EUROPEAN STANDARD

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EUROPÄISCHE NORM

EN ISO 11137-1

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English Version

Sterilization of health care products - Radiation - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices (ISO 11137-1:2006, including Amd 1:2013)

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 (ISO 11137-1:2006, y compris Amd 1:2013)

Sterilisation von Produkten für die Gesundheitsfürsorge - Strahlen - Teil 1: Anforderungen an die Entwicklung, Validierung und Lenkung der Anwendung eines Sterilisationsverfahrens für Medizinprodukte (ISO 11137-1:2006, einschließlich Amd 1:2013)

This European Standard was approved by CEN on 20 May 2015.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration. Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the CEN-CENELEC Management Centre or to any CEN member.

This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the CEN-CENELEC Management Centre has the same status as the official versions.

CEN members are the national standards bodies of Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and United Kingdom.

EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

CEN-CENELEC Management Centre: Avenue Marnix 17, B-1000 Brussels

Ref. No. EN ISO 11137-1:2015 E

Foreword

The text of ISO 11137-1:2006, including Amd 1:2013 has been prepared by Technical Committee ISO/TC 198 “Sterilization of health care products” of the International Organization for Standardization (ISO) and has been taken over as EN ISO 11137-1:2015 by Technical Committee CEN/TC 204 “Sterilization of medical devices” the secretariat of which is held by BSI.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by December 2015, and conflicting national standards shall be withdrawn at the latest by December 2015.

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

This document supersedes EN ISO 11137-1:2006.

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

For relationship with EU Directives, see informative Annexes ZA, ZB, ZC, which are an integral part of this document.

The following referenced documents are indispensable for the application of this document. For undated references, the edition of the referenced document (including any amendments) listed below applies. For dated references, only the edition cited applies. However, for any use of this standard within the meaning of Annex ZA, ZB or ZC, the user should always check that any referenced document has not been superseded and that its relevant contents can still be considered the generally acknowledged state-of-art.

When an IEC or ISO standard is referred to in the ISO standard text, this should be understood as a normative reference to the corresponding EN standard, if available, and otherwise to the dated version of the ISO or IEC standard as listed below.

NOTE The way in which these referenced documents are cited in normative requirements determines the extent (in whole or in part) to which they apply.

Table — Correlation between normative references and dated EN and ISO standards

Normative references as listed in Clause 2 of the ISO standard	Equivalent dated standard	
	EN	ISO
ISO 10012-1	EN ISO 10012:2003	ISO 10012:2003
ISO 11137-2	EN ISO 11137-2:2013	ISO 11137-2:2013
ISO 11737-1	EN ISO 11737-1:2006 + AC:2009	ISO 11737-1:2006 + Cor 1:2007
ISO 11737-2	EN ISO 11737-2:2009	ISO 11737-2:2009
ISO 13485	EN ISO 13485:2012	ISO 13485:2003

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

Endorsement notice

The text of ISO 11137-1:2006, including Amd 1:2013 has been approved by CEN as EN ISO 11137-1:2015 without any modification.

Annex ZA
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 90/385/EEC on active implantable medical devices

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

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

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with 90/385/EEC, as amended by 2007/47/EC. This means that risks have to be reduced 'as far as possible', 'to a minimum', 'to the lowest possible level', 'minimized' or 'removed', according to the wording of the corresponding essential requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with essential requirements 1, 4, 5, 8, 9 and 10 of the Directive.

NOTE 3 This Annex ZA is based on normative references according to the table of references in the European foreword, replacing the references in the core text.

NOTE 4 When an Essential Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

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

Clauses of this EN	Essential Requirements (ERs) of Directive 90/385/EEC	Qualifying remarks/Notes
4,5,6,7,8,9,10,11,12	7	Only a sterilization process using ionizing radiation is considered by this standard. This relevant Essential Requirement is only partly addressed in this European Standard. Design and packaging for maintenance of sterility during transportation and storage are not covered. Aspects of manufacture other than those related to sterilization are not covered.

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

Annex ZB
(informative)

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

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

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

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with 93/42/EEC, as amended by 2007/47/EC. This means that risks have to be reduced 'as far as possible', 'to a minimum', 'to the lowest possible level', 'minimized' or 'removed', according to the wording of the corresponding essential requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with essential requirements 1, 2, 5, 6, 7, 8, 9, 11 and 12 of the Directive.

NOTE 3 This Annex ZA is based on normative references according to the table of references in the European foreword, replacing the references in the core text.

NOTE 4 When an Essential Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

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

Clauses of this EN	Essential Requirements (ERs) of Directive 93/42/EEC	Qualifying remarks/Notes
4,5,6,7,8,9,10,11,12	8.3	Only a sterilization process using ionizing radiation is considered by this standard. This relevant Essential Requirement is only partly addressed in this European Standard. Design and packaging for maintenance of sterility during transportation and storage are not covered. Aspects of manufacture other than those related to sterilization are not covered.
4,5,6,7,8,9,10,11,12	8.4	This relevant Essential Requirement is only partly addressed in this European Standard. Aspects of manufacture other than those related to sterilization are not covered.

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

Annex ZC
(informative)

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

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

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

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with 98/79/EC. This means that risks have to be reduced 'as far as possible', 'to a minimum', 'to the lowest possible level', 'minimized' or 'removed', according to the wording of the corresponding essential requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with essential requirements Part A: 1, 2 and 5; Part B: 1.2, 2, 3, 5, 6, and 7 of the Directive.

NOTE 3 This Annex ZA is based on normative references according to the table of references in the European foreword, replacing the references in the core text.

NOTE 4 When an Essential Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

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

Clauses of this EN	Essential Requirements (ERs) of Directive 98/79/EC	Qualifying remarks/Notes
4,5,6,7,8,9,10,11,12	B.2.3	Only a sterilization process using ionizing radiation is considered by this standard. This relevant Essential Requirement is only partly addressed in this European Standard. Design and packaging for maintenance of sterility during transportation and storage are not covered. Aspects of manufacture other than those related to sterilization are not covered.

4,5,6,7,8,9,10,11,12	B.2.4	This relevant Essential requirement is addressed only with regard to: - sterilization, not covering other special microbiological state - devices for which sterilization by radiation is appropriate

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

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Foreword

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

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

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

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.

ISO 11137-1 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care product*.

This first edition, together with ISO 11137-2 and ISO 11137-3, cancels and replaces ISO 11137:1995.

ISO 11137 consists of the following parts, under the general title *Sterilization of health care products — Radiation*:

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

— *Part 2: Establishing the sterilization dose*

— *Part 3: Guidance on dosimetric aspects*

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

The kinetics of inactivation of a pure culture of microorganisms by physical and/or chemical agents used to sterilize medical devices can generally best be described by an exponential relationship between the numbers of microorganisms surviving and the extent of treatment with the sterilizing agent; inevitably this means that there is always a finite probability that a microorganism may survive regardless of the extent of treatment applied. For a given treatment, the probability of survival is determined by the number and resistance of microorganisms and by the environment in which the organisms exist during treatment. It follows that the sterility of any one 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 part of ISO 11137 describes requirements that, if met, will provide a radiation sterilization process intended to sterilize medical devices, that has appropriate microbicidal activity. Furthermore, compliance 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 may vary from country to country (see, for example, EN 556-1 and ANSI/AAMI ST67).

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

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

a) the microbiological status of incoming raw materials and/or components;

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

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

d) the control of equipment and processes;

e) the control of personnel and their hygiene;

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

g) the conditions under which product is stored.

This part of ISO 11137 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 radiation process will consistently yield sterile products on treatment with doses falling within the predetermined limits.

The requirements are the normative parts of this part of ISO 11137 with which compliance is claimed. The guidance given in the 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 suitable means for complying with the requirements. Methods other than those given in the guidance may be used, if they are effective in achieving compliance with the requirements of this part of ISO 11137.

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, operational qualification and performance qualification. While the activities required by this part of ISO 11137 have been grouped together and are presented in a particular order, this part of ISO 11137 does not require that the activities be performed in the order that they are presented. The activities required are not necessarily sequential, as the programme of development and validation may be iterative. It is possible that performing these different activities will involve a number of separate individuals and/or organizations, each of whom undertake one or more of these activities. This part of ISO 11137 does not specify the particular individuals or organizations to carry out the activities.

Sterilization of health care products — Radiation —

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

1 Scope

1.1 This part of ISO 11137 specifies requirements for the development, validation and routine control of a radiation sterilization process for medical devices.

NOTE Although the scope of this part of ISO 11137 is limited to medical devices, it specifies requirements and provides guidance that may be applicable to other products and equipment.

This part of ISO 11137 covers radiation processes employing irradiators using,

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

b) a beam from an electron generator

or

c) a beam from an X-ray generator.

