TECHNICAL SPECIFICATION

ISO/TS 19930

First edition
2017-12

Guidance on aspects of a risk-based approach to assuring sterility of terminally sterilized, single-use health care product that is unable to withstand processing to achieve maximally a sterility assurance level of 10^{-6}

Document d'orientation sur les aspects d'une approche, fondée sur l'appréciation du risque, permettant d'assurer la stérilité des produits de santé à usage unique, soumis à une stérilisation terminale y compris ceux ne pouvant pas supporter un traitement atteignant un niveau d'assurance de la stérilité maximal de 10^{-6}

Reference number
ISO/TS 19930:2017(E)

ISO copyright office
Ch. de Blandonnet 8 • CP 401
CH-1214 Vernier, Geneva, Switzerland
Tel. +41 22 749 01 11
Fax +41 22 749 09 47
copyright@iso.org
www.iso.org

Contents

Page

Foreword

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

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

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

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

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

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

Introduction

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

Compliance with the requirements of International Standards for development, validation and routine control of sterilization processes ensures that the sterilization process is both reliable and reproducible so that predictions can be made, with reasonable confidence, that there is a low probability of there being a viable microorganism present on a health care product after sterilization.

Specification of this probability is a matter for regulatory authorities and can vary from country to country.

For example, the European Standards Organization has published EN 556-1. EN 556-1 has been harmonized in the European Union and also been adopted in a number of countries outside Europe, for example Australia and China. EN 556-1 specifies that a sterility assurance level (SAL) of 10^{-6} or less (e.g. 10^{-7}) has to be achieved in order to designate a terminally sterilized medical device as sterile. EN 556-1 includes an explanatory note that specifies that permission for acceptance of a sterility assurance level of greater than 10^{-6} (e.g. 10^{-5}) may be sought through appropriate regulatory bodies and such permission requires consideration of the individual situation, including consideration of the risk assessment undertaken by the manufacturer of the medical device.

In the USA, the American National Standard ANSI/AAMI ST67 specifies that a maximal sterility assurance level of 10^{-6} is required for the majority of terminally sterilized health care product. ST67 also indicates that

a) there are circumstances for which a greater maximal sterility assurance level of 10^{-3} can be acceptable for certain product, e.g. product that does not contact breached skin or compromised tissue, and

b) when product cannot withstand a terminal sterilization process that achieves maximally a SAL of 10^{-6}, a greater sterility assurance level (e.g. 10^{-5}) might be acceptable for that product.

There is health care product that is unable to withstand a terminal sterilization process achieving maximally a SAL of 10^{-6}. This might be because some or all of the materials that constitute the product are sensitive to one or more traditional sterilization processes, for example cellular or biologically-based components.

The purpose of this document is to provide general guidance on the considerations to be taken into account in selecting a SAL for health care product that is unable to withstand terminal sterilization to meet the general requirement to achieve maximally a SAL of 10^{-6}. Particularly, the document gives advice in relation to fulfilling the EN 556-1:2001, Note to 4.1 and AAMI ST67:2011, 4.2.4.

It is recognized that this topic is contentious for some regulatory agencies, conformity assessment bodies, manufacturers, contract sterilizers and national standards bodies. Some see development of this document as a potential move to relax the current regulatory quality requirements to supply product as sterile. This is not the intention. This document states clearly that a decision to approve a SAL other than 10^{-6} for a specific product resides solely with the relevant regulatory agency. A cautious approach has been taken during development of this document and ongoing diligence is maintained to ensure that the spirit in which this document is intended is not misconstrued. The purpose of this document is to promote discussion between interested parties and to bridge a gap in existing standards and regulations. This document provides much-needed guidance on technical aspects when considering an

alternative SAL to 10^{-6} for identified high clinical need, terminally sterilized product that is unable to withstand the processing conditions necessary to achieve maximally a SAL of 10^{-6}.

This document is intended to be applied by process developers, manufacturers of health care product to be sterilized and organizations responsible for the sterilization of health care product.

Guidance on aspects of a risk-based approach to assuring sterility of terminally sterilized, single-use health care product that is unable to withstand processing to achieve maximally a sterility assurance level of 10^{-6}

1 Scope

This document provides guidance on identifying the aspects to be considered as part of a risk-based approach to selecting a sterility assurance level (SAL) for terminally sterilized, single-use health care product that is unable to withstand processing to achieve maximally a SAL of 10^{-6}.

In addition, this document provides

a) background information on the assurance of sterility and sterility assurance level, and

b) guidance on strategies that can allow the achievement of a maximal SAL of 10^{-6}.

This document describes the elements of a quality management system which are applied to enable the appropriate selection of a SAL for terminally sterilized, single-use health care product that is unable to withstand processing to achieve maximally a SAL of 10^{-6}.

NOTE It is not a requirement of the International Standards for development, validation and routine control of a sterilization process to have a full quality management system. Attention is drawn to the standard for quality management systems (see ISO 13485) that controls all stages of the lifecycle of health care product.

This document is applicable to sterilization processes in which microorganisms are inactivated by physical and/or chemical means.

This document does not apply

— to selecting a maximal SAL greater than 10^{-6} for health care product that is able to withstand processing to achieve maximally a SAL of 10^{-6};

— in cases where a maximal SAL of 10^{-6} is required and an alternative SAL is not allowed;

— in cases where a maximal SAL of greater than 10^{-6} (e.g. 10^{-3}) has been accepted by regulatory authorities within their jurisdiction for health care product for defined use;

— to the sterilization of used or reprocessed health care product;

— to sterilization of health care product by filtration.

This document does not describe detailed procedures for assessing microbial inactivation.

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

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

This document does not supersede or modify published International Standards for particular sterilization processes.

This document neither recommends a SAL for a given health care product nor identifies a maximal SAL for a health care product to be labelled “sterile”.

