International Standard

ISO 11137-1

Sterilization of health care products — Radiation —

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

Stérilisation des produits de santé — Irradiation —

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

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Foreword

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

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

The main changes are as follows:

— addition of ISO 13004 as a normative reference;

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

— update of Clause 4 to align with ISO/TC 198 documents;

— increase of the allowable limits above which the potential induced radioactivity shall be assessed to 11 MeV for electrons and 7,5 MeV for X-rays (see 5.1.2);

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

— simplification of content on transference of verification dose or sterilization dose based on published data that demonstrates that differences in operating conditions of the two radiation sources have no effect on microbicidal effectiveness for product that does not promote microbial growth (see 8.4.2);

— clarification on the use of dose measurements and the recording of process variables for process control (see 10.6 and 10.7);

— clarification has been provided on the allowable interval of time for quarterly dose audits, allowing for an interval of four months provided there are four dose audits per year (see 12.1.2);

— addition of references for all VD_{max}^{SD} dose levels contained in both ISO 11137-2 and ISO 13004 (see 8.2.2 and 12.1.2);

— additional information has been included on bioburden determination for products with very low bioburden (see 12.1.2.2 and A.12.1.2.2);

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

— addition of references to the Bibliography.

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

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Introduction

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

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

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

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

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

a) the microbiological quality (microorganism numbers and characterization) of incoming raw materials and 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 document describes the requirements for ensuring that the activities associated with the process of radiation sterilization are performed properly. These activities are described in documented work programmes designed to demonstrate that the irradiation process will consistently yield sterile medical devices on treatment with doses falling within the predetermined limits.

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

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

Sterilization of health care products — Radiation —

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

1 Scope

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

NOTE Although the scope is limited to medical devices, this document can be applicable to other products and equipment.

This document 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 document is not applicable to processes for inactivating viruses or the causative agents of spongiform encephalopathies, such as scrapie, bovine spongiform encephalopathy and Creutzfeldt-Jakob disease.

NOTE For information on such processes, see ISO 22442-1, ISO 22442-2, ISO 22442-3, ISO 13022 and ICH Q5A.

1.2.1 This document does not specify requirements for designating a medical device as sterile.

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

1.2.2 This document does not specify a quality management system for the control of all stages of production of medical devices.

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

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

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

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

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

2 Normative references

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

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

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

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

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

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

3 Terms and definitions

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

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

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

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

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

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

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

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

[SOURCE: ISO 11139:2018, 3.23]

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

[SOURCE: ISO 11139:2018, 3.29]

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

[SOURCE: ISO 11139:2018, 3.31]

3.5
correction
action to eliminate a detected nonconformity

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

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

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

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

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

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

3.7
development
act of elaborating a specification

[SOURCE: ISO 11139:2018, 3.79]

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

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

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

[SOURCE: ISO 11139:2018, 3.89]

3.10
dosimetry
measurement of absorbed dose by the use of dosimeters

[SOURCE: ISO 11139:2018, 3.90]

3.11
establish
determine by theoretical evaluation and confirm by experimentation

[SOURCE: ISO 11139:2018, 3.107]

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

[SOURCE: ISO 11139:2018, 3.116]

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

[SOURCE: ISO 11139:2018, 3.132]

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

[SOURCE: ISO 11139:2018, 3.220.2]

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

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

[SOURCE: ISO 11139:2018, 3.146]

3.16
irradiator operator
company or body responsible for irradiation of product

[SOURCE: ISO 11139:2018, 3.147]

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

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

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

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

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

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

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

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

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

— supporting or sustaining life;

— control of conception;

— disinfection of medical devices;

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

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

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

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

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

— disinfection substances;

— aids for persons with disabilities;

— devices incorporating animal and/or human tissues;

— devices for in vitro fertilization or assisted reproduction technologies.

[SOURCE: ISO 11139:2018, 3.166]

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

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

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

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

[SOURCE: ISO 11139:2018, 3.220.3]

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

[SOURCE: ISO 11139:2018, 3.220.4]

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

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

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

[SOURCE: ISO 9000:2015, 3.12.1]

3.24
process interruption
intentional or unintentional stoppage of the irradiation process

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

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

3.26
process parameter
specified value for a process variable

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

[SOURCE: ISO 11139:2018, 3.211]

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

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

[SOURCE: ISO 11139:2018, 3.213, modified — EXAMPLE has been changed to a list of process variables specific to radiation processes.]

3.28
processing category
collection of different product or product families that can be processed together

Note 1 to entry: Processing categories can be based on, for instance, composition, homogeneity, density or dose requirements.

[SOURCE: ISO 11139:2018, 3.215, modified — Note 1 to entry has been added.]

3.29
product
tangible result of a process

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

[SOURCE: ISO 11139:2018, 3.217]

3.30
product family
group or subgroup of product characterized by similar attributes determined to be equivalent for evaluation and processing purposes

Note 1 to entry: Members of a radiation sterilization product family can be given the same sterilization dose.

[SOURCE: ISO 11139:2018, 3.218, modified — Note 1 to entry has been added.]

3.31
requalification
repetition of part or all of validation for the purpose of confirming the continued acceptability of a specified process

[SOURCE: ISO 11139:2018, 3.220.5]

3.32
services
supplies from an external source needed for the function of equipment

EXAMPLE Electricity, water, compressed air, drainage.

[SOURCE: ISO 11139:2018, 3.252, modified — EXAMPLE has been added.]

3.33
simulated product
material with attenuation and scattering properties similar to those of product, material, or substance to be irradiated

Note 1 to entry: Simulated product is used as a substitute for the actual product, material, or substance to be irradiated. When used in routine production runs to compensate for the absence of product, simulated product is sometimes referred to as compensating dummy. When used for dose mapping, simulated product is sometimes referred to as phantom material.

[SOURCE: ISO 11139:2018, 3.254, modified — Deleted <radiation sterilization> domain.]

