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Sterilization of health care products — Radiation —

Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices

Stérilisation des produits de santé — Irradiation —

Partie 1: Exigences relatives à la mise au point, à la validation et au contrôle de routine d'un procédé de stérilisation pour les dispositifs médicaux

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Contents

Foreword iv

Introduction vi

1 Scope 1

2 Normative references 2

3 Terms and definitions 2

4 General 10

5 Sterilizing agent characterization 10
5.1 Sterilizing agent 10
5.2 Microbicidal effectiveness 11
5.3 Material effects 11
5.4 Environmental considerations 11

6 Process and equipment characterization 11
6.1 Process 11
6.2 Equipment 11

7 Product definition 12

8 Process definition 13
8.1 Establishing the maximum acceptable dose, $D_{max,acc}$ 13
8.2 Establishing the sterilization dose, D_{ster} 13
8.3 Specifying the maximum acceptable dose and the sterilization dose 14
8.4 Transference of maximum acceptable, verification or sterilization dose between radiation sources 14

9 Validation 14
9.1 Installation qualification (IQ) 14
9.2 Operational qualification (OQ) 15
9.3 Performance qualification (PQ) 16
9.4 Review and approval of validation 17

10 Routine monitoring and control 17

11 Product release from sterilization 18

12 Maintaining process effectiveness 18
12.1 Demonstration of continued effectiveness 18
12.2 Recalibration 21
12.3 Maintenance of equipment 21
12.4 Requalification of equipment 21
12.5 Assessment of change 21

Annex A (informative) Guidance on this document 22

Annex ZA (informative) Relationship between this European standard and the General Safety and Performance Requirements of Regulation (EU) 2017/745 aimed to be covered 39

Annex ZB (informative) Relationship between this European standard and the General Safety and Performance Requirements of Regulation (EU) 2017/746 aimed to be covered 43

Bibliography 46

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 document should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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

This second edition cancels and replaces the first edition (ISO 11137-1:2006), which has been technically revised.

The main changes are as follows:

— ~~—~~addition of ISO 13004 as a normative reference;

— ~~—~~addition of ISO/ASTM 52628 ~~standard practice~~ as a normative reference for dosimetry in radiation processing ~~as a normative reference~~ and alignment of terminology across the document to ASTM standards terminology;

— ~~—replacement~~update of Clause 4~~Clause 4~~ to align with ~~the updated common Clause 4 for~~ ISO/TC 198 documents;

— ~~—~~increase of the allowable limits above which the potential induced radioactivity shall be assessed to 11 MeV for electrons and 7.5 ~~7.5~~ MeV for X-rays (see 5.1.2~~5.1.2);~~;

— ~~—~~addition of a requirement to ensure that failure of a control function does not lead to a failure in recording process parameters such that an ineffective process appears effective (see 6.1~~6.1);~~;

— ——simplification of content on transference of verification dose or sterilization dose based on published data that demonstrates that differences in operating conditions of the two radiation sources have no effect on microbicidal effectiveness for product that does not promote microbial growth (see 8.4.28.4.2););

— ——clarification on the use of dose measurements and the recording of process variables for process control has been clarified (see 10.610.6 and 10.710.7););

— ——clarification has been provided on the allowable interval of time for quarterly dose audits, allowing for an interval of four months provided there are four dose audits per year (see 12.1.212.1.2););

— ——addition of references for all VD_{max}^{SD} dose levels contained in both ISO 11137-2 and ISO 13004 (see 8.2.28.2.2 and 12.1.212.1.2););

— ——additional information has been included on bioburden determination for productproducts with very low bioburden (see 12.1.2.212.1.2.2););

— ——addition of guidance related to new or modified normative content;

— ——addition of references to the Bibliography.

A list of all parts in the ISO 11137 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

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

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

This document describes requirements that, if met, will provide a radiation sterilization process, intended to sterilize medical devices. Furthermore, conformance with the requirements ensures that this activity is both reliable and reproducible so that predictions can be made, with reasonable confidence, that there is a low level of probability of there being a viable microorganism present on product after sterilization. Specification of this probability is a matter for regulatory authorities and can vary from country to country (see, for example, EN 556~~-~~-1 and ANSI/AAMI ST67).

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

Exposure to a properly validated, accurately controlled sterilization process is not the only factor associated with the provision of reliable assurance that the medical devices are sterile and~~, in this regard,~~ suitable for its intended use. Attention is therefore given to a number of considerations, including:

a) ~~a)~~ the microbiological quality (microorganism numbers and characterization) of incoming raw materials and components;

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

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

d) ~~d)~~ the control of equipment and processes;

e) ~~e)~~ the control of personnel and their hygiene;

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

g) ~~g)~~ the conditions under which product is stored.