1.2 This part of ISO 11137 does not specify requirements for development, validation and routine control of a process for inactivating the causative agents of spongiform encephalopathies such as scrapie, bovine spongiform encephalopathy and Creutzfeld-Jakob disease. Specific recommendations have been produced in particular countries for the processing of materials potentially contaminated with these agents.

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

1.2.1 This part of ISO 11137 does not detail specified requirements for designating a medical device as sterile.

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

1.2.2 This part of ISO 11137 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 part of ISO 11137 to have a complete quality management system during manufacture, but the elements of a quality management system that are the minimum necessary to control the sterilization process are normatively referenced at appropriate places in the text (see, in particular, Clause 4). Attention is drawn to the standards for quality management systems (see ISO 13485) that control all stages of production of medical devices, including the sterilization process. Regional and national regulations for the provision of medical devices might require implementation of a complete quality management system and the assessment of that system by a third party.

1.2.3 This part of ISO 11137 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 This part of ISO 11137 does not specify requirements for occupational safety associated with the design and operation of irradiation facilities.

NOTE Attention is also drawn to the existence, in some countries, of regulations laying down safety requirements for occupational safety related to radiation.

1.2.5 This part of ISO 11137 does not specify requirements for the sterilization of used or reprocessed devices.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10012-1, *Quality assurance requirements for measuring equipment — Part 1: Metrological confirmation system for measuring equipment*

A1 ISO 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose* A1

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

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

ISO 13485:2003, *Medical devices — Quality management systems — Requirements for regulatory purposes*

3 Terms and definitions

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

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

NOTE 1 The unit of absorbed dose is the gray (Gy) where 1 Gy is equivalent to the absorption of 1 J/kg.

NOTE 2 For the purposes of this part of ISO 11137, the term dose is used to mean “absorbed dose”.

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

[ISO/TS 11139:2006]

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

[ISO/TS 11139:2006]

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

[VIM:1993, definition 6.11]

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

[ISO/TS 11139:2006]

3.6
correction
action to eliminate a detected nonconformity

NOTE A correction can be made in conjunction with corrective action (3.7).

[ISO 9000:2005]

3.7
corrective action
action to eliminate the cause of a detected nonconformity or other undesirable situation

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

NOTE 2 Corrective action is taken to prevent recurrence whereas “preventive action” (3.24) is taken to prevent occurrence.

NOTE 3 There is a distinction between correction and corrective action.

[ISO 9000:2005]

3.8
D **value**
D_{10} **value**
time or radiation dose required to achieve inactivation of 90 % of a population of the test microorganism under stated conditions

NOTE For the purpose of the ISO 11137 series, the D value refers to the radiation dose necessary to achieve the 90 % reduction.

[ISO/TS 11139:2006]

3.9
development
act of elaborating a specification

[ISO/TS 11139:2006]

3.10
dose mapping
measurement of dose distribution and variability in material irradiated under defined conditions

3.11
dosimeter
device having a reproducible, measurable response to radiation, which can be used to measure the absorbed dose in a given system

[ISO/TS 11139:2006]

3.12
dosimetry
measurement of absorbed dose by the use of dosimeters

3.13
establish
determine by theoretical evaluation and confirm by experimentation

[ISO/TS 11139:2006]

3.14
fault
one or more of the process parameters lying outside of its/their specified tolerance(s)

[ISO/TS 11139:2006]

3.15
health care product(s)
medical device(s), including *in vitro* diagnostic medical device(s), or medicinal product(s), including biopharmaceutical(s)

[ISO/TS 11139:2006]

3.16
installation qualification
IQ
process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification

[ISO/TS 11139:2006]

3.17
irradiation container
holder in which product is transported through the irradiator

NOTE The holder can be a carrier, cart, tray, product carton, pallet or other container.

3.18
irradiator operator
company or body responsible for irradiation of product

3.19
maximum acceptable dose
dose given in the process specification as the highest dose that can be applied to a defined product without compromising safety, quality or performance

3.20
medical device
instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, 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 for medical purposes by means of in vitro examination of specimens derived from the human body;

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

[ISO 13485:2003]

NOTE This definition from ISO 13485:2003 has been developed by the Global Harmonization Task Force (GHTF 2002).

3.21
microorganism
entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

NOTE A specific standard might 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.

[ISO/TS 11139:2006]

3.22
operational qualification
OQ
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[ISO/TS 11139:2006]

3.23
performance qualification
PQ
process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification

[ISO/TS 11139:2006]

3.24
preventive action
action to eliminate the cause of a potential nonconformity or other undesirable potential situation

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

NOTE 2 Preventive action is taken to prevent occurrence whereas “corrective action” (3.7) is taken to prevent recurrence.

[ISO 9000:2005]

3.25
primary manufacturer
body responsible for the design and manufacture of a medical device, together with the safety and performance of that medical device when placed on the market

3.26
process interruption
intentional or unintentional stoppage of the irradiation process

3.27
process parameter
specified value for a process variable

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

[ISO/TS 11139:2006]

3.28
process variable
condition within a sterilization process, changes in which alter microbicidal effectiveness

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

〈A1〉 **3.29**
processing category
collection of different product or product families that can be sterilized together

NOTE Processing categories can be based on, for instance, composition, density or dose requirements. 〈A1〉

3.30
product
result of a process

[ISO 9000:2005]

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

〈A1〉 **3.31**
product family
group of product possessing characteristics that allow them to be sterilized using given defined process conditions

NOTE Bioburden on members of a product family destined for radiation sterilization has to comprise similar numbers and types of microorganisms. 〈A1〉

3.32
requalification
repetition of part of validation for the purpose of confirming the continued acceptability of a specified process

[ISO/TS 11139:2006]

3.33
services
supplies from an external source, needed for the function of equipment

EXAMPLES Electricity, water, compressed air, drainage.

3.34
specification
approved document stipulating requirements

3.35
specify
stipulate in detail within an approved document

[ISO/TS 11139:2006]

3.36
sterile
free from viable microorganisms

[ISO/TS 11139:2006]

3.37
sterility
state of being free from viable microorganisms

NOTE In practice, no such absolute statement regarding the absence of microorganisms can be proven (see **sterilization**) 3.39.

[ISO/TS 11139:2006]

3.38
sterility assurance level
SAL
probability of a single viable microorganism occurring on an item after sterilization

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

[ISO/TS 11139:2006]

3.39
sterilization
validated process used to render product free from viable microorganisms

NOTE In a sterilization process, the nature of microbial inactivation is exponential and thus the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number it can never be reduced to zero [see **"sterility assurance level"** (3.38)].

[ISO/TS 11139:2006]

3.40
sterilization dose
minimum dose to achieve the specified requirements for sterility

3.41
sterilization process
series of actions or operations needed to achieve the specified requirements for sterility

NOTE This series of actions includes pretreatment of product (if necessary), exposure under defined conditions to the sterilizing agent and any necessary post treatment. The sterilization process does not include any cleaning, disinfection or packaging operations that precede sterilization.

[ISO/TS 11139:2006]

3.42
sterilizing agent
physical or chemical entity, or combination of entities having sufficient microbicidal activity to achieve sterility under defined conditions

[ISO/TS 11139:2006]

3.43
test for sterility
technical operation defined in an official pharmacopoeia performed on product following exposure to a sterilization process

[ISO/TS 11139:2006]

3.44
test of sterility
technical operation performed as part of development, validation or requalification to determine the presence or absence of viable microorganisms on product or portions thereof

[ISO/TS 11139:2006]

3.45
transit dose
dose absorbed during travel of product or source to or from the non-irradiation to the irradiation position

3.46
uncertainty of measurement
parameter, associated with the result of a measurement, that characterizes the dispersion of values that could reasonably be attributed to the measurand

[VIM 1993]

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

[ISO/TS 11139:2006]

4 Quality management system elements

4.1 Documentation

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

4.1.2 Documents and records required by this part of ISO 11137 shall be reviewed and approved by designated personnel (see 4.2.1). Documents and records shall be controlled in accordance with the applicable clauses of ISO 13485.

4.2 Management responsibility

4.2.1 The responsibility and authority for implementing and meeting the requirements described in this part of ISO 11137 shall be specified. Responsibility shall be assigned to competent personnel in accordance with the applicable clauses of ISO 13485.

4.2.2 If the requirements of this part of ISO 11137 are undertaken by organizations with separate quality management systems, the responsibilities and authority of each party shall be specified.

4.3 Product realization

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

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

4.3.3 A system complying with the applicable clauses of ISO 13485 or ISO 10012-1 shall be specified for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this part of ISO 11137.

4.3.4 Dosimetry used in the development, validation and routine control of the sterilization process shall have measurement traceability to national or International Standards and shall have a known level of uncertainty.

