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)

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Foreword

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

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

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

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

For an explanation 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

