifications of any special pre-conditioning requirements related to product or SBS [see F.9.4.4 b)];

NOTE 2 Some medical devices need pre-treatment such as equilibration to atmospheric or other specific temperature and humidity.

f) specification of any restrictions to load size or configuration based on IQ or OQ results.

NOTE 3 Each sterilization cycle available on the sterilizer is validated separately. For example, when an acute or immediate use process for single unpackaged instruments is available on the sterilizer, it is validated separately as the cycle typically does not include a pre- or post-vacuum phase.

NOTE 4 If moisture remains on a medical device, specific orientation and/or location can be necessary.

F.9.4.5 PQ tests include the following:

a) Tests to demonstrate that limiting values for each process variable is delivered and meets the established process definition, a constant level of pressure and temperature is obtained during the holding time or the process parameters fall within predetermined tolerances.

NOTE Holding time is the time at which all sensors show that they (i.e. those within the load chamber and reference measurement point) have reached the sterilization temperature.

b) A demonstration that the steam has a temperature within the temperature tolerances specified for the sterilization cycle and that the theoretical temperature calculated from measured pressure according to steam tables (see Annex E) is within specified values. The temperature and pressure in the chamber should be within the specified tolerance to maintain the condition of the product and SBS.

c) Assessment of the temperature profile throughout load; heat penetration into each type of load is determined either from the temperature measured within a number of medical device packages or in a reference load. At least one temperature sensor should be situated adjacent to the temperature sensors connected to the recording instrument, indicating instrument and controller. If a sensor or indicator cannot be located at a position on a medical device known to be difficult to sterilize, the medical device may be substituted by a different type of medical device or PCD dedicated for this purpose. The number and the locations of the sensors to be used will depend on the type of load and the size of the chamber. The sensors placed within the load should be located on or within those parts of the load configuration and its individual items from which air is difficult to remove. Caution should be exercised when

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interpreting thermometric data from within hollow or porous medical devices capable of entrapping air. Temperature measurement alone cannot differentiate between hot air and saturated steam. The presence of saturated steam can be confirmed from the evaluation of the results from biological indicators or chemical indicators, if used.

NOTE In most cases the holding time is the part of the operating cycle used to establish lethality.

d) The response of the chemical indicator. The chemical indicator instructions for use and colour change reference examples should be referred to for the interpretation of the end point indication.

e) The response of the indicator inside a PCD instruction for use for interpretation of the result. Local or national recommended practices can contain requirements that apply to use of PCDs. If a biological indicator is used in the PCD, a positive control should be incubated according to the instructions for use.

f) Assessment of the SBS/product used for compatibility to the process and integrity post processing.

F.9.4.6 No additional guidance.

F.9.4.7 No additional guidance.

F.9.4.8 No additional guidance.

F.9.4.9 No additional guidance

F.9.5 Review and approval of the validation

F.9.5.1 The data and final validation report should be reviewed, approved and signed by a responsible person, organizationally independent of those conducting the tests, preparing the report or responsible for production and knowledgeable in sterilization science and practices. It should also be reviewed and approved by the health care facility management. The completed validation report review verifies that:

— there is a specification for each test used during OQ and PQ, and that acceptance criteria for each test has been met;

— the tests are conducted routinely to verify that the efficiency of the sterilization process remains within specification, and that each test and its performance requirements have been derived from data gained during OQ, PQ and requalification if necessary;

— the product family(ies) represented is one of the most challenging loads for sterilization; if a restriction on presentation and/or location has been identified, this restriction is reflected in the description of the load configuration.