4.4 Measurement, analysis and improvement — Control of nonconforming product

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

5 Sterilizing agent characterization

5.1 Sterilizing agent

5.1.1 The type of radiation to be used in sterilization processing shall be specified.

5.1.2 For electrons or X-rays, the energy level of the electron beam shall be specified. If the energy level for electrons exceeds 10 MeV or the energy level for electrons used to generate X-rays exceeds 5 MeV, the potential for induced radioactivity in product shall be assessed. The outcome of the assessment and the rationale for decisions reached shall be documented.

5.2 Microbicidal effectiveness

The inactivation of microorganisms by radiation and the use of radiation in sterilization processes have been comprehensively documented in the literature. This literature provides knowledge of the manner in which the process variables affect microbial inactivation. Reference to these general studies on microbial inactivation is not required by this part of ISO 11137.

5.3 Material effects

The effects of radiation on a wide variety of materials used to manufacture medical devices have been comprehensively documented and the resultant documentation is of value to those designing and developing medical devices that are to be sterilized by radiation. This part of ISO 11137 does not require the performance of studies on material effects, but does require performance of studies of the effects of radiation on product (see 8.1).

5.4 Environmental considerations

The potential effect on the environment of the operation of the radiation sterilization process shall be assessed and measures to protect the environment shall be identified. This assessment, including potential impact (if any) shall be documented and measures for control (if identified), shall be specified and implemented.

6 Process and equipment characterization

6.1 Process

Process variables shall be identified and means of monitoring and controlling them shall be specified.

6.2 Equipment

6.2.1 The irradiator and its method of operation shall be specified. The specification of the irradiator shall be revised as necessary (see 12.5.1) and retained for the life of the irradiator (see 4.1.2).

6.2.2 Software used to control and/or monitor the process shall be prepared in accordance with a quality management system that provides documented evidence that the software meets its design intention.

6.2.3 For gamma irradiators, the specification shall at least describe:

a) the irradiator and its characteristics;

b) the type of radionuclide and its activity and the geometry of the gamma source;

c) the premises, including the location of the irradiator;

d) the means provided for the segregation of non-irradiated product from irradiated product (see 10.3 and 10.4);

e) the construction and operation of any associated conveyor system;

f) the conveyor path(s) and the range of conveyor speed;

g) the dimensions, materials and nature of construction of the irradiation container(s);

h) the manner of operating and maintaining the irradiator and any associated conveyor system;

i) the means of indicating the position of the gamma source;

j) the means of automatically returning the gamma source to the storage position and automatically ceasing conveyor movement if the process control timer or the conveyor system fails;

k) the means of returning the gamma source to the storage position and automatically ceasing conveyor movement or identifying affected product if the gamma source is not at its intended position.

6.2.4 For electron beam irradiators the specification shall at least describe:

a) the irradiator and its characteristics;

b) the characteristics of the beam (electron energy and, if applicable, average beam current, scan width and scan uniformity);

c) the premises including the location of the irradiator;

d) the means provided for the segregation of non-irradiated product from irradiated product (see 10.3 and 10.4);

e) the construction and operation of any associated conveyor system;

f) the conveyor path(s) and the range of the conveyor speed;

g) the dimensions, materials and nature of construction of the irradiation container(s);

h) the manner of operating and maintaining the irradiator and any associated conveyor system;

i) the means of indicating that the beam and the conveyor are operating;

j) the means of ceasing irradiation if any failure of the conveyor occurs which affects the dose;

k) the means of ceasing conveyor movement or identifying affected product if any fault in the beam occurs.

6.2.5 For X-ray irradiators, the specification shall at least describe:

a) the irradiator and its characteristics;

b) the characteristics of the beam (electron or X-ray energy and, if applicable, average beam current, scan width and scan uniformity);

c) the dimension, materials and nature of construction of the X-ray converter;

d) the premises including the location of the irradiator;

e) the means provided for the segregation of non-irradiated product from irradiated product (see 10.3 and 10.4);

f) the construction and operation of any associated conveyor system;

g) the conveyor path(s) and the range of the conveyor speed;

h) the dimensions, materials and construction of the irradiation container(s);

i) the manner of operating and maintaining the irradiator and any associated conveyor system;

j) the means of indicating that the beam and the conveyor are operating;

k) the means of ceasing irradiation if any failure of the conveyor occurs which affects the dose;

l) the means of ceasing conveyor movement or identifying affected product if any fault in the beam occurs.

A1 m) the means of ceasing irradiation if failure of the target cooling system occurs. A1

7 Product definition

7.1 Product to be sterilized, including the packaging materials, shall be specified.

7.2 Changes to product, product package or configuration of product within the package shall be specified (see 12.5.2).

7.3 A system shall be specified and implemented to ensure that the condition of product presented for sterilization, including its bioburden, is controlled so that the effectiveness of the sterilization process is not compromised. The effectiveness of the system shall be demonstrated and shall include determination of bioburden in accordance with ISO 11737-1.

7.4 If a sterilization dose is to be established for a product family, requirements for defining a product family in [A1] ISO 11137-2 [A1], shall be met.

7.5 If a processing category is to be used for the purpose of routine processing, product shall be assessed against documented criteria as to whether it is to be included in a processing category. Assessment shall include consideration of product-related variables that affect dose to product and processing specification. The outcome of the assessment shall be recorded (see 4.1.2).

7.6 Periodic reviews of the criteria for assessing product for inclusion in a processing category and of the group of product that constitutes a processing category shall be conducted. The outcome of such reviews shall be recorded (see 4.1.2).

8 Process definition

8.1 Establishing the maximum acceptable dose

8.1.1 The maximum acceptable dose for product shall be established. When treated with the maximum acceptable dose, product shall meet its specified functional requirements throughout its defined lifetime.

8.1.2 Basic technical requirements to establish the maximum acceptable dose shall include:

a) a facility capable of assessing product with regard to its intended function;

b) product representative of that to be produced routinely;

c) an appropriate source of radiation capable of precisely and accurately delivering the required doses (see also 8.4.1).

8.2 Establishing the sterilization dose

8.2.1 The sterilization dose shall be established for product.

8.2.2 One of two approaches, as described in a) and b) below, shall be taken in establishing the sterilization dose:

a) a knowledge of the number and/or resistance to radiation of the bioburden is obtained and used to set the sterilization dose

NOTE Methods of setting the sterilization dose and circumstances under which these methods may be applied are detailed in [A1] ISO 11137-2 [A1].

or

b) a sterilization dose of 25 kGy or 15 kGy is selected and substantiated; in substantiating a sterilization dose of 25 kGy or 15 kGy, the primary manufacturer shall have evidence that the selected sterilization dose is capable of achieving the specified requirements for sterility (see 1.2.2).

NOTE Methods VD_{max}^{25} and VD_{max}^{15} for substantiation of the sterilization dose and circumstances under which these methods may be applied are detailed in [A1] ISO 11137-2 [A1]. Methods VD_{max}^{25} and VD_{max}^{15} are linked to achievement of a sterility assurance level of 10^{-6}.

8.2.3 Basic technical requirements to establish the sterilization dose shall include:

a) a competent microbiological laboratory to perform determinations of bioburden in accordance with ISO 11737-1 and tests of sterility in accordance with ISO 11737-2;

b) product representative of that to be produced routinely;

c) an appropriate source of radiation capable of precisely and accurately delivering the required doses (see also 8.4.2).

NOTE Guidance on dosimetric aspects of radiation sterilization can be found in ISO 11137-3.

8.3 Specifying the maximum acceptable dose and the sterilization dose

The sterilization dose and the maximum acceptable dose shall be specified for product.

8.4 Transference of maximum acceptable, verification or sterilization dose between radiation sources

8.4.1 Transference of maximum acceptable dose

In transferring a maximum acceptable dose to a radiation source different from that on which the dose was originally established, an assessment shall be made demonstrating that differences in irradiation conditions of the two radiation sources do not affect the validity of the dose. The assessment shall be documented and the outcome shall be recorded (see 4.1.2).

8.4.2 Transference of verification dose or sterilization dose

8.4.2.1 Transference of a verification dose or a sterilization dose to a radiation source different from that on which the dose was originally established shall not be permitted unless:

a) data are available to demonstrate that differences in operating conditions of the two radiation sources have no effect on microbicidal effectiveness

or

b) 8.4.2.2 or 8.4.2.3 applies.

8.4.2.2 For product that does not contain water in the liquid state, transference of the verification dose or sterilization dose is permitted between:

a) one gamma irradiator and another gamma irradiator,

b) one electron beam generator and another electron beam generator

or

c) one X-ray generator and another X-ray generator.

8.4.2.3 For product that contains water in the liquid state, transference of the verification dose or sterilization dose is permitted between:

a) one gamma irradiator and another gamma irradiator,

b) two electron radiation sources operating under identical operating conditions

or

c) two X-ray radiation sources operating under identical operating conditions.

