BS EN ISO 20857:2013

BSI Standards Publication

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

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National foreword

This British Standard is the UK implementation of EN ISO 20857:2013. It is identical to ISO 20857:2010.

The UK participation in its preparation was entrusted to Technical Committee CH/198, Sterilization of medical devices.

A list of organizations represented on this committee can be obtained on request to its secretary.

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English Version

Sterilization of health care products - Dry heat - Requirements for the development, validation and routine control of a sterilization process for medical devices (ISO 20857:2010)

Stérilisation des produits de santé - Chaleur sèche - Exigences pour l'élaboration, la validation et le contrôle de routine d'un processus de stérilisation pour dispositifs médicaux (ISO 20857:2010)

Sterilisation von Produkten für die Gesundheitsfürsorge - Trockene Hitze - Anforderungen an die Entwicklung, Validierung und Lenkung der Anwendung von industriellen Sterilisationsverfahren für Medizinprodukte (ISO 20857:2010)

This European Standard was approved by CEN on 5 April 2013.

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Ref. No. EN ISO 20857:2013: E

Foreword

The text of ISO 20857:2010 has been prepared by Technical Committee ISO/TC 198 “Sterilization of health care products” of the International Organization for Standardization (ISO) and has been taken over as EN ISO 20857:2013 by Technical Committee CEN/TC 204 “Sterilization of medical devices” the secretariat of which is held by BSI.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by October 2013, and conflicting national standards shall be withdrawn at the latest by October 2013.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. CEN [and/or CENELEC] shall not be held responsible for identifying any or all such patent rights.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directives.

For relationship with EU Directives, see informative Annex ZA, B and C, which are integral parts of this document.

According to the CEN-CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Endorsement notice

The text of ISO 20857:2010 has been approved by CEN as EN ISO 20857:2013 without any modification.

Annex ZA
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 90/385/EEC on Active Implantable Medical Devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 90/385/EEC on active implantable medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this standard given in Table ZA.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZA.1 — Correspondence between this European Standard and Directive 90/385/EEC

Clauses of this EN	Essential Requirements (ERs) of Directive 90/385/EEC	Qualifying remarks/Notes
4,5,6,7,8,9,10,11,12	7	This relevant Essential Requirement is only partly addressed in this European Standard. Packaging for maintenance of sterility during transportation and storage are not covered

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this Standard.

Annex ZB
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 93/42/EEC on Medical Devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 93/42/EEC on medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this standard given in Table ZB.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZB.1 — Correspondence between this European Standard and Directive 93/42/EEC

Clauses of this EN	Essential Requirements (ERs) of Directive 93/42/EEC	Qualifying remarks/Notes
4,5,6,7,8,9,10,11,12	8.3	This relevant Essential Requirement is only partly addressed in this European Standard. Packaging for maintenance of sterility during transportation and storage are not covered
4,5,6,7,8,9,10,11,12	8.4	

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this Standard.

Annex ZC
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 98/79/EC on *in vitro* diagnostic medical devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 98/79/EC on *in vitro* diagnostic medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this standard given in Table ZC.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZC.1 — Correspondence between this European Standard and Directive 98/79/EC

Clauses of this EN	Essential Requirements (ERs) of Directive 98/79/EC	Qualifying remarks/Notes
4,5,6,7,8,9,10,11,12	B.2.3	This relevant Essential Requirement is only partly addressed in this European Standard. Packaging for maintenance of sterility during transportation and storage are not covered
4,5,6,7,8,9,10,11,12	B.2.4	

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this Standard.

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Foreword

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

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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ISO 20857 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

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Introduction

A sterile medical device is one that is free of viable microorganisms. International Standards that specify requirements for development, validation and routine control of sterilization processes, require, when it is necessary to supply a sterile medical device, that adventitious microbiological contamination of a medical device prior to sterilization be minimized. Even so, medical devices produced under standard manufacturing conditions in accordance with the requirements for quality management systems (see, for example, ISO 13485) may, prior to sterilization, have microorganisms on them, albeit in low numbers. Such products are non-sterile. The purpose of sterilization is to inactivate the microbiological contaminants and thereby transform the non-sterile products into sterile ones.

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

This International Standard describes requirements that, if met, will provide a dry heat sterilization process capable of sterilizing medical devices through appropriate microbicidal activity. This International Standard also describes requirements that, if met, will provide a dry heat depyrogenation process through an appropriate denaturation activity. Furthermore, such compliance permits prediction, with reasonable confidence, that there is a low probability of there being a viable microorganism present on the product after processing. Specification of this probability is a matter for regulatory authorities and may vary from country to country (see for example EN 556-1 and ANSI/AAMI ST67). Additionally, there will be a low probability of pyrogenic material of bacterial origin being present on the product after the application of a depyrogenation process.

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

Exposure to a properly validated, accurately controlled sterilization process is not the only factor associated with the provision of reliable assurance that 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 incoming raw materials and/or components;

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;

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

g) the conditions under which product is stored.

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These factors also need consideration for the provision of reliable assurance of depyrogenation.

The type of contamination on the product to be sterilized varies and this variation influences the effectiveness of a sterilization and depyrogenation process. Product that has been used in a health care setting and is being presented for resterilization in accordance with the manufacturer's instructions (see ISO 17664) should be regarded as a special case. There is potential for such product to possess a wide range of contaminating microorganisms and residual inorganic and/or organic contamination in spite of the application of a cleaning process. Hence, particular attention has to be given to the validation and control of the cleaning and disinfection processes used during reprocessing.

The requirements are the normative parts of this International Standard with which compliance is claimed. The guidance given in the informative annexes is not normative and is not provided as a check list for auditors. The guidance provides explanations as well as methods that are accepted as being suitable means for complying with the requirements. Approaches other than those given in the guidance may be used if they are effective in achieving compliance with the requirements of this International Standard.

The development, validation and routine control of a sterilization process and/or a depyrogenation process comprise a number of discrete but interrelated activities, for example calibration, maintenance, product definition, process definition, installation qualification, operational qualification and performance qualification. While the activities required by this International Standard have been grouped together and are presented in a particular order, this International Standard does not require that the activities be performed in the order that they are presented. The activities required are not necessarily sequential, as the programmes of development and validation might be iterative. It is possible that performing these different activities will involve a number of separate individuals and/or organizations, each of whom undertake one or more of these activities. This International Standard does not specify the particular individuals or organizations to carry out the activities.

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INTERNATIONAL STANDARD ISO 20857:2010(E)

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

1 Scope

1.1 Inclusions

1.1.1 This International Standard specifies requirements for the development, validation and routine control of a dry heat sterilization process for medical devices.

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

1.1.2 Although this International Standard primarily addresses dry heat sterilization, it also specifies requirements and provides guidance in relation to depyrogenation processes using dry heat.

NOTE Dry heat is often used for the depyrogenation of equipment, components and health care products and its effectiveness has been demonstrated. The process parameters for sterilization and/or depyrogenation are time and temperature. Because the conditions for depyrogenation are typically more severe than those required for sterilization, a process that has been validated for product depyrogenation will result in product sterility without additional validation.

1.2 Exclusions

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

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

1.2.2 This International Standard does not apply to processes that use infrared or microwaves as the heating technique.

1.2.3 This International Standard does not detail a specified requirement for designating a medical device as "sterile."

NOTE Attention is drawn to national or regional requirements for designating medical devices as “sterile.” See, for example, EN 556-1 or ANSI/AAMI ST67.

1.2.4 This International Standard does not specify a quality management system for the control of all stages of production of medical devices.

NOTE It is not a requirement of this International Standard to have a complete quality management system during manufacture, but the elements of a quality management system that are the minimum necessary to control the sterilization process are normatively referenced at appropriate places in the text (see, in particular, Clause 4). Attention is drawn to the standards for quality management systems (see ISO 13485) that control all stages of production of medical devices, including the sterilization process. Regional and national regulations for the provision of medical devices might require implementation of a complete quality management system and the assessment of that system by a third party.

1.2.5 This International Standard does not specify requirements for occupational safety associated with the design and operation of dry heat sterilization and/or depyrogenation facilities.

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NOTE Requirements for operational safety are specified in IEC 61010-2-040. Additionally, safety regulations exist in some countries.

2 Normative references

The following referenced documents are indispensable for the application 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 10012, *Measurement management systems — Requirements for measurement processes and measuring equipment*

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

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

ISO 11138-1:2006, *Sterilization of health care products — Biological indicators — Part 1: General requirements*

ISO 11138-4:2006, *Sterilization of health care products — Biological indicators — Part 4: Biological indicators for dry heat sterilization processes*

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

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 medical devices — Microbiological methods — Part 1: Determination of a population of microorganisms on products*

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

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

IEC 61010-1, *Safety requirements for electrical equipment for measurement, control, and laboratory use — Part 1: General requirements*

IEC 61010-2-040, *Safety requirements for electrical equipment for measurement, control and laboratory use — Part 2-040: Particular requirements for sterilizers and washer-disinfectors used to treat medical materials*

3 Terms and definitions

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

3.1
batch
defined quantity of product, intended or purported to be uniform in character and quality, which has been produced during a defined cycle of manufacture

[ISO/TS 11139:2006, definition 2.1]

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3.2
bioburden
population of viable microorganisms on or in product and/or sterile barrier system

[ISO/TS 11139:2006, definition 2.2]

3.3
biological indicator
BI
test system containing viable microorganisms providing a defined resistance to a specified sterilization process

[ISO/TS 11139:2006, definition 2.3]

3.4
calibration
set of operations that establish, under specified conditions, the relationship between values of a quantity indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards

[ISO/TS 11139:2006, definition 2.4]

3.5
change control
assessment and determination of the appropriateness of a proposed alteration to product or procedure

[ISO/TS 11139:2006, definition 2.5]

3.6
chemical indicator
non-biological indicator
test system that reveals change in one or more pre-defined process variables based on a chemical or physical change resulting from exposure to a process

[ISO/TS 11139:2006, definition 2.6]

3.7
correction
action to eliminate a detected nonconformity

NOTE A correction can be made in conjunction with a **corrective action** (3.8).

[ISO 9000:2005, definition 3.6.6]

3.8
corrective action
action to eliminate the cause of a detected nonconformity or other undesirable situation

NOTE 1 There can be more than one cause for a nonconformity.

NOTE 2 Corrective action is taken to prevent recurrence whereas **preventive action** (3.27) is taken to prevent occurrence.

NOTE 3 There is a distinction between **correction** (3.7) and corrective action.

[ISO 9000:2005, definition 3.6.5]

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3.9
D **value**
D_{10} **value**
time or radiation dose required to achieve inactivation of 90 % of a population of the test microorganism under stated conditions

NOTE 1 For the purposes of this International Standard, D value refers to the exposure time necessary to achieve the 90 % reduction of the population of test microorganisms.

NOTE 2 Adapted from ISO/TS 11139:2006.

3.10
depyrogenation
validated process designed to remove or inactivate pyrogenic material, by a specified quantity, which is monitored by inactivation of endotoxin

NOTE For the purposes of the depyrogenation process, “inactivation” refers to loss of ability of biological material to cause a pyrogenic reaction.

3.11
depyrogenation process
series of actions or operations needed to achieve the specified requirements for removal or inactivation of pyrogens

3.12
establish
determine by theoretical evaluation and confirm by experimentation

[ISO/TS 11139:2006, definition 2.17]

3.13
exposure time
period for which the process parameters are maintained within their specified tolerances

[ISO/TS 11139:2006, definition 2.18]

3.14
F **value**
microbiological lethality of a sterilization process expressed in terms of the equivalent time, in minutes, at a temperature of 160 °C with reference to microorganisms with a z value of 20 °C.

NOTE 1 For dry heat, the F value for specific values of sterilization temperature, T, and z is referred to as F_H. Usually, F_H is the equivalent time in minutes at 160 °C delivered to product at temperature, T, assuming a z value of 20 °C. F_H can be determined by biological (F_{Bio}) or physical (F_{phys}) methods.

NOTE 2 The F_H for a process at temperature T, where T is other than 160 °C, may be determined by multiplying the lethal rate by the time at temperature T:

$$F_H = \Delta t \times L$$

where

F_H is the equivalent time in minutes at 160 °C, that has been delivered to the product by the process over time t;

Δt is the time in minutes at temperature T;

L is the lethal rate at temperature T.

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3.15
fault
one or more of the process parameters lying outside of its/their specified tolerance(s)

[ISO/TS 11139:2006, definition 2.19]

3.16
fraction positive
quotient derived from the number of positive tests of sterility observed and the total number of tests of sterility performed (number of positive tests of sterility plus number of negative tests of sterility)

3.17
health care product(s)
medical device(s), including *in vitro* diagnostic medical device(s), or medicinal product(s), including biopharmaceutical(s)

[ISO/TS 11139:2006, definition 2.20]

3.18
inactivation
loss of ability of microorganisms to grow and/or multiply

[ISO/TS 11139:2006, definition 2.21]

NOTE For purposes of depyrogenation processes, “inactivation” refers to loss of ability of biologic material to cause a pyrogenic reaction.

3.19
inoculated carrier
supporting material on or in which a defined number of test microorganisms have been deposited

3.20
installation qualification
IQ
process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification

[ISO/TS 11139:2006, definition 2.22]

3.21
lethal rate
L
expression of inactivation per unit time at temperature, T, expressed in terms of a reference temperature, T_{ref}

NOTE 1 L is expressed as minutes at the reference temperature, T_{ref}, per minute at T.

NOTE 2 Lethal rate at any temperature can be calculated using the equation $L = 10^{\frac{(T - T_{\text{ref}})}{z}}$

where

T is the delivered temperature;

T_{ref} is the reference temperature;

z is the change in temperature in degrees Celsius required to change a D value by a factor of 10.

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3.22
medical device
instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other related article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of

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

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

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

— supporting or sustaining life,

— control of conception,

— disinfection of medical devices,

— providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body

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

[ISO 13485:2003, definition 3.7]

NOTE This definition has been developed by the Global Harmonization Task Force (GHTF 2002).

3.23
microorganism
entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

[ISO/TS 11139:2006, definition 2.26]

NOTE A specific standard might not require demonstration of the effectiveness of the sterilization process in inactivating all types of microorganisms, identified in this definition, for development, validation and/or routine control of the sterilization process.