F.9.5.2 The report can include:

a) no additional guidance;

b) no additional guidance;

c) the product family(ies) represented by one of the most challenging loads for sterilization has been identified; the products and load configurations are defined;

d) the load configurations including any limits to load size or weight including total surface area;

e) any pre-conditioning requirements for the loads prior to processing in the sterilization cycle. After the sterilization cycle the products, including their SBS, are dry and intact at the completion of the process;

f) a description of all validated SBSs, e.g. wraps, pouches, rigid container systems. Each should have been tested with reference to the most challenging loads;

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g) if a restriction on presentation and/or location (e.g. orientation) has been identified, this restriction is reflected in the description of the load configuration;

h) results from all tests including steam penetration, leak test, steam quality and appropriately responding biological and/or chemical indicators (when used);

i) no additional guidance;

j) bioburden tests are not routinely carried out in health care facilities.

The reports can also include national guidance requirements and any additional product release criteria established during PQ.

F.10 Routine monitoring and control

F.10.1 Routine monitoring

F.10.1.1 Data for identifying limits for process parameters and acceptance criteria for periodic tests and routine monitoring and control are determined from data obtained from the tests carried out during PQ. This includes physical parameters, thermometric data and data from the results from any chemical indicators and/or biological indicators placed in the locations that are difficult for the sterilizing agent to gain access and any other tests used.

F.10.1.2 No additional guidance.

F.10.1.3 The results of all indicators used for routine monitoring and control of the sterilization process (physical monitors, chemical indicators and biological indicators) should demonstrate a successful operating cycle was accomplished.

F.10.2 Operational status

The physical monitors will indicate that the correct sterilization cycle was carried out and that the expected parameters for temperature and holding time were achieved. Any chemical indicators used, including external process indicators (type 1), should have reached their end point response indicating a pass result. Any biological indicators used, including those used inside PCDs, should show no growth and therefore indicate a pass result.

F.10.3 Process verification

Any fault indication, failure message and further relevant information provided by the routine monitoring system during the current cycle should be evaluated with respect to possible detrimental impact on the reliability of the process according to the recommendation in the sterilizers instructions for use.

A failure message may indicate the need to quarantine the load until investigated and resolved.

F.10.4 Evaluation of additional data for saturated steam sterilization processes

The cycle parameters should be examined to confirm that the intended sterilization cycle was selected and successfully carried out. Key information to assess includes the correct air removal process (gravity or dynamic air removal; the number of air removal pulses including pressure set points), the sterilization stage temperature and holding time, the vacuum level attained and time of the drying stage. The results of air leakage tests and the daily Bowie and Dick type test should be considered for pre-vacuum cycles.

The daily steam penetration test such as a Bowie and Dick type for dynamic air removal sterilizers will judge the effect that residual air and NCG has on the efficiency of the sterilization cycle and is typically used in an otherwise empty chamber.

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If the Bowie and Dick test is used, the user should verify if the Bowie and Dick test should be run in a specific validated cycle for its purpose.

NOTE 1 An extended conditioning phase will prevent the Bowie and Dick test from detecting residual air and NCG. The steam penetration test is designed to assess the ability of the sterilization cycle to effect air removal and rapid and even steam penetration into the load. Use of special test cycles such as one in which the air removal stage is different to that which will be employed in the production cycle can give erroneous results, i.e. the special test cycle provides an acceptable result, but the sterilization cycle is inadequate.

Routine monitoring activities include, when appropriate:

a) a review of the time at or above the sterilization temperature as noted on physical parameter data or printed charts;

b) a review of the cycle record to confirm that the correct cycle was run and that the process parameters were correct;

c) no additional guidance;

d) confirmation that all air removal or steam penetration tests (when used), including chemical indicators and/or biological indicators, including those contained in a PCD, indicate a pass result;

NOTE 2 Other types of steam penetration tests can be used. Refer to applicable instructions for use.

e) no additional guidance;

f) assessment that the load has sufficiently cooled, that all the packages are undamaged, dry, correctly labelled and that the process chemical indicators (if used) on each pack have reached their end point response.

A periodic review of records should be carried out to ensure the equipment calibration and equipment maintenance requirements have been completed according to policies and procedures and the sterilizer's instructions for use.

F.10.5 Not typically applicable to health care processes.