9 Validation

9.1 Installation qualification

9.1.1 Operating procedures for the irradiator and associated conveyor system shall be specified.

9.1.2 Process and ancillary equipment, including associated software, shall be tested to verify operation to design specifications. The test method(s) shall be documented and the results shall be recorded (see 4.1.2).

9.1.3 Any modifications made to the irradiator during installation shall be documented (see 6.2.1).

9.1.4 For gamma irradiators, the activity of the source and a description of the location of individual components of the source shall be recorded (see 4.1.2).

9.1.5 For electron beam irradiators, the characteristics of the beam (electron energy, average beam current and, if applicable, scan width and scan uniformity) shall be determined and recorded (see 4.1.2).

9.1.6 For X-ray irradiators, the characteristics of the beam (electron or X-ray energy, average beam current and, if applicable, scan width and scan uniformity) shall be determined and recorded (see 4.1.2).

9.2 Operational qualification

9.2.1 Prior to operational qualification (OQ), the calibration of all instrumentation, including test instrumentation used for monitoring, controlling, indicating or recording, shall be confirmed (see 4.3.3).

9.2.2 OQ shall be carried out by irradiating homogeneous material representative of product to be processed to demonstrate the capability of the equipment to deliver the range of doses required for the sterilization process that has been specified (see Clause 8). OQ shall demonstrate that the irradiator, as installed, is capable of operating and delivering appropriate doses within defined acceptance criteria.

9.2.3 Dose mapping shall be carried out to characterize the irradiator with respect to the distribution of dose (see 9.2.4) and variability of dose (see 9.2.5).

NOTE Guidance on dose mapping is given in ISO 11137-3.

9.2.4 Dose mapping shall be carried out using an irradiation container filled to the upper limit of its design specification with material of homogeneous density. Dosimeters shall be used to determine the dose at various known depths in the material. During dose mapping, irradiation containers, filled to the upper limit of their design specifications with the same material as that present in the container being dose mapped, shall be present in the irradiator in sufficient numbers to mimic effectively a fully loaded irradiator.

9.2.5 Dose mapping shall be carried out on a sufficient number of irradiation containers to allow determination of the distribution and variability of dose between irradiation containers.

9.2.6 If there is more than one conveyor path, dose mapping shall be carried out for each path to be used for processing product.

9.2.7 The effect of a process interruption on the dose shall be determined and recorded (see 4.1.2).

9.2.8 Records of dose mapping shall include a description of irradiation containers, irradiator operating conditions, materials used, measurements of dose and conclusions drawn (see 4.1.2).

9.2.9 For gamma irradiators, the relationship between the timer setting, conveyor speed and dose shall be established.

9.2.10 For electron beam and X-ray irradiators, variations in the characteristics of the beam (see 9.1.5 or 9.1.6) during dose mapping shall be within the limits of the irradiator specification (see 6.2.4 or 6.2.5).

9.2.11 For electron beam and X-ray irradiators, the relationship between the characteristics of the beam (see 9.1.5 and 9.1.6), the conveyor speed and dose shall be established.

9.3 Performance qualification

9.3.1 Dose mapping shall be carried out using product loaded in irradiation containers in accordance with a specified loading pattern in order to

a) identify the location and magnitude of the minimum and maximum dose and

b) determine the relationships between the minimum and maximum dose and the dose(s) at the routine monitoring position(s).

9.3.2 The manner of presenting product for sterilization shall be specified. This shall include:

a) the dimensions and density of packaged product;

b) the orientation of product within the package;

c) a description of the irradiation container (if multiple types of irradiation containers are used within the irradiator);

d) a description of the conveyor path (if multiple conveyor paths are used within the irradiator).

9.3.3 Dose mapping shall be carried out for each processing category (see 7.5).

9.3.4 If partially-filled irradiation containers are to be used during routine processing, the effect of partial filling on

a) dose distribution within irradiation containers and

b) dose and dose distribution in other irradiation containers present in the irradiator,

shall be determined and recorded (see 4.1.2).

9.3.5 Dose mapping shall be carried out on representative irradiation containers sufficient in number to determine the variability of dose between containers.

9.3.6 Dose mapping shall be carried out for each conveyor path to be used for processing the defined product.

9.3.7 For gamma and X-ray irradiators, dose mapping shall be carried out to identify product, or processing categories if used, that can be processed with the product being mapped. The effect on dose to product of different densities present in the irradiator shall be determined to define product that can be processed together.

9.3.8 Records of dose mapping shall include a description of the irradiation container, loading pattern, conveyor path, irradiator operating conditions, measurements of dose and conclusions drawn (see 4.1.2).

9.4 Review and approval of validation

9.4.1 Information generated during installation qualification (IQ), OQ and performance qualification (PQ) shall be reviewed. The outcome of the review shall be recorded (see 4.1.2).

9.4.2 From a consideration of the information and its review, a process specification shall be prepared (see 4.1.2).

9.4.3 For gamma irradiation, the process specification shall include:

a) the description of packaged product, including dimensions, density and orientation of product within the package (see Clause 7 and 9.3.2) and acceptable variations;

b) the loading pattern of product within the irradiation container (see 9.3.1);

c) the conveyor path(s) to be used (see 9.3.6);

d) the maximum acceptable dose (see 8.1);

e) the sterilization dose (see 8.2);

f) for product that support microbial growth, the maximal interval of time between manufacture and completion of irradiation;

g) the routine dosimeter monitoring position(s);

h) the relationships between the dose at the monitoring position(s) and the minimum and maximum doses (see 9.3.1);

i) for product that is to be given multiple exposures to the radiation field, any required re-orientation between exposures.

9.4.4 For electron beam and X-ray irradiation, the process specification shall include:

a) the description of packaged product, including dimensions, density and orientation of product within the package (see Clause 7 and 9.3.2) and acceptable variations;

b) the loading pattern of product within the irradiation container (see 9.3.1);

c) the conveyor path(s) to be used (see 9.3.6);

d) the maximum acceptable dose (see 8.1);

e) the sterilization dose (see 8.2);

f) for product that support microbial growth, the maximal interval of time between manufacture and completion of irradiation;

g) the routine dosimeter monitoring position(s);

h) the relationships between the dose at the monitoring position(s) and the minimum and maximum doses (see 9.3.1);

i) the irradiator operating conditions and limits (i.e. beam characteristics and conveyor speed);

j) for product that is to be given multiple exposures to the radiation field, any required re-orientation between exposures.

10 Routine monitoring and control

10.1 Procedures for handling of product and maintaining product integrity before, during and after irradiation shall be specified.

10.2 Systems for counting product and checking product count shall be implemented throughout product receipt, loading, unloading, handling and release. Any discrepancies in the count shall be resolved before processing and/or release.

10.3 Non-irradiated and irradiated product shall be segregated.

10.4 Radiation sensitive visual indicators shall not be used as proof of adequate radiation processing or as the sole means of differentiating irradiated products from non-irradiated products.

10.5 Product shall be loaded into the irradiation container in accordance with the process specification (see 9.4.3 or 9.4.4).

10.6 A dosimeter or dosimeters shall be placed at the predetermined routine monitoring position(s). Following irradiation, the dosimeters shall be measured and the results recorded (see 4.1.2) and analysed.

10.7 The frequency of dosimeter placement shall be sufficient to verify that the process is in control. The frequency and its rationale shall be specified.

10.8 For gamma irradiators:

a) the timer setting and/or conveyor speed shall be adjusted in accordance with a documented procedure to take account of radionuclide decay and

b) the source position, timer setting and/or conveyor speed and the movement of irradiation containers shall be monitored and recorded (see 4.1.2).

10.9 For electron beam and X-ray irradiators, the electron beam characteristics (see 9.1.5 and 9.1.6) and conveyor speed shall be monitored and recorded (see 4.1.2).

10.10 If process interruption(s) and/or process non-conformance(s) occur, they shall be recorded, together with any actions taken (see 4.1.2).

10.11 Records of radiation processing shall state the date of irradiation and be traceable to batch records (see 4.3.2).

11 Product release from sterilization

11.1 Prior to product release from sterilization, any specific periodic tests, calibrations, maintenance tasks and necessary requalification shall have been performed and outcomes recorded (see 4.1.2).

11.2 Procedures for review of records and product release from sterilization shall be specified (see 4.1.2). The procedure(s) shall define the requirements (see 9.4.3 or 9.4.4 as appropriate) for designating a sterilization process as conforming, taking into account the uncertainty of the measurement system(s). If these requirements are not met, product shall be considered as nonconforming and handled in accordance with 4.4.

Additional records of manufacture and inspection of product will be required as specified in a quality management system (see ISO 13485) in order for product to be released as sterile and distributed.