3.24
operational qualification
OQ
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[ISO/TS 11139:2006, definition 2.27]

3.25
parametric release
declaration that product is sterile, based on records demonstrating that the process parameters were delivered within specified tolerances

[ISO/TS 11139:2006, definition 2.29]

3.26
performance qualification
PQ
process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification

[ISO/TS 11139:2006, definition 2.30]

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3.27
preventive action
action to eliminate the cause of a potential nonconformity or other undesirable potential situation

NOTE 1 There can be more than one cause for a potential nonconformity.

NOTE 2 Preventive action is taken to prevent occurrence whereas **corrective action** (3.8) is taken to prevent recurrence.

[ISO 9000:2005, definition 3.6.4]

3.28
process challenge device
PCD
item designed to constitute a defined resistance to a sterilization process and used to assess performance of the process

[ISO/TS 11139:2006, definition 2.33]

3.29
process parameter
specified value for a process variable

NOTE The specification for a sterilization process includes the process parameters and their tolerances.

[ISO/TS 11139:2006, definition 2.34]

3.30
process variable
condition within a sterilization process, changes in which alter microbicidal effectiveness

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

[ISO/TS 11139:2006, definition 2.35]

3.31
product
result of a process

[ISO 9000:2005, definition 3.4.2]

NOTE For the purposes of sterilization standards, product is tangible and can be raw material(s), intermediate(s), sub-assembly(ies) and health care product(s)

3.32
product family
group or subgroup of product characterized by similar attributes such as mass, material, construction, shapes, lumens and/or packaging and that present a similar challenge to the sterilization process

3.33
requalification
repetition of part of validation for the purpose of confirming the continued acceptability of a specified process

[ISO/TS 11139:2006, definition 2.40]

3.34
specify
stipulate in detail within an approved document.

[ISO/TS 11139, definition 2.42]

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3.35
spore log reduction
SLR
factor, expressed as the logarithm to base 10, describing the reduction in the number of spores on a biological indicator produced by exposure to specified conditions

NOTE SLR can be calculated as the log of the initial spore population minus the log of the final spore population of the biological indicator as follows:

$$\text{SLR} = \log N_o - \log N_u$$

where

N_o is the initial population;

N_u is the final population.

If N_u is zero, the true SLR cannot be calculated. If N_u is assumed to be 1 for the purposes of calculation, the SLR is reported as greater than log N_o.

3.36
sterile
free from viable microorganisms

[ISO/TS 11139:2006, definition 2.43]

3.37
sterile barrier system
minimum package that prevents ingress of microorganisms and allows aseptic presentation of the product at the point of use

[ISO/TS 11139:2006, definition 2.44]

3.38
sterility
state of being free from viable microorganisms

NOTE In practice, no such absolute statement regarding the absence of microorganisms can be proven. See **sterilization** (3.40).

[ISO/TS 11139:2006, definition 2.45]

3.39
sterility assurance level
SAL
probability of a single viable microorganism occurring on an item after sterilization

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

[ISO/TS 11139:2006, definition 2.46]

3.40
sterilization
validated process used to render product free from viable microorganisms

NOTE 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. See **sterility assurance level** (3.39).

[ISO/TS 11139:2006, definition 2.47]

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3.41
sterilization load
product to be, or that has been, sterilized together using a given sterilization process

NOTE In dry heat processing, a sterilization load might be subjected to **depyrogenation** (see 3.10) in a given sterilization system (see 3.43).

[ISO/TS 11139:2006, definition 2.48]

3.42
sterilization process
series of actions or operations needed to achieve the specified requirements for sterility

NOTE This series of actions includes pre-treatment of product (if necessary), exposure under defined 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.

[ISO/TS 11139:2006, definition 2.49]

3.43
sterilization system
sterilizer and ancillary equipment associated with delivering the sterilization process

NOTE In dry heat processing, a sterilization system might be used for **depyrogenation** (3.10).

3.44
sterilizing agent
physical or chemical entity, or combination of entities, having sufficient microbicidal activity to achieve sterility under defined conditions

[ISO/TS 11139:2006, definition 2.50]

3.45
survivor curve
graphical representation of the inactivation of a population of microorganisms with increasing exposure to a microbicidal agent under stated conditions

[ISO/TS 11139:2006, definition 2.51]

3.46
terminal sterilization
process whereby product is sterilized within its sterile barrier system

[ISO/TS 11139:2006, definition 2.52]

3.47
validation
documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications

[ISO/TS 11139:2006, definition 2.55]

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3.48
z **value**
temperature change required to effect a ten fold change in D value, expressed in degrees Celsius

NOTE The z value is a measure of how the response to heat treatment of a microorganism changes with changes in temperature. The z value can be calculated or obtained from the equation

$$z = \frac{T_2 - T_1}{\log_{10} D_1 - \log_{10} D_2}$$

where

T_1 is the lower of the temperatures;

T_2 is the higher of the temperatures;

D_1 is the D value obtained at T_1;

D_2 is the D value obtained at T_2.

4 Quality management system elements

4.1 Documentation

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

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

4.2 Management responsibility

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

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

4.3 Product realization

4.3.1 Procedures for purchasing shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.

4.3.2 Procedures for identification and traceability of product shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.

4.3.3 A system complying with the applicable clauses ISO 13485 or ISO 10012 shall be specified for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this International Standard.

4.4 Measurement, analysis and improvement — Control of nonconforming product

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

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5 Sterilizing agent characterization

5.1 Sterilizing agent

For the purposes of this International Standard, the sterilizing agent shall be dry heat.

5.2 Microbicidal effectiveness

The microbicidal effectiveness of dry heat and its use in sterilization processes has been comprehensively documented and is available in the published literature. See, for example, Pflug and Holcomb[28]. If dry heat is employed outside the range of conditions that are widely recognised, then microbicidal effectiveness shall be demonstrated.

5.3 Material effects

The effects of exposure to dry heat on the physical and/or chemical properties of materials and on the biological safety of exposed materials shall be assessed in accordance with the requirements of Clauses 6 and 7. During this assessment, the effect of the rate and range of temperature change of the process shall be determined.

5.4 Environmental considerations

Dry 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 Process characterization

The dry heat sterilization process shall be specified. The specification shall include:

a) the process parameters and their tolerances;

b) requirements for the conditioning of product prior to sterilization, if such conditioning is necessary to ensure the efficacy of the sterilization process;

c) the location of the reference point for temperature measurement.

6.2 Equipment characterization

6.2.1 Equipment specification

The sterilization system shall be specified.

6.2.2 Identification

The sterilization system shall be permanently and indelibly labelled with at least the following information in the language agreed to by the user:

a) name and address of the manufacturer;

b) serial number or other identifier;

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c) minimum and maximum working temperatures;

d) stamp of inspection authority and vessel identification mark (if applicable).

6.2.3 Safety

Compliance of the sterilization system with the safety requirements specified in IEC 61010-1, IEC 61010-2-040 and any other standards or regulatory requirements applicable in the country of use, shall be documented.

6.2.4 Manuals and instructions

At a minimum, the following information shall be available for each identified sterilization system:

a) instructions that facilitate safe and effective installation;

b) list of materials of construction;

c) instructions for operation, including temperature limits and safety precautions;

d) instructions and schedules for routine preventive maintenance;

e) repair manual or instructions;

f) drawings defining configuration and hardware, ductwork and control systems;

g) parts list defining all significant components;

h) process control logic and/or software documentation necessary for operation and maintenance.

6.2.5 Utilities

6.2.5.1 Gases shall be specified and the specification shall be such that the safety and quality of product are not impaired and the sterilization system operates as intended.

6.2.5.2 The requirements for the electrical supply shall be specified.

NOTE Generally, the manufacturer of the sterilizer or applicable ancillary equipment specifies the requirements for the electrical supply. Conformance with this specification is confirmed in installation qualification (IQ) (see 9.2).

6.2.6 Components

The materials and components of the sterilization system shall not contribute to microbiological or chemical contamination of the sterilization system.

6.2.7 Accessories

6.2.7.1 The carrier supporting product in the sterilization system shall be designed to allow uniform heat penetration, heat transfer or both. It shall also maintain the integrity of the sterilization load.

6.2.7.2 Means of cooling the sterilization system and removing exhaust gases shall be specified.

6.2.7.3 If the sterilization system is connected to or located within a controlled environment, appropriate filtration of incoming and/or exhaust gases shall be specified.

6.2.7.4 If the sterilization system is equipped with a means of forced air circulation, the means of circulation shall be specified.

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6.2.8 Control and recording systems

6.2.8.1 The sterilization system shall be equipped with instrumentation to control, monitor and record the following process variables:

a) temperature (dry heat sterilizer and/or sterilization load, as applicable);

b) exposure time;

c) speed of the conveyor system, if applicable;

d) pressure and airflow, if applicable;

e) rate of change of temperature, if it affects product integrity.

6.2.8.2 The process control and recording systems shall either be independent or be designed in a manner that will cause a warning to occur if the difference between a measured process parameter and a recorded process parameter exceeds a specified limit.

6.2.8.3 The control and recording systems shall incorporate means to detect failure of a sensor.

6.2.8.4 Means shall be provided to prevent unauthorized changes to process set points and ensure selection of the correct sterilization process.

6.2.8.5 Software shall be identified by revision level and accompanied by documentation supporting its validation.

6.2.8.6 Accuracy of instruments used in development, validation, and routine monitoring and control shall be specified such that attainment of process specifications can be demonstrated.

6.2.8.7 Temperature and, where applicable, airflow or pressure sensors shall be selected, installed and used in a manner that will ensure that the stated accuracy is maintained.

6.2.9 Control programs

6.2.9.1 If microprocessor or electromechanical programs are used to execute and control the sterilization process, they shall be documented and validated. The correctness of program logic in both simulated and actual use shall be demonstrated.

6.2.9.2 Changes to such programs shall be evaluated and the evaluation recorded (see 4.1.2 and 12.5).

7 Product definition

7.1 General

NOTE The purpose of product definition is to define the product to be sterilized/depyrogenated, including the quality of the product prior to sterilization/depyrogenation and the manner in which product is to be packaged and presented for sterilization/depyrogenation.

Product to be sterilized/depyrogenated shall be specified. Changes to product, package or product configuration within the package shall be specified (see 12.5.2).

7.2 Product safety and performance

7.2.1 Any treatment of product required before the sterilization/depyrogenation process, e.g., cleaning, washing, lubrication or disinfection, shall be specified.

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7.2.2 It shall be confirmed that the product and its packaging meet specified requirements for safety, quality and performance following application of the defined sterilization/depyrogenation process at the most challenging process parameters for product. If exposure to multiple sterilization/depyrogenation processes is to be permitted, the effects of such processing on the product and its packaging shall be evaluated to ensure that there are no adverse effects.

This can be achieved by employing a quality management system complying with ISO 13485 throughout the manufacture of the medical device, or by employing a defined and controlled cleaning process of demonstrated effectiveness, together with a disinfection process (if specified) prior to sterilization, and thereafter preventing recontamination of the medical device.

NOTE 1 There are International Standards published for equipment to be used in cleaning and disinfecting medical devices (ISO 15883 series) and which include methods of demonstrating the effectiveness of a cleaning and disinfecting process.

NOTE 2 Health care users of re-usable medical devices should follow manufacturers' directions for reprocessing unless they independently validate an alternate approach.

7.3 Packaging considerations

7.3.1 Packaging materials and procedures shall be specified.

7.3.2 Packaging materials, if present at the time of sterilization/depyrogenation, shall be compatible with the conditions of the sterilization/depyrogenation process.

7.3.3 Packaging shall protect the product from physical damage and maintain the sterility of the product until use.

7.3.4 Packaging shall comply with ISO 11607-1 and ISO 11607-2.

7.3.5 For product labelled sterile, the packaging shall consist of at least a sterile barrier system.

7.4 Microbiological quality

7.4.1 A system shall be specified and maintained to ensure that the biological quality and cleanliness of the product presented for sterilization/depyrogenation is controlled and does not compromise the effectiveness of the sterilization/depyrogenation process.

7.4.2 The effectiveness of the system defined in 7.4.1 shall be demonstrated. For medical devices to be supplied for single use, this demonstration shall include an estimation of bioburden at a defined interval in accordance with ISO 11737-1. For re-usable medical devices, this demonstration shall include an assessment of the effectiveness of the specified cleaning and, if applicable, disinfecting process. This shall also include an assessment of organic and inorganic contamination.

NOTE Requirements for information to be provided for the reprocessing of resterilizable devices are given in ISO 17664. The intention is that bioburden be stable and low, taking account of the nature of the raw materials, product and manufacturing or reprocessing procedures prior to sterilization.

7.5 Product family

If applicable, criteria for the assignment of product to a product family shall be specified. The product family to which product, including its packaging system, is assigned, shall be recorded (see 4.1.2).

7.6 Biological safety

The biological safety of the product following exposure to the sterilization process shall be demonstrated in accordance with ISO 10993-1.

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NOTE The evaluation of the biocompatibility or biological safety of a medical device is normally performed by the product manufacturer prior to the introduction of the product.

8 Process definition

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

8.1 The method to be used for establishing the sterilization process shall be specified. The method shall be either one of those described in Annexes B, C or D, or an alternative method of equal effectiveness. Application of the method shall provide evidence that, on delivery of the specified sterilization process, the pre-selected sterility assurance level (SAL) is achieved.

The method to be used for establishing the depyrogenation process shall be specified. Application of the method shall provide evidence that, on delivery of the specified depyrogenation process, the required level of depyrogenation is achieved.

8.2 Process parameters and their tolerances for the sterilization/depyrogenation process shall be specified. The lower tolerance shall be based on minimum effective process parameters established during process definition. Upper tolerances shall be selected to ensure that product safety, quality and performance are maintained.

NOTE Some product can be made of materials that have high endurance to dry heat process temperatures (e.g. glass, metal). Therefore, tolerances for process parameters for these types of product can have a wide range.

8.3 The required sterility assurance (SAL) to be achieved by the sterilization process for defined product shall be specified.