NOTE These are matters for regulatory authorities and can vary from country to country.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

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

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

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

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

3.1
aseptic processing
handling of *sterile* (3.29) product, containers and/or devices in a controlled environment, in which the air supply, materials, equipment and personnel are regulated to maintain sterility

3.2
assurance of sterility
qualitative concept comprising all activities that provide confidence that product is *sterile* (3.29)

3.3
bioburden
population of viable microorganisms on or in product and/or *sterile barrier system* (3.30)

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

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

3.6
chemical indicator
test system that reveals change in one or more pre-defined *process variables* (3.20) based on a chemical or physical change resulting from exposure to a process

3.7
correction
action to eliminate a detected nonconformity

Note 1 to entry: A correction can be made in conjunction with a *corrective action* (3.8).

[SOURCE: ISO 9000:2015, 3.12.3]

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

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

Note 2 to entry: Corrective action is taken to prevent recurrence whereas *preventive action* (3.18) is taken to prevent occurrence.

[SOURCE: ISO 9000:2015, 3.12.2, modified — "detected" and "or other undesirable situation" have been added to the definition and the Note 3 to entry has been deleted.]

3.9
development
act of elaborating a specification

3.10
establish
determine by theoretical evaluation and confirm by experimentation

3.11
fault
situation in which one or more of the *process parameters* (3.19) or cycle parameters is/are outside its/their specified tolerance(s)

3.12
health care product
medical device(s) (3.14), including *in vitro* diagnostic medical device(s), or medicinal product(s), including biopharmaceutical(s)

3.13
load
product, equipment or materials to be processed together within an operating cycle

3.14
medical device
instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

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

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

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

— supporting or sustaining life;

— control of conception;

— disinfection of medical devices;

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

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

Note 1 to entry: Product which can be considered to be medical devices in some jurisdictions but not in others include:

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

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

— disinfection substances;

— aids for persons with disabilities;

— devices incorporating animal and/or human tissues;

— devices for *in vitro* fertilization or assisted reproduction technologies.

[SOURCE: ISO 13485:2016, 3.11, modified — The first two list items in the Note 1 to entry have been added.]

3.15
medical device manufacturer
natural or legal person with responsibility for design and/or manufacture of a *medical device* (3.14) with the intention of making the medical device available for use, under their name, whether or not such a medical device is designed and/or manufactured by that person themselves or on their behalf by another person(s)

[SOURCE: GHTF/SG1/N055:2009, 5.1 — modified.]

3.16
overkill approach
method of defining a sterilization process that achieves a maximal *sterility assurance level (SAL)* (3.32) for product substantially less than 10^{-6}

3.17
parametric release
declaration that product is *sterile* (3.29), based on records demonstrating that the *process variables* (3.20) were delivered within specified tolerances

3.18
preventive action
action to eliminate the cause of a potential nonconformity or other potential undesirable situation

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

Note 2 to entry: Preventive action is taken to prevent occurrence, whereas *corrective action* (3.8) is taken to prevent recurrence.

[SOURCE: ISO 9000:2015, 3.12.1]

3.19
process parameter
specified value for a *process variable* (3.20)

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

3.20
process variable
chemical or physical attribute within a cleaning, disinfection, packaging or sterilization process, changes in which can alter its effectiveness

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

3.21
product
tangible result of a process

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

3.22
requalification
repetition of part or all of *validation* (3.38) for the purpose of confirming the continued acceptability of a specified process

3.23
risk
combination of the probability of occurrence of harm and the severity of that harm

[SOURCE: ISO/IEC Guide 51:2014, 3.9]

3.24
risk analysis
systematic use of available information to identify hazards and to estimate the risk

[SOURCE: ISO/IEC Guide 51:2014, 3.10]

3.25
risk assessment
overall process comprising a *risk analysis* (3.24) and a *risk evaluation* (3.26)

[SOURCE: ISO/IEC Guide 51:2014, 3.11]

3.26
risk evaluation
procedure based on the *risk analysis* (3.24) to determine whether tolerable risk has been exceeded

[SOURCE: ISO/IEC Guide 51:2014, 3.12]

3.27
risk management
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

[SOURCE: ISO 14971:2007, 2.22]

3.28
specify
stipulate in detail within an approved document

3.29
sterile
free from viable microorganisms

3.30
sterile barrier system
minimum package that minimizes the risk of ingress of microorganisms and allows aseptic presentation of the *sterile* (3.29) product at the point of use

3.31
sterility
state of being free from viable microorganisms

Note 1 to entry: In practice, no such absolute statement regarding the absence of microorganisms can be proven [see *sterilization* (3.33)].

3.32
sterility assurance level
SAL
probability of a single viable microorganism occurring on an item after sterilization

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

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

3.33
sterilization
process used to render product free from viable microorganisms

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

3.34
sterilization process
series of actions or operations needed to achieve the specified requirements for sterility

Note 1 to entry: This series of actions includes pre-treatment of product (if necessary), exposure under 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.

3.35
sterilizing agent
physical or chemical entity, or combination of entities, having sufficient microbicidal activity to achieve sterility under defined conditions

3.36
terminal sterilization
process whereby product is sterilized within its *sterile barrier system* (3.30)

3.37
test of sterility
technical operation performed as part of *development* (3.9), *validation* (3.38) or requalification to determine the presence or absence of viable microorganisms on product or portions thereof

3.38
validation
confirmation process, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

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

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

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

[SOURCE: ISO 9000:2015, 3.8.13]

4 Assurance of sterility and sterility assurance level (SAL)

4.1 Sterility is defined as the state of being free from viable microorganisms. The term is an absolute one and descriptions implying degrees of sterility are not only confusing but erroneous. Sterilization is the process by which sterility is achieved, i.e. the process of inactivating or removing all viable microorganisms. Normally, sterilization is achieved by exposure to a physical or chemical sterilizing agent for a predetermined extent of treatment. Terminal sterilization, comprising exposure of product to the sterilization process in a packaged or assembled form that maintains the sterility of the product, is the common practice. When terminal sterilization is not possible, aseptic processing provides an alternative approach to produce sterile product.