12 Maintaining process effectiveness

12.1 Demonstration of continued effectiveness

12.1.1 General

The continued effectiveness of the established sterilization dose shall be demonstrated through the conduct of

[A1] a) determinations of bioburden to monitor the number of microorganisms present on product in relation to a specified bioburden limit, and [/A1]

b) sterilization dose audits to monitor the radiation resistance of the bioburden on product.

NOTE The method for the performance of a sterilization dose audit, described in ISO 11137-2, includes the conduct of a bioburden determination.

12.1.2 Frequency of determinations of bioburden

12.1.2.1 For product of average bioburden greater than or equal to 1,5, the maximum interval of time between determinations of bioburden shall be three months.

12.1.2.2 For product of average bioburden less than 1,5 and for which a) the sterilization dose has been set using Method 2 (see ISO 11137-2), or b) a sterilization dose of 25 kGy has been selected (see 8.2.2), the maximum interval of time between determinations of bioburden shall be three months.

12.1.2.3 For product of average bioburden less than 1,5 and for which a) the sterilization dose has been set using Method 1 (see ISO 11137-2), or b) a sterilization dose of 15 kGy has been selected (see 8.2.2), the maximum interval of time between determinations of bioburden shall be one month.

12.1.2.4 If the interval of time between the manufacture of batches of product is more than either one month or three months, as applicable (see 12.1.2.1, 12.1.2.2 and 12.1.2.3), determinations of bioburden shall be performed on each production batch.

〈A1〉 **12.1.2.5** If the outcome of determinations of bioburden exceeds the specified bioburden limit, an investigation in accordance with ISO 11737-1 shall be performed. If the outcome of the investigation indicates that the bioburden determination is a true result, procedures specified in 4.4 shall be implemented and a sterilization dose audit shall be performed immediately. Depending on the outcome of the sterilization dose audit, a) or sterilization dose audit, a) or b) below shall be followed.

a) If the sterilization dose audit is unsuccessful, action shall be taken in accordance with 12.1.3.5.

b) If the outcome of the sterilization dose audit is successful and the bioburden continues to exceed the specified bioburden limit, sterilization shall continue using the dose used prior to the sterilization dose audit. Also

   1) if the sterilization dose has been established using Method 1 (see ISO 11137-2), a three-month interval for the sterilization dose audit shall be used until either the bioburden is returned to the specified bioburden limit or the sterilization dose is re-established; 〈A1〉

   2) if the sterilization dose has been established using Method 2 (see ISO 11137-2), a three-month interval for the sterilization dose audit shall be used until compliance with 12.1.3.2 is achieved;

   3) if a sterilization dose of 25 kGy has been selected and substantiated using Method VD_{max}^{25} and the average bioburden is less than 1 000, the sterilization dose audit frequency currently used shall be continued;

   4) if a sterilization dose of 25 kGy has been selected and substantiated using Method VD_{max}^{25} and the average bioburden is greater than 1 000, the sterilization dose shall be established using another method;

   5) if a sterilization dose of 15 kGy has been selected and substantiated using Method VD_{max}^{15} and the average bioburden is less than 1,5, the sterilization dose audit frequency currently used shall be continued;

   6) if a sterilization dose of 15 kGy has been selected and substantiated using Method VD_{max}^{15} and the average bioburden is greater than 1,5, the sterilization dose shall be established using another method.

12.1.3 Frequency of sterilization dose audits

12.1.3.1 One of two possible approaches, described in a) and b) below, shall be made in initially determining the interval of time between the performance of sterilization dose audits:

a) an interval of time of three months between sterilization dose audits is selected

or

b) a rationale is prepared and documented for the selection of the initial interval of time between the performance of sterilization dose audits; in preparing the rationale, account shall be taken, and records made, of a review and conclusions reached with respect to, at least:

[A1] 1) the specified bioburden limit; [A1]

2) available data from determinations of bioburden, the period of time over which these data were obtained and the characterization of the microorganisms that comprise the bioburden;

NOTE Characterization may be based, for example, on colony or cellular morphology, staining properties or selective culturing.

3) available data on the resistance of microorganisms that comprise the bioburden;

4) the method used to establish the sterilization dose and the conservativeness associated with the method;

5) the difference between the dose to be used in routine processing and the sterilization dose, together with any conservativeness associated with this difference;

6) the materials comprising the product, particularly the use of materials of natural origin, and the control of the microbiological quality of materials;

7) the manufacturing process, particularly manufacturing steps that affect bioburden or its resistance;

8) the control and monitoring procedures for the manufacturing process;

9) the interval of time between manufacture of batches of product;

10) the manufacturing environment, particularly the extent of microbiological control and monitoring and available data on the stability of the manufacturing environment over time;

11) the controls on the health, cleanliness and clothing of personnel in the manufacturing area; and

12) available data on the microbiological quality of other products in the same product family.

12.1.3.2 An increase in the interval of time between the performance of sterilization dose audits shall only be permitted if:

a) at least four consecutive sterilization dose audits, whose outcomes have required neither dose augmentation nor sterilization dose re-establishment, have been performed at the previously selected interval of time;

b) data are available that demonstrate the stability of bioburden within the bioburden specification over the same period of time as item a) above; these include

[A1] 1) bioburden determinations performed at least every three months or every month in the case of product of average bioburden less than 1,5 for which the sterilization dose has been set using Method 1 or a sterilization dose of 15 kGy has been selected and substantiated and [A1]

2) characterization of bioburden (e.g. use of colony or cellular morphology, staining properties or selective culturing);

c) the manufacture of the product in relation to bioburden is controlled and the effectiveness of this control is demonstrated through the implementation of the elements of a quality management system identified for sterile medical devices in ISO 13485.

12.1.3.3 Unless 12.1.3.4 applies, the maximum interval of time between performance of sterilization dose audits shall be twelve months.

12.1.3.4 If the interval of time between manufacture of batches of product is more than that determined in accordance with 12.1.3.1 and/or 12.1.3.2, a sterilization dose audit shall be performed on each production batch.

12.1.3.5 If a sterilization dose audit is unsuccessful, action shall be taken in accordance with [A1] ISO 11137-2. [A1] The frequency of performance of sterilization dose audits shall be an interval of time of not greater than three months until:

a) the cause of the sterilization dose audit failure or the increase in bioburden has been investigated and correction and/or corrective action implemented;

b) the rationale (see 12.1.3.1) for the interval of time between the performance of sterilization dose audits has been reviewed and, if necessary, a new interval of time specified; [A1] and [A1]

c) the criteria for increasing the interval of time between the performance of sterilization dose audits in 12.1.3.2 have been met.

12.2 Recalibration

The accuracy and reliability of instrumentation used to control, indicate or record the sterilization process shall be verified periodically in accordance with 4.3.3.

12.3 Maintenance of equipment

12.3.1 Preventative maintenance shall be planned and performed in accordance with documented procedures. Records of maintenance shall be retained (see 4.1.2).

12.3.2 The maintenance scheme, maintenance procedures and maintenance records shall be reviewed at specified intervals by a designated person and the results of the review shall be documented.

12.4 Requalification of equipment

12.4.1 Requalification of a sterilization process shall be carried out for defined product and specified equipment; it shall be performed at defined intervals and after the assessment of any change (see 12.5). The extent to which requalification is carried out shall be justified.

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

12.4.3 Requalification data shall be reviewed against specified acceptance criteria in accordance with documented procedures. Records shall be retained (see 4.1.2) of reviews of requalification data, together with corrections made and corrective actions taken when the specified acceptance criteria are not met.

12.5 Assessment of change

12.5.1 Any change in the irradiator which could affect dose or dose distribution shall be assessed. If one or both of these is judged to be affected, then a repeat of part or all of IQ, OQ and/or PQ shall be carried out (see 9.1, 9.2 or 9.3). The outcome of the assessment, including the rationale for decisions reached, shall be recorded (see 4.1.2).

12.5.2 A change in product, its package or the presentation of product for sterilization shall be assessed for its effect on the appropriateness of the sterilization process. Those parts of process definition or PQ that have to be undertaken shall be determined based on the nature of the change. The outcome of the assessment, including the rationale for decisions reached, shall be recorded (see 4.1.2).

Annex A
(informative)

Guidance

NOTE 1 The guidance given in this annex is not intended as a checklist for assessing compliance with this part of ISO 11137. This guidance is intended to assist in obtaining a uniform understanding and implementation of this part of ISO 11137 by providing explanations and acceptable methods for achieving compliance with specified requirements. Methods other than those given in the guidance may be used. However, the use of alternative methods has to be demonstrated to be effective in achieving compliance with this part of ISO 11137.

NOTE 2 For ease of reference, the numbering in this annex corresponds to that in the normative part of this part of ISO 11137.