3.34
specification
approved document stipulating requirements

3.35
specify
stipulate in detail within an approved document

[SOURCE: ISO 11139:2018, 3.259]

3.36
sterile
free from viable microorganisms

[SOURCE: ISO 11139:2018, 3.271]

3.37
sterile barrier system
SBS
minimum package that minimizes the risk of ingress of microorganisms and allows aseptic presentation of the sterile contents at the point of use

[SOURCE: ISO 11139:2018, 3.272]

3.38
sterility
state of being free from viable microorganisms

Note 1 to entry: In practice, no such absolute statement regarding the absence of microorganisms can be proven.

[SOURCE: ISO 11139:2018, 3.274]

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

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

Note 2 to entry: The term SAL takes a quantitative value, generally 10^{-6} or 10^{-3}.

[SOURCE: ISO 11139:2018, 3.275, modified — Note 2 to entry has been added.]

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

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

[SOURCE: ISO 11139:2018, 3.277]

3.41
sterilization dose
SD
D_{ster}
minimum dose to achieve the specified requirements for sterility

[SOURCE: ISO 11139:2018, 3.280, modified — Deleted <radiation> domain and added the symbol D_{ster}]

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

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

[SOURCE: ISO 11139:2018, 3.284]

3.43
sterilizing agent
physical or chemical entity, or combination of entities, having sufficient microbicidal activity to achieve sterility under specified conditions

[SOURCE: ISO 11139:2018, 3.288]

3.44
test for sterility
technical operation specified in a pharmacopoeia performed on product following an aseptic process or exposure to a sterilization process

[SOURCE: ISO 11139:2018, 3.298]

3.45
test of sterility
technical operation performed as part of development, validation, or requalification to determine the presence or absence of viable microorganisms on a product or portions thereof

[SOURCE: ISO 11139:2018, 3.299]

3.46
validation
confirmation process, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

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

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

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

[SOURCE: ISO 9000:2015, 3.8.13, modified — “process” has been added to the definition.]

3.47
verification dose
dose of radiation predicted to give a predetermined sterility assurance level (SAL) greater than or equal to 10^{-2} used in establishing the sterilization dose

[SOURCE: ISO 11139:2018, 3.315]

4 General

4.1 The development, validation and routine control of a sterilization process is a critical element in product realization of health care product. To ensure the consistent implementation of the requirements specified in this document, the necessary processes need to be established, implemented and maintained. Processes of particular importance in relation to the development, validation and routine control of a sterilization process include but are not limited to:

— control of documentation, including records,

— assignment of management responsibility,

— provision of adequate resources, including competent human resources and infrastructure,

— control of product provided by external parties,

— identification and traceability of product throughout the process, and

— control of non-conforming product.

NOTE ISO 13485 covers all stages of the lifecycle of medical devices in the context of quality management systems for regulatory purposes. National and/or regional regulatory requirements for the provision of health care product can require the implementation of a full quality management system and the assessment of that system by a recognized conformity assessment body.

4.2 A process shall be specified for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this document.

4.3 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. Processes for dosimetry shall meet the requirements of ISO/ASTM 52628.

5 Sterilizing agent characterization

5.1 Sterilizing agent

5.1.1 The type of radiation to be used in sterilization processing shall be specified (e.g. gamma ray, electron beam or X-ray).

5.1.2 For electrons or X-rays, the energy level of the electron beam shall be specified. The potential for induced radioactivity in product and packaging system shall be assessed if:

— the energy level for electrons exceeds 11 MeV; or

— the energy level for electrons used to generate X-rays exceeds 7,5 MeV.

The outcome of the assessment and the rationale for decisions reached shall be documented.

NOTE Additional guidance can be found in Annex A.

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 process variables affect microbial inactivation. Reference to these general studies on microbial inactivation is not required by this document.

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 (see, for example, AAMI TIR17). This document does not require the studies to be carried out on material effects, but does require studies on the effects of radiation on product and packaging system to be carried out (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 parameters, together with their tolerances, are part of the process specification (see 9.4.3). The means of monitoring and controlling process variables shall be specified. Means shall be provided to ensure that failure in a control function does not lead to failure in the recording of process variables such that an ineffective process appears effective. This can be achieved either by the use of independent systems for control and monitoring, or by a cross-check between control and monitoring that identifies any discrepancies that indicate a fault.

NOTE Guidance for identifying, monitoring and controlling process variables relevant to the establishment and control of a radiation sterilization process is given in ISO/TS 11137-4.

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).

6.2.2 Software used to control or monitor the process shall be validated.

6.2.3 Table 1 lists what the equipment design specification for gamma, electron beam and X-ray irradiators shall describe at a minimum.

Table 1 — Equipment design specifications for gamma, electron beam and X-ray irradiators

Equipment design specification	Gamma	Electron beam	X-ray
a) The irradiator and its characteristics.	✓	✓	✓
b) The type of radionuclide, its maximum specified activity and the geometry of the gamma source(s).	✓		
c) The characteristics of the beam, including the applicable range of electron energy, beam current and beam width profile.		✓	✓
d) The dimension, materials and nature of construction of the X-ray converter.			✓
e) The premises, including the location of the irradiator.	✓	✓	✓
f) The means provided for the segregation of non-irradiated product from irradiated product (see 10.3 and 10.4).	✓	✓	✓
g) The construction and operation of any associated conveyor system.	✓	✓	✓

Table 1 *(continued)*

Equipment design specification	Gamma	Electron beam	X-ray
h) The conveyor path(s), the mechanism(s) of conveyance and associated specification(s).	✓	✓	✓
i) The dimensions, materials and nature of construction of the irradiation container(s) and their allowable range of process load dimensions and weights.	✓	✓	✓
j) The manner of operating and maintaining the irradiator and any associated conveyor system.	✓	✓	✓
k) The means of indicating the position of the gamma source(s).	✓		
l) The means of returning the gamma source(s) to the storage position and automatically ceasing conveyor movement or identifying affected product if the gamma source(s) is/are not at the intended position(s).	✓		
m) The means of indicating that the beam and the conveyor are operating.		✓	✓
n) The means of ceasing irradiation if any failure of the conveyor occurs which affects the dose.	✓	✓	✓
o) The means of ceasing conveyor movement or identifying affected product if any fault in the beam occurs.		✓	✓
p) The means of ceasing irradiation if failure of the X-ray converter cooling system occurs.			✓

7 Product definition

7.1 The product that is to be sterilized, including the packaging materials and configuration of product within the package, shall be specified.