This document describes the requirements for ensuring that the activities associated with the process of radiation sterilization are performed properly. These activities are described in documented work programmes designed to demonstrate that the irradiation process will consistently yield sterile medical devices on treatment with doses falling within the predetermined limits.

The requirements are the normative parts of this document with which conformance is claimed. The guidance given in Annex A~~the~~ is informative~~ annexes is not normative~~ and is not provided as a checklist for auditors. The guidance provides explanations and methods that are ~~regarded as being a~~an example of suitable means for conforming with the requirements. Methods other than those given in the guidance may be used, if they are effective in achieving conformance with the requirements of this document.

The development, validation and routine control of a sterilization process comprise a number of discrete but interrelated activities, e.g. calibration, maintenance, product definition, process definition, installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). ~~While the~~The activities required by this document ~~have been grouped together and are presented in a particular order, this document does~~do not ~~require that the activities~~need to be performed in the order ~~that~~in which they are presented. The activities required are not necessarily sequential, as the programme of development and validation may be iterative. It is possible that performing these different activities will involve a number of separate individuals or organizations, or both, each of whom undertake one or more of these activities. This document does not specify the particular individuals or organizations to carry out the activities.

Sterilization of health care products — Radiation— —

Part 1:
Requirements for the development, validation and routine control of a sterilization process for medical devices

1 Scope

1.1 ~~**1.1**~~ This document specifies requirements for the development, validation and routine control of a radiation sterilization process for medical devices.

NOTE Although the scope ~~of this document~~ is limited to medical devices, ~~it specifies requirements and provides guidance that~~this document can be applicable to other products and equipment.

This document covers radiation processes employing irradiators using:

a) ~~a)~~ the radionuclide ^{60}Co or ^{137}Cs;

b) ~~b)~~ a beam from an electron generator; or

c) ~~c)~~ a beam from an X-ray generator.

1.2 ~~**1.2**~~ This document ~~**does**~~is not ~~**specify requirements for development, validation and routine control of a process**~~applicable to processes for inactivating viruses or 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, for example,~~For information on such processes, see ISO 22442-1, ISO 22442-2, ISO 22442-3, ISO 13022 and ICH Q5A.

1.2.1 ~~**1.2.1**~~ This document does not ~~**detail specified**~~specify requirements for designating a medical device as sterile.

NOTE Regional and national requirements can designate medical devices as ~~"~~sterile~~."~~. See, for example, EN 556~~-~~-1 or ANSI/AAMI ST67.

1.2.2 ~~**1.2.2**~~ This document 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 document 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~~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 can require implementation of a complete quality management system and the assessment of that system by a third party.

1.2.3 ~~**1.2.3**~~ This document does not require that biological indicators be used for validation or monitoring of radiation sterilization, nor does it require that a pharmacopoeial test for sterility be carried out for product release.

1.2.4 ~~**1.2.4**~~ This document does not specify requirements for occupational safety associated with the design and operation of irradiation facilities.

NOTE Regulations on safety requirements for occupational safety related to radiation can exist in some countries.

1.2.5 ~~1.2.5~~ This document does not specify requirements for the sterilization of used or reprocessed devices.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

~~ISO 11137-2:2013, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*~~

ISO 13004, *Sterilization of health care products — Radiation — Substantiation of selected sterilization dose: Method VD_{max}^{SD}*

ISO 11137-2:2013, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

ISO 11737-1, *Sterilization of health care products — Microbiological methods — Part 1: Determination of a population of microorganisms on products*

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

ISO/ASTM 52628, *Standard practice for dosimetry in radiation processing*

3 Terms and definitions

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

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

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

— ~~—~~ IEC Electropedia: available at https://www.electropedia.org/

3.1 ~~3.1~~
dose
absorbed dose
quantity of ionizing radiation energy imparted per unit mass of a specified material

Note 1 to entry: The unit of absorbed dose is the gray (Gy~~)~~), where 1 Gy is equivalent to the absorption of 1 J/kg.

[SOURCE: ISO 11139:2018, 3.3, modified — Deleted <radiation> domain, added "~~"~~dose~~"~~" as a preferred term, added ~~notes~~Note 1 to entry.]

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

[SOURCE: ISO 11139:2018, 3.23]

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

[SOURCE: ISO 11139:2018, 3.29]

3.4 ~~3.4~~
calibration
operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication

[SOURCE: ISO 11139:2018, 3.31]

3.5 ~~3.5~~
correction
action to eliminate a detected nonconformity

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

[SOURCE: ISO 9000:2015, 3.12.3, modified — Note 2 to entry has been deleted.]

3.6 ~~3.6~~
corrective action
action to eliminate the cause of a nonconformity and to prevent recurrence

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

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

[SOURCE: ISO 9000:2015, 3.12.2, modified — Note 3 to entry has been deleted.]