4.2 In practice, a microorganism is considered inactivated when it cannot be detected using culture media in or on which it has been shown previously to proliferate. Detection generally requires the

production of turbidity in liquid culture medium or a colony on the surface of solid medium. A single microorganism has to be able to proliferate through many generations to be detected and a microorganism that cannot reproduce or can only reproduce through a few generations would be classified as inactivated on applying either of these detection criteria. However, there is no culture medium capable of culturing all known microorganisms. Furthermore, microorganisms that have survived a potentially lethal process can have specific metabolic requirements and, if these requirements are not met by supplementation, it might not be possible to get microbial recovery in a standard culture medium. The absence of all viable microorganisms is therefore a negative state that can never be practically proved.

4.3 Microorganisms exposed to a sterilizing agent are not all inactivated at the same instant. Laboratory studies have shown that the kinetics of inactivation of a pure culture of microorganisms by physical and/or chemical sterilizing agents generally can be best described by an exponential relationship between the number of microorganisms surviving and the extent of treatment with the sterilizing agent. These findings indicate that after any given treatment, regardless of extent, there is always a finite probability a microorganism will survive. For a sterilization treatment, this probability is determined by the level of the bioburden, its inherent resistance and by the environment in which the organisms reside during treatment. Even when viable organisms cannot be detected, the probability of survival exists. Inevitably, the probability of microbial survival decreases as the extent of treatment is increased, but never reaches zero. Thus, sterility is an absolute state, the achievement of which cannot be guaranteed absolutely.

4.4 The probability of a single microorganism surviving on a product after exposure to a given sterilization process is defined as the sterility assurance level (SAL). SAL can also be regarded as the probability of a single viable microorganism in a population of terminally sterilized product items. Assurance of sterility is a qualitative concept that comparatively can be described as greater or lesser assurance of sterility. SAL, however, has a quantitative value and a SAL of 10^{-6} takes a lesser value than a SAL 10^{-4}. This is a mathematical fact. Hence, when all other factors influencing assurance of sterility are equal, there is a greater assurance of sterility associated with a lesser SAL (see Figure 1). Standards for sterilization processes should always express a specified SAL as a maximum value and use terms "less than" or "greater than" when comparing different values for SAL. The use of terms such as "better than", which implies a difference in quality rather than a difference in quantity, or "higher" and "lower", which relate to height and not quantity, should be avoided when referring to SAL.

Processes with decreasing numerical values of SAL have increasing assurance of sterility (see Figure 1).

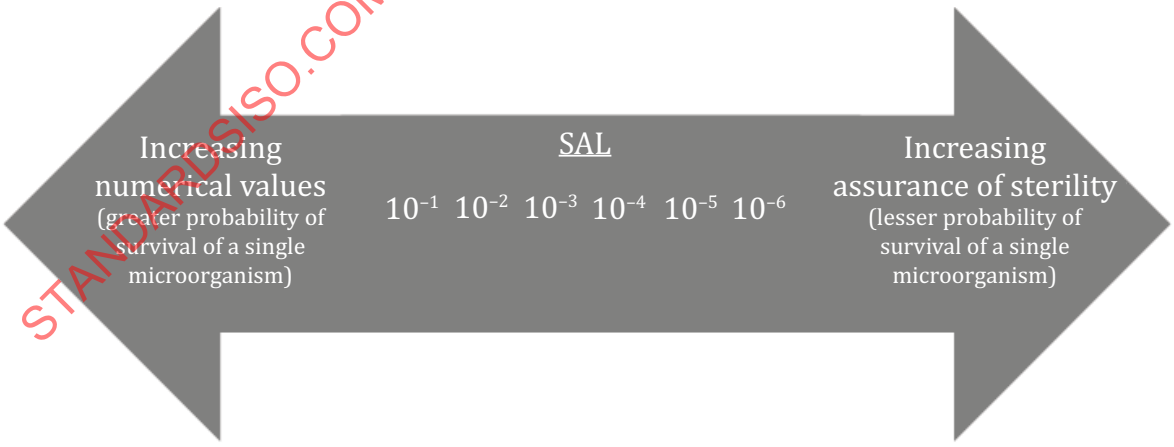

Figure 1 — Numerical values of sterility assurance level (SAL) together with the concept of assurance of sterility

4.5 A non-sterile product item has one or more viable microorganisms present. Due to the nature of microbial inactivation, the decline in the number of surviving microorganisms on subjecting a microbial population to increasing levels of treatment with a sterilizing agent can be extrapolated to determine the treatment to achieve the probability of survival of any particular number of microorganisms. However,

it is important to note that SAL is the probability of survival of a single microorganism. As the presence of a single microorganism on a product item cannot be demonstrated in practice, SAL is a mathematical extrapolation. The term SAL is applicable exclusively to a terminal sterilization process.

In practical terms during establishment and validation of a sterilization process, the numbers and/or resistance of microorganisms surviving on product are estimated. This is usually by recovery and enumeration techniques, or by use of the test of sterility to determine the proportion of product items having viable microorganisms on them following an extent of treatment less than that employed for sterilization. These practical techniques determine the occurrence of a non-sterile product item remaining after treatment. For this reason, there is a difference between SAL, an extrapolation to the probability of a single microorganism surviving a defined treatment, and the probability of a non-sterile unit (PNSU), which is the probability of one or more microorganisms being present on a product item in a population of items. The terms SAL and PNSU are often misused as being synonymous.

It is not appropriate to compare a SAL for a terminal sterilization process with a rate of occurrence of a contaminated unit estimated by process simulation for an aseptic process. Aseptic processing relies on a number of independent factors for prevention of recontamination of previously sterilized components during the assembly or filling of product into a final container and is not based on known and predictable inactivation kinetics. Recontamination can occur, for example, by contact with an operator, contact with a contaminated surface, or chance contamination by an airborne particle. Aseptic processes are generally qualified by process simulation during which microbiological growth medium is used to simulate product during the filling process or used to test assembled product for sterility. The number of contaminated units is used as an estimate of the effectiveness of the process. As each aseptic processing run is slightly different due to operator interventions and variation in environmental conditions, the results of a process simulation apply to that simulation run and only indicate what might be expected during routine operations. Due to the variability and chance nature of occurrence of contamination during aseptic processing, aseptic process simulation does not give a true probability of there being a contaminated unit but rather an indication of what might happen in the routine processing of the next batches.