7.2 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. For products that promote microbial growth, careful consideration shall be given to control of the microbial population until the start of sterilization. Considerations include the maximal interval of time and environmental conditions between manufacture and completion of irradiation. The effectiveness of the system shall be demonstrated and shall include determination of bioburden, including characterization, and also establishment of bioburden alert and action levels in accordance with ISO 11737-1.

7.3 If a sterilization dose is to be established for a product family, requirements for defining a product family shall be met in either ISO 11137-2 or ISO 13004 based on which standard was used in establishing the dose (see 8.2).

7.4 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).

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

8 Process definition

8.1 Establishing the maximum acceptable dose, $D_{max,acc}$

8.1.1 The maximum acceptable dose, $D_{max,acc}$, for product shall be established. When treated with the maximum acceptable dose, product shall meet its specified functional requirements throughout its specified lifetime.

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

a) a facility capable of assessing product and packaging to meet criteria for acceptance;

b) product in its sterile barrier system physically representative of that to be produced routinely;

c) an irradiator capable of delivering precise and accurate doses relevant to routine processing conditions (see also 8.4.1).

8.2 Establishing the sterilization dose, D_{ster}

8.2.1 The sterilization dose, D_{ster} shall be established for product.

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

a) knowledge of either the number or resistance to radiation of the bioburden, or both, is obtained and used to set the sterilization dose; or

NOTE 1 Methods of setting the sterilization dose and the circumstances under which these methods can be applied are detailed in ISO 11137-2 and include Method 1 and Methods 2A and 2B.

b) a sterilization dose is selected and substantiated; in substantiating a sterilization dose, the manufacturer shall have evidence that the selected sterilization dose is capable of achieving the specified requirements for sterility.

NOTE 2 Method VD_{max}^{SD} for substantiation of the sterilization dose and circumstances under which these methods can be applied are detailed in ISO 11137-2 for selected sterilization doses of 15 kGy and 25 kGy and in ISO 13004 for selected sterilization doses of 17,5 kGy 20 kGy, 22,5 kGy, 27,5 kGy, 30 kGy, 32,5 kGy and 35 kGy. The selection of dose is valid only for a specified upper limit of average bioburden. These methods are linked to achievement of a SAL 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 and characterization in accordance with ISO 11737-1 and tests of sterility in accordance with ISO 11737-2;

b) product in its sterile barrier system microbiologically representative of that to be produced routinely;

c) an irradiator capable of delivering precise and accurate doses in the required dose range (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 the 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).

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 is permitted provided that the product does not contain water in the liquid state.

NOTE For product that promotes microbial growth, see 7.2.

8.4.2.2 For product that contains water in the liquid state, transference of the verification dose or sterilization dose is not permitted unless data are available to demonstrate that differences in operating conditions of the two radiation sources have no effect on microbicidal effectiveness.

9 Validation

9.1 Installation qualification (IQ)

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).

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).

9.1.5 For electron beam irradiators, the characteristics of the beam, including electron energy, beam current and beam width profile shall be determined and recorded (see 4.1).

9.1.6 For X-ray irradiators, the characteristics of the beam, including X-ray converter, electron energy, beam current and beam width profile shall be determined and recorded (see 4.1).

9.2 Operational qualification (OQ)

9.2.1 Prior to OQ, the calibration of all instrumentation, including test instrumentation used for monitoring, controlling, indicating or recording, shall be confirmed (see 4.2).

9.2.2 OQ shall be carried out by irradiating homogeneous material to demonstrate the capability of the equipment to deliver the range of doses required for the specified sterilization process (see Clause 8). OQ shall demonstrate that the irradiator, as installed, is capable of operating and delivering appropriate doses within specified 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 1 Guidance on dose mapping is given in ISO 11137-3, ASTM E3270 (gamma), and ISO/ASTM 52303. Guidance on the interpretation of dose mapping results is given in ISO/TS 11137-4.

NOTE 2 Mathematical models can be used to calculate dose distributions, and therefore supplement or complement the measurement of dose associated with dose mapping. See ASTM E2232, ISO 11137-3, and ISO/TS 11137-4 for guidance on the use of mathematical models.

9.2.4 Dose mapping shall be carried out using an irradiation container filled to the upper limit of its intended use with material of homogeneous density. Dosimeters shall be used to determine the dose at various known depths in the material. For gamma and X-ray irradiators, there shall be a sufficient number of irradiation containers to effectively mimic a fully loaded irradiator. The irradiation containers shall have similar density and homogeneity as that present in the container being dose mapped.

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.

A minimum number of three replicates should be dose mapped, however a larger number will reduce the measurement uncertainty and increase confidence in the result.

NOTE Further guidance can be found in ISO 11137-3 and ISO/TS 11137-4.

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 If there is more than one irradiation container type used, dose mapping shall be carried out for each irradiation container type and its associated conveyor path(s).

9.2.8 The effect of a process interruption on the dose shall be determined and recorded (see 4.1).

9.2.9 Records of dose mapping shall include a description of:

— irradiation containers;

— irradiator operating conditions;

— materials used;

— measurements of dose;

— conclusions drawn (see 4.1).

9.2.10 The relationship between the process parameters and dose shall be established.

NOTE Guidance on the choice of target processing parameters can be found in ISO/TS 11137-4.