8.4 For sterilization processes based on bioburden, there shall be a determination of bioburden in accordance with ISO 11737-1 and investigation of the resistance of microorganisms comprising the bioburden. The frequency of bioburden determinations shall be specified to ensure that significant changes in bioburden are detected. When investigating the resistance of microorganisms comprising the bioburden, a test of sterility complying with ISO 11737-2 shall be performed.

8.5 If biological indicators are used for establishing the sterilization process, they shall comply with ISO 11138-1 and ISO 11138-4.

8.6 If chemical indicators are used for establishing the sterilization process, they shall comply with ISO 11140-1.

8.7 If a process challenge device (PCD) is used in establishing the sterilization process, the appropriateness of the PCD shall be demonstrated and recorded (see 4.1.2).

8.8 If tests of sterility are performed in establishing the sterilization process, such tests shall comply with ISO 11737-2.

8.9 A health-based risk assessment shall be conducted in accordance with ISO 10993-17 to identify and specify any limits for residues associated with the sterilization process.

8.10 If application of the dry heat process is also intended to achieve depyrogenation, the reduction of endotoxins to an appropriate specified level shall be demonstrated. The appropriateness of the level of the endotoxin challenge used for development or validation of the depyrogenation process shall be demonstrated.

NOTE Attention is drawn to national or international requirements for endotoxin reduction (see A.8.10 and A.9.4.4 for additional guidance).

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9 Validation

9.1 General

9.1.1 Procedures for validation shall be specified. IQ, OQ and PQ shall be performed.

9.1.2 Equipment used for measuring and/or recording process parameters shall be calibrated (see 4.3.3).

9.2 Installation qualification

9.2.1 IQ shall demonstrate that the sterilization system has been installed according to its specifications. The demonstration shall include:

a) compliance with equipment specifications after installation;

b) conformance of services/utilities to specified requirements (see 6.2.5).

9.2.2 In addition, the following should be reviewed, approved and documented:

a) equipment design;

b) prints, drawings and manuals;

c) software, if applicable;

d) programmes for calibration, preventive maintenance and cleaning.

9.3 Operational qualification

9.3.1 OQ shall demonstrate that the installed sterilization system, including control and recording systems and control programmes, operate according to specification.

9.3.2 OQ shall be performed using an empty sterilization system or one that contains appropriate test material. OQ shall include:

a) demonstration that process parameters (e.g., temperature, time, airflow, pressure) are within the specified limits for the defined usable space;

b) demonstration that preprogrammed sterilization cycles operate as specified;

c) demonstration that equipment, such as alarms, set-point controllers, safety devices, monitoring systems and door interlocks, perform as specified;

d) confirmation of the relationship between set control values and measured process parameters;

e) review of documentation of operational procedures for the sterilization system.

9.4 Performance qualification

9.4.1 General

9.4.1.1 PQ shall be performed with a sterilization load in the sterilization system.

PQ shall be performed on the introduction of new or altered products, packaging, loading patterns, equipment or process parameters, unless equivalence to a previously validated product, packaging, load pattern or equipment has been demonstrated. The demonstration of equivalence shall be recorded (see 4.1.2).

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9.4.1.2 PQ shall demonstrate that the sterilization process (and, where applicable, the depyrogenation process) is consistently delivered to product.

9.4.1.3 The sterilization load used for PQ shall be representative of the most challenging load and configuration that is to be sterilized routinely.

9.4.1.4 Product used for PQ shall be packaged in the same manner as that to be routinely processed.

9.4.1.5 PQ shall include a series of at least three successful exposures of product to the sterilization/depyrogenation process, within defined tolerances, in order to demonstrate the reproducibility of the process. Results from PQ outside of defined tolerances shall be reviewed and corrective actions determined and instituted before initiating a new series of exposures.

The series of three successful exposures shall be performed consecutively, unless findings outside defined tolerances can be attributed to factors not relevant to the effectiveness of the process being validated. Such findings shall be documented as unrelated to performance of the sterilization/depyrogenation process.

9.4.2 Performance qualification — Physical

9.4.2.1 Physical PQ shall demonstrate that the sterilization or depyrogenation process is reproducibly applied over the range of conditions proposed for routine processing. Physical PQ shall include:

a) demonstrating the relationship between set control values and process parameters measured in the sterilization load;

b) demonstrating uniformity of temperature throughout the sterilization load;

c) identifying the relationship between conditions in the sterilization load and at the routine monitoring position(s);

d) demonstrating the acceptability of different loading configurations;

e) demonstrating the acceptability of minimum product temperature before processing, if process is not controlled from measurements of sterilization load temperature;

f) demonstrating acceptability of product mix within the sterilization load;

g) demonstrating appropriateness of simulated product to comprise the sterilization load, if used;

h) demonstrating conformance to specification of product and packaging after sterilization, depyrogenation or resterilization as applicable.

9.4.2.2 If chemical indicators are used as part of PQ, they shall comply with ISO 11140-1.

9.4.2.3 The number and location of temperature sensors shall be specified and shall be sufficient to measure the temperature range throughout the sterilization load.

9.4.2.4 The results of the physical PQ shall be recorded (see 4.1.2).

9.4.3 Performance qualification — Microbiological

9.4.3.1 If, in addition to the measurement of physical parameters, the dry heat sterilization process is to be based on bioburden, or verified by microbiological methods, a microbiological PQ shall be performed which demonstrates that the sterilization process consistently delivers appropriate microbial inactivation over the range of conditions proposed for routine processing. The microbiological PQ shall:

a) demonstrate the appropriateness of the BI or other PCD and its relationship to the bioburden;

b) identify the acceptable maximum bioburden level on the product before sterilization;

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c) identify the relationship of the delivered physical parameters to microbiological lethality;

d) demonstrate the inactivation of BIs or resistant bioburden isolates under conditions selected to deliver less lethality than the conditions used for routine processing;

e) demonstrate the achievement of required lethality throughout the sterilization load.

9.4.3.2 Product used for microbiological PQ shall be packaged in the same manner as that to be routinely processed.

9.4.3.3 The number and location of BIs or other PCDs, if used, shall be specified. Specified locations shall include placement at the locations in the sterilization load where sterilizing conditions are most difficult to achieve, as identified in the physical PQ.

9.4.3.4 If BIs are used as part of microbiological PQ, these shall comply with Clause 5 and subclause 9.5 of ISO 11138-4:2006.

9.4.3.5 The results of the microbiological PQ shall be recorded (see 4.1.2).

9.4.4 Performance qualification — Depyrogenation

9.4.4.1 For a depyrogenation process, PQ shall demonstrate that the specified process parameters ensure that the required endotoxin inactivation (see 8.10) is achieved at the location which is the slowest to heat up in the items being processed.

9.4.4.2 For depyrogenation processes, the number and location of the endotoxin challenges shall be specified.

9.5 Additional sterilization systems

Sterilization systems delivering a sterilization/depyrogenation process the same as that delivered by a previously qualified sterilization system, shall undergo PQ either:

a) in the same manner as the original sterilization system

or

b) using a reduced PQ that demonstrates the attainment of the required process parameters in the sterilization load and, if applicable, the required level of microbiological lethality. The rationale for reduced PQ shall be recorded (see 4.1.2).

9.6 Review and approval of validation

NOTE The purpose of this activity is to undertake and document a review of the validation data to confirm the acceptability of the sterilization process and to approve the validation report and the process specification.

9.6.1 Information gathered or produced during IQ, OQ and PQ shall be documented and reviewed for acceptability (see also 4.1.2). The results of this review shall be recorded.

9.6.2 A process specification for the defined product or product family, including the process parameters and their tolerances, shall be documented and approved. The process specification shall stipulate the criteria an individual sterilization/depyrogenation process used for a particular sterilization load as compliant. The process specification shall include:

a) the minimum temperature of the sterilization load to be introduced into the sterilization system (unless the process is controlled by load temperature);

b) the loading pattern;

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c) the time to reach sterilization temperature;

d) the exposure time;

e) the circulation (airflow);

f) if F_H is to be used:

1) the location of the monitoring position for F_H;

2) the minimum F_H;

3) the acceptable range within the sterilization load.

10 Routine monitoring and control

10.1 Routine control

10.1.1 Procedures for the routine monitoring of the sterilization process shall be specified.

10.1.2 The sterilization load and the load configuration shall be specified.

10.1.3 The sterilization process shall be delivered within the tolerances defined in the process specification.

10.1.4 Process parameters shall be recorded throughout the sterilization process.

10.1.5 The correct loading of the sterilization system shall be confirmed.

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

10.1.7 If BIs or PCDs are used for routine monitoring, they shall comply with 8.5 or 8.7 (whichever is applicable).

10.1.8 The number and locations for placement of BIs and PCDs shall be specified.

NOTE Typically, fewer BIs or PCDs are used for routine monitoring than for validation.

10.1.9 If chemical indicators are used in routine monitoring, they shall comply with ISO 11140-1.

10.2 Routine monitoring

10.2.1 At a minimum, a record shall be made of the following for each sterilization process:

a) the date;

b) identification of the sterilization system;

c) sterilization process identification;

d) product and loading configuration;

e) operator and signature;

f) product temperature before introduction to the sterilizer, if applicable;

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g) heat-up and cool-down characteristics of sterilization load, if applicable;

h) temperature at routine monitoring position(s);

i) exposure time or conveyor speed;

j) F_H, if applicable;

k) airflow rate, if applicable;

l) fault identified, if any.

10.2.2 Table 1 identifies process variables evaluated during process definition, OQ and PQ, and identifies the process variables that shall be monitored during routine processing.

10.2.3 Records shall be retained as specified in 4.1.2.

10.3 Process monitoring locations

The sterilization process shall be monitored at specified representative locations in the sterilization system [see also 9.4.2.1 c)].

Table 1 — Process variables to be monitored

Process variables	During validation	For routine processing
Program logic verification (if applicable)	Yes	No
Load identification	Yes	Yes
Load configuration	Yes	Yes
Load temperature before entering sterilizer[a]	Yes	Yes
Sterilizer temperature heat-up time	Yes	Yes, if F_H is used for release
Load temperature heat-up time	Yes	No
Airflow setting (if applicable)	Yes	Yes
Airflow (metres per minute) (if applicable)	Yes	Yes
Fan revolutions per minute (if applicable)	Yes	No
Conveyor speed (if applicable)	Yes	Yes
Exposure temperature	Yes	Yes
Temperature distribution	Yes	No
Exposure time	Yes	Yes
Exposure pressure (if applicable)	Yes	Yes
Sterilizer cool-down time	Yes	Yes, if F_H is used for release
Load cool-down time	Yes	No
Accumulated F_H of the sterilizer (if applicable)	Yes	Yes
Accumulated F_H of the load (if applicable)	Yes	No

[a] Unless process is controlled by load temperature or alternate means of control have been demonstrated (i.e. equilibration time prior to processing, standard storage and/or manufacturing conditions).

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11 Product release from sterilization/depyrogenation

11.1 For release of product, the process parameters monitored during sterilization/depyrogenation shall comply with the process specification. Data from microbiological/endotoxin challenges, if used, shall be acceptable.

11.2 For parametric release, process parameters, in addition to being specified and controlled, shall be monitored directly.

11.3 Records demonstrating that the sterilization/depyrogenation process has been delivered in accordance with its specification shall be retained (see 4.1.2).

11.4 If the conditions specified in 11.1 are not met, product shall be considered as nonconforming and shall be handled in accordance with documented procedures (see 4.4).

12 Maintaining process effectiveness

12.1 General

The continued effectiveness of the system for ensuring the condition of the product presented for sterilization or depyrogenation (see 7.4) shall be demonstrated. This can include routine monitoring of product bioburden and/or monitoring the effectiveness of the cleaning process.

12.2 Recalibration

The accuracy and reliability of the instrumentation used to control and monitor the sterilization process shall be verified periodically (see 4.3.3).

12.3 Maintenance of equipment

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

12.3.2 Equipment shall not be used to process product until all specified maintenance tasks have been satisfactorily completed and recorded or otherwise addressed by a risk management approach within the quality management system.

12.3.3 The maintenance scheme, maintenance procedures and maintenance records shall be reviewed periodically by a designated person. The results of the review shall be recorded (see 4.1.2).

12.4 Requalification

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

12.4.2 Requalification procedures shall be specified and records of requalification shall be retained (see 4.1.2).

12.4.3 Requalification data shall be reviewed against specified acceptance criteria in accordance with documented procedures. Records shall be retained of reviews of requalification data together with corrections made and corrective actions taken if specified acceptance criteria are not met (see 4.4).

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12.5 Assessment of change

12.5.1 Any change in the sterilization system which could affect delivery of the sterilization or depyrogenation process shall be assessed. If the sterilization or depyrogenation process is judged to be affected, then a repeat of part or all of IQ, OQ or PQ shall be carried out (see Clause 9). The outcome of this assessment, including the rationale for decisions reached, shall be recorded (see 4.1.2).

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

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Annex A
(informative)

Guidance on the application of this International Standard

A.1 Scope

A.1.1 Inclusions

No guidance offered.

A.1.2 Exclusions

A.1.2.1 No guidance offered.

A.1.2.2 No guidance offered.

A.1.2.3 No guidance offered.

A.1.2.4 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. This International Standard identifies and specifies those elements of a quality management system that are essential for the effective control of sterilization by normative reference to the quality management system standard for medical devices, ISO 13485. This International Standard does not require that a full quality management system complying with ISO 13485 be implemented, nor does it require that those quality management system elements that are specified be subject to third party assessment. Attention is drawn to the existence of national and regional regulatory requirements for quality management systems in the manufacture of medical devices and for third party assessment of such systems.

A.1.2.5 No guidance offered.

A.2 Normative references

The requirements given in documents that are included as normative references are requirements of this International Standard only to the extent that they are cited in normative parts of this International Standard. The citation may be to a whole standard or limited to specific clauses.

A.3 Terms and definitions

No guidance offered.

A.4 Quality management system elements

A.4.1 Documentation

A.4.1.1 No guidance offered.

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A.4.1.2 In 4.2.3 and 4.2.5 of ISO 13485:2003, requirements are specified for the generation and control of documentation (including specifications and procedures) and records.

A.4.2 Management responsibility

A.4.2.1 Requirements for responsibility and authority are specified in 5.5 of ISO 13485:2003 and requirements for human resources are specified in 6.2 of ISO 13485:2003.