4.6 A SAL is an outcome of the inactivation of product bioburden at a rate determined by the resistance of the microorganisms comprising that bioburden. SAL is expressed as a negative exponent of the base 10. On applying theoretically two sequential microbicidal processes, each treatment associated with a process inactivates the bioburden independently, by its individual mechanism of action, according to its own inactivation rate and achieves its own characteristic SAL. Given these theoretical considerations, it follows that arithmetic addition of the SAL exponents associated with the two processes does not provide a value that represents the total SAL achieved by the two microbicidal treatments.

4.7 In practice, a sterilization process is established and validated to predict achievement of a SAL equal to or less than a specified value. In establishing and validating the process, account is taken of variations in the delivery of the sterilization process, such that the specified SAL is achieved. This includes, but is not limited to, achievement of the maximal SAL

a) at positions on product at which the attainment of sterilization conditions is most difficult to achieve,

b) using process conditions that deliver reduced microbicidal activity, and

c) at locations in the sterilization equipment at which the conditions deliver the least microbicidal activity.

4.8 There are examples of product that have portions that are hermetically sealed and do not come into patient contact, such as the interior of an implantable cardiac pacemaker or implantable defibrillator. Such portions of product are not required or intended to be sterile and the development and validation of the sterilization process does not apply in such locations. Furthermore, there is product for which a claim of sterility applies only to a portion of that product, such as the fluid path in an administration set for intravenous infusion. In such situations, the development and validation of the sterilization process

does not apply to any portion of product not intended to be sterile and the sterile barrier system or design of product is not intended to maintain sterility of those portions of product.

4.9 Assurance of sterility comes from actions taken in all phases of development, validation and routine control of a terminal sterilization process together with the control of the microbiological quality of product materials and manufacturing environment. Typically, such actions include but are not limited to

a) specifying sterility requirements as design and development input,

b) selecting material combinations that can withstand exposure to a sterilizing agent,

c) identifying the nature of the product to be sterilized and its presentation to the sterilization process,

d) defining an appropriate sterilizing agent,

e) defining sterilization conditions that have adequate microbicidal effectiveness,

f) controlling the microbiological status of incoming raw materials and/or components,

g) validating and routinely controlling any cleaning and disinfection procedures used on product,

h) controlling the environment in which product is manufactured, assembled and packaged,

i) controlling manufacturing equipment and processes,

j) controlling personnel and their hygiene,

k) controlling the manner in which product is packaged,

l) specifying the equipment that is needed to control the sterilization conditions,

m) showing that the defined sterilization process is effective and reproducible,

n) demonstrating that the validated process has been delivered during routine processing,

o) maintaining the continued effectiveness of the sterilization process over time, and

p) controlling the conditions under which product is stored.

5 Management responsibility

5.1 The implementation of a quality management system is often a regulatory requirement for a range of activities in the lifecycle of product, from design and development, through production and service provision, to distribution and post market surveillance. Within such a quality management system, responsibility and authority for implementing and meeting the guidance described in this document are specified and the applicable responsibility is assigned to competent personnel.

5.2 If the guidance described in this document is implemented by organizations with separate quality management systems, the responsibility and authority of each party are specified. Examples of situations where organizations with separate quality management systems are involved include one organization undertaking design and development, another organization undertaking production activities and a third delivering the sterilization process.

5.3 In relation to assurance of sterility, the overall responsibility generally resides with the manufacturer who places the product onto the market or maintains the registration for the product. Roles and responsibilities are defined within the quality management system of this manufacturer. The manufacturer will work with a conformity assessment body or regulatory authority in order to achieve the necessary authorization to make the product available. In situations where a standard such as EN 556-1 or AAMI/ANSI ST 67 is accepted as providing conformity with the regulatory requirements,

this will entail demonstrating conformance with the standard. In situations where a recognized standard is not complied with because the product is unable to withstand the extent of treatment necessary to achieve maximally the specified SAL, the manufacturer has to agree with the appropriate authority

a) the requirements to be met to justify a claim of sterility, and

b) the need and rationale for the selected SAL when a SAL greater than 10^{-6} (e.g. 10^{-5}) is applied.

5.4 In situations in which maximally a SAL of 10^{-6} cannot be applied and a SAL greater than 10^{-6} (e.g. 10^{-5}) is under consideration, the associated risk assessment and risk mitigations that are adopted within the manufacturer's risk management process will be of great importance. The manufacturer needs to identify aspects determining the selection of SAL to be considered in the risk assessment. In such cases, the manufacturer has to assign responsibility for the risk management activities to appropriately qualified individuals and the considerations of risk-benefit assessment are likely to require the input of an individual or individuals with appropriate clinical expertise. Annex A provides an illustration of the sequence of activities in selecting and justifying an alternative SAL.

6 Compatibility of product with a sterilization process

6.1 Requirements in sterilization standards

6.1.1 ISO 14937:2009, 5.4.1 requires that the effects of exposure to the sterilizing agent on the properties of materials be studied and ISO 14937:2009, 8.10 requires a demonstration that product meets its specified requirements for safety, quality and performance following application of the specified sterilization process.

6.1.2 Standards for traditional sterilization methods (for example, radiation, ISO 11137-1:2015, 8.1; ethylene oxide, ISO 11135:2014, 7.2; moist heat, ISO 17665-1:2006, 7.6; dry heat, ISO 20857:2013, 7.2.2; liquid chemicals, ISO 14160:2011, 7.6; low temperature steam and formaldehyde, ISO 25424:2009, 7.4) require product performance to be demonstrated after the product is exposed to process parameters likely to maximize effects on materials. ISO 11137-1:2006, 8.1, explicitly requires product performance to be demonstrated over the defined lifetime of the product.

6.2 Selecting and assessing materials and product

6.2.1 Nine strategies to achieve maximally a SAL of 10^{-6} for product that has limited compatibility with terminal sterilization methods are outlined in 7.3. Some approaches might not require modification or significant re-assessment of materials, e.g. reducing bioburden through control of personnel and cleanroom modification, or adoption of sterilization process parameters that have less detrimental effects. Other strategies might require reassessment of materials, selection of new materials, redesigning of product or changing the sterilization method.