9.3 Performance qualification (PQ)

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

a) identify the zones and magnitudes of the minimum and maximum dose;

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

c) define the relationship between process parameters and routine monitoring dose(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(s) within the package;

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

d) the orientation of the package(s) within the irradiation container;

e) a description of any materials to be used with the irradiation container for the purpose of positioning, temperature management or attenuating dose to product;

f) a description of the conveyor path (for each conveyor paths used within the irradiator).

9.3.3 Dose mapping shall be carried out for each processing category (see 7.4).

9.3.4 If partially-filled irradiation containers are to be used during routine processing, the effect of partial filling on the following shall be determined and recorded:

a) dose distribution within irradiation containers;

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

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

A minimum number of three replicates should be dose mapped, however a larger number will reduce the measurement uncertainty and increase confidence in the results.

NOTE 1 Further guidance can be found in ISO 11137-3 and ISO/TS 11137-4.

NOTE 2 Mathematical models can be used to calculate dose distributions, and therefore supplement or complement the measurement of dose associated with dose mapping. See ASTM E2232, ISO 11137-3, and ISO/TS 11137-4 for guidance in the use of mathematical models.

9.3.6 Dose mapping shall be carried out for each conveyor path and associated irradiation container type to be used for processing the specified product.

9.3.7 For gamma and X-ray irradiators, the effect on dose to product of different densities present in the irradiator shall be determined to specify 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, placement of dosimeters, measurements of dose and conclusions drawn (see 4.1).

9.4 Review and approval of validation

9.4.1 Information generated during IQ, OQ and PQ shall be reviewed. The outcome of the review shall be recorded (see 4.1).

9.4.2 A process specification shall be prepared for each product or processing category (see 4.1).

9.4.3 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, including any added materials within the irradiation container (see 9.3.2);

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 promote microbial growth, the maximal interval of time between manufacture and completion of irradiation;

g) the method and frequency of routine process monitoring;

h) the acceptable limits for the routine monitoring dose(s) (see 9.3.1);

i) the irradiator operating conditions (acceptable ranges of process parameters);

NOTE There can be multiple combinations of operating conditions to achieve the same process definition.

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

k) any actions to be taken as a result of process interruptions (see 9.2.8).

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 either before processing 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).

10.6 A method for routinely monitoring the process shall be specified. Measurements shall be recorded and analysed against specified acceptance criteria.

10.7 Traceable dose measurements, in conjunction with the monitoring of process variables, shall be carried out at sufficient frequency to verify that the process is in a state of control. The frequency and its rationale shall be specified.

NOTE Guidance on process control is given in ISO/TS 11137-4.

10.8 For gamma irradiators:

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

b) the source position, timer setting or conveyor speed and the movement of irradiation containers shall be monitored and recorded (see 4.1).

10.9 For electron beam and X-ray irradiators, the process variables shall be monitored and recorded (see 4.1).

10.10 If process interruption(s) or process non-conformance(s) occur, they shall be recorded, together with any actions taken (see 4.1).

10.11 Records of radiation processing shall state the date of irradiation and be traceable to product batch records (see 4.1).

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 the outcomes recorded (see 4.1).

11.2 Procedures for review of records and for product release from sterilization shall be specified (see 4.1). The procedure(s) shall define the requirements (see 9.4.3) for designating a sterilization process as conforming. If these requirements are not met, product shall be considered as nonconforming (see 4.1).

NOTE Additional records of manufacture and inspection of product can be required 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:

a) determinations of bioburden to monitor the number and types of microorganisms present on product (see A.7.2);

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 and ISO 13004, includes the conduct of a bioburden determination in accordance with ISO 11737-1.

12.1.2 Frequency of determinations of bioburden

12.1.2.1 Bioburden determinations shall be performed at least four times per year, with the interval not exceeding four months from the previous sampling.

12.1.2.2 For product bioburden having a high level of variability or where there is limited data, or for bioburden associated with a sterilization dose less than or equal to 17,5 kGy, consideration shall be given to either increased frequency of bioburden determinations or increased bioburden characterization or both, based on a risk assessment.

12.1.2.3 If the interval of time between the manufacture of batches of product is more than the maximum interval of time identified in 12.1.2.1 or 12.1.2.2 as applicable, determinations of bioburden shall be performed on the next production batch.

12.1.2.4 If a bioburden result of a batch exceeds an established action level, an investigation in accordance with ISO 11737-1 shall be performed and the bioburden characterized (see ISO 11737-1:2018 A.6.2). The extent of characterization is determined during the investigation. If the outcome of the investigation indicates that the results are due to a sampling or laboratory error, the test may be repeated. If the original result is confirmed as a true finding and differs from the expected routine bioburden, a sterilization dose

audit shall be performed on the same batch, if possible, or the next manufacturing batch. Depending on the outcome of the sterilization dose audit, 12.1.2.4 a) or b) shall be followed.

a) If the sterilization dose audit is unsuccessful, action shall be taken in accordance with 12.1.3.4.

b) If the sterilization dose audit is successful and the average bioburden continues to exceed the established action level, sterilization may continue using the dose used prior to the sterilization dose audit. If the frequency of sterilization dose audits is less often than four times per year, a frequency of four times per year shall be implemented until either the bioburden is returned to below the established value or the sterilization dose is re-established.

NOTE If the bioburden continues to exceed the established action level, more frequent monitoring of the bioburden can identify negative trends at an early stage in order to initiate corrective actions.

12.1.3 Frequency of sterilization dose audits

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

a) Dose audits shall be performed at least four times per year, with the interval not to exceed four months from the time period of the previous sampling.

b) A rationale shall be prepared and documented for the selection of the interval of time between the performance of sterilization dose audits. In preparing the rationale, a review shall be conducted and recorded along with conclusions reached with respect to, at least:

1) the established bioburden alert and action levels;

2) available data from the 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 can be based, for example, on colony or cellular morphology, staining properties or selective culturing or genus and species identifications.