F.10.6 Local, national and facility guidelines for record retention policy, regulation and timeframe should be taken into consideration.

F.11 Product release from sterilization

Product release procedures and acceptance criteria for test results can be defined. Some examples can include:

a) the sterilizer's physical parameters indicate acceptable results;

b) results from a daily Bowie and Dick type air removal test are satisfactory;

c) biological indicators contained within a PCD do not show growth when incubated;

d) other steam penetration tests show a satisfactory result;

e) when inspected, SBSs are dry and intact.

Product release can only occur after the defined product release verification procedures have been successfully performed.

Product release documentation needs to include confirmation that the sterilization process acceptance criteria were met and that traceability of individual loads is possible (e.g. by attachment of batch numbers to individual packages). Procedures should describe the release criteria including the requirement that sterilizer printouts are verified and approved and that chemical indicator and biological indicator results are documented.

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A sterilization process that fails to meet any of the acceptance criteria (see examples above) for product release, should result in quarantine of the load and removal of the sterilizer from use until the cause of the failure is identified, corrective action taken, and any identified requalification has been appropriately completed (e.g. conducting an air leakage flow rate test). The investigation can result in a decision to recall already released load(s)/ products up to the date when the last successful process was carried out.

F.11.1 The policies and procedures of the health care facility and national and local regulatory requirements should be taken into consideration when preparing documentation relating to the sterilization process and the load contents. Traceability of the load contents to the point of use including to the patient if specified per the policy and procedures of the health care facility and regulatory requirements should be maintained. A recall procedure should be established., in the event that a sterilization process is subsequently deemed to be inadequate based on monitoring results or procedural review.

An audit trail for equipment, product and sterilization process should be in place. For example, the sterilizer should be fit for purpose and this should be noted on the release documentation if applicable. This declaration should be based on and include confirmation of:

— successful scheduled equipment maintenance;

— conformity to the performance requirements for the current periodic tests and routine tests;

— no change to the steam supply system and other services;

— conformity to the performance requirements for routine processing has been met for recent production cycles.

F.11.2 The markings or labelling on each pack or product/ medical device should enable:

— identification of the date of the sterilization process and if applicable an expiry date;

— identification of the pack contents;

— identification of the load number indicating the sterilizer used and the cycle;

— identification of the person who assembled the package (when applicable);

— confirmation of conformance with the facility policy and any product release requirements established in an electronic tracking or traceability system.

F.11.3 Identification of item as 'processed' is commonly some form of visible indicator attached to the outside of the package unless the indicator is integrated on the package, e.g. pouch.

F.12 Maintaining process effectiveness

F.12.1 If an existing sterilization process is to be used to treat either a new medical device or loading configuration, or both, conformity to the performance requirements established during the original or subsequent OQ should be verified before PQ is carried out. This may be done by reference to data obtained during routine processing and/or periodic tests or by a repeat of OQ.

Whenever new equipment is installed, existing equipment is modified to deliver a new sterilization cycle, or a service is changed, the sterilizer manufacturer, or the party having responsibility for the sterilization process, should assess the need for the repetition of operational and/or PQ studies. Modifications to the sterilization process that can affect efficacy include for example changes to process parameters.

F.12.2 Demonstration of continued effectiveness

F.12.2.1 No additional guidance.

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F.12.2.2 The health care facility's policies should describe recommended tests, sensor calibration schedules, equipment maintenance schedule and tasks, including required parts replacement and requalification tests (see F.12.5, Table F.2).

F.12.2.3 No additional guidance.

F.12.2.4 The steam penetration test is designed to assess the ability of the production process to effect air removal and rapid and even steam penetration into the PCD. The success of a steam sterilization process depends on the combination of the sterilizer, process, load, load configuration and SBS. If the sterilization process relies on the removal of air from the chamber and load in order to achieve rapid and even penetration of steam into the load, a PCD should be used in every production cycle of the sterilizer [see 10.4 d)] to establish the adequacy of air removal and steam penetration. The PCD should be proven to have a known relationship to the load with regard to air removal and steam penetration.