3.7 ~~3.7~~
development
act of elaborating a specification

[SOURCE: ISO 11139:2018, 3.79]

3.8 ~~3.8~~
dose mapping
measurement of dose distribution and variability in material irradiated under specified conditions

[SOURCE: ISO 11139:2018, 3.87, modified — Deleted <radiation> domain.]

3.9 ~~3.9~~
dosimeter
device having a reproducible, measurable response to radiation that can be used to measure the absorbed dose in a given system

[SOURCE: ISO 11139:2018, 3.89]

3.10 ~~3.10~~
dosimetry
measurement of absorbed dose by the use of dosimeters

[SOURCE: ISO 11139:2018, 3.90]

3.11 ~~3.11~~
establish
determine by theoretical evaluation and confirm by experimentation

[SOURCE: ISO 11139:2018, 3.107]

3.12 ~~3.12~~
fault
situation in which one or more of the process or cycle parameters is/are outside its/their specified tolerance(s)

[SOURCE: ISO 11139:2018, 3.116]

3.13 ~~3.13~~
health care product
medical device, including in vitro diagnostic medical device, or medicinal product, including biopharmaceutical

[SOURCE: ISO 11139:2018, 3.132]

3.14 ~~3.14~~
installation qualification
IQ
process of establishing by objective evidence that all key aspects of the process equipment and ancillary system installation comply with the approved specification

[SOURCE: ISO 11139:2018, 3.220.2]

3.15 ~~3.15~~
irradiation container
holder in which product is transported through the irradiator

Note 1 to entry: The holder can be a carrier, cart, tray, product carton, pallet or other container.

[SOURCE: ISO 11139:2018, 3.146]

3.16 ~~3.16~~
irradiator operator
company or body responsible for irradiation of product

[SOURCE: ISO 11139:2018, 3.147]

3.17 ~~3.17~~
maximum acceptable dose
$D_{max,acc}$
dose given in the process specification as the highest dose that can be applied to a specified product without compromising safety, quality or performance

Note 1 to entry: The specification for maximum acceptable dose can apply to an entire product or a specified portion of a product.

[SOURCE: ISO 11139:2018, 3.161, modified — The symbol ($D_{max,acc}$) and Note 1 to entry ~~has~~have been added.]

3.18 ~~3.18~~
measurement uncertainty
uncertainty of measurement
non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used

[SOURCE: VIM:2012, definition 2.26, modified — The notes to entry have been deleted.]

3.19 ~~3.19~~
medical device
instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, or software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific purpose(s) of:

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

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

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

— ~~—~~supporting or sustaining life;

— ~~—~~control of conception;

— ~~—~~disinfection of medical devices;

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

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

Note 1 to entry: Products which may be considered to be medical devices in some jurisdictions, but not in others include:

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

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

— ~~—~~disinfection substances;

— ~~—~~aids for persons with disabilities;

— ~~—~~devices incorporating animal and/or human tissues;

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

[SOURCE: ISO ~~13485:2016~~ 11139:2018, 3.~~11, modified — The first two list items in Note 1 to entry have been added.~~]166]

3.20 ~~3.20~~
microorganism
entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

Note 1 to entry: ~~A specific standard might~~ It is possible that other standards do not require demonstration of the effectiveness of the sterilization process in inactivating all types of microorganisms, identified in the definition above, for validation and/or routine control of the sterilization process.

[SOURCE: ISO 11139:2018, 3.176, modified — Note 1 to entry has been added.]

3.21 ~~3.21~~
operational qualification
OQ
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[SOURCE: ISO 11139:2018, 3.220.3]

3.22 ~~3.22~~
performance qualification
PQ
process of establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements

[SOURCE: ISO 11139:2018, 3.220.4]

3.23 ~~3.23~~
preventive action
action to eliminate the cause of a potential nonconformity or other potential undesirable situation

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

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

[SOURCE: ISO 9000:2015, 3.12.1]

3.24 ~~3.24~~
process interruption
intentional or unintentional stoppage of the irradiation process

3.25 ~~3.25~~
process load
volume of material with a ~~specified~~specified product loading ~~configuration~~configuration irradiated as a single entity

[SOURCE: ISO/ASTM 52303:2015, 3.1.10]

3.26 ~~3.26~~
process parameter
specified value for a process variable

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

~~Note 2 to entry: In the context of this document the term "tolerances" is used as "limits".~~

[SOURCE: ISO 11139:2018, 3.211~~, modified — Note 2 to entry has been added.]~~]

3.27 ~~3.27~~
process variable
chemical or physical attribute within a cleaning, disinfection, packaging, or sterilization process, changes in which can alter its effectiveness

EXAMPLE Conveyor speed, beam current, electron energy, beam width.