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, environment and personnel;

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

12.1.3.2 An increase in the interval of time between the performance of sterilization dose audits shall only be permitted up to a maximum of 12 months 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 established action level over the same period of time as 12.1.3.2 a), these include:

   1) bioburden determinations performed in accordance with 12.1.2.1;

   2) characterization of bioburden;

c) the manufacture of the product in relation to bioburden is controlled and the effectiveness of this control is demonstrated.

Even after sufficient data have been obtained to reduce the frequency of sterilization dose audits, determinations of bioburden shall be performed at the frequency determined per 12.1.2.

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

12.1.3.4 If a sterilization dose audit is unsuccessful, action shall be taken in accordance with either ISO 11137-2 or ISO 13004 based on which standard was used in establishing the dose (see 8.2). The frequency of performance of sterilization dose audits shall be a frequency of not less than four times per year until:

a) the cause of the unsuccessful sterilization dose audit or the increase in bioburden has been investigated and correction 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;

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 at a frequency specified in accordance with 4.2.

12.3 Maintenance of equipment

12.3.1 Preventive maintenance shall be planned and performed in accordance with documented procedures. Records of maintenance shall be retained (see 4.1).

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

12.4 Requalification of equipment

12.4.1 Requalification of equipment shall be carried out at specified 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).

12.4.3 Requalification data shall be reviewed against specified acceptance criteria in accordance with documented procedures. Records shall be retained (see 4.1) 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 can affect dose or dose distribution shall be assessed. If one or both of these is judged to potentially be affected, then a repeat of part or all of IQ, OQ and 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).

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 specification (see 9.4.3). 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). The product specification shall be updated based on the change (see 7.5).

Annex A
(informative)

Guidance on this document

NOTE 1 The guidance given in this annex is not intended as a checklist for assessing conformance with this document. This guidance is intended to assist in obtaining a uniform understanding and implementation of this document by providing explanations and acceptable methods for achieving conformance with specified requirements. Methods other than those given in the guidance can be used if the use of alternative methods is demonstrated to be effective in achieving conformance with this document.

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

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 No guidance offered.

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 of the product bioburden and dose is well established. In addition, tests for sterility are not appropriate as criteria for releasing product from sterilization. As stated in the introduction to this document, for certain processes used in manufacturing, the effectiveness of the process cannot be fully verified by subsequent inspection and testing of the product. For this reason, sterilization processes are validated for use, the performance of the sterilization process is monitored routinely and the equipment is maintained.

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 document only to the extent that they are cited in a normative part of this document; the citation can be to an entire standard or limited to specific clauses.

A.3 Terms and definitions

No guidance offered.

A.4 General

A.4.1 Requirements for control of documents and records are specified in ISO 13485.

In ISO 13485, the requirements for documentation relate to the generation and control of documentation (including specifications and procedures) and records. Procedures required to be specified by this document are established, documented, implemented and maintained.

Procedures are specified for the development, validation and routine control of a radiation sterilization process and product release from sterilization.

Documents, including records, required by this document are reviewed and approved by designated personnel prior to issue and following changes.

Documents are controlled to ensure that relevant versions of applicable documents are available for use. Records are maintained to provide evidence of conformity to the requirements of this document. The controls needed for the identification, storage, security and integrity, retrieval, retention and disposition of records are specified.

The period for which documents, including records, are to be retained is specified.

The responsibility and authority for implementing and meeting the requirements described in this document are specified. Responsibility is assigned to competent personnel on the basis of appropriate education, training, skills and experience. See ISO 13485 for requirements on responsibility, authority and human resources. Requirements are specified for management responsibility related to management commitment, customer focus, quality policy, planning, responsibility, authority, communication and management review. The level of qualification, training and experience required by personnel will depend upon the activities being performed. General guidance on training as part of the overall quality management system is given in ISO 9004. Specific qualifications and training are appropriate for personnel with the responsibilities for:

a) microbiological testing;

b) establishing the sterilization dose;

c) dosimetry;

d) installation of equipment;

e) equipment maintenance;

f) PQ;

g) routine irradiator operation;

h) calibration;

i) process design;

j) equipment specification.

If the requirements of this document are undertaken by organizations with separate quality management systems, the responsibilities and authority of each party are specified in a written agreement.

Procedures for purchasing are specified to ensure that purchased product conforms to specified purchasing information.

Procedures for identification and traceability of product are specified. These procedures ensure the identification of the status of product throughout product realization. Identification of product status is maintained throughout production and storage to ensure that only product that has passed the required inspections and tests is dispatched.

Procedures for control of product designated as non-conforming and for correction, corrective action and preventive action are specified. These procedures ensure that product which does not conform to

requirements is identified and controlled to prevent its unintended use or delivery. Records of the nature of the nonconformities and any subsequent action taken, including the evaluation, any investigation and the rationale for decisions are maintained.

Action is taken to eliminate the cause of nonconformities in order to prevent recurrence and of potential nonconformities to prevent occurrence. Any necessary corrective actions are taken without undue delay. Corrective actions and preventive actions are proportionate to the effects of the nonconformities encountered.

A.4.2 A calibration system conforming with ISO 13485:2016, 7.6 or ISO 10012-1 can be specified for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this document.

A.4.3 Additional guidance is given in ISO 11137-3 and ISO/TS 11137-4. See ISO/ASTM 51261 for guidance in the calibration of dosimetry systems. See ISO/ASTM 51707 for guidance in estimating dosimetry system measurement uncertainty.

A.5 Sterilizing agent characterization

A.5.1 Sterilizing agent

For electron beam and X-ray sterilization, the energy threshold above which there is the potential for induced radioactivity depends on the material composition of the medical device.

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 or modelling of induced radioactivity. Examples of such literature include Grégoire et al.[34], Smith (2008)[45], Smith (2012)[46], Stichelbaut et al.[48] and Michel et al.[43]

In each of these documents, both theoretical and experimental assessments have been performed to determine induced radioactivity based on materials commonly found in medical devices. Michel et al.[43] specifically looks at the potential for induced radioactivity with X-rays below 7,5 MeV and concludes that most products exhibit no induced radioactivity, while radioactivity that has been measured in a limited number of products has been well below exemption limits specified in the IAEA International Basic Safety Standard.[35] This is further supported by IAEA-TECDOC-1287[36] in which a similar analysis was conducted on induced radioactivity in food, which concludes that food irradiated with X-ray energy up to 7,5 MeV has a level of radioactivity well below the natural radioactivity found in unirradiated food.