F.12.2.5 No additional guidance.

F.12.2.6 Not typically applicable to health care facilities.

F.12.3 Recalibration

Calibration and recalibration of the sterilizer sensors should be conducted according to the recommendations provided with the sterilizer and advice provided by professional service support as documented in the health care facility policy and procedures.

Procedures can require verification of calibration of each sensor and its associated measuring and indication or recording equipment (the measuring chain). Calibration should be carried out:

— at specified intervals, typically annually;

— after unscheduled equipment maintenance or repair of the sensor and/or associated equipment;

— if there is evidence of inaccuracy of the sensor or associated equipment.

F.12.4 Equipment maintenance

Equipment maintenance or changes to a service, such as a central steam generator, should be notified to the user because, for example, changes to the water treatment to a boiler can cause the level of non-condensable gas, moisture and/or chemical contaminants to exceed the specified maximum. Such changes should be assessed for their impact on creating a non-conformity with the process specification and if necessary, corrective action taken and documented.

F.12.4.1 Policy and procedure should be established for equipment maintenance. The recommendations provided with the sterilizer and professional service support should be consulted. All equipment maintenance should only be performed by trained and qualified service personnel.

F.12.4.2 No additional guidance.

F.12.4.3 No additional guidance.

F.12.5 Requalification

F.12.5.1 Requalification should be completed at frequencies provided with the sterilizer information and professional service support and is performed to confirm that process changes have not compromised the effectiveness of the sterilization process and the data acquired during validation remains valid. Typically, requalification is performed annually or according to local or national standards and health care facility policies and procedures.

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F.12.5.2 An example is provided in Table F.3 of a test schedule for validation and periodic test for large steam sterilizers. Operational requalification may repeat some or all of the OQ tests based on a change that can impact process and reproducibility.

Performance requalification is a repeat of a PQ study for at least one of the loads routinely processed and for which PQ records are available. If the values established are within the same limits as in the original validation study or in the preceding requalification study, reproducibility should be deemed to be acceptable.

Operational requalification is performed after any major repairs. See F.12.5 and Table F.2.

Performance requalification is performed due to changes that can include materials, packaging, etc. which potentially or is suspected to have affected the necessary sterilization parameters.

To facilitate the comparison of PQ and performance requalification data, test data, should be presented in the same format as used in the PQ report.

It can be sufficient to analyse only a reduced number of sterilization cycles of the process product family and/or load configurations if no changes have been made since the last PQ. Reproducibility may be able to be assessed by comparison of the repeat cycles with previous process records. However, in the event of deviations from previous validation, the full PQ should be repeated and documented.

Repeat PQ demonstrates and documents the following:

a) the products are loaded into the sterilizer as defined;

b) the sterilization conditions are achieved throughout the load;

c) the measurements from the sterilizer's physical parameter recording and the physical measurements taken using independent recording systems is aligned;

d) the packaging, the load carrier, and the products are intact and dry;

e) the planned maintenance and personnel training program have been implemented and documented throughout the year;

f) incoming steam is of satisfactory quality and water treatment meets specification;

g) the products and loads sterilized conform with previous documentation and results of established routine monitoring including biological indicator and chemical indicator results if used in previous qualification or routine monitoring.

F.12.5.3 The effect of equipment maintenance activities on the process should be evaluated. A successful repair should be confirmed by requalification.

F.12.5.4 No additional guidance.

F.12.6 Assessment of change

F.12.6.1 Any change to the sterilization process should raise doubt about the effectiveness of the sterilization process and initiate a review by a suitably qualified sterilization professional with knowledge of the equipment in operation, quality of the steam provided and practical knowledge of the departmental processes and procedures. Consultation with a quality control department representative and an infection prevention professional is also advisable.