In ISO 13485, the requirements for management responsibility relate to management commitment, customer focus, quality policy, planning, responsibility, authority and communication, and management review.

A.4.2.2 The development, validation and routine control of a sterilization process can involve a number of separate parties, each of whom is responsible for certain elements. This International Standard requires that the party accepting particular responsibilities be defined and that this definition of responsibilities be documented. This definition of authority and responsibility is documented within the quality management system(s) of the identified parties. The party accepting responsibilities for defined elements is required to assign these elements to competent personnel, with competence demonstrated through appropriate training and qualification.

A.4.3 Product realization

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

A.4.3.1 Requirements for purchasing are specified in 7.4 of ISO 13485:2003. In particular, it should be noted that the requirements in 7.4.3 of ISO 13485:2003 for verification of purchased product apply to all product and services received from outside the organization.

A.4.3.2 Requirements for identification and traceability are specified in 7.5.3 of ISO 13485:2003.

A.4.3.3 Requirements for calibration of monitoring and measuring devices are specified in 7.6 of ISO 13485:2003.

A.4.4 Measurement, analysis and improvement — Control of nonconforming product

Procedures for the control of nonconforming product and corrective action are specified in 8.3 and 8.5.2, respectively, of ISO 13485:2003.

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

A.5 Sterilizing agent characterization

A.5.1 Sterilizing agent

No guidance offered.

A.5.2 Microbicidal effectiveness

The purpose of sterilizing agent characterization is to demonstrate the microbicidal effectiveness of the sterilizing agent, assess the effects that exposure to the sterilizing agent has on materials, and to identify requirements for safety of personnel and protection of the environment.

The microbicidal effectiveness of dry heat is well-characterized in the literature.

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A.5.3 Material effects

The material effects of dry heat are caused by exposure to heat for predetermined times. Material effects can include:

— changes in physical properties, such as softening, cracking, deformation or shape changes;

— changes in chemical properties, such as decomposition, generation of gases, polymerization or formation of toxic compounds;

— differences in expansion rates that could cause damage to mated parts;

— changes in material functionality or product performance.

Dry heat is a relatively slow-acting sterilizing agent, generally requiring higher temperatures than other modes of sterilization. However, one of the distinct advantages of dry heat is its ability to penetrate different types of materials, including oils, petrolatum jelly and closed containers that are not permeable to steam.

The rate of microbiological destruction can be influenced by the temperature, uniformity of the heating medium during sterilization, permeability of the packaging material to the heating medium, accessibility of the device or component fluid pathway to the heating medium, and physiological state of the bioburden associated with the product.

A.5.4 No guidance offered.

A.6 Process and equipment characterization

A.6.1 Process characterization

Development of a dry heat sterilization cycle for health care products needs to take into account the sensitivity of the process to significant variations in load configuration, load initial temperature and the specific heat of the load components. Factors that can influence dry heat sterilization of health care products are listed in Table A.1.

Table A.1 — Factors that can influence dry heat sterilization of health care products

Variables	Factors	Considerations
Packaging	Density per unit volume	Heat penetration
	Hermetic seals	Seal strengths
	Porosity	Maintenance of sterility
	Labelling	Retention of product labels during process
Device or component	Composition	Heat tolerance
	Complexity	Design
		Thermal degradation
		Maintenance of sterility potential
		Loss of function
Sterilizer	Sterilizer load density (e.g., fully loaded or partially loaded sterilizer)	Rate of heat penetration in the load
		Rate of post-sterilization cooling

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Dry heat sterilization processes generally occur at a temperature of 160 °C or higher, although sterilization processes at significantly lower temperatures have been developed and validated, Depyrogenation processes typically occur at 250 °C or higher.

Depending on the equipment used, the process may require different process parameters to be specified.

Process parameters and tolerances: the high temperature of typical dry heat processes limits the materials that can be used for the product and packaging. The maximum temperature, exposure time and number of allowable resterilizations should be determined from an evaluation of product stability, the materials of construction, manufacturers' data or from development and validation studies. Conversely, the relative insensitivity of the materials used can allow wide tolerances in process parameters, as compared with other sterilization processes.

The minimum temperature for sterilization or depyrogenation should be determined during the process development or validation studies. The tolerance of the process parameters is determined by the control capability of the sterilization system and material being sterilized. Products made of glass and metal can withstand higher temperatures and permit the use of greater temperature and heating-time tolerances. In these situations, temperature ranges of greater than 5 °C are not unusual. See A.6.2 for a discussion of batch and continuous sterilizers. For continuous dry heat sterilizers, the time at temperature is determined by conveyor speed. While conveyor speeds are adjustable, once set they maintain speeds with close tolerances, provided that the mechanical and control systems function properly. Tolerances in the conveyor speed should be included in the minimum time required for sterilization or depyrogenation.

In batch dry heat sterilizers, time is generally the parameter that can best be controlled. Appropriate tolerances should be determined. If F_H is used to calculate the sterilization time, the temperature ramp-up and ramp-down rates need to be controlled.

The gaseous heating media used in dry heat sterilization have a low heat capacity. The temperature distribution within the sterilizer is influenced by:

— loading (loading should be consistent with that used during the validation);

— airflow rate and distribution (e.g., dampers);

— blower speed;

— operation of the heating elements;

— for continuous sterilization systems, the temperature of adjacent zones (or ambient temperature at the entrance to and exit from the tunnel), and the rate of conveyor movement through the tunnel.

The mechanical elements associated with the sterilization system are generally not adjusted for a particular cycle. Proper performance of these elements (e.g., blower, dampers, heaters) should be ensured.

The requirements for the conditioning of product prior to sterilization, if such conditioning is necessary to ensure the efficacy of the sterilization process, need to be considered during the validation. The minimum temperature of product allowed to be submitted to the sterilization process should be determined as this will impact the heating delivered by the process equipment.

Location of the reference measuring point and process monitoring locations: locations of temperature monitoring devices are determined during the process validation. The location should be at the worst-case site (lowest-temperature and/or slowest-to-heat zone) in the load (or sterilizer). A convenient location that can be related to this zone may also be used. The latter is determined during the validation. If a convenient location is used, the sterilization (or depyrogenation) time is set to ensure that the worst-case location receives the required time at temperature.

It is typical to measure sterilizer temperatures rather than load temperatures. In continuous systems, it may be impossible to measure load temperatures. At least two temperature measurement devices are recommended

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for routine production cycles; these devices can be placed together in the selected location. If the two devices are separately positioned, the allowable difference between the devices should be determined.

When required, the speed of a conveyor should be monitored at the conveyor surface or a location as close as possible to the conveyor surface. Such monitoring will detect any problems that develop with the drive mechanism. However, the drive mechanism can be evaluated and alternate speed sites determined as acceptable (i.e., shaft rotation) if it can be ensured that such alternate sites represent the conveyor speed.

If the pressure in the sterilizer is controlled, the site for pressure monitoring should represent the worst-case location for leakage out of the sterilizer. For example, if the sterilizer is pressurized to maintain an aseptic environment and it is not hermetically sealed, the pressure monitor should be placed at the openings to the external environment.

When performing dry heat sterilization of sealed containers with liquid and gas phases, it could be necessary to add external pressure higher than ambient to compensate for internal pressure caused by liquid expansion and gas vapour pressure.

A.6.2 Equipment characterization

A.6.2.1 Equipment specification

There are two general categories for dry heat sterilization systems: batch and continuous (continuous systems are often referred to as “tunnel” or “conveyor” sterilization systems). Continuous sterilization systems are often used for the sterilization or depyrogenation of containers for aseptic fill. In these cases, no packaging is used, and the product is sterilized in an aseptic environment and delivered into an aseptic area. (Batch dry heat sterilization systems can also be used for this function.)

A.6.2.2 Identification

No guidance offered.

A.6.2.3 Safety

Written instructions should be available to alert the user to potential hazards associated with equipment use.

The equipment, including the sterilizer, should comply with national safety regulations in the country of intended use.

For batch sterilization systems, means should be provided of ensuring that the system cannot be accidentally operated unless the sterilizer doors are closed, sealed and locked. The sterilization system should be provided with a means of preventing the door from being unsealed if the sterilizer is heated or pressurized. Unless a fault condition is indicated, the sterilization system doors should be able to be unsealed, unlocked and opened only at the end of a sterilization cycle. The sterilization system should also be provided with a means of returning the sterilizer to atmospheric conditions and opening the loading doors if a failure or critical fault of the automatic cycle occurs.

If a loading, unloading or maintenance operation requires entrance into the sterilization system (whether batch or continuous), a lockout procedure and equipment should be provided to ensure that the sterilization system cannot be started while it is being worked on, except by the personnel conducting the work.

Unloading procedures should be developed to prevent damage to the package and danger to personnel, from hot materials. Sterilizer loads should be removed from the sterilizer and allowed to cool further before handling. This equilibrium should take place in an area free of draughts and with restricted traffic patterns.

A.6.2.4 Manuals and instructions

Information should be supplied to enable safe and proper installation, operation and routine maintenance of the sterilization system.

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The installation instructions should include a description of:

— the overall dimensions and masses of the sterilization system;

— the type of electrical supply, voltage, frequency and power;

— the flow and pressure for air supplies;

— the emitted sound intensity for operator safety;

— the cooling system, if applicable.

The instructions for safe and effective system operation should include a description of:

— the range of application, type of load and kind of packaging;

— sterilizer capacity;

— the available sterilizing cycles;

— the controls and indicating devices;

— safety devices;

— the exhaust system, if applicable;

— safety instructions;

— what to do in the event of a malfunction.

The maintenance and repair manual and instructions should include:

— what to do in the maintenance procedures;

— the recommended maintenance interval, timetable or schedule;

— electrical diagrams and circuits;

— hydraulic plans and circuits;

— a spare-parts list.

The process-control logic and/or software documentation necessary to operate and maintain the equipment control system (or any other software supplied) should be provided and accompanied by proof of validation. This validation may be performed by either an independent party or, where applicable, the manufacturer of the software in accordance with the requirements of the appropriate parts of the ISO 9000 series.

A.6.2.5 Utilities

A.6.2.5.1 The sterilization system should be designed to operate with an air or other gaseous heating medium supply which is free of liquid water, filtered to 5 µm, and contains not more than 0,5 mg of oil per cubic meter of free air. If an aseptic environment is required in the sterilizer, the heating medium should be passed through a microbiologically retentive filter.

For sealed products, it may not be necessary for air admitted to the sterilizer to be microbiologically filtered. Under conditions of high heat, however, permeable packaging can allow microbiological penetration that would not occur under normal conditions.

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A.6.2.5.2 The purchase specification for the sterilization system should include the characteristics of the electrical power that is available at the installation site. The required voltage should be tested and specified by the manufacturer. The sterilization system should be designed to operate with an electrical supply provided with means to simultaneously isolate all poles from the main supply and fuse each pole separately. The electrical installation should comply, for example, with applicable regional, national or local codes.

A.6.2.6 Components

The materials used in the sterilization system should resist the adverse effects of heat, and should not lead to deterioration of the quality of the heating medium or release any substances known to be toxic, in quantities that could create a health hazard. Ductwork and other surfaces that personnel could touch and which have a temperature higher than 70 °C should be thermally insulated. Connections should be provided so that temperature or other monitoring sensors can be inserted for testing temperature distribution and product heat penetration. Components that needs be replaced (e.g., HEPA or other filters) should be conveniently located, and the sterilization system should be installed in a manner that allows easy access.

A.6.2.7 Accessories

A.6.2.7.1 Trays, racks, carts and, where applicable, conveyors should be designed to allow uniform contact of all products with the heating medium. They should ensure that the product and package are not damaged or their sterility compromised. They should also be designed to hold the product securely and prevent movement of the product resulting from gas flow or movement of a conveyor.

A.6.2.7.2 Hot exhaust gases should be safely vented.

A.6.2.7.3 Filters, if used, should be appropriate for the intended use. They should be tested or replaced periodically. If HEPA filters are used, they should be tested at least every six months and certified and any cooling systems specified and controlled in accordance with this International Standard.

A.6.2.7.4 No guidance offered.

A.6.2.8 Control and recording systems

A.6.2.8.1 The sterilization cycle should be controlled by an automatic program control that has one or more preset sterilization cycles. The recording system should produce permanent, legible records of the values of the specified process parameters throughout the sterilization cycle at sufficient time intervals to characterize the rate of change of temperature and pressure, the speed of the conveyor, and time of exposure.

A.6.2.8.2 No guidance offered.

A.6.2.8.3 No guidance offered.

A.6.2.8.4 Access to the selection and change to the control device programmes should be restricted through the use of a special key, code, tool or other administrative and user access rights.

A.6.2.8.5 The monitoring and control instruments should be demonstrated as sufficient for their intended use. The measurement equipment should be part of the measurement management system in compliance with ISO 10012.

The following recommended instrument capabilities should be sufficient but may vary according to the requirements of the measurement process and capabilities of the sterilization equipment.

The temperature control device should:

— have an accuracy of ±1 % or better over the operating range;

NOTE The accuracy should be sufficient to demonstrate compliance with specifications.

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— be adjusted to ±0,5 °C at the sterilization temperature;

— be adjustable *in situ* by the use of a key, code or tool without dismantling the instrument.

The pressure control device (if used) should have an accuracy of ±1,6 % or better over the scale range of 0 to 3 bar (300 kPa); and be adjustable *in situ* by the use of a key, code or tool without dismantling the instrument.

The time control device should have an accuracy of ±1 % or better for time periods longer than 5 min and have an accuracy of ±2,5 % or better for time periods of up to 5 min.

Where possible, systematic errors should be quantified and corrected by applying the appropriate correction factors.

A.6.2.8.6 No guidance offered.

A.6.2.8.7 No guidance offered.

A.6.2.9 Control programs

A.6.2.9.1 The sterilization system manufacturer is usually responsible for the quality of any of the software provided. For proprietary reasons, the sterilization system manufacturer may decide not to disclose the software source list. In this case, the manufacturer should supply the user with a validation statement that includes a reference indicating on which points and to which standards the validation was performed. The logic of electromechanical or other means of control should also be validated.

A.6.2.9.2 The sterilizer user is responsible for all validations in support of all changes.