Similarly, Smith (2012)[45] provides evidence that the amount of induced radioactivity remains below the exempt concentration limitations at initial electron energies up to 12,1 MeV. This implies that, under irradiation conditions typical for single use medical device sterilization, the electron energy can be higher than 10 MeV without creating significant induced radioactivity. For the purposes of this document, the limit for assessment is specified as 11 MeV to allow for irradiations higher than 10 MeV while staying below a threshold where induced radioactivity is more probable and should be assessed. Guidance on performing assessments when required can be found in Michel et al.[43] and Smith et al.[47]

A.5.2 Microbicidal effectiveness

The resistance against radiation of many microorganisms has been studied. Published data are for example summarized in Block[41] and the Irradiation Panel database of D_{10} values.[38] However, resistances are not known for all microorganisms on all products and in all environments. Therefore, the sterilization dose has to be established and its continued effectiveness demonstrated through the periodic performance of bioburden determination and sterilization dose audits.

A.5.3 Material effects

See AAMI TIR17 for further guidance on material effects.

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. Users of radiation are advised that there can be applicable local, national, and international requirements regarding the handling and disposal of source materials, as well as any by-products.

A.6 Process and equipment characterization

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

A.6.1 See ISO/TS 11137-4 for guidance on process control.

A.6.2 The specification of the irradiator is typically kept on file and managed by the irradiation facility. In such cases, it is not necessary for the device manufacturer to maintain these records.

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 The intention is that the bioburden is stable in both numbers and types (i.e. see ISO 11737-1 for microbial characterization) of microorganisms, taking into account the nature of the raw materials, product packaging and processes prior to sterilization. Demonstration of stability in bioburden numbers and types is critical for radiation sterilization. This is best achieved by engaging personnel who are competent in microbiology and sterility assurance throughout the manufacture of the product, and in data interpretation. Based on risk associated with low bioburden or low sterilization dose, testing at an increased sample size or frequency and more detailed characterization should be considered to help establish a more robust baseline of product bioburden.

Demonstrating stability in bioburden numbers is often accomplished by establishing alert and action levels and consistently obtaining results below these levels. Bioburden levels are established based on historical data and risk and are used to detect shifts in the product bioburden during routine monitoring.[52]

The determination of bioburden action and alert levels is addressed in ISO 11737-1:2018, A.8.6, and additionally can include but is not limited to the consideration of:

a) level of bioburden control necessary based on product requirements (e.g. product requires a low sterilization dose);

b) if using VD_{max}^{SD}, the maximum allowed bioburden value on the selected dose substantiation table;

c) the level of risk associated with the established sterilization dose.

NOTE If using VD_{max}^{SD}, a lower action level is appropriate to detect shifts in routine bioburden monitoring.

Because radiation sterilization is bioburden based, the bioburden action and alert levels should be assessed periodically to determine their appropriateness in detecting shifts that can affect the sterilization dose and which indicate a need for re-establishment of the sterilization dose.

Demonstrating stability in bioburden types is more complex than demonstrating stability in bioburden numbers because interpreting bioburden type data requires an understanding of microbiology and potential microorganism resistance to radiation. Bioburden type stability can be determined empirically (entirely

based on data), or empirically combined with microbiological knowledge and information from literature, see A.5.2.

In demonstrating stability in bioburden types, competent microbiology and sterility assurance personnel can consider the following:

— performing more in-depth bioburden characterization, e.g. through selective plating or culturing, performing Gram stains, and characterizing Gram-positive rods into spore-forming and non-spore-forming categories;

— performing bioburden testing and characterization on raw materials and components;

— assessing the radiation resistance of microorganisms comprising the product bioburden through the performance of microbial identifications;

— gathering radiation resistance data in literature that is applicable to the materials and environment that make up the product bioburden;

— performing identifications when positive test of sterility results are obtained;

— performing tests of sterility during dose establishment with greater sample sizes (e.g. 10 samples from multiple batches), or a test of sterility using a greater number of test samples than 10 (e.g. as described in AAMI TIR76).

While microbial identification to genus and species is not required for microbial characterization, it can be advantageous under certain circumstances, for example:

— when initially establishing a bioburden baseline for a new product, cleanroom, or manufacturing line;

— following bioburden alert or action level excursions;

— when bioburden results indicate spreaders or too numerous to count (TNTC) (wherein the plate is covered by spreading organism);

— when positive tests of sterility are obtained from dose audits; and

— when using a sterilization dose that is 17,5 kGy or less.

The standard distribution of resistances in ISO 11137-2:2013 Table 3 assumes a certain percentage of a wide variety of resistances (i.e. ≤ 1,0 kGy to 4,2 kGy D values). Thus, the presence of a small percentage of microorganisms that are higher in radiation resistance is expected and should not be considered unacceptable when recovered from product, whether from a bioburden test or a test of sterility. In a dose audit, it is the number of positives out of the number tested that determines whether the results are acceptable or not.

A.7.3 See ISO 11137-2 and ISO 13004.

A.7.4 The criteria for assessing product for inclusion in processing categories are unique to radiation sterilization and are not necessarily appropriate for use with other sterilization methods (e.g. ethylene oxide or moist heat).

In general, product is included in a processing category based on the ability to process product using the same processing parameters without violating the specified dose limits for product within the processing category. The two main criteria for assessing product for inclusion in a processing category for gamma and X-ray irradiators are compatible dose requirements (sterilization dose and maximum acceptable dose) and dose absorption characteristics (e.g. density and loading pattern).

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 can be 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.