If biological indicators are used during requalification, their performance should present a similar challenge to those used during operational and PQ. Use of biological indicators which have a significantly different microbial population or *D* value can result in a challenge which is greater or less than that used during validation. If a biological indicator is used during requalification which has significantly different characteristics, then this should be justified and documented. ISO 11138-3 identifies minimum requirements

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for population count and *D* value but does not specify maxima, however the information accompanying the biological indicator will specify these values.

NOTE With the approach shown in B.4, the sterilization time varies depending on the *D* value and the number of the biological indicator used. Therefore, it is necessary to pay attention to the selection of biological indicators when conducting microbiological requalification.

Requalification frequency period may be reduced depending on inconsistency factors that affect sterilization performance. These factors can be analysed based on the assessment of changes (see 12.5). Table F.2 provides some examples with common recommended actions.

F.12.6.2 No guidance offered.

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Table F.2 — Assessment of change examples

Assessment of change examples and suggested actions			Requalification	
			OQ	PQ
a)	Replacement of a part which could cause a process parameter to change;			
	1)	Temperature sensor replacement – calibrated after substitution (required)	N/A	N/A
	2)	Replacement or repairs of solenoid valves and actuators	X	X
	3)	Major replacement of solenoid valves or actuators	X	X[a]
b)	Replacement of a part which could cause an increase in leakage into the chamber;			
	1)	Door gasket	X	N/A
	2)	Replacement or repair of solenoid valves or actuators	X	X
c)	Variation of homogeneity in the chamber;			
	1)	Increase in the difference between maximum and minimum temperatures during exposure (maximum Tolerance equipment specification or OQ/PQ records)	X	X[a]
	2)	Registered pressure maximum and minimum during exposure above or below previous qualified records (maximum Tolerance equipment specification or OQ/PQ records)	X	X[a]
	3)	Non-condensable gases (NCGs)Mixture tolerance changes in the process	X	X[a]
d)	New or modified software and/or hardware;			
	1)	Software update	X	X[a]
	2)	Controller (partial or total) replacement	X	X
e)	Any change to a process parameter;			
	1)	Exposure temperature and/or duration time increase	X	X
	2)	Drying phase duration increase or decrease		X
	3)	Conditioning phase pulse quantities and/or levels		X
f)	Any change to services and the outcome of equipment maintenance on a service;			
	1)	Calibration error above previous calibrated certificate	X	X[a]
	2)	Steam generator replacement (if fitted)	X	X[a]
	3)	Sequential wet loads occurrence	X	X[a]
g)	Any change of the SBS or procedures used;			
	1)	Same sterile barrier but from different supplier		X
	2)	Replacement of sterile barrier types		X
	3)	Addition of new sterile barrier		X
h)	Any change of load configuration;			
	1)	Increase maximum load limit		X
	2)	New cart supports or shelves		X
	3)	New content location		X
i)	Any change of product manufacturing processes, product materials or source of materials or design of product.			
	1)	Addition of a new medical device to be sterilized		X
	2)	Material changes in the medical device, product supports and boxes		X

[a] If the requalification is within previous qualification results and tolerance this step in not required.

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Table F.3 — Routine monitoring and control of sterilizing equipment in a health care facility

Application	Saturated steam sterilization process	Reference
Steam penetration test for every operating cycle	Can be performed on every load	10.4 d), e)
Periodic steam penetration test (e.g. Bowie and Dick test)	Can be performed every day	10.2 d)
Temperature	Measured for every load	10.4 b), c)
Pressure	Measured for every load	10.4 b), c)
Time	Measured for every load	10.4 a)
Air leakage flow rate test	Measured at specified intervals	10.2 a)
Product package integrity	Each load, item can be inspected	10.4 f)
Process exposure indicator, system for control and identification of processed and unprocessed loads/items	Used on each load item	11.3

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Annex G
(informative)

Guidance on the designation of a medical device to a product family and processing category for sterilization by moist heat

G.1 Classification

G.1.1 General

G.1.1.1 This Annex describes fundamental principles of classification of medical devices intended for sterilization by moist heat into product families. These principles are applicable for industrial sterilization (e.g. performed by a manufacturer of a medical device delivered sterile) or for sterilization as part of a processing process (e.g. performed in a health care facility) as well as for demonstration of the suitability of a medical device for sterilization intended for processing (as specified by the scope of ISO 17664-1:2021). The guidance given in this Annex relates only to sterilization by moist heat.