A.7 Product definition

A.7.1 General

Product definition involves documentation of essential information about the medical device to be sterilized. Product definition includes the medical device itself, the sterile barrier system containing the device, and any accessories, instructions or other items included in the sterile barrier system. It also includes a description of the intended functionality of the medical device and the manufacturing and sterilization processes, as well as an assessment as to whether the product is a new design or part of an existing product family. The following should be considered as part of product definition:

— physical description of the medical device (composition and configuration);

— intended use of the medical device;

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

— design characteristics that might affect choice of sterilization process;

— raw materials/manufacturing conditions that might affect microbiological quality;

— compatibility with sterilization process and sterilization specification for the product;

— required SAL;

— packaging;

— sterilization loading pattern;

— documentation of the above.

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A.7.2 Product safety and performance

A.7.2.1 No guidance offered.

A.7.2.2 During the design of medical devices, attention should be given to product functionality, design tolerances, product composition and configuration, and packaging materials to ensure effective delivery of the sterilant to all parts of the product. Product design should ensure that functionality and safety are not compromised by exposure to the anticipated range of sterilization conditions.

A.7.3 Packaging considerations

A.7.3.1 Packaging materials for dry heat sterilization should:

— be able to withstand high temperatures;

— permit easy heat penetration;

— provide a barrier to microorganisms after sterilization for the duration of product shelf life;

— resist tearing and puncturing;

— be able to be adequately sealed;

— be free of toxic ingredients and non-fast dyes and be low-linting.

A.7.3.2 Packaging materials that are not designed for dry heat sterilization temperatures might melt or burn causing damage to the sterilizer and/or product, and can present a fire hazard.

Health care facilities: small packages or containers are recommended with product density to be kept as low as possible to minimize the potential for adverse effects on air flow rate and distribution within the sterilizer.

A.7.3.3 The primary functions of packaging for a sterilized medical device are to allow sterilization of the package contents, to maintain sterility of the package contents until the package is opened, and to provide for removal of the contents without contamination.

A.7.3.4 No guidance offered.

A.7.3.5 No guidance offered.

A.7.4 Microbiological quality

Factors such as entrapment of microorganisms in the product, product contact with contaminated liquids during manufacturing, and use of materials that could support microbiological growth should be considered when developing a dry heat sterilization cycle. Recovery of heat-treated spores can also vary with time between treatment and culturing, and with culturing conditions. Therefore, such conditions should be carefully controlled and documented.

Health care facilities: attention to microbiological quality will necessitate strict procedures for collection and handling of used, re-usable medical devices, and for validation and control of cleaning processes for re-usable medical devices in accordance with the medical device manufacturer's instructions. For further information refer to ISO 17664 and ISO 15883-1. For instruments predating the publication of ISO 17664, regional or national guidelines for cleaning, decontamination and sterilization of such medical devices should be followed. Additionally, caution is given on the use of lubricants with medical devices, as they can add microbial contaminants to products and increase the difficulty of sterilant penetration.

A.7.4.1 No guidance offered.

A.7.4.2 No guidance offered.

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A.7.5 Product family

Products may be grouped into families for selection of the sterilization cycle, for validation activities and for routine control of dry heat sterilization. Product families should be established on the basis of the product bioburden, complexity of the product and packaging, and configuration and density of the sterilization load. The general approach is to classify individual products and packages by their similarities and then evaluate which conditions within a given classification provide the greatest challenge. A family of products may be represented by the master product, an equivalent product, or a simulated product. The studies or rationale used to place a product in a particular product classification should be documented.

The master product may represent the product family if assessment indicates that one member of the product family presents a challenge to the sterilization process that is greater than all of the other family members. In some situations, there may be several products in the family that could be considered the master product. In such circumstances, any one of these products may be selected as the master product to represent the family.

A group of equivalent products may represent the product family if assessment indicates that members of a product family are considered equivalent. Selection of the equivalent product should be either at random or in accordance with a planned schedule to include the equivalent family members. The manufacturing volume and availability of the product should be considered in selecting the product to represent the family.

The individual with responsibility for sterilization should participate in periodic reviews of the product families to assess the impact of any modifications to the product or process. The outcome of such assessments and reviews should be documented.

A formal review should be performed at a defined interval to ensure that all product families and products used to represent each family remain valid.

Health care facilities: a health care facility will often combine several 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 known to be the one most difficult to sterilize.

A.7.6 Biological safety

No guidance offered.

A.8 Process definition

A.8.1 Establishing the sterilization process: process definition is undertaken to define the process parameters for a dry heat sterilization process that will achieve the specified requirements for sterility for a defined product without adversely affecting product performance. Therefore, process definition includes at least two bodies of work: one directed at assessing the effect (if any) of a range of candidate values for the process variables on the product and packaging, and the other directed at defining the process parameters that will achieve the specified requirements for product sterility.

A.8.2 Process parameters: selection of the duration and temperature of the sterilization cycle to be used depends on the product configuration and the ability of the product and package to withstand temperatures and total heat input. Dry heat processes should be developed with the narrowest practical range of temperatures in the sterilizer. Process development studies may be performed in a research sterilizer if the production sterilizer is able to deliver the same processing parameters.

A.8.3 Sterility assurance level: no guidance offered.

A.8.4 Bioburden: see Annex E for additional guidance on bioburden.

A.8.5 Biological indicator: see Annexes C, D and E.

A.8.6 Chemical indicator: no guidance offered.

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A.8.7 Process challenge device (PCD): PCDs usually consist of a known spore population of *Bacillus atrophaeus* or another strain of microorganism known to have a resistance to dry heat that has been demonstrated to be equivalent to or greater than that of var. *B. atrophaeus*. There are several types of PCDs, including but not limited to the following.

— Inoculated product: the actual product may be inoculated directly or indirectly with spores of a known population and resistance. Direct inoculation is accomplished by applying a liquid suspension on the product. Indirect inoculation is accomplished by placing an inoculated carrier in or on the product or in the package.

  Direct inoculation of a product can result in variable resistance of the inoculum because of the occlusion of the spores on or in the product, surface phenomena and/or other environmental factors. Therefore, it is important to validate this practice to ensure that the resistance of the inoculated simulated product is reasonably correlated to the natural product. The inoculum recovery needs also to be validated. See Gillis and Schmidt[21], West[32] and ISO 11737-1 for additional information.

— Inoculated simulated product: a simulated product consists of portions of a device or a combination of components known to represent the greatest challenge to the process while still adequately representing all products in a product family. The simulated product may be inoculated by direct or indirect means.

— Inoculated carrier: a carrier such as a paper strip, disc or other substrate may be inoculated with spores of a known population and resistance. In order to use the inoculated carrier for cycle development, the resistance of the inoculated carrier should be correlated with the resistance of the inoculated product, simulated product or natural product.

— Natural product: a product with naturally occurring bioburden may be used as the microbiological challenge system for the absolute bioburden method of cycle development. When a natural product is used, there should be a bioburden monitoring programme that complies with ISO 11737-1 and determines the numbers, distribution and resistance of the bioburden before sterilization.

A simulated product may represent a product family if it constitutes a challenge to the sterilization process which is equivalent to or greater than the challenge associated with the products in the family. A simulated product is not intended for clinical use; it is fabricated solely for the development of the sterilization cycle, validation, and routine production sterilization. A simulated product may be one that:

a) is similar to the actual product in terms of materials, size, complexity and packaging, and is subjected to similar manufacturing processes (for example, a piece of the material used for implants that goes through the entire manufacturing process);

b) is a packaged combination of components from products in the family which would not typically be combined for use (for example, a tubing set containing multiple filters, clamps and stopcocks that are components of other products in the product family);

c) has similar heat transfer characteristics.

A.8.8 Tests of sterility: no guidance offered.

A.8.9 Risk Assessment: no guidance offered.

A.8.10 Depyrogenation: thermal destruction by dry heat (convection, conduction or radiant heat ovens) is the most common and effective way to destroy pyrogenic material of bacterial origin (endotoxin). Dry heat depyrogenation is the method of choice for heat-resistant materials such as glassware, metal equipment and instruments, as well as heat-stable chemicals, waxes and oils.

The standard method of depyrogenation, as described in many reference texts and compendia, is exposure at not less than 250 °C for more than 30 min (Sweet and Huxsoll[30]). Temperatures in excess of 180 °C for not less than 3 h have also been shown to effectively destroy bacterial endotoxin. Lower dry heat temperatures (i.e., 175 °C or less) are relatively insufficient to destroy at least 2 log units of pyrogen (Akers, et al.,[17];

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Ludwig and Avis[24]). For example, at 170 °C, a 3-log to 5-log reduction in endotoxin was shown to require processing times greater than 1 000 min.

Validation should be completed by demonstrating a 3-log reduction in endotoxin. One or more challenge articles should be treated with 1 000 or more USP international units (IU). A positive control, not exposed to thermal destruction, and the exposed challenge articles should be measured for endotoxin. The endotoxin assay should be the Limulus Amebocyte Lysate (LAL) test.

If a lower level of IU reduction is validated, a program should be in place for routine monitoring of endotoxin levels on articles before processing to ensure that they do not exceed the validated level.

When depyrogenation cycle validation is being conducted, the nature of the endotoxin should be considered. Different rates of endotoxin destruction have been found. Commercial endotoxin preparations formulated without fillers (i.e., lactose, polyethylene glycol) have been shown to be most resistant to dry heat exposure and, therefore, are regarded as worst-case challenges (Ludwig and Avis[25]). Destruction of endotoxin does not follow the simple logarithmic decline exhibited in sterilization studies on homogeneous spore suspensions. The inactivation kinetics of endotoxin from *E. coli*, *S. typhosa*, *Serratia marcescens*, and *Pseudomonas aeruginosa* have been demonstrated to be a non-linear, second-order process (Tsuji and Harrison[31]). Ensuring reliable endotoxin recovery from the challenge articles is crucial in endotoxin inactivation or removal studies (Avis, et al.[18]; Ludwig and Avis[24]).

So that depyrogenation is ensured, it is important that every article in the oven or tunnel be exposed to at least the stated temperature for not less than the stated time.

A.9 Validation

A.9.1 General

The validation programme is performed to evaluate the reliability of a sterilization or depyrogenation process. (Further references to “sterilization” will include depyrogenation where applicable.) Therefore, the validation protocol should be explicit in what, when, and how to measure. A major part of the protocol will also need to address the interpretation of the results. True objective validation is possible only if the requirements on which the sterilization process will be judged are determined and established before the validation. Compliance with a quality system such as ISO 13485 will ensure clear and objective validation.

Careful attention should be given to ensuring that physical parameters throughout the entire sterilization cycle (not just the exposure phase) are comparable to those set during cycle development. The conditioning (heat-up) phase could deliver significant lethality to the load.

The analysis of the data obtained during validation will demonstrate that a given sterilization cycle in an identified sterilization system will or will not render a specified load sterile. Therefore, validation is not related just to the sterilization system but also to such factors as the load and its configuration.

The homogeneity of the load and the loading pattern largely determine the number of temperature sensors needed. Using mixed loads could require an increase in the number of sensors being used. At least one sensor should be placed next to the monitoring and control sensors. Additional sensors may be used.

A good interpretation of the results is possible only if the criteria have been set before validation is performed. Adapting the requirements to the validation results contradicts any quality system or principle. If the sterilization process is not within the preset limits, experience and expertise are necessary to interpret the results and identify the problems causing noncompliance.

Validation may be scheduled as measurement sessions (or runs) among production runs of already validated loads. However, the interruption of validation sessions for scheduling purposes does not preclude the necessity to demonstrate process reproducibility throughout multiple consecutive validation runs. Thus, a new series of validation runs should be initiated following the investigation and correction of any failed validation run. However, such new series need not be initiated where a validation run has been disqualified because of an unforeseen failure of something peripheral to the system being validated. Peripheral failures include, for

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example, power failures, loss of services, and failure of external monitoring equipment. A peripheral failure would be documented as a disqualification and not as a failed validation test if the factor responsible for the failure is truly unrelated to the control or performance of the process or equipment being validated. Normally, a disqualified run would simply be rescheduled.

The IQ, OQ and PQ are part of the design control process and should be conducted using approved protocols.

The reliability of the validation results depends on the accuracy and reproducibility of the process delivered and measured. Calibration in conjunction with validation should ensure the accuracy, precision and sensitivity of the measuring equipment that is used in validation, as well as the equipment that delivers, senses, records or otherwise controls the specified process parameters. Specifications associated with calibration for validation should include detection values and tolerance limits for accuracy and precision. The validation programme should include provisions for addressing out-of-calibration conditions that might be encountered. Calibration standards should be traceable to a national or international standard.

A.9.1.1 No guidance offered.

A.9.1.2 No guidance offered.

A.9.2 Installation qualification

The IQ plan should include procedures that will ensure that the sterilization system and its connected service utilities comply with the specifications, and the sterilizer is safe and fit for use.

Upon completion of the IQ, “as built” drawings should be prepared because the actual installation may not be the same as that planned in the design or installation drawings.

A.9.2.1 No guidance offered.

A.9.2.2 No guidance offered.

A.9.3 Operational qualification

A.9.3.1 The OQ plan should include a study that demonstrates that the sterilization system will perform the required process without product. Any carts trays or racks used to hold the product should be in the sterilizer. OQ demonstrates that the sterilization equipment and any auxiliary items have been supplied and installed in accordance with their specification.

A.9.3.2 Temperature sensors should be distributed throughout the volume occupied by the load. Locations should include

— expected hot zones (e.g., near heating medium inlets);

— expected cold zones (e.g., near doors or locations farthest from heating medium inlets);

— areas next to fixed sterilizer temperature sensors;

— the top, geometric centre, and bottom of the load volume, distributed uniformly.

For small batch sterilizers, a minimum of three temperature sensors, or one temperature sensor per 0,028 m^3 (1 ft^3), should be used up to 0,28 m^3 (10 ft^3) of sterilizer volume. A minimum of ten temperature sensors should be used for sterilizer volumes of 0,28 m^3 or more. The number of sensors should be based on the temperature range found and the specification required. The smaller the temperature range in the sterilizer, the fewer temperature sensors will be needed. Temperature should be monitored throughout the entire cycle using the longest anticipated exposure time.