For electron beam irradiators, more individual product dose mapping during PQ is often performed than for X-ray or gamma irradiators. Product can be grouped into processing categories for products that can be irradiated with the same processing parameters in a compatible loading pattern.

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;

g) the mass distribution within the carton.

A.7.5 No guidance offered.

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 The specified functional requirements for product should be documented. These requirements can include, but are not limited to:

— physical properties;

— chemical properties;

— biocompatibility;

— effective sterile barrier system.

Assurance of the quality, safety and performance of product throughout defined lifetime should begin with designing a test programme to establish the effect of radiation on these properties.

It is generally not adequate to test materials comprising the product at, for example, elongation at break. This parameter can give a first estimate of radiation compatibility of a given material, but it is not always directly related to the specified functional requirements.

Appropriate test methods for each of the functional requirements of the product to be tested should be established, as well as their acceptance criteria.

The number of product samples to be tested should be selected in sufficient quantity, with supporting rationale, to adequately support product meeting its specified functional requirements throughout its defined lifetime. A risk-based approach based on understanding the product and its properties as well as the expected influence of radiation on these properties should be used for the selection.

Grouping of product with similar functional requirements can reduce the number of tests to be carried out.

Different approaches can be used for establishment of maximum acceptable dose ($D_{max,acc}$) and a few examples are given here:

a) For product where the maximum delivered dose (D_{max}) to product during processing is not known because:

   1) packaging geometry has not yet been selected;

   2) PQ dose mapping has not yet been carried out; or

   3) process irradiation type or irradiator has not yet been decided.

   Irradiate product samples at a single dose level or at a number of increasing doses.

   NOTE 1 Irradiation of product samples at a number of increasing doses is sometimes referred to as a dose ranging study. It can result in an accurate estimate of the highest dose at which the defined acceptance criteria are achieved.

   $D_{max,acc}$ can be selected from any of the doses at which the defined acceptance criteria are achieved.

   This approach is generally applicable for products that are intended to be irradiated at gamma or X-ray irradiation, where homogeneous dose distribution typically is not difficult to obtain for irradiation of product samples.

   If an irradiation source is chosen for irradiation processing that differs from the one used for testing, 8.4.1 should be taken into account.

   NOTE 2 It can generally be assumed the radiation effects on product properties are cumulative. See AAMI TIR17.

   NOTE 3 Irradiating at a number of increasing doses can lead to effects of irradiating temperatures that can differ from those at process conditions.

b) For product where D_{max} to product during processing is known because:

   1) irradiation type and irradiator for sterilization has been selected;

   2) sterilization dose D_{ster} has been established;

   3) PQ dose mapping has been carried out.

   Determine the maximum dose to be delivered to product for routine processing. Irradiate product samples so that the minimum dose to product exceeds this maximum dose.

   $D_{max,acc}$ can be taken as the minimum dose delivered to the product samples if the defined acceptance criteria are achieved following this irradiation.

   Process specification should be updated according to the study results.

c) Alternatives to the methods in A.8.1.1 a) or A.8.1.1 b) can be needed for product where these methods do not provide an attainable solution to establish $D_{max,acc}$ because, for example, one or more of the following applies:

   1) the product size or heterogeneity prohibit a homogeneous dose distribution for product sample irradiation in the radiation type chosen as required in a) and b);

   2) PQ dose mapping has been carried out as required in b) and demonstrates that D_{max} is expected at different locations within a given product;

   3) the maximum doses that can be delivered to the product sample during irradiation based on b) above are high enough to have a negative effect on product functionality;

   4) the product composition is made up of different material and the D_{max} defined during PQ dose mapping is located in a portion of the product which does not contain a component sensitive to ionizing radiation.

A suggested approach can be:

— Irradiate a process load using the maximum process target dose that can be selected for routine processing as defined during PQ dose mapping. Assess the functionality of the product.

— If the defined acceptance criteria are achieved following this irradiation, then $D_{max,acc}$ for that process is the measured D_{max} from the irradiated process load.

This approach can be considered as stress testing corresponding to worst case conditions under normal process conditions. Further guidance on this method can be found in Craven.[33]

Dose measurements made during testing for establishing $D_{max,acc}$ should be traceable to national standards. See ISO 11137-3 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 and ISO 13004.

NOTE Guidance on modified methods of dose establishment have been provided in national standards, including AAMI TIR76, AAMI TIR35 and AAMI TIR40.

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:

a) knowledge of the number and resistance of microorganisms comprising the bioburden is used in establishing the sterilization dose (see ISO 11137-2:2013, Method 1);

b) knowledge of the resistance of microorganisms comprising the bioburden is used in establishing the sterilization dose for product having any level of average bioburden (see ISO 11137-2:2013, Method 2).

With regard to 8.2.2 b), appropriate methods for substantiation of sterilization doses are given in ISO 11137-2 and ISO 13004.

NOTE Guidance on modified methods of dose establishment have been provided in national standards, including AAMI TIR76, AAMI TIR35 and AAMI TIR40.

A.8.2.3 Product which is representative of that to be produced routinely also includes representative bioburden in type and quantity.

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

NOTE The term radiation source is used to differentiate between irradiators, their operational characteristics including dose rate and irradiation environment, and their locations. This includes differences between irradiators that operate with the same type of radiation.

A.8.4.1 Transference of maximum acceptable dose

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) typically requires minimal qualification to demonstrate product compatibility at a high dose rate (electron beam). Conversely,

a material qualified at a high dose rate can require more substantial qualification in the low or intermediate dose rate application.

If dose rate and product temperature are acceptable with respect to product, transfer between the same type of radiation sources is appropriate.

A risk assessment is one tool that can be used in determining the validity of the transfer of maximum dose. An example of a risk assessment framework is found in Montgomery et al.[44] Further information on transfer of maximum dose can also be found in AAMI TIR104.