G.1.1.2 Each medical device intended for moist heat sterilization should be classified using selected attributes.

The applicable classification criteria relate to the medical device itself and to the applied SBS and/or packaging system including applied label(s).

G.1.2 Attributes

G.1.2.1 General

It is known that at least the attributes shown in G.1.2.1 to G.1.2.6 will significantly influence the outcome of sterilization by moist heat.

The process variables for a moist heat sterilization process are exposure time at a specified temperature in the presence of moisture. The degree of air removal and steam penetration will influence the presence of moisture on surfaces which need to be sterilized. Thermal resistance to heating will influence the attainment of the temperature required to achieve sterilizing conditions assuming moisture is present. Air removal, steam penetration and thermal resistance are factors which should be considered.

The steam penetration resistance will be different for each design when air is to be removed and replaced by moist heat. The thermal resistance to heating will also be different for each design when a sterilizing temperature is required on surfaces to be sterilized. The following aspects are relevant for effective sterilization by moist heat:

— a SBS and labelling which does not impede the flow of air out of and steam into the packaged product so enabling air removal and moist heat access without significant delay;

— medical device design which enables rapid removal of air and replacement by moist heat onto surfaces and into cavities which need to be sterilized;

— sufficient temperature on inner surfaces in order to avoid excessive condensation;

— moist heat access to all outer and inner surfaces (e.g. not hindered by some types of lubrication);

— the thermal mass and thermal conductivity of the material(s) of which the device is manufactured;

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— the presence of narrow channels or cavities surrounded by material of low thermal conductivity which can allow condensate build up thereby retarding thermal penetration.

Dependent upon the applied operating cycle (see Annex D) some of the listed attributes (e.g. mass) can be more relevant than others. This can be the case when considering the differences between passive and active or dynamic air removal saturated steam sterilization processes. Specific medical devices can require consideration of additional or alternative attributes. The attributes described in G.1.2.1 to G.1.2.6 are not listed in any particular order of effect on the ability of a medical device to be sterilized by moist heat and each is judged for its challenge to sterilization when creating product families.

G.1.2.2 Design of the medical device

The design will influence the access and the removal of moist heat, e.g. the steam penetration resistance will be different for each design when air is to be removed and replaced by moist heat. The following in combination with aspects of weight/density (see G.1.2.4), material (see G.1.2.5) and surface treatment (see G.1.2.6) should be considered when assessing the medical device design:

— some geometric aspects will prevent or hinder access and removal of moist heat;

— some geometric aspects will prevent or hinder replacement of air by steam;

— some geometric aspects will increase the risk of condensation and therefore retardation of air removal and / or thermal penetration.

Along with other aspects, the attributes in Table G.1 can be considered.

Table G.1 — Attributes of medical device design — Examples

Design attribute	More critical	Less critical
Cavities and channels within instruments including open ended cylindrical cavities, closed (blind) ended cylindrical cavities. Complex cavities	The published literature is contradictory. PQ should always be considered for any instrument having a cavity or channel whether open or closed ended. All factors associated with cavities and channels are evaluated including material type, wall thickness, length. See G.4 for further information.	
Cock / tap / spigot	— wider overlapping — higher pressure resistance	— smaller overlapping — lower pressure resistance — specific position for sterilization
joints	— wider overlapping — washer between	— smaller overlapping — no washer
ball bearings	— greater volume inside/ smaller access area — ball tightens the volume inside during sterilization	— smaller volume inside/ greater access area — ball does not tighten the volume inside during sterilization
gaskets	— wider overlapping — better tightening — no movement possible during sterilization	— smaller overlapping — looser tightening — movement possible during sterilization

NOTE Instructions for specific procedures (e.g. open position, specific orientation) can assist sterilization and can be considered for assessment of the geometric design (see References [72] and [73]).