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For continuous (tunnel) sterilization systems, the temperature across the conveyor belt should be monitored. Sensors should be fastened to the belt to include the edges of the product area and the centre. If the sterilization system is set with different temperature zones, each zone should be monitored. The monitoring location should be above the maximum product height. If the temperature sensors are rotated (i.e., the zones are not monitored simultaneously), a reference position is needed to compare temperatures from different zones. If the sterilizer is not zoned, the temperatures should be monitored in the heat-up (entrance) area, exposure area and cool-down (exit) area. Locations should include the area above the maximum height of the product and across the width occupied by the product. Locations next to control probes should also be included. A minimum of ten temperature locations should be monitored. In larger sterilizers, a minimum of five temperature locations per 2,8 m^3 (100 ft^3) of product volume should be monitored. Temperature should be measured at equilibrium operating conditions for the maximum exposure time. It could be necessary to bring a continuous sterilization system to operating temperature before conducting heat mapping.

If pressurization of the sterilizer or tunnel is required, measurements should be conducted in areas where the gaseous heating medium is expected to leak out. In tunnel units, these areas are typically the exit and entrance locations.

Additional process parameters that should be measured during validation include:

— heating medium flow rates and uniformity;

— amperage draw of electrical heater(s);

— conveyor speed, if applicable.

A.9.4 Performance qualification

A.9.4.1 General

A.9.4.1.1 PQ demonstrates that the equipment consistently operates in accordance with predetermined criteria and the process produces product that meets its specification. Performance qualification should be performed in the equipment used to sterilize the product. The PQ includes a physical qualification and microbiological qualification.

Examples of significant changes that should be qualified include:

— packaging;

— product design;

— sterilization load configuration or density;

— sterilizing equipment;

— sterilization process.

The effects of such changes on all stages of the sterilization process should be determined.

A.9.4.1.2 The performance qualification is performed to demonstrate the ability of the process to attain defined physical conditions, within specified tolerances, throughout the load.

A.9.4.1.3 Different loads and modifications of loads should be evaluated to determine the acceptable range of product and packaging types and densities that can be sterilized by a specific process.

A.9.4.1.4 See A.9.4.1.3.

A.9.4.1.5 No guidance offered.

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A.9.4.1.6 No guidance offered.

A.9.4.2 Performance qualification — Physical

A.9.4.2.1 Temperature profiles of the sterilization load should be determined for each representative loading pattern. The number of temperature sensors recommended for the empty sterilizer during the OQ should provide an adequate profile of the load. Product should be at or below the minimum specified temperature (see 9.4.1) before it is introduced into the sterilizer, unless the process is controlled using load temperature. Temperature sensors should be distributed throughout the volume occupied by the load, with particular attention to any suspected hot and cold spots or zones.

Simultaneous internal (penetration) and external (distribution) temperature monitoring may be conducted during the physical PQ. This monitoring might indicate the presence of unforeseen problems that could occur in loaded versus empty sterilizers; in this case, twice the number of temperature sensors recommended above should be used.

It should be confirmed that the product meets its specified requirements for safety, quality and performance after application of the sterilization process at the upper tolerances of the process parameters.

A.9.4.2.2 No guidance offered.

A.9.4.2.3 The reproducibility of the production cycle is demonstrated by conducting a minimum of three cycles at nominal process parameters, using the worst-case full sterilizer load for each cycle. At least one minimum load cycle should be run to confirm that the parameters at minimum loading are consistent with the maximum loading. If mixed product loads are to be processed, sufficient cycles should be run to demonstrate that the mix of products results in consistent process parameters.

A.9.4.2.4 No guidance offered.

A.9.4.3 Performance qualification — Microbiological

A.9.4.3.1 The microbiological qualification should include a minimum of three fractional cycles that demonstrate reproducible kill from cycle to cycle and uniform kill throughout the sterilizer or tunnel using a full sterilizer load of worst-case product. The cycles should provide less lethality than the production process, which can be accomplished by reducing the exposure time, temperature or both.

The type of BI or PCD is determined by the type of microbiological validation that has been selected (see 8.3 and 8.4). If an external or different microbiological monitor is to be used in routine production, it should be included in the microbiological qualification.

A.9.4.3.2 No guidance offered.

A.9.4.3.3 Biological indicators or other PCDs should be placed in the load on the basis of data acquired during the physical performance qualification (A.9.4.1).

The number of BI or PCD locations should be based on the temperature range found and the specification required. The smaller the temperature range in the sterilizer, the fewer BI or PCD locations will be needed. For small batch sterilizers (those having a sterilizer volume less than or equal to 0,28 m^3), a minimum of ten BI or PCD locations should be used. For larger batch sterilizers (those having a sterilizer volume more than 0,28 m^3), a minimum of twenty BI or PCD locations should be used. Each of the temperature sensors should be placed next to a BI or PCD location.

For continuous (tunnel) sterilization systems, the microbiological kill across the conveyor belt should be determined. Biological indicators or other PCDs should be placed in the product on the belt to include the edges of the product area and the centre. In addition, BIs or PCDs should be included at the beginning, middle, and end of each processing run. Biological indicators or other PCDs should be placed in the worst-case product, which is generally the largest. A minimum of ten BIs or other PCDs should be passed through the tunnel during each of three runs with the tunnel at equilibrium conditions. The runs should be conducted on three different days with the tunnel shut down between each run. It may be necessary to bring a

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continuous sterilization system to operating temperature before the microbiological qualification is conducted. The microbiological monitoring should be conducted at a fractional exposure time, which is established by adjusting the conveyor speed. Each of the temperature sensors should be placed next to a BI or PCD location. Because it is not practical to continuously monitor the load temperature throughout the entire processing run for continuous (tunnel) sterilization systems, the load temperatures should be monitored, at minimum, at the beginning, middle and end of each processing run.

A.9.4.3.4 No guidance offered.

A.9.4.3.5 No guidance offered.

A.9.4.4 Performance qualification — Depyrogenation

For validation of depyrogenation processes, a standard endotoxin challenge is used in place of BIs or other PCDs. The number and placement of the endotoxin challenge should follow the guidance given in A.9.4.3.3 for BIs or PCDs. A 3-log reduction of a standard endotoxin challenge is typical; however, a lower level of reduction can be validated, provided that a programme is in place to ensure that pyrogen levels are controlled to the validated limits.

A.9.4.4.1 No guidance offered.

A.9.4.4.2 No guidance offered.

A.9.5 Additional sterilization systems

The equivalency of a specific sterilization process can be established by comparing the data obtained when the sterilization process is run in the candidate sterilization process equipment with the data obtained when the same sterilization process is run in the existing equipment. This comparison should include an evaluation of the equipment's ability to deliver the desired specifications reproducibly to a worst-case product load. The specifications should be those that were previously validated in the performance qualification of the sterilization process in the existing equipment. The candidate sterilization process equipment should also be compared with the existing equipment to determine how significant the differences are. The IQ and OQ for all candidate equipment should be reviewed to ensure that the equipment is suitable for the sterilization process.

The evaluation of equivalency is a three-phase process consisting of design and engineering evaluation (Phase 1), process analysis and evaluation (Phase 2), and microbiological evaluation (Phase 3).

Phase 1: the design and engineering evaluation consists of a comparison of the equipment used in the candidate sterilization process system to the existing validated sterilization process system. Some of the factors to be considered include:

— volume of the sterilizers;

— volume used in the sterilizers;

— available joules per cubic metre of the heat source for the sterilizers;

— capacity of the circulation system of the sterilizers;

— equilibration time in the sterilizers;

— temperature uniformity in the sterilizers;

— overall cycle time in the sterilizers;

— conveyor speed, if applicable.

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The outcome of this evaluation is a basis for determining the extent of further qualification testing required in the second and third phases. If the evaluation shows that the equipment is not similar, it is still possible to establish process equivalency on the basis of the results of the second and third phases. Typically, the greater the similarity between the candidate equipment and existing equipment, the less testing will be required in those phases.

Phase 2: the second phase in establishing equivalency is an analysis of all process data associated with a validated process in the candidate equipment. These data should be compared to the specification limits for that specific sterilization process. The specification limits are those established in the initial validation of the sterilization process in the existing equipment. The specifications, acceptance criteria and load configuration should be the same as defined for the initial process validation studies. Statistical methods that evaluate both the central tendencies of the test data and their degree of variability may be used to assist in this evaluation.

An evaluation that compares the load profiles within each candidate sterilizer should be performed. This evaluation should be performed using the existing process parameters. The critical parameters for the process should be defined before the evaluation is performed. These parameters should include distribution and control of product temperature in the load throughout the cycle, as well as heat-up and cool-down times of the product.

A comparison of the processes from the sterilizer runs should indicate that the processes are equivalent in their ability to meet the existing process specification limits and any additional acceptance criteria. If the analysis of the data meets the acceptance criteria, then a reduced microbiological PQ with product may be performed (see Table A.2) to validate the candidate sterilizers. The data generated should be analysed and compiled in a format that allows its use in future process equivalency determinations.

If the acceptance criteria are not met in the process analysis and evaluation, then it is not possible to demonstrate process equivalency even though the results of the other phases may be equivalent.

Phase 3: the third phase of the analysis of process equivalency is the performance of a microbiological evaluation. This evaluation consists of the consideration of any factors that would affect the lethality of the sterilization process.

The factors that should be evaluated include any changes to the sterilization location or manufacturing location that could affect the bioburden level of the product as presented for sterilization. An increased distance between the manufacturing facility and sterilization site could result in higher bioburden levels, particularly if the product supports microbiological growth. Differences in manufacturing environments could lead to the production of product with higher bioburden levels than previously validated, even if the product does not support microbiological growth.

Results evaluation: the results of the microbiological evaluation, in conjunction with the results of Phase 1 and Phase 2, are used to determine if a microbiological PQ should be performed (see Table A.2). If the conclusions of the design and engineering evaluation (Phase 1), process analysis and evaluation (Phase 2), and microbiological evaluation (Phase 3) are equivalent, then the performance of a microbiological PQ is not necessary.

Table A.2 — Evaluation of results

Phase 1 Design and engineering evaluation	Phase 2 Process analysis and evaluation	Phase 3 Microbiological evaluation	Minimum number of microbiological PQ runs
Equivalent	Equivalent	Equivalent	None
Not equivalent	Equivalent	Equivalent	1
Equivalent	Equivalent	Not equivalent	1
Not equivalent	Equivalent	Not equivalent	1
Equivalent or not equivalent	Not equivalent	Equivalent or not equivalent	3

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If Phase 2 and either Phase 1 or Phase 3 concluded that the processes are equivalent, or if only Phase 2 concluded that the processes are equivalent, then at least one microbiological PQ run should be performed (see Table A.2). This microbiological performance qualification should be sufficient to demonstrate that the desired SAL of the process is achieved even if the equipment or microbiological evaluation is not equivalent.

If the conclusion of Phase 2 was that the processes are not equivalent, then the process should be declared "not equivalent" and should be fully validated according to the requirements of this International Standard before the candidate equipment is used. The results of Phase 1 or Phase 3 do not change this declaration of "not equivalent."

If the performance of one or more microbiological PQ runs is required, then the type of cycle, specification limits, and lethality requirements established in the validation of the existing process should be used to evaluate the performance of the candidate equipment. The specification limits, lethality requirements, and acceptance criteria should be defined before the performance of the microbiological PQ.

Maintenance of equivalency: the established process equivalency programme should define the requirements that the equipment needs to meet to produce repeatable performance characteristics annually. The analysis should define the acceptable range of the operating parameters and level of variability to maintain equivalency from year to year. All decisions related to the outcome of the analysis to determine if candidate equipment may be declared equivalent to the existing sterilization process equipment need to be documented. At a minimum, the documentation package should include:

— the complete specification for the candidate equipment, which should fully describe the equipment, operating specifications and tolerances, and reference or provide a list of applicable operating procedures, calibration procedures and maintenance schedules;

— evidence or assessment of the ability of the equipment to deliver the intended process, including a reference to the current OQ;

— the results of the comparison between the candidate process equipment and the existing, validated process equipment, which comparison should clearly demonstrate that all major systems and critical parameters were assessed, and include statistical analyses, if used;

— evidence or assessment of the product conditions during processing in the candidate equipment to demonstrate equivalence to the existing process;

— the results of evaluation of additional factors that could affect the lethality of the sterilization process;

— the documented conclusion that the candidate equipment is equivalent to the equipment specifically referenced in the current validation study to achieve the specified SAL, which statement should include or reference the results of any additional testing performed to supplement the existing validation study and any further testing performed for confirmation/qualification of routine release of product from the existing, validated cycle;

— approval by the sterilization specialist and other individuals as required by the normal change control practices within the organization;

— the listing of applicable sterilizer operating procedures and specifications issued or changed to authorize use of the candidate equipment for routine processing of product.

A.9.6 Review and approval of validation

A.9.6.1 The validation report should be approved by the same functions that approved the original protocol.

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A.9.6.2 On completion of the validation programme, the test results should be compiled into a validation report. The validation report should include or reference the following:

— details of products sterilized (including packaging and load patterns in the sterilizer);

— the specification of the sterilizer;

— the IQ/OQ data;

— the records, physical and biological, of all PQ runs;

— an indication that all gauges, recorders, etc. were within calibration at the time of the PQ;

— provision for future review and requalification;

— the validation protocol(s);

— the documented procedures used;

— documented operating procedures including process control limits;

— maintenance and calibration procedures;

— if a biological or equipment failure occurred, this occurrence and the corrective action taken.

A.10 Routine monitoring and control

A.10.1 Routine control

A.10.1.1 In the development and qualification phase, the process is established as capable and reproducible. During this evaluation, control variables are identified and referred to in a process validation file. Documented procedures are developed from the validation data for routine process execution and control. In accordance with documented procedures, the key control variables (materials, loading, operating parameters and so forth) are read and monitored during routine sterilizer use to verify process control and acceptability.

The relationships between temperature controller, control programme (if applicable), sterilizer temperature probe and load temperature distribution are established to ensure that materials at all locations in the sterilizer meet the required time at temperature during exposure.

The timer setting should reflect the minimum exposure time at the location in the sterilizer that is the last to reach the set point. When manual timing is required, temperature documentation intervals should be appropriately determined on the basis of the length of the exposure period.