A.1 Scope

A.1.1 No guidance offered.

A.1.2 No guidance offered.

A.1.2.1 No guidance offered.

A.1.2.2 The effective implementation of defined and documented procedures is necessary for the development, validation and routine control of a sterilization process for medical devices. Such procedures are commonly considered to be elements of a quality management system. This part of ISO 11137 identifies and specifies those elements of a quality management system that are essential for the effective control of sterilization by normative reference to the quality management system standard for medical devices, ISO 13485. This part of ISO 11137 does not require that a complete quality management system complying with ISO 13485 be implemented, nor does it require that those quality management system elements that are specified be subject to third party assessment. Attention is drawn to the existence of national and regional regulatory requirements for quality management systems in the manufacture of medical devices and for third party assessment of such systems.

A.1.2.3 The use of biological indicators for validation and process monitoring is not recommended for radiation sterilization because the relationship between the microbicidal action and radiation dose is well established.

A.1.2.4 No guidance offered.

A.1.2.5 No guidance offered.

A.2 Normative references

The requirements given in documents included as normative references are requirements of this part of ISO 11137 only to the extent that they are cited in a normative part of this document; the citation may be to an entire standard or limited to specific clauses.

A.3 Terms and definitions

No guidance offered.

A.4 Quality management system elements

NOTE See also A.1.2.2.

A.4.1 Documentation

Requirements for control of documents and records are specified in 4.2.3 and 4.2.4 respectively, of ISO 13485:2003.

In ISO 13485:2003, the requirements for documentation relate to the generation and control of documentation (including specifications and procedures) and records.

A.4.2 Management responsibility

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

In ISO 13485:2003, the requirements for management responsibility relate to management commitment, customer focus, quality policy, planning, responsibility, authority and communication, and management review.

The development, validation and routine control of a sterilization process can involve a number of separate parties, each of whom is responsible for certain elements. This part of ISO 11137 requires that the party accepting particular responsibilities be defined and that this definition of responsibilities be documented. This definition of authority and responsibility is documented within the quality management system(s) of the identified parties. The party accepting responsibilities for defined elements is required to assign these elements to competent personnel, with competence demonstrated through appropriate training and qualification.

In radiation sterilization, there can be two principal parties involved; the primary manufacturer and the irradiator operator. The irradiator operator might be a specialist contractor offering a sterilization service or it might be part of the same firm as the primary manufacturer. In these instances, the primary manufacturer and the irradiator operator have separate quality management systems and the definition of authority and responsibility is within a contract or technical agreement. Some of the principal responsibilities that can be allocated to the primary manufacturer and irradiator operator are:

a) Primary manufacturer

- establishing the sterilization dose;
- developing product families;
- establishing the maximum acceptable dose;
- PQ;
- controlling the manufacturing process(es), including meeting the specifications for products submitted to the irradiator's operator, i.e. product density, orientation, dimensions;
- revision of specifications submitted to the irradiator's operator;
- change control of the product to include a review of product-related variables that affect processing categories;
- control of product labelled “sterile” prior to sterilization;
- product release.

b) Irradiator operator

— IQ;

— OQ;

— controlling the irradiation process;

— change control of the irradiator;

— certification of the radiation dose;

— developing processing categories.

A.4.3 Product realization

NOTE In ISO 13485:2003, the requirements for product realization relate to the product lifecycle from the determination of customer requirements, design and development, purchasing, control of production and calibration of monitoring and measuring devices.

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

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

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

A.4.3.4 Guidance on dosimetric aspects of radiation sterilization is given in ISO 11137-3.

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

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

In ISO 13485:2003, the requirements for measurement, analysis and improvement relate to process monitoring, control of nonconforming product, analysis of data, and improvement (including corrective and preventive actions).

A.5 Sterilizing agent characterization

A.5.1 Sterilizing agent

The assessment of the potential of electrons or X-rays above the specified energy level for inducing radioactive radionuclides in irradiated product should be based on available literature, measurement of induced radioactivity and/or modelling of induced radioactivity.

An example of an assessment using both experimental and theoretical treatments is that of Grégoire *et al.* [21]. Measured and calculated values of the induced radioactivity in many materials used in medical devices and irradiated with X-rays generated with a 7,5 MeV electron beam at doses up to 50 kGy are reported. Such materials are:

a) materials that have very small potential for becoming radioactive (non-metallic hydrocarbon-based materials, e.g. polyethylene and polystyrene);

b) materials that have a potential to be activated at a measurable but low level (e.g. stainless steel and brass);

c) materials that have a potential to be activated to comparatively higher levels (e.g. tantalum) requiring detailed evaluation.

Materials not covered in the publication of Grégoire *et al.* [21] could require detailed evaluation due to their potential for activity (e.g. silver and gold).

A.5.2 Microbicidal effectiveness

No guidance offered.

A.5.3 Material effects

No guidance offered.

A.5.4 Environmental considerations

Principles of an environmental management system can be applied to the radiation sterilization process. ISO 14001 provides a specification for an environmental management system. ISO 14040 provides guidance on designing a life cycle assessment study. An assessment should be made regarding any explosive or inflammable properties of materials to be irradiated.

A.6 Process and equipment characterization

NOTE The purpose of this activity is to define the equipment used in the sterilization process and its operation.

A.6.1 No guidance offered.

A.6.2 No guidance offered.

A.7 Product definition

NOTE The purpose of product definition is to define the product to be sterilized and to determine its microbiological quality prior to sterilization.

A.7.1 No guidance offered.

A.7.2 No guidance offered.

A.7.3 The intention is that the bioburden is stable and low, taking into account the nature of the raw materials, product packaging and procedures prior to sterilization. This is typically achieved by using a quality management system complying with ISO 13485 throughout the manufacture of the medical device.

A.7.4 See A1 ISO 11137-2. A1

A.7.5 The criteria for assessing product for inclusion in processing categories are unique to radiation sterilization and would not necessarily be appropriate for use with other sterilization methods (e.g. ethylene oxide or moist heat).

For gamma or an X-ray irradiator, routine processing of product is performed in an irradiation facility that typically contains a large number of irradiation containers. The effect of product in adjacent irradiation containers on the dose is determined during OQ dose mapping and can provide information regarding products that can be processed together. Typically, this dose mapping information is also used to assess product for inclusion in a processing category that can be used by the irradiator operator to schedule the product being processed.

The two main criteria for assessing product for inclusion in a processing category for gamma and X-ray irradiators are possession of similar dose requirements (sterilization dose and maximum acceptable dose) and dose absorption characteristics (e.g. density and loading pattern). In general, product is included in a processing category based on the ability to process product at the same timer setting without violating the specified dose limits for product within the processing category. If OQ dose mapping has not been performed to determine the ranges of products that may be included in a processing category, each product to be included in the processing category should be dose mapped.

For electron beam irradiators, more individual product dose mapping during PQ is performed than for X-ray or gamma irradiators. However, to reduce the amount of dose mapping required, product may be grouped into processing categories. Grouping of product into processing categories is only appropriate if the product, packaging and the loading pattern of product in irradiation containers result in an ability to process product at the same process parameters without exceeding the specified dose limits for product within the processing category. The number, distribution and orientation of product within the irradiation container and density and distribution of mass should be considered.

Modifications of the product-related variables that affect dose to product and processing specifications can alter the basis on which product was included in the processing category; when this occurs, a new processing category should be defined. Examples of these product-related variables include:

a) the dimensions of the carton;

b) the weight of the carton including product;

c) the orientation of product within the carton;

d) the number of product items per carton;

e) the sterilization dose;

f) the maximum acceptable dose.

A.7.6 Periodic reviews of processing categories are typically carried out annually.

A.8 Process definition

NOTE The purpose of process definition is to establish the maximum acceptable dose and the sterilization dose for the sterilization process to be applied to defined product (see Clause 7).

A.8.1 Establishing the maximum acceptable dose

A.8.1.1 Assurance of the quality, safety and performance of product throughout defined lifetime should begin with the selection of appropriate materials (see AAMI TIR17 [16]). Typically, in designing a test programme, variations in the following should be assessed:

— raw materials;

— manufacturing processes;

— radiation dose;

— type of radiation;

— storage conditions after irradiation.

The programme should include assessment of functionality and safety, including biological safety (see ISO 10993-1), using appropriate tests with specific acceptance criteria.

The dose derived from the test programme is used to determine the maximum acceptable dose for product.

A further necessary step in the test programme is to obtain supporting evidence that the product will meet its acceptance criteria throughout its defined lifetime. One method designed to obtain this information more rapidly than by real time experience is through the institution of an accelerated aging programme. The adverse effects of radiation on product develop more rapidly at higher temperatures and proposals have been made for relating the heat induced changes to those occurring in real time (see AAMI TIR17 [16]). Accelerated ageing, however, is not a substitute for real time ageing.