6.2.2 A general assessment of compatibility of materials with sterilization methods, particularly the effects on aspects critical to product performance, can eliminate options for the sterilization method, or give guidance for selecting materials when investigating a new sterilization method. For example:

a) moist and dry heat cause many plastic materials to undergo thermal deformation;

b) radiation sterilization can cause some electronic components/systems to undergo significant changes;

c) oxidative gas sterilization methods can cause some drugs and biologics to undergo loss of activity or function;

d) gaseous sterilization methods can fail to achieve sterility of product that has locations that cannot be penetrated by the sterilizing agent;

e) sterilization methods that use light as the sterilizing agent can fail to achieve sterility for product that has opaque or translucent components.

While all materials require clinically relevant testing after sterilization, materials with limited compatibility with a given sterilization method, e.g. as included in tables in AAMI TIR 17 and related annexes, require additional testing.

6.2.3 The following provides guidance using the approach provided in AAMI TIR 17 for selecting and assessing materials.

6.2.3.1 Product design and material processing are intimately related to the choice of sterilization method. The functional performance of many polymeric materials can be affected by the manufacturing process, e.g. injection moulding or extrusion temperature or cooling rate. Some sub-optimal conditions will cause generic product functionality defects, while some will cause functionality defects that particular sterilization methods can worsen. Reviewing processing issues related to materials from which product is manufactured will help prevent problems and increase the probability of designing and implementing sterilization-compatible product for a given sterilization method.

6.2.3.2 Understanding and investigating clinically relevant product performance outputs, including biocompatibility (see ISO 10993 series on biological evaluation of medical devices), is essential while investigating the compatibility of product with a sterilization method. Tests should evaluate specific properties that are essential to the intended function of the product. General material compatibility information derived from reference sources alone is inadequate.

6.2.3.3 Product performance over the shelf-life of the product should be considered during investigation of product compatibility. Certain sterilization methods produce chemical effects with the potential for the production of long-lived active species that can affect product performance over time, e.g. radiation sterilization can produce long-lived free radicals.

6.2.3.4 See Bibliography for AAMI TIR17, Annex J; ASTM F 1980; ICH Q1A(R2).

7 Strategies to achieve a maximal SAL of 10^{-6}

7.1 Within the manufacturer's quality management system, the requirement for product to be sterile will initially be identified as an input to the design and development process. When sterility is so identified, the first requirement for consideration is the achievement of a maximal SAL of 10^{-6}. With this requirement defined as a design input, consideration of the choice of materials of construction and of the sterilization process needs to be included as essential requirements for product. The choice of materials for product should be such that it can withstand a sterilization process that will provide maximally a SAL of 10^{-6}. This material choice should include elements such as packaging materials that will undergo sterilization. When product is able to withstand a sterilization process that can achieve maximally a SAL of 10^{-6}, that process should be selected. Furthermore, exposure to the sterilization processing conditions should not detrimentally affect the ability of sterilized product to meet its intended performance requirements.

7.2 For sterilization of sensitive product or materials, the point at which the product is detrimentally affected by a sterilization process might only be the magnitude of the process parameters necessary to achieve a 10^{-6} SAL as opposed to the process itself. For example, a 12 kGy sterilization radiation dose might provide an acceptable maximal SAL for tissue-based product, whereas radiation doses above 12 kGy would prove detrimental to the biological performance of the product. Alternatively, a novel material in product might be acceptable if sterilized by moist heat at 112° C, but it would be structurally degraded at the traditional temperature of 121° C.

7.3 Prior to considering an alternative to a maximal SAL of 10^{-6}, a manufacturer should investigate the feasibility of the strategies that might be employed to overcome the detrimental effects on product of a

sterilization process capable of achieving maximally a SAL of 10^{-6}. Such strategies might include a) to i) below. A combination of these strategies might be considered before it is determined that the product cannot be sterilized to achieve maximally a SAL of 10^{-6}. Using two or more strategies might be necessary to overcome the detrimental effects of a particular process or to allow the use of an alternative process.

a) Changing materials to enable product, including the sterile barrier system, to withstand the processing conditions necessary to achieve maximally a SAL of 10^{-6}. Selecting different materials might allow a different sterilization process to be used without detrimentally affecting the intended performance requirements. Choosing alternative polymer materials or using polymers which have additives can change their resistance to certain sterilization processes

EXAMPLE 1 Selecting a radiation-stabilized polypropylene.

b) Redesigning product to enable it to withstand the processing conditions necessary to achieve maximally a SAL of 10^{-6}. Modifying product, including changing its sterile barrier system, might allow a different sterilization process to be used without adversely affecting the intended performance requirements.

EXAMPLE 2 Modifying the diameter or length of lumen to improve penetration of gaseous sterilizing agent, or removal of air and penetration of steam.

EXAMPLE 3 Selecting a porous rather than a non-porous sterile barrier system to improve ingress and outflow of a gaseous sterilizing agent or removal of air and penetration of steam.

c) Changing the presentation of product to the sterilization process to reduce the extent of treatment. This might include changes to the orientation of product within its packaging or changes to the orientation of product in the sterilization load to improve ingress and outflow of a gaseous sterilizing agent.

EXAMPLE 4 Reducing the size of the sterilization load for radiation sterilization, or changing the configuration of product within its packaging, can be used to achieve a lower dose uniformity ratio, thereby lowering the maximum dose.

d) Changing conditions in the sterilization process to reduce the detrimental effects on product. This might include consideration of the change of one or more process parameter, e.g. time, temperature, humidity, sterilizing agent concentration or sterilization dose to reduce the detrimental effect on the product.

EXAMPLE 5 Use of a higher temperature for a shorter time in moist heat sterilization can have less detrimental effects on pharmaceutical stability and deliver the same lethality.

EXAMPLE 6 Use of a lower temperature for a longer time in dry heat sterilization might cause less material degradation.