The time required to reach the set point (heat-up time) is reviewed and documented for each cycle to verify process control and ensure that product integrity has been maintained.

The airflow settings for sterilizers so equipped are documented and should reflect the specification. A pressure reading for sterilizers so equipped should also be reviewed and documented for each sterilizer run.

For continuous systems, the speed of the conveyor is verified and documented for each sterilization run.

A.10.1.2 The load configuration is inspected to verify that it reflects the configuration established during qualification. A new load size qualification can be established by comparing the temperature distribution during minimum and maximum load validation studies. If the minimum and maximum loads are determined to be equivalent, then loads of intermediate sizes can be considered qualified.

A.10.1.3 No guidance offered.

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A.10.1.4 Automated control systems produce a record of the events of the sterilization process. This record is compared to the operational parameters included in documented procedures and signed by the individual verifying process acceptability. Manual system records include a predetermined recording format to document the sterilizer load and configuration, cycle identification, run date and cycle events such as time, temperature, airflow and (if applicable) pressure readings. This information is gathered during the cycle or derived from remote monitoring devices.

A.10.1.5 No guidance offered.

A.10.1.6 No guidance offered.

A.10.1.7 No guidance offered.

A.10.1.8 No guidance offered.

A.10.1.9 No guidance offered.

A.10.2 Routine monitoring

No guidance offered.

A.10.3 Process monitoring locations

Biological indicators are placed in the product load in locations determined to be the most difficult to sterilize. Alternatively, the appropriate PCDs may be used. The locations in the sterilizer shown to have the shortest time at temperature should be challenged by the BI or PCD.

If parametric release has been established, then microbiological monitoring with BI or PCD and microbiological testing of product after sterilization are not required.

A.11 Product release from sterilization/depyrogenation

A.11.1 If the process parameters are outside their specified tolerances, product should not be released. Product should be evaluated in accordance with nonconforming product procedures. The decision on the disposition of the product should be documented.

The suitability of the product and packaging for resterilization and the effect of repeated exposures to the dry heat sterilization process on product functionality should be included in the validation exercises. If product is sterilized again because the initial exposure to the dry heat sterilization process was outside of the specification, records of the initial sterilization process should be included or referenced in the sterilization file or batch record.

A.11.2 If a dry heat sterilization cycle operating within specified tolerances has been demonstrated to be both effective and reproducible, then confirmation that the process parameters were within specification limits is taken as evidence of the reliability of the cycle. Parametric release is the declaration of adequacy of sterilization of product on the basis of direct measurement and evaluation of physical parameters in the sterilizer. No other samples or indicator testing are required for parametric release.

If BIs or other PCDs are used to monitor the sterilization cycle for product release, records of the physical sterilization process parameters and results of indicator testing are reviewed to demonstrate the effective delivery of the dry heat sterilization process. Guidance on the selection, use and interpretation of results of BIs is contained in ISO 14161.

A.11.3 No guidance offered.

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A.11.4 Failure to meet the physical specification or failure of the BI or other PCD to meet its specified requirements should lead to the sterilization load being placed in quarantine, the cause of failure investigated, and the investigation documented.

A.12 Maintaining process effectiveness

A.12.1 General

The purpose of this activity is to identify and implement the periodic checks and tests necessary to ensure that the specified sterilization process is reproducibly delivered to product during routine processing.

To ensure that the sterilization process continues to deliver the required SAL, it is necessary to evaluate any changes to product and product packaging, to the processes and to equipment. The use of a comprehensive product and process change control system is recommended. Any change that raises doubt about the lethality that will be delivered to a sterilization load should initiate a review.

For health care facilities reprocessing re-usable medical devices, the effectiveness of the cleaning process should be periodically reviewed to confirm that the process is still effective and provides an adequate reduction in bioburden prior to resterilization of the medical device. Decontaminated medical devices should be visually examined for cleanliness prior to resterilization. Medical devices that are not clean should not be resterilized.

A.12.2 Recalibration

Documented programmes for calibration of controlling and monitoring equipment are necessary to ensure that the sterilization process continues to deliver product with the required SAL and performance characteristics.

A procedure should be written to cover calibration and calibration frequencies. All instruments or gauges that are not part of the calibration system should be clearly marked to indicate that calibration is not required.

The frequency of calibration should be based on the manufacturer's recommendations, instrument operational experience, use of redundant or secondary instrumentation for product release and risk assessment.

Instrumentation and gauges found to be out of calibration should be identified and documented in a report that is reviewed by appropriate engineering and quality assurance personnel to assess the effect of the error on the sterility of the product processed during the period of time since the previous calibration.

Periodic audits of the calibration programme should be performed to assess the adequacy of the reported data, calibration frequency, training of the technicians and compliance of the system with the quality assurance programme.

A.12.3 Maintenance of equipment

A.12.3.1 Preventive maintenance is a critical component of the system and should be covered in an SOP. This procedure should address the schedule for review of critical equipment parts, using the equipment manufacturer's instructions and historical information. A log should be maintained and provide a chronological record of all preventive and corrective maintenance activities performed. Equipment components that typically require preventive maintenance include (but are not limited to):

— door gaskets;

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— control equipment;

— air filters;

— moving belts (for product transfer);

— motors;

— alarms;

— insulation.

A.12.3.2 Sterilization equipment that is not properly maintained can generate an inaccurate record of process parameters during the sterilization cycle. If these data are used for product release it could result in loads being released that have not been adequately sterilized.

A.12.3.3 The review of maintenance records should focus on identifying:

— trends in component failure;

— whether changes are required in the maintenance schedule;

— whether changes have occurred to any maintenance procedure;

— whether additional training is required by maintenance persons;

— the effectiveness of actions taken.

A.12.4 Requalification

Requalification is performed to confirm that inadvertent process changes have not compromised the effectiveness of the sterilization process.

Validation data, any subsequent revalidation data and routine processing data should be reviewed at least annually to ensure that inadvertent process changes have not occurred and to demonstrate that the original validation study remains valid. Procedures for review and results of the review should be documented.

Requalification is necessary if significant changes are made in the sterilization system (hardware or software), process, product or packaging that could affect sterilization efficacy. The following are examples (not necessarily all-inclusive) of changes that could necessitate performance requalification unless data are available to establish equivalency:

— product tolerances: a significant change in the product material or design tolerances which could affect the heating rate of the product;

— product design: a significant change in the product design, including product materials, composition, or thickness, which could affect the efficacy of the sterilization process;

— packaging: changes that could affect microbiological barrier efficacy, substantive changes in packaging design or changes in vendors which could significantly affect physical properties and heat transfer;

— equipment: changes that could affect specified operating parameters or substantially change the rate of heat transfer into the product;

— process: alterations in the process which could substantially change the manner in which process parameters are achieved and controlled (e.g., changes in process control software);

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— product loading or density: changes in the previously validated loading configurations that could affect heat transfer into the load;

— product bioburden: any change in raw materials, the environment or processing that could influence the efficacy of the sterilization cycle.

To determine if requalification is required, process changes should be reviewed by a sterilization specialist. The sterilization specialist should determine the extent of requalification required. The review and extent of requalification necessary should be documented.

A.12.4.1 No guidance offered.

A.12.4.2 No guidance offered.

A.12.4.3 No guidance offered.

A.12.5 Assessment of change

No guidance offered.

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Annex B
(informative)

Process definition based on inactivation of the microbial population in its natural state (bioburden-based approach)

B.1 General

The bioburden-based approach is applicable in cases where the effects of the sterilization process on the product need to be minimized.

This approach is not suitable for sterilization of re-usable medical devices as the bioburden challenge to the sterilization process from re-usable medical devices is difficult to define.

The bioburden-based approach requires extensive knowledge of the naturally occurring product bioburden. This approach necessitates ongoing enumeration and characterization of product bioburden. Bioburden of product samples representative of production should be determined in accordance with ISO 11737-1. Bioburden isolates should be screened for heat resistance. Resistance can be determined by exposing product samples and or bioburden isolates to graded exposure times and or process temperatures. The product samples or bioburden isolates are then subject to microbiological tests to determine the number of survivors or fractional positives present post-exposure. When the number and resistance of the naturally occurring bioburden has been identified, the process parameters necessary to achieve the specified SAL for the product can be established.

The ongoing bioburden monitoring programme for the product should be designed to detect any changes in bioburden that might adversely affect the sterilization process.

Guidance and discussion on this method are given in the literature such as Halvorson and Ziegler[22], Pflug and Holcomb[28], PDA TR3[16] and Pflug[27].

B.2 Product selection

Product selected for studies on process definition should be representative of routine production.

B.3 Procedure

B.3.1 Determine the product bioburden in accordance with ISO 11737-1.

B.3.2 To characterize the resistance, expose product to dry heat in predetermined time and or temperature increment(s) of the anticipated sterilization process utilizing equipment and procedures for the fractional exposure of product samples or bioburden isolates. (See Annex C of ISO 18472:2006 and Annex A of ISO 11138-4:2006).

NOTE Although the above references are indicated for biological and or chemical indicators, the guidance provided would be appropriate for naturally occurring bioburden and product samples.

B.3.3 The required accuracy and precision of increments should be established, and the delivery of dry heat should be controlled and monitored to meet defined limits. See 4.7 of ISO 18472:2006.

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B.3.4 After time graded exposures to dry heat, determine the lethality of the sterilization process by at least two of the following methods a) or b) and c). (See Annex C and Annex D of ISO 11138-1:2006.)

a) direct enumeration (see Annex C of ISO 11138-1:2006)

b) the fraction negative method (see Annex D of ISO 11138-1:2006)

c) survival-kill response characteristics.

From these results, the rate of inactivation of the product bioburden can be calculated.

B.3.5 From a knowledge of the product bioburden (established in accordance with 7.4.2), its resistance to the sterilization process and its rate of inactivation, determine the extent of treatment necessary to achieve the specified SAL for the product. An example of this type of calculation is given in Pflug[27] and in Section 17.B.4.0 or 6.2.1.9 of PDA TR3:1981[16].

B.3.6 The level of treatment identified should be carried out in triplicate to demonstrate reproducibility.

B.4 Maintaining process effectiveness

B.4.1 This approach requires on-going monitoring of, and control over, the product bioburden.

B.4.2 Confirm the continued appropriateness of the sterilization process at defined intervals using product representative of routine production.

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Annex C
(informative)

Process definition based on the inactivation of reference microorganisms and knowledge of bioburden (combined bioburden/biological indicator approach)

C.1 General

The combined bioburden/biological indicator approach combines knowledge of the resistance of a biological indicator to a given sterilization process, with knowledge of the product bioburden population and resistance, to establish sterilization process parameters. This approach is applicable where the product bioburden is known and controlled.

The combined bioburden/biological indicator approach requires product bioburden to be monitored at frequent intervals, the bioburden levels to be relatively consistent over time and resistance of this bioburden to be demonstrated to be equal to, or less resistant than, the resistance of the biological indicator.

Resistance of the biological indicator is demonstrated by exposing the biological indicator to graded exposure times at the proposed process temperature and determining the lethal rate (rate of inactivation) of the sterilization process. Knowledge of this rate of inactivation, the population and the relative resistance of the bioburden allows the exposure time to be established for the sterilization process so that an SAL can be predicted.

Guidance and discussion on this method can be found in ISO 14161[4] and also in the literature such as Halvorson and Ziegler[22], Pflug and Holcomb[28], PDA TR3[16], and Pflug[27].

C.2 Procedure

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

C.2.2 Create a challenge to the sterilization process comprising a known number of microorganisms with known resistance to dry heat by either:

a) placing biological indicators within the product at position(s) where sterility is most difficult to achieve or by placing them within a PCD

   or

b) by inoculating the product with reference microorganisms at position(s) within the product where sterility is most difficult to achieve.

NOTE An inoculated product can be considered to be a biological indicator. (See 8.4 and ISO 11138-1.)

If the location of the challenge is not the most difficult-to-sterilize position, its relationship to the most difficult-to-sterilize position should be established.

C.2.3 Package the challenge in the same manner as product produced routinely and include it within the sterilization load in the location where sterility is most difficult to achieve.

C.2.4 Expose the sterilization load to dry heat under conditions selected to deliver less lethality than is delivered during routine sterilization, so that not all reference microorganisms will be inactivated.

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C.2.5 After time graded exposures to dry heat, determine the lethality of the sterilization process by one of the following methods:

a) direct enumeration (see C.3.1)

or

b) the fraction-negative method (see C.3.2).

From this result, the rate of inactivation of the reference microorganisms can be calculated.

C.2.6 From a knowledge of the product bioburden (established in accordance with 7.4.2), bioburden resistance to the sterilization process and the rate of inactivation of the reference microorganisms, determine the extent of treatment necessary to achieve the specified SAL for the product. The resistance of the product bioburden can be demonstrated by information provided in published literature and/or a test of sterility for fractionally exposed product and comparison to reference organisms or the PCD.

C.3 Process lethality determination

C.3.1 Direct enumeration

C.3.1.1 Determine the lethality of the sterilization cycle by construction of a survivor curve using direct enumeration of survivors.

C.3.1.2 Further details on this method are given in ISO 14161 and C.3 of ISO 11138-1:2006.

Subclause C.3 of ISO 11138-1:2006 requires a minimum of five exposure points covering:

a) one exposure in which the sample is not subjected to the sterilant (e.g. zero time exposure);

b) at least one exposure in which the viable population is reduced to 0,01 % of the original inoculum (4 $\log_{10}$ reduction);

c) a minimum of three exposures covering the intervals between exposure a) and exposure b) above.

C.3.2 Fraction-negative method using Holcomb-Spearman-Karber procedure (HSKP)

Expose biological indicators to time graded exposures to dry heat with all other parameters remaining constant. After exposure, assay the test samples by direct immersion using an appropriate culture medium. Score the samples as to the proportion of samples showing no growth after incubation. Further details on this method are given in ISO 14161 and D.3.1 of ISO 11138-1:2006.

Subclause D.3.1 of ISO 11138-1:2006 requires a minimum of five exposure conditions covering:

a) at least one set of samples in which all tested samples show growth;

b) at least two sets in which a fraction of the samples show growth (quantal region);

c) at least two sets of samples in which no growth is observed.