See ISO 11137-3:2006, Clause 6, for further guidance on dosimetry aspects.

A.8.1.2 Guidance on dosimetric aspects of radiation sterilization is given in ISO 11137-3.

A.8.2 Establishing the sterilization dose

A.8.2.1 See ISO 11137-2.

A.8.2.2 With regard to 8.2.2 a), in order to establish the sterilization dose with this approach, the following can apply:

1) a knowledge of the number and resistance of microorganisms comprising the bioburden may be used in establishing the sterilization dose for product having an average bioburden greater than or equal to 0,1 (see [A1] Method 1 of ISO 11137-2 [A1]);

2) a knowledge of the resistance of microorganisms comprising the bioburden may be used in establishing the sterilization dose for product having any level of average bioburden, (see [A1] Method 2 of ISO 11137-2 [A1] .)

With regard to 8.2.2 b), an appropriate method for substantiation of 25 kGy for product having an average bioburden less than or equal to 1 000 or for substantiation of 15 kGy for product having an average bioburden [A1] less than or equal to [A1] 1,5 is given in [A1] ISO 11137-2. [A1]

A.8.2.3 No guidance offered.

A.8.3 Specifying the maximum acceptable dose and the sterilization dose

No guidance offered.

A.8.4 Transference of maximum acceptable, verification or sterilization dose between radiation sources

A.8.4.1 Transference of maximum acceptable dose

[A1] The assessment of the validity of the maximum acceptable dose for a radiation source other than that on which the dose was originally established should take into consideration dose rate and product temperature during irradiation. For example, the higher the dose rate, the less likely are unwanted effects upon product.

A product qualified at a low dose rate (gamma rays) or intermediate dose rate (X-rays) will typically require minimal qualification to demonstrate material compatibility at a high dose rate (electron-beam). Conversely, a material qualified at a high dose rate may require more substantial qualification in the low or intermediate dose rate application. [A1]

If dose rate and product temperature are equivalent, transfer between the same type of radiation sources is appropriate.

A.8.4.2 Transference of verification or sterilization dose

[A1] **A.8.4.2.1** There is a concern in transferring between types of radiation source with widely differing dose rates that can provide different microbicidal effects. Demonstrating that the microbicidal effectiveness is not affected by changes in dose rate provides the necessary data for the transference to be permitted. A demonstration that transference does not alter microbicidal effectiveness can be accomplished by the performance of a successful verification dose experiment (see ISO 11137-2) using the radiation source to which transfer is being considered. [A1]

A.8.4.2.2 Experimental evidence indicates that when irradiation occurs under "dry" conditions, microbicidal effectiveness is independent of the operating conditions of the sources; hence the granting of this permission.

[A1] *Text deleted* [A1]

[A1] **A.8.4.2.3** Experimental evidence indicates that when irradiation occurs in the presence of liquid water, microbicidal effectiveness can be affected by the operating characteristics of the radiation sources, hence the restrictions on permission being granted. [A1]

A.9 Validation

NOTE 1 For the purpose of this part of ISO 11137, validation has at least the three main elements, IQ, OQ and PQ.

NOTE 2 For major installations or new items of equipment, it is common practice to begin by defining and documenting the user requirements. When potential suppliers of equipment have been identified, the equipment specifications and facility layout are formally reviewed against the user requirements and any discrepancies resolved. This process is generally designated Design Qualification (DQ). This part of ISO 11137 does not specify requirements for DQ.

A.9.1 Installation qualification

IQ is carried out to demonstrate that the sterilization equipment and any ancillary items have been supplied and installed in accordance with their specification.

IQ begins with production of documentation describing the design and installation requirements (see also A.9, NOTE 2). IQ should be based on written requirements. Construction and installation should be assessed against these requirements. IQ documentation should include drawings and details of all the construction materials, the dimensions and tolerances of the equipment, support services and power supplies.

IQ should be completed prior to performance of OQ.

Radiation plants that operated prior to the publication of ISO 11137:1995 might not have records of modifications made to the irradiator during installation. Retrospective generation of such records is not required.

A.9.2 Operational qualification

See ISO 11137-3 for dosimetric aspects for radiation sterilization.

A.9.3 Performance qualification

PQ is the stage of validation which uses defined product to demonstrate that equipment consistently operates in accordance with predetermined criteria to deliver doses within the range of the specified doses, thereby giving product that meets the specified requirement for sterility.

See ISO 11137-3 for dosimetric aspects for radiation sterilization.

With regard to 9.3.2 b), orientation of the product within the package is critical in electron-beam processing. Furthermore, orientation can be critical in gamma and X-ray processing where density could affect dose distribution (e.g. containers of liquids or metal hip implants).

With regard to 9.3.2 c), if a system is used to secure the product in the irradiation container, a description of the materials used and the method of securing should be included in the specification.

A.9.4 Review and approval of validation

This activity involves undertaking and documenting a review of the validation data to confirm the acceptability of the sterilization process and to develop and approve a process specification.

A.10 Routine monitoring and control

NOTE The purpose of routine monitoring and control is to demonstrate that the validated and specified sterilization process has been delivered to product.

A.10.1 No guidance offered.

A.10.2 ISO 13485 specifies requirements for handling and preservation of product.

A.10.3 When segregating product, consideration can be given to:

a) the physical separation of product

and/or

b) the use of a reliable inventory control system.

The use of labels and/or stamps could be part of the procedure.

A.10.4 No guidance offered.

A.10.5 If product could move within the irradiation container and, in so doing, affect dose distribution, then product should be secured and packing material should be utilized to prevent undue movement during processing.

A.10.6 A review of the results from the monitoring of the process parameters and from routine dosimetry is used to ascertain that product has been processed according to specification. The review should include, if appropriate, actions to be taken when measurements fall outside specified limits.

For measurements outside of specified limits, a procedure describing the actions to be taken in such cases (e.g. reprocessing, checking of the reliability of the transgressing reading, product discard, further processing needs) should be documented and implemented.

Electron beam irradiators vary in their characteristics and in the way they are monitored. The relative contribution of the monitoring of operating parameters and of the performance of routine dosimetry to assure that the sterilization dose is delivered to product inevitably varies from irradiator to irradiator. The irradiator operator should design a monitoring procedure, including the monitoring of operating parameters and the performance of routine dosimetry, which will provide the necessary confidence that sterilization processing is properly carried out.

A.10.7 See ISO 11137-3 for guidance on dosimetric aspects.

A.10.8 No guidance offered.

A.10.9 No guidance offered.

A.10.10 A review of the results from the monitoring of the process parameters and from routine dosimetry is used to ascertain that product has been processed according to specification. The review should also include, if appropriate, actions to be taken in case of process interruption.

Deviations from normal operating conditions (such as power loss or incorrect conveyor movements) should result in immediate interruption of the process and automatic safe storage of the source. The reason for and the duration of process interruption should be recorded, and procedures regarding restart should be documented and implemented.

In case of failure of the irradiator or conveyor system, a documented procedure should be followed to ensure that subsequent actions provide product that has received the sterilization dose and that the maximum acceptable dose has not been exceeded.

For process interruption occurring with product incapable of supporting microbial growth, interruption without moving product in the irradiator does not generally necessitate action. Nevertheless, such process interruptions should be documented and reviewed to ensure that dosimetry measurements are valid.

For process interruption occurring with product capable of supporting microbial growth:

— the maximal interval of time that can elapse between completion of manufacture and completion of sterilization processing and

— the conditions of storage and transportation to be applied during this interval of time

are stated in the process specification.

The maximal interval of time and conditions are chosen to ensure that the microbiological quality of the product is at a level that would not compromise product sterility. If process interruption occurs during sterilization and this delays the completion of sterilization beyond the specified time, its effect on the microbiological quality of the product should be ascertained and appropriate action taken. This can include product discard.

If a process deviation occurs resulting in a dose less than the desired dose, additional dose may be given to the product if a) the ability of the product to support microbial growth has been taken into consideration and b) the dose can be delivered in such a way to assure that the minimum dose is achieved and the maximum acceptable dose is not exceeded. See ISO 11137-3 for further guidance.

See ISO 11137-3 for guidance on dosimetric aspects.

A.10.11 No guidance offered.

A.11 Product release from sterilization

No guidance offered.

A.12 Maintaining process effectiveness

A.12.1 Demonstration of continued effectiveness

A.12.1.1 General

For the sterilization dose to remain valid, product has to be manufactured under controlled conditions that yield stable bioburden in terms of numbers and types of microorganisms. To demonstrate continued validity of the sterilization dose, sterilization dose audits are carried out at a pre-defined interval of time.