EXAMPLE 7 Modified atmosphere and/or low temperature irradiation can reduce the effects on materials that result from high radiation doses.

e) Considering an alternative method of establishing the sterilization process if using a conservative overkill approach to process definition does not achieve maximally a SAL of 10^{-6} without a detrimental effect on product. A different approach to establishing the sterilization process might provide a process with less severe conditions that can achieve a maximal SAL of 10^{-6}.

EXAMPLE 8 Use of a combined bioburden-biological indicator approach to process definition rather than an overkill approach for EO sterilization (see ISO 11135)

EXAMPLE 9 Use of a bioburden-based approach for dry or moist heat sterilization (see ISO 17665-1 or ISO 20857) instead of use of a standard time-temperature combination.

EXAMPLE 10 Use of Method 2 instead of Method VD_{max}^{SD} to establish the sterilization dose for radiation sterilization (see ISO 11137-2).

f) Considering another sterilization process that could achieve maximally a SAL of 10^{-6}. Based on the particular process parameter(s) that would be detrimental to product, consideration should be given to the use of a different sterilization process that might mitigate these effects.

EXAMPLE 11 If the temperature or humidity required for EO sterilization is an issue, then a radiation sterilization process could be considered.

EXAMPLE 12 If radiation effects in the product are an issue, then an EO, dry heat or moist heat sterilization process could be considered.

EXAMPLE 13 If radiation, EO, dry heat or moist heat sterilization process are not appropriate, sterilization processes for which currently there are no specific standards for validation and routine control, such as exposure to hydrogen peroxide vapour or chlorine dioxide gas, could be considered.

g) Reducing and controlling product bioburden to allow the use of sterilizing conditions that have less detrimental effect. This might enable a different approach to establishment of the sterilization process to achieve maximally a SAL of 10^{-6} [see e) above].

EXAMPLE 14 For radiation sterilization, reducing the bioburden might allow use of a lower sterilization dose. If the packaging is contributing to bioburden, then pre-sterilization or inclusion of a microbiological reduction process for internal packaging materials could be a means of reducing the bioburden to enable the use of sterilizing conditions that have less detrimental effect.

h) Applying microbiological inactivation processes sequentially. Consideration might be given to using two microbicidal processes in sequence, if there is evidence that product can withstand the process conditions and that the combination of two processes decreases the likelihood of survival of contaminants. Applying two microbicidal processes that individually cannot achieve a maximal SAL of 10^{-6} in sequence might allow the maximal SAL of 10^{-6} to be achieved. Demonstrating achievement of a maximal SAL of 10^{-6} with multiple processes is likely to be complex.

EXAMPLE 15 This scenario is illustrated by sequential microbicidal treatments comprising irradiation and ethylene oxide, applied to product having an average bioburden of 10 (10^1) colony forming units per item. For the irradiation process, with this bioburden of 10, achieving a SAL of 10^{-2} corresponds to three log cycles of inactivation; one log cycle covering survivors and two log cycles covering a probability of survival. For the irradiation process, the radiation dose required could be obtained and substantiated using the Method 1 table from ISO 11137-2. For the second treatment using ethylene oxide, the treatment needed to achieve at least a further four log cycles of probability of survival would be obtained and validated using a biological indicator approach as described in ISO 11135. In using this approach, the assumption is made that microorganisms surviving the irradiation treatment are not more resistant to ethylene oxide than the microorganisms of the biological indicator. In this example, the total number of log cycles of inactivation is seven resulting from a combination of outcomes from less severe treatments than those employed traditionally and that have been shown not to affect product detrimentally. Applying seven log cycles of inactivation to an initial bioburden of 10 (10^1) results in a maximal SAL of 10^{-6}.

While the desired assurance of sterility can, in principle, be achieved by treating product by two processes, each achieving a SAL greater than 10^{-6}, it is not valid to combine the SALs associated with the individual processes to arrive at a maximal SAL of 10^{-6}.

i) Applying a microbiological inactivation process as an adjunct to aseptic processing. It might be possible to deliver a terminal sterilization process by applying a microbicidal process that on its own would not achieve a maximal SAL of 10^{-6} following an aseptic process. It is important to note that combining the rate of occurrence of a contaminated unit estimated from process simulation with the microbiological reduction delivered by the terminal microbicidal process does not calculate a SAL for the two applied processes. Using the rate of occurrence of a contaminated unit from the process simulation data of the aseptic process to derive a most probable number of microorganisms per unit after the aseptic process is unlikely to be acceptable because of

   i) the random nature by which contamination occurs, and

   ii) the possibility that an individual contaminated product item was due to contamination with more than one microorganism, invalidate the assumptions in the most probable number calculation.

EXAMPLE 16 This scenario is illustrated by aseptic filling a fluid and subsequently applying a moist heat process. The adequacy of the aseptic process is demonstrated by process simulation with a contamination rate of 1 non-sterile unit in 10 000 units filled. A moist heat process of 115°C for 15 min is selected based as the greatest time-temperature combination that the product can withstand, on the assumption that any contaminating microorganisms following the aseptic process are not as resistant to moist heat as the standard reference microorganisms for moist heat sterilization. This could be confirmed by culturing the microorganisms from the positive process simulation and determining their moist heat resistance.

7.4 Wherever possible, product intended to be sterile should be sterilized in its sterile barrier system, i.e. terminal sterilization should be applied. When product is intended to be sterile and cannot be terminally sterilized, aseptic processing provides an alternative. Sterilization of product, product parts and/or components and all equipment coming into direct contact with the aseptically processed product is required. Aseptic processing maintains the sterility of pre-sterilized components, materials and product through strict control of the environment, air supply, equipment and personnel. Requirements and guidance on aseptic processing are given in the ISO 13408 series.

7.5 The level of effort required in investigating the feasibility of the strategies that might be employed to overcome the detrimental effects on product of a sterilization process capable of achieving maximally a SAL of 10^{-6} should be determined by risk assessment and should also be directly related to the nature of the product and the clinical benefit of its being available to patients. Too little effort might not be in the patient's best interests from an overall risk-benefit perspective. Too much effort might not be in the patient's best interest due to limiting or delaying the availability of critical product; in extreme circumstances, this might make a critical care product commercially non-viable.