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G.1.2.3 Design of packaging

The packaging design influences the access and the removal of moist heat. For example, the steam penetration resistance will be different for each design when air is to be removed and replaced by steam. The following, in combination with aspects of weight/density (see G.1.2.4) and material (see G.1.2.5) as well as some aspects of surface treatment (see G.1.2.6), should be considered when assessing the packaging design:

— some aspects will prevent or hinder access and removal of moist heat;

— some aspects will prevent or hinder replacement of air by steam.

NOTE Instructions for specific procedures (e.g. open position, specific orientation) can assist sterilization.

Rigid sterilization containers will add additional complexity when assigning product families depending on their design, for example whether they use single use or reusable filters or valve-based systems to enable air removal and steam entry. The size of air removal and steam entry ports should be considered (see Table G.2), but cannot be the sole arbiter when assigning to a product family. Users cannot migrate to a rigid container SBS from flexible SBSs without a reassessment of product family assignments.

Along with other aspects, the attributes in Table G.2 can be considered.

Table G.2 — Attributes of packaging design — Examples

Attribute	More critical	Less critical
Porosity	— lower	— higher
Share of porous packaging part	— greater volume/ smaller access area (porous packaging part)[a] — greater label on the porous part of the packaging	— smaller volume/ greater access area (porous packaging part)[a] — smaller label on the porous part of the packaging
Type of porous packaging part	— high weighted (g/m^2) paper or non-woven fabric — thicker nonwoven fabric — sterilization container with less/ small openings	— low weighted (g/m^2) paper — thinner packaging nonwoven fabric — sterilization container with more/large openings
Additional inner protective packaging	— with inner protective packaging — lower porosity	— without inner protective packaging — higher porosity
Outer protective packaging	— with outer protective packaging — lower porosity	— without outer protective packaging — higher porosity
[a] In some regions this is termed the vent-to-volume ratio.		

G.1.2.4 Weight/density

The weight of a medical device, or part of a medical device (if sterilized separately), or for a collection of medical devices grouped into a single SBS and/or packaging system, can have significant influence on the amount of condensate and its effect on steam penetration and thermal penetration (and by consequence the extent of the required time for heat-up, exposure and/or cooling/drying).

NOTE 1 Comparison of the parameter weight is only permitted if the medical devices are made out of the same material or made out of materials having comparable heat capacity and heat transfer coefficient.

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NOTE 2 The higher the mass of the device(s) to be sterilized, the higher the amount of condensate and hence the amount of NCGs in the close vicinity of the device(s). The NCGs can form an insulating layer inhibiting further direct condensation on the outer or inner surface(s) of the device(s) and hence a lower than necessary amount of energy released through condensation for effective heating and inactivation of microorganisms. Considerations regarding this effect are advisable.

Along with other aspects, the attributes in Table G.3 can be considered.

Table G.3 — Influence of weight — Examples

Attribute	More critical	Less critical
Weight of a medical device	greater	lower
The thermal mass surrounding a cavity in a medical device	greater	lower
The thermal conductivity surrounding a cavity in a medical device	lower	greater
Weight of the complete sterilization container	greater	lower
Weight of the load	greater	lower

G.1.2.5 Material

Materials with low thermal conductivity exhibit higher temperature differences throughout the material when compared to materials with high thermal conductivity. Both types of material present challenges to the sterilization process. The moisture content of the material can also influence the heat transfer into the medical device. This should be taken into account during PQ with the material in its most challenging state.