These specified maximal intervals of time have been based on:

a) experience gained in applying dose setting methods;

b) the need to detect changes in manufacturing processes and materials and a consensus on an accepted degree of risk associated with the frequency of seeking such changes;

c) the potential for seasonal changes or other variations in the microbiological quality of materials or the manufacturing environment;

d) the generally accepted frequency of revalidation for a sterilization process.

A.12.1.2 Frequency of determinations of bioburden

A.12.1.2.1 No guidance offered.

A.12.1.2.2 No guidance offered.

A.12.1.2.3 No guidance offered.

A.12.1.2.4 No guidance offered.

A1 **A.12.1.2.5** Setting the specified bioburden limit for the purpose of demonstrating the continued effectiveness of the sterilization dose should be based on the consequences of exceeding the specified bioburden limit on the achievement of the specified requirements for sterility. A1

A.12.1.3 Frequency of sterilization dose audits

A.12.1.3.1

a) Historically, a three-month time interval has been used to detect seasonal variations in bioburden. Product manufactured under controlled conditions may not exhibit seasonal variation in bioburden. If control over bioburden in terms of numbers and types of microorganisms can be demonstrated with no seasonal variation, a reduction in the frequency of dose audits may be considered. This consideration has to include those aspects of processing and monitoring specified in 12.1.3. It is noted that all the aspects have to be considered, but not all of them will necessarily provide definitive outcomes or carry equal weight (i.e. be of equal importance).

b) No guidance offered.

A.12.1.3.2 As experience of product and its manufacture is gained, increases in the interval of time between the performance of sterilization dose audits have occurred as follows – initially an interval of time of three months, then an interval of time of six months and finally an interval of time of twelve months.

It should be recognized that a reduction in the frequency of performance of the sterilization dose audit results in a reduction in the ability to detect a change within the manufacturing process, over time. Consequently, the effect of such a reduction in frequency should be considered before proceeding.

A.12.1.3.3 No guidance offered.

A.12.1.3.4 No guidance offered.

A.12.1.3.5 No guidance offered.

A.12.2 Recalibration

No guidance offered.

A.12.3 Maintenance of equipment

During the review of the maintenance records, the maintenance schedule and procedures should be revised as necessary to address information learned about the equipment.

A.12.4 Requalification of equipment

The intervals for requalification of the irradiator should be chosen to provide assurance that the irradiator is consistently operating within specifications. For gamma irradiators, the requalification is typically carried out in connection with replenishment of sources. For electron beam and X-ray irradiators, requalification is typically carried out on an annual cycle, with specific parts of requalification at shorter time intervals within this cycle. If requalification measurements show that the IQ and/or OQ status of the irradiator has changed, then PQ might have to be repeated.

A.12.5 Assessment of change

A.12.5.1 For gamma irradiators, examples of when OQ should be performed after a change include:

— replenishment of the source;

— changes in source geometry and position;

— changes to the conveyor;

— a change in product path;

— a change in irradiation container.

The extent of the OQ will depend on the type and degree of the change (see Table A.1).

For electron beam irradiators, OQ should be performed when changes are made to the irradiator, which can affect performance. Examples of such changes include:

— changes to the conveyor;

— an increase of maximal designed dimensions of the irradiation container;

— repair or replacement of scanning magnet;

— repair or replacement of bending magnet;

— repair or replacement of parallel beam magnet;

— changes in the elements of the irradiator creating scattering effects.

The extent of the OQ will depend on the type and extent of the change (see Table A.2). For example, an increase of the maximal designed dimensions of the irradiation container will require a complete requalification, whereas replacement of a conveyor part could only require confirmation of the proper functioning of the conveyor.

For X-ray irradiators, OQ should be performed when changes are made to the irradiator, which can affect performance. Examples of such changes include:

— changes to the conveyor;

— an increase of maximal designed dimensions of the irradiation container;

— repair or replacement of scanning magnet;

— repair or replacement of bending magnet;

— repair or replacement of parallel beam magnet;

— changes in the elements of the irradiator creating scattering effects;

— changes to the X-ray target.

The extent of the OQ will depend on the type and extent of the change (see Table A.3). For example, an increase of the maximal designed dimensions of the irradiation container will require a complete requalification, whereas replacement of a conveyor part could only require confirmation of the proper functioning of the conveyor.

A.12.5.2 No guidance offered.

Table A.1 — Guidance on qualification of changes to a gamma irradiator

Irradiator change	Installation qualification	Operational qualification			
	Installation testing and equipment documentation	Equipment testing	Equipment calibration	Irradiator dose mapping	Type of dose mapping
Addition, removal or reconfiguration of/to radionuclide	✓			✓	Homogeneous material to design limits
Carrier/irradiation container redesign	✓	✓		✓	Homogeneous material to design limits
Removal or relocation of overhead conveyor inside irradiation cell	✓	✓		✓	Homogeneous material to design limits
Removal or relocation of stop units in the critical product path	✓	✓		✓	Homogeneous material to design limits
Removal or relocation of stop units outside of the critical product path	✓	✓			
Replacement of source cables	✓	✓			
Redesign of the source drive system	✓			✓	Transit dose
Redesign that affects the source to product distance	✓	✓		✓	Homogeneous material to design limits Transit dose
Redesign of the source rack system	✓	✓		✓	Homogeneous material to design limits Transit dose
Changes to type of irradiator cycle timer	✓	✓	✓		
Changes to type of irradiator radiation safety monitoring devices	✓	✓	✓		
Changes to type of irradiator pool water monitoring devices	✓	✓	✓ (if applicable)		

NOTE 1 Addition of radionuclide without reconfiguration of the source geometry might only require that part of the homogeneous dose mapping study be performed to confirm the results of mathematical modelling or modification objectives. Whereas addition of radionuclide with change of source geometry might require that all homogeneous dose maps be repeated in addition to some of the ancillary studies such as centre loading or partial load.

NOTE 2 Pending results of operational testing (e.g. verification of source position), irradiator dose mapping may be required after source cable replacement.

NOTE 3 OQ dose mapping results may lead to a repeat of PQ.

Table A.2 — Guidance on qualification of changes to an electron beam irradiator

Irradiator change	Installation qualification	Operational qualification			
	Installation testing and equipment documentation	Operational testing	Equipment calibration	Irradiator dose mapping	Type of dose mapping
Accelerator mechanical alignment	✓			✓	Scan uniformity in the direction of beam scan and depth-dose in the direction of beam travel
Steering or focusing magnet systems	✓			✓	Scan uniformity in the direction of beam scan and depth-dose in the direction of beam travel
Bending magnet systems	✓		✓	✓	Scan uniformity in the direction of beam scan and depth-dose in the direction of beam travel
Beam current monitoring system	✓		✓	✓	Scan uniformity in the direction of product travel
Scanning magnet system	✓		✓	✓	Scan uniformity in the direction of beam scan
Conveyor speed monitoring and/or control circuitry	✓		✓	✓	Scan uniformity in the direction of product travel Process interruption testing
Conveyor system motors, belts, and gearing.	✓	✓			
NOTE OQ dose mapping results may lead to a repeat of PQ.					

Table A.3 — Guidance on qualification of changes to an X-ray irradiator

Irradiator change	Installation qualification	Operational qualification			
	Installation testing and equipment documentation	Equipment testing	Equipment calibration	Irradiator dose mapping	Type of dose mapping
Accelerator mechanical alignment	✓			✓	Scan uniformity in the direction of beam scan and depth-dose in the direction of beam travel
Steering or focusing magnet systems	✓			✓	Scan uniformity in the direction of beam scan and depth-dose in the direction of beam travel
Bending magnet systems	✓		✓	✓	Scan uniformity in the direction of beam scan and depth-dose in the direction of beam travel
Beam current monitoring system	✓		✓	✓	Scan uniformity in the direction of product travel
Scanning magnet system	✓		✓	✓	Scan uniformity in the direction of beam scan
Conveyor speed monitoring and/or control circuitry	✓		✓	✓	Scan uniformity in the direction of product travel Process interruption testing
Conveyor system motors, belts and gearing.	✓	✓			
Carrier/irradiation container redesign	✓	✓		✓	Scan uniformity in the direction of product travel Depth-dose in the direction of product travel
Removal or relocation of conveyor inside irradiation cell	✓	✓		✓	Scan uniformity in the direction of product travel Depth-dose in the direction of product travel
Redesign that affects the source-to-product distance	✓	✓		✓	Scan uniformity in the direction of product travel Scan uniformity in the direction of beam scan Depth-dose in the direction of product travel
Changes to type of irradiator radiation safety monitoring devices	✓	✓	✓		
Replacement, redesign, or realignment of the X-ray target	✓	✓		✓	Scan uniformity in the direction of beam scan and beam travel Scan uniformity in the direction of product travel Depth-dose in direction of beam travel
NOTE OQ dose mapping results may lead to a repeat of PQ.					

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