The examples of factors to consider and document during performance of the risk management activities described in 8.2.5 to support the use of a SAL greater than 10^{-6} for a particular product have been identified taking into account the level of effort that is reasonably practicable. The justification can be a combination of literature review, associated theoretical analysis and experimental work.

8 Considerations if a maximal SAL of 10^{-6} cannot be achieved

8.1 General

8.1.1 The regulatory authority is responsible for approving a SAL for a terminally sterilized, single-use health care product that is unable to withstand processing to achieve maximally a SAL of 10^{-6}.

8.1.2 If product is not able to withstand a sterilization process that can achieve maximally a SAL of 10^{-6}, the manufacturer should ensure that the product design and development phases included investigation and documentation of the feasibility of the strategies that might be employed to overcome the detrimental effects on product of a sterilization process capable of achieving maximally a SAL of 10^{-6}. Such strategies are outlined in 7.3. Annex A provides an illustration of the sequence of activities in selecting and justifying an alternative SAL.

8.1.3 Having completed the review of the strategies to achieve maximally a SAL of 10^{-6}, it might be concluded that a terminal sterilization process providing such a maximal achievement is not suitable for a particular product or product type. Some examples are product containing materials of biological origin, including tissue and cell-based product, or active pharmaceutical ingredients; product incorporating active electronics; and product made of novel materials. The effects of exposure to sterilizing conditions on these types of product can result in drug degradation, reduced stability, material ageing and structural mechanical changes, as well as reduced biological performance for cell-based product. The detrimental effects of the sterilization process on product might be due to sensitivity to one or more of the process variables that constitute the sterilization process or to the extent of treatment needed to achieve maximally a SAL of 10^{-6}.

8.1.4 Having found that product is not able to withstand the sterilization process required to achieve maximally a SAL of 10^{-6}, it could be necessary for a manufacturer to propose an alternative SAL for consideration by regulatory authorities. In this regard,

a) the product should offer a clear significant benefit to patient diagnosis, treatment or care, and

b) the validated sterilization process for the product should be the one that does not affect detrimentally the intended performance requirements of the product over its lifetime and achieves the lowest possible SAL greater than 10^{-6}.

8.2 Risk management considerations

8.2.1 If product is unable to withstand, or cannot be redesigned to withstand, the processing conditions necessary to achieve maximally a SAL of 10^{-6} and the manufacturer proposes consideration of an alternative SAL for that product, then the manufacturer should conduct risk management activities and identify, assess, mitigate, control and document risks that might affect assurance of sterility.

8.2.2 Factors related to the microbiological contamination on product prior to sterilization that should be considered include, but are not restricted to as follows.

a) The nature of the bioburden of the product as well as that of environmental isolates from the production area, e.g.:

   — the types of microorganisms present;

   — their resistance to the sterilization process.

b) The potential for the bioburden to change over time (including the potential for the bioburden of individual components of the health care product to fluctuate over time) and the ability of the monitoring procedures to detect such changes.

c) Microorganisms that might be considered irregular if detected as bioburden isolates and which might potentially render product non-conforming.

d) The potential for bioburden on or in product to decrease or increase after completion of product manufacturing but prior to product sterilization.

e) Assessment and management of risks associated with the outsourcing of product manufacturing and sterilization processes.

The data considered during these risk management activities should be specific to the product for which an alternative SAL is being proposed.

ISO 14971 and ICH Q9 provide guidance on risk management.

8.2.3 Other factors that should be considered as part of the manufacturer's overall risk management process but which do not directly affect microbicidal effectiveness include, but are not restricted to:

a) the patient population for which the product is intended, e.g. vulnerable patients susceptible to infection;

b) the intended use of the product in terms of the potential routes of infection;

c) the portion of product intended to have patient contact versus the portion of product which is not intended to have patient contact;

d) the clinical benefit(s) offered to patients by the product in comparison to existing product;

e) the availability of clinically suitable alternative product;

f) the scale of production, e.g. is supply of the health care product industrial scale, clinical trial scale or patient-specific scale?

8.2.4 In addressing such factors in the risk management process, the manufacturer might address the scale of the risk in terms of an individual patient and the wider population. For example, the risk of infection for an individual patient undergoing a cell therapy treatment presents different considerations compared to the large-scale preparation of saline solution for intravenous infusion; consequently, the risk-benefit assessment might be different.

8.2.5 In evaluating the use of a maximal SAL greater than 10^{-6}, there are certain practicalities that need to be taken into account, including

a) the availability of technology to implement strategies to achieve maximally a SAL of 10^{-6};

b) the availability of a sterilization facility that can

— deliver a sterilization process with a SAL greater than 10^{-6} SAL within specified parameters (for example, the availability of an irradiation facility able to deliver a narrow dose range), and

— handle the capacity needed to deliver a sterilization process with a SAL greater than 10^{-6} (for example, the ability to handle either small or large volumes of product).

c) The time required to obtain regulatory approval for supply of product with significant advantages to patient care and the impact of delay in supply of such a product on patient care.

8.3 Risk management output

8.3.1 Justification to support selection of a SAL greater than 10^{-6} should be directly related to the nature of the product and the clinical benefit of it being available to patients. This justification should be linked to the product risk assessment, which can vary from product to product, and the investigations into strategies to achieve maximally a SAL of 10^{-6} in 7.3.

Cogent technical reasoning should support the selection of an alternative SAL for product. Where a 10^{-6} SAL is not achievable, this should be because the product cannot physically or chemically withstand a sterilization process and cannot be re-engineered to withstand such a process. Selection of an alternative SAL should not be based on a business decision solely related to financial cost. Additionally, it has been argued that the environment in which product is used might pose a significantly greater risk to assurance of sterility than introduced by that particular product, irrespective of the maximal SAL to which it is processed; this argument should not be used solely to justify a SAL greater than 10^{-6}.