When compared to materials with low thermal conductivity, materials with high thermal conductivity and equal heat capacity do the following:

— initially generate more condensate in a given time period;

— absorb and release energy faster;

— attain a state of equilibrium faster.

Along with other aspects, the attributes in Table G.4 can be considered.

Table G.4 — Influence of material — Examples

Attribute	More critical	Less critical
Thermal conductivity	— lower (e.g. plastic material)	— greater (e.g. metals)
Isolation properties	— greater (e.g. metals)	— lower (e.g. plastic material)
Material thickness	— greater	— lower
Material porosity	— lower	— greater

G.1.2.6 Surface treatment

The type and amount of an applied surface treatment can have an influence on the heat transfer to the medical device and/or moist heat access to the medical device surface.

Along with other aspects, the attributes in Table G.5 can be considered.

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Table G.5 — Influence of surface treatment — Examples

Attribute	More critical	Less critical
Lubrication	— with	— without
Type of lubrication	— silicone oil — grease	— paraffinic white oil
Amount of lubrication	— greater	— lower
Type of coating	— plastic material	— inorganic, carbon
Thickness of coating	— greater	— lower

NOTE The aspects type and thickness of coating can apply to porous packaging materials as well.

G.2 Classification systems

In practice different types of classification systems, each with advantages and disadvantages, are used.

NOTE For validation of sterilization in industrial settings (e.g. performed by a manufacturer of a medical device delivered sterile) or validation of sterilization as part of a processing process (e.g. performed by a processing unit in a health care facility) or validation of the suitability of a medical device for sterilization intended for processing (as specified in the scope of ISO 17664-1) application of different classification systems can be required.

The rationale for the selected and applied classification system and the discrete classification levels, if applied, should be documented. The rationale can be assisted by, but not restricted to:

— fundamentally accepted information given by this document or other standards;

— information given in published literature;

— documented experience;

— results of comparative studies.

G.3 Product family

The product families to which a medical device is assigned should be based on attributes identified from the ones shown in Table G.1 considering the following rules (if applicable but not limited to):

— apply one product family only to medical devices intended for identical or directly comparable sterilization processes (considering type of moist heat sterilization process, sterilizer and operating cycle as well as cycle parameters);

— apply one product family only to medical devices with the same types of attributes;

— if a direct ranking of two aspects of an attribute is not possible, apply two different product families for both aspects of that attribute;

— consider the number or aspect of the same attribute type occurring on the product family.

G.4 Documentation

G.4.1 General

Documentation should illustrate the type and status of the attributes applicable to each medical device or group of directly comparable medical devices, as well as the allocation of each medical device, or group of directly comparable medical devices, to a product family.

NOTE Similar medical devices with identical attributes except one aspect of one attribute, e.g. a different length, can be covered by the medical device with the worst-case aspect with respect to this attribute, e.g. the greatest length.

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G.4.2 Instruments with channels and cavities

Due to advances in surgical techniques, instruments with complex geometries, e.g. hollow devices, are becoming increasingly employed. Such instruments pose challenges to decontamination processes including moist heat sterilization, and in particular, the adequacy of air removal and steam penetration. Air removal and steam penetration is affected by several factors. Some examples can include but are not limited to the:

a) physico/chemical conditions in the usable chamber space;

b) load characteristics;

c) load configuration including the SBS used;

d) characteristics of the sterilization cycle.

The diameter and length alone do not account for all the issues related to air removal from, and steam penetration into, channels in medical devices. The conclusions in the published literature on the air removal from, and steam penetration into channels and cavities, are in part conflicting (e.g. see References [55] and [69]). PQ should be considered for any instrument or instruments of a similar design having a cavity or channel whether open- or closed-ended.

G.4.3 Example of a classification system for identifying the level of challenge to air removal and steam penetration posed by medical devices

An example of a classification system identifying the level of challenge to air removal and steam penetration is shown in Table G.6. Additional information and published references used to support the classification are also provided:

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