A modification of the HSKP, the Limited Holcomb-Spearman-Karber Procedure (LHSKP), may be used if the same number of samples is exposed at each time point and the time interval is constant. For further guidance, see D.3.2 of ISO 11138-1:2006.

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C.3.3 Fraction-negative method using Stumbo Murphy Cochran Procedure (SMCP)

The formula for the Stumbo Murphy Cochran Procedure (SMCP) requires one result in the fraction negative range consisting of time, t, the number of units negative for growth, r, the number of replicates, n, at one exposure time within the fraction-negative range, and the initial number of microorganisms per replicate, N_0.

To obtain valid data using SMCP, D.3.3 of ISO 11138-1:2006 requires that the D value be calculated as the average of at least three runs in the fraction negative range in order to confirm reproducibility.

For further guidance, see ISO 14161.

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Annex D
(informative)

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

D.1 General

D.1.1 The overkill approach is based on the inactivation of high numbers of resistant reference microorganisms. In this approach, a biological indicator is used to present a significant microbial challenge to a defined dry heat sterilization process. Process conditions established to inactivate the biological indicator challenge are significantly more severe than those conditions necessary to inactivate the naturally occurring product bioburden. Generally, the overkill approach provides an SAL in excess of 10^{-6}. The overkill approach does not require extensive knowledge about the naturally occurring product bioburden, or for the product bioburden to be determined at frequent intervals. However, it is prudent for product bioburden to be monitored periodically.

The overkill approach can be used where packaged product is able to withstand the excessive thermal conditions and exposure necessary to achieve sterilization. It can also be used where the actual microbial challenge is unknown or cannot be reliably measured, as is the case with reprocessing of re-usable medical devices. It is widely employed for sterilization of both virgin product and re-usable medical devices.

Qualifying a sterilization process for re-usable medical devices requires an approach different to that used for virgin product as the challenge to the sterilization process is difficult to define and pre-sterilization treatments (such as cleaning) are difficult to validate and control. A sterilization process in this situation needs to be conservative and designed to deliver a large safety margin, exceeding that required to achieve the specified SAL. This type of “overkill” treatment can be determined either mathematically based on an empirical microorganism (full cycle approach) or from a reduced level of treatment delivered to a defined microorganism (partial cycle approach).

D.1.2 The overkill method is best suited to sterilization processes where linear inactivation kinetics can be demonstrated. This method is particularly applicable in health care applications where the challenge to the sterilization process is difficult to define.

D.1.3 Guidance and discussion on the overkill method are given in, ISO 14161[4] and in literature, such as Halvorson and Ziegler[22], Pflug and Holcomb[28], PDA TR3[16] and Pflug[27].

D.1.4 Overkill process definition should use either the approach given in a) or b) below.

a) Half-cycle approach: a total of three consecutive experiments resulting in total inactivation of the biological indicator (with a population of not less than 10^6) should be performed in order to confirm the minimum exposure time. The specified exposure time should be at least double this minimum time.

   NOTE In a dry heat sterilization process, microbial inactivation starts to occur at a temperature below the specified sterilization temperature (during the heat-up phase) and increases in rate as the temperature increases to the sterilization temperature. Microbial inactivation continues to occur during the exposure time at the sterilization temperature and also continues to occur into the cool-down phase. The half-cycle approach requires the exposure time of routine sterilization cycles to be at least double that used during microbiological PQ studies thereby building a good margin of safety into routine production sterilization cycles.

b) Cycle calculation approach*:* the routine processing parameters that deliver minimally a 12 spore log reduction (SLR) of the biological indicator should be established using one of the methods described in C.3. The number of cycles is dictated by the method used.

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D.1.5 The resistance of the product bioburden should be shown to be equal to or less than the resistance of the biological indicator.

D.2 Product selection

Product selected for studies on process definition should be representative of routine production.

D.3 Procedure

D.3.1 Identify a worst-case product or PCD which is at least as difficult to sterilize as the most difficult item anticipated for the process.

D.3.2 Establish the location(s) within the product at which sterility is most difficult to achieve.

D.3.3 Create a challenge to the sterilization process comprising a known number of microorganisms with known resistance to dry heat by either:

a) placing biological indicators within the product at position(s) where sterility is most difficult to achieve or by placing them within a PCD

   or

b) by inoculating with reference microorganisms the position(s) within the product where sterility is most difficult to achieve.

NOTE An inoculated product can be considered to be a biological indicator. (See 8.5 and ISO 11138-1.)

If the location of the challenge is not the most difficult-to-sterilize position, its relationship to the most difficult-to-sterilize position should be established.

D.3.4 Package the challenge in the same manner as product produced routinely and include it within the sterilization load in the location where sterility is most difficult to achieve.

D.4 Partial cycle approach

D.4.1 Expose the sterilization load to dry heat under conditions designed to deliver less lethality than is delivered during routine sterilization.

D.4.2 Confirm the extent of treatment necessary to inactivate 10^6 reference microorganisms on a biological indicator that complies with ISO 11138-4.

D.4.3 The level of treatment identified should be carried out in triplicate to demonstrate reproducibility.

D.4.4 If the inactivation of 10^6 reference microorganisms is confirmed, determine the extent of treatment necessary to achieve the specified SAL taking into account the number and resistance of the reference microorganisms on the biological indicator.

D.4.5 The extent of treatment necessary can be defined conservatively as twice that used by the reduced level of treatment.

D.5 Full cycle approach

D.5.1 Expose the sterilization load to dry heat under conditions designed to deliver sufficient lethality to inactivate a biological indicator complying with ISO 11138-4.

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D.5.2 The nominal population on the biological indicator should exceed by at least $0{,}5 \times \log_{10}$ of the population, calculated from F_{Bio}[12] and the certified D_{160} value for the biological indicator. This takes into account variations in microbiological manipulations and changes in D value for the test microorganism, which can be caused by contact with the product or a contaminating material.

F_{Bio} is determined using Equation (D.1)

$$F_{Bio} = D_{160}(\log N_o - \log N_u) \quad \text{(D.1)}$$

where

D_{160} is the D value of the biological indicator at an exposure temperature of 160 °C;

N_o is the pre-exposure viable population of the biological indicator;

N_u is the post-exposure viable population of the biological indicator.

NOTE ISO 11138-4 specifies a D_{160} value of 2,5 min with a z value $\geqslant$ 20 °C. Thus the F_{Bio} of a process should be at least $2{,}5 \times 12 = 30$, where the overkill approach is used and an SAL of 10^{-6} is required.

D.5.3 *Bacillus atrophaeus* is an example of a reference microorganism that demonstrates high resistance to dry heat and which is suitable for use in this approach.

D.5.4 Variations in delivered lethality that may occur within the sterilization system and the probability that this could result in a positive test result should be included in the calculation to determine the target F_H.

The minimum F_H required to achieve a particular SAL can be calculated from using Equation (D.2).

$$F_H = D_{160}(\log_{10} a - \log_{10} b) \quad \text{(D.2)}$$

where

a is the viable population of the biological indicator;

b is the specified SAL (10^{-6}).

D.5.5 Expose the sterilization load to dry heat under conditions selected to deliver the target F_H to confirm that there are no survivors. If results of the test establish that this level of treatment is acceptable, then perform two further repeat tests to demonstrate reproducibility.

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Annex E
(informative)

Process development

E.1 Process development — Biological methods

Following are three methods used to determine process lethality. The overkill approach has the greatest margin of safety and is the easiest method to use.

The overkill method: the overkill approach is based on the use of a resistant BI with a known population to demonstrate a specific SLR. Overkill methods traditionally have been used to establish industrial dry heat sterilization cycles. This approach is based on the premise that the sterilization process will inactivate a high microbiological challenge (e.g., between 10^3 and 10^6) that is not necessarily related to the presterilization bioburden. This method is called “overkill” because the cycle conditions established to kill the microbiological challenge, with an additional safety factor, should be much more severe than those required to inactivate the product bioburden.

The D value of the microbiological challenge and product bioburden microorganisms can vary in different environments and at different sites. Thus, the initial count or challenge concentration is selected on the basis of the resistance of the spore population under the conditions of use.

When the overkill method is used, the potential thermal degradation of the product and its package or container should be considered. Increased chemical and physical degradation, increased formation of particulates, and limited product shelf life may result from excessive thermal exposure.

The manufacturer should obtain data for the typical bioburden loading associated with the product. Those data need not be as extensive nor need they be obtained as frequently as when bioburden cycle development methods are used.

The combined biological indicator/bioburden method: the combined BI/bioburden approach is based on the use of a resistant BI or PCD with a population that is equal to or greater than that of the natural product bioburden. This method is appropriate when sufficient bioburden data are available from the bioburden monitoring programme to demonstrate that a BI or PCD with a population of less than 10^6 can be used.

In the combined BI/bioburden approach, the microbiological sterilization challenge of the product could necessitate inactivation of the initial inoculum concentration to an established logarithmic level. The relative resistance and population of the initial challenge inoculum of the microbiological challenge microorganism should be compared with the mean number and thermal resistance of the bioburden typically associated with the product. The comparison should demonstrate that inactivation of a predetermined level of microbiological challenge ensures that the desired probability of a bioburden survivor is achieved. This method is considered to be based on bioburden, therefore, the bioburden should be enumerated and the resistance determined as in the absolute bioburden method.

The absolute bioburden method: representative product samples that are indicative of the highest levels of bioburden and most resistant organisms are subjected to incremental dwell periods. Following exposure, a test of sterility will need to be performed in accordance with ISO 11737-2.

The absolute bioburden method involves screening product for thermally resistant microorganisms – for example, by using a bioburden isolate (recovered for purposes of challenging product sterilization) that is representative of the most resistant bioburden population. The isolate may be propagated, inoculated onto or into the product, and used in product sterilization challenge studies to directly demonstrate the desired probability of survival for the product bioburden. Typical bioburden counts used in the calculation are based on the mean bioburden count plus three times the standard deviation.

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Bioburden resistance can be determined by exposing product samples containing the bioburden to fractional exposure time increments at proposed cycle conditions and then conducting sterility tests to determine the number of survivors or fractional positives present at various durations of exposure (Halvorson and Ziegler[22], Pflug and Holcomb[28]).

Product bioburden usually consists of a mixture of organisms that typically have different D values. In this case, the logarithmic reduction of each organism after the same exposure time will be different. Thus, the cumulative log reduction after each exposure interval will also not be the same and the curve will not be linear. A straight line from the original count to any single point after exposure will either under- or over-estimate the end point and the SAL.

Alternatively, isolation and propagation, followed by inoculation onto the product or an appropriate carrier, may be used to determine the resistance of bioburden organisms; however, propagation can change the resistance of the bioburden. The resistance of other microbiological challenge systems that could be used for routine biological monitoring should also be determined.

A cycle based on bioburden requires frequent bioburden screening to determine bioburden counts and species associated with the products. The frequency of bioburden screening depends on the quality and variability of the historical data, the kinds of products being sterilized, the manufacturing process, and the type of sterilization process. Representative products from each manufacturing facility should be sampled during routine production. A bioburden monitoring programme should be designed to evaluate any changes in product components and manufacturing, the environment or production processes that could significantly affect bioburden. If a change in the manufacturing environment occurs, additional bioburden monitoring should be considered.

E.2 Process development — Physical methods

Mathematical techniques and graphing methods have been developed by which the process lethality (often expressed as F_{phys}) can be calculated from product temperature data. The calculation of an F value derived from physical process parameters is explained in such publications as PDA TR3[16], Stumbo[29], and Pflug[27]. Definitions of D value, F value, F_{bio}, F_{H} value, F_{phys}, and z value are given in Clause 3 of this International Standard. Both the reference temperature and z value are needed to calculate the F value.

The larger the D value, the more resistant the microorganism is to thermal destruction. The value can be derived by plotting the logarithm of the number of microbiological survivors against sterilization exposure time; the time corresponding to a 1-log reduction in numbers can then be directly measured.

The use of F_{H} to express cycle lethality assumes a reference temperature. The standard reference temperature for dry heat is 160 °C, with a z value of 20 °C. It should be noted, however, that with the variety of temperatures used in dry heat processes, any reference temperature can be selected. Product temperature data accumulated during the entire process (heating, exposure, cooling) is converted to the equivalent lethality at 160 °C and mathematically or graphically integrated to derive a physical lethality value expressed as the equivalent minutes of exposure at 160 °C. For example, each minute at 140 °C has a lethal rate equivalent to 0,1 min at 160 °C if $z = 20$ °C. Some software programs can calculate the process F value continuously during the sterilization cycle using input from one or more temperature sensors in the product. Specific techniques to calculate F_{H} are described in the references included with this International Standard and in other literature.

Preliminary studies should be conducted to select the locations for monitoring temperatures to calculate F_{H} so that the F values used in process development represent the greatest challenge to the system. These studies should include temperature distribution studies in the loaded sterilization system to find slow-to-heat regions in the sterilizer sterilizing zone, determine whether they are reproducible, and find the lowest-temperature regions in the sterilizing zone during exposure. These studies should demonstrate that the temperature sensor is in the product's low-temperature zone, or a documented technical rationale should be given for the selected location of the temperature sensor. If the size of the package or container or the volume of fill is small, consideration should be given to the possible effects of heat conduction along the probe and into the product, and to the need to insert the probe to the proper depth in order to minimize stem conduction errors. Small-gauge sensor wire can be used to minimize this heating effect.

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Accurate estimation of a process F_{phys} value requires that the temperature measurement system be properly calibrated. Correction factors need to be applied to individual readings before calculating cycle lethality. The validity of the F_{phys} value is based on the assumption that the resistant species in the product bioburden have a z value of approximately 20 °C. The relationship between the F_{phys} value and the F_{bio} value of organisms in the product/sterilization environment (D and z values) should be determined. Validation depends on first-order death kinetics. The death of microorganisms from dry heat has been demonstrated to follow first-order kinetics for a population consisting of a single species of organism.

Lethality using physical process data should be determined in conjunction with appropriate microbiological studies. Whereas the F_{phys} is determined by temperature probes and the resulting physical data, the F_{bio} is determined by the PCD and the resulting biological data (D values and z values). By using the biological data together with the F_{phys}, one can predict the effectiveness of a sterilization cycle.

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