Examples of factors to consider and document in this justification for a particular product should include, but are not limited to

a) the feasibility of applying bioburden reduction to the raw materials and/or the product, without affecting the materials or effectiveness of the finished product,

b) the extent of investigations across a range of alternative process parameters,

c) investigations into the feasibility of using alternative approaches to a traditional conservative approach to process definition for a sterilization process,

d) the extent of investigations into the use of an alternative sterilization method,

NOTE 1 National regulatory bodies have published guidance on established and novel sterilization methods, e.g. US Food and Drug Administration Submission and Review of Sterility Information in Premarket Notification [510(k)] Submissions for Devices Labeled as Sterile.

NOTE 2 Due to the number of potential sterilization methods, appropriate screening and justification, as opposed to testing, is acceptable.

e) the practicability of changing the specification of product, its materials or its manufacturing processes, and

f) the evaluation of biocompatibility, product performance and/or stability.

8.3.2 Having specified the necessary maximal sterility assurance level, the design and development process will examine the achievement of that SAL as a design and development output, and verify and validate the achievement of that SAL. The published International Standards on development, validation and routine control for particular sterilization processes provide requirements to be met in conducting this verification and validation.

9 Label claims

9.1 It is an essential principle that health care product, and the manufacturing processes used to produce them, are designed in a way that eliminates, or reduces as far as possible, the risk of infection to the patient, user and third parties. In order to achieve this, the design of product needs to allow easy handling and, where necessary, minimize contamination of the patient by the product or vice versa during use. Packaging systems are intended to keep product without deterioration at the level of cleanliness stipulated. Product is accompanied by the information needed to use it safely and properly, taking account of the training and knowledge of the potential users.

One approach to reduce the risk of infection to the patient is for the manufacturer to provide product in a sterile state. When a claim of sterile is made, a number of regulatory requirements apply. These include, but are not limited to, that product

a) is designed, manufactured and packed in a non-reusable pack and/or according to appropriate procedures to ensure that it is sterile when placed on the market and remains sterile, under the storage and transport conditions laid down, until the protective packaging is damaged or opened,

b) is manufactured in appropriately controlled environmental conditions,

c) is manufactured and sterilized by an appropriate, validated method,

d) is labelled with the word "STERILE" or an accepted symbol indicating sterility, and

e) has packaging and/or labelling that distinguishes between identical or similar product sold in both a sterile and a non-sterile condition.

The ISO 11607 series provides requirements and guidance for packaging for terminally sterilized health care product.

9.2 For a terminally sterilized product, a claim that the product is sterile is linked to the delivery of a sterilization process that has been established, validated and is routinely controlled to predict attainment of a specified maximal SAL. Specifying a value for that SAL is a matter for regulatory authorities. It is important to note, however, that:

a) product sterilized using a validated process achieving maximally a SAL of 10^{-6} is generally regarded as sterile and is labelled as such;

b) some jurisdictions accept a label claim of sterile for product for certain defined applications when a sterilization process achieves maximally a SAL of 10^{-3};

c) regulatory authorities may permit product processed to achieve maximally a SAL greater than 10^{-6} (e.g. 10^{-5}) to be labelled as sterile based on individual analysis of the risk-benefit of that particular product if a maximal SAL of 10^{-6} cannot be achieved;

d) generally, product processed to achieve maximally a SAL greater than 10^{-3}, such as 10^{-2}, is not labelled as sterile. It should be noted that there might be individual situations in which such product

(such as cell-based therapies) is appropriate for a particular intended use and has regulatory approval for that use.

9.3 When a regulatory body accepts that a maximal SAL greater than 10^{-6} may be used (e.g. 10^{-5}), its consideration will also address how that product should be labelled.

10 Establishing the sterilization process

10.1 Irrespective of the maximal SAL, the sterilization process appropriate for defined product should be established by

a) defining the process parameters and demonstrating their delivery by measurements,

b) delivering the sterilizing agent as an increment or increments of treatment that provide less lethality than the intended sterilization process. Such an approach is described in each of the standards for validation and routine control of particular sterilization methods, for example:

   1) ethylene oxide: ISO 11135: 2014, Clause 8, Annexes A and B;

   2) radiation: ISO 11137-1: 2015, Clause 8 and ISO 11137-2;

   3) moist heat: ISO 17665-1: 2006, Clause 8, Annexes B, C and D;

   4) dry heat: ISO 20857: 2013, Clause 8, Annexes B, C, and D;

   5) low temperature steam and formaldehyde: ISO 25424: 2009 Clause 8, Annexes A and B;

   6) liquid chemical sterilants: ISO 14160: 2011, Clause 8 and Annex B;

   7) other sterilization methods: ISO 14937: 2009, Clause 8, Annexes B, C and D.

10.2 It is unlikely that traditional conservative approaches to process definition that use biological indicators will provide sufficient precision in predicting the achievement of the specified maximal SAL, and, if this applies, biological indicator/bioburden or bioburden-based approaches should be considered.

10.3 In establishing the sterilization process, it is necessary to measure the attainment of the process parameters. The methods and instrumentation used for these measurements need to have sufficient accuracy and precision, recognizing that when an alternative SAL is being established, the process parameters required to give incremental treatments for process establishment will be less than those process parameters used in sterilization processes aiming for achievement of a maximal SAL of 10^{-6}.

11 Specific considerations for validation, routine monitoring and control, and product release from sterilization

11.1 The purpose of validation is to demonstrate that the established sterilization process can be delivered effectively and reproducibly to the sterilization load. For sterilization processes delivering maximally a SAL of 10^{-6}, validation in accordance with the international standards for development, validation and routine control of sterilization processes for health care product (see Bibliography) is required and has been widely accepted as a tool to ensure the effectiveness of the sterilization process. For processes delivering a SAL greater than 10^{-6} (e.g. 10^{-5}) validation in accordance with these international standards is also necessary to ensure the effectiveness of the sterilization process.

11.2 The considerations of the required accuracy and precision for measurement systems in process establishment described in 10.3, as well as the performance requirements for biological indicators and chemical indicators, will also be relevant to the selection of instrumentation and any indicators to be used in validation and routine monitoring of the sterilization process. The requirements for systems for use in validation are likely to be similar to those used for process establishment.