A.8.4.2 Transference of verification or sterilization dose

A.8.4.2.1 Experimental evidence indicates that for products which do not promote microbial growth, microbicidal effectiveness is independent of the radiation source. Hansen et al.[40] evaluated radiation resistance across a matrix of differing radiation types, microbial challenges, and dose rates, with the result that no significant differences were seen in the rate of microbial lethality across the range of radiation types and dose rates evaluated.

Additionally, Tallentire, Miller and Helt-Hansen[50] verified that the radiation resistance of a test organism with known radiation resistance characteristics did not vary among gamma and electron beam irradiation under wet conditions. Tallentire and Miller[49] expanded that study to include X-rays, showing that the radiation resistance was consistent across all three radiation types. McEvoy et al.[42] published a similar comparative study using dry spores which concluded that dose rate has no impact on sterilization efficacy.

These studies indicate that the operating conditions of different irradiators, specifically as related to dose rate and radiation type, do not have an effect on microbicidal effectiveness such that the transfer of sterilization and verification dose can be made without further assessment. For limitations, see A.8.4.2.2.

A.8.4.2.2 Two situations can result in the need for further assessment to determine if transferring sterilization or verification doses between sources is permitted:

a) product that promotes microbial growth with inadequate microbial control;

b) product that has the presence of liquid water.

For a product that promotes microbial growth (e.g. high-moisture devices or devices containing biological material), it is necessary to ensure that the condition of product presented for sterilization, including its bioburden, is controlled until the time of sterilization (7.2). In transferring verification and sterilization doses to different sources, variables known to influence microbial growth (e.g. time, temperature and humidity) can change. Their effects on continued growth of microorganisms should be considered and controlled. When control is effective, verification and sterilization dose may be transferred between sources. When control is not effective, new controls are required or transfer is not allowed.

For product that contains liquid water, it is possible that microbicidal effectiveness varies with dose rate, hence the requirement for further assessment. Tallentire and Powers[51] is interpreted to indicate that the presence of water in liquid form with a product can cause a variation in microbicidal effectiveness with dose rate. Studies with a single organism in water, as noted above, do not indicate a variation in microbial effectiveness with dose rate (Tallentire, Miller and Helt-Hansen[50] and Tallentire and Miller[49]).

In both A.8.4.2.2 a) and b), a verification dose experiment carried out at the radiation source to which the product is being transferred can be a means to demonstrate that the sterilization and verification doses are still valid or to document that they should be re-established. This verification dose experiment should be repeated if historic dose audits have demonstrated seasonal variations in bioburden, if bioburden action level excursions occur or if a shift in bioburden types is observed.

If a validated time between manufacture and sterilization is changed, this time should be re-established (see 9.4.3).

See AAMI TIR104 for further guidance.

A.9 Validation

NOTE 1 For the purpose of this document, 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 document does not specify requirements for DQ.

A.9.1 Installation qualification (IQ)

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 be maintained at the irradiation facility and 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 completion of OQ.

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

A.9.2 Operational qualification (OQ)

See ISO 11137-3 for dosimetric aspects for radiation sterilization, and ASTM E3270 for gamma OQ test methods.

A.9.3 Performance qualification (PQ)

PQ is the stage of validation which uses defined product or simulated 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 and performance through the defined lifetime.

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 can affect dose distribution (e.g. containers of liquids or metal implants).

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

See the Irradiation Panel report on performance qualification dose mapping[38] for further guidance.

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;

b) the use of a reliable inventory control system.

The use of labels or stamps can be part of the procedure.

A.10.4 No guidance offered.

A.10.5 If product can 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. In some cases, the product shipper box is the irradiation container and the same principals apply.

A.10.6 A review of the results from the monitoring of the process variables 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.

Irradiators vary in their characteristics and in the way they are monitored. The relative contribution of the monitoring of process variables, the presence of other products in the irradiator, and of the performance of routine dosimetry to ensure that the sterilization process is delivered to product inevitably varies from irradiator to irradiator. The irradiator operator should design a monitoring procedure, including the monitoring of process variables and the performance of routine dosimetry, which will provide the necessary confidence that sterilization processing is carried out in accordance with this document.

See ISO/TS 11137-4 for guidance on process control.

A.10.7 See ISO 11137-3 for guidance on dosimetric aspects and ISO/TS 11137-4 for guidance on process control.

A.10.8 See ISO/TS 11137-4 for guidance on process control.

A.10.9 See ISO/TS 11137-4 for guidance on process control.

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 or shut-down of the radiation 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 the product specifications have been met.

For process interruption occurring with product capable of promoting microbial growth, the following should be stated in the process specification:

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

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

The maximal interval of time and conditions are chosen to ensure that the microbiological quality of the product is not affected. 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 sterilization dose, additional dose may be given to the product if:

a) the ability of the product to promote microbial growth has been taken into consideration;

b) the dose can be delivered in such a way to ensure that the sterilization 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, and ISO/TS 11137-4 for guidance on process control.

A.10.11 No guidance offered.

A.11 Product release from sterilization

For guidance on exclusions to product release from sterilization, see A.1.2.3.

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 is 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 establishment 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 The interval of bioburden determinations is targeted at three months but can vary based on logistics such as availability of parts or production schedules, hence the allowance for an interval not to exceed four months from the previous sampling. Initiation of sampling for bioburden determinations can be different based on manufacturing situations, but initiation can include actions such as placing a work order,

pulling samples, instructing a third party to manufacture product, shipping samples to the laboratory, or other conditions.

A.12.1.2.2 A product risk assessment performed as part of product definition or as an investigational or situational tool, can indicate a need for more frequent bioburden determinations, including increased characterization. Situations where more frequent bioburden determination, such as monthly, should be considered are:

a) new manufacturing environment or product with limited bioburden data;

b) products in which a low sterilization dose has been established based on very low bioburden levels that need increased monitoring to ensure control;

NOTE Where the risk assessment has shown that low bioburden levels are well controlled and well characterized, there can be justification for the frequency of monitoring.

c) highly variable bioburden population or microorganism types (see A.7.2);

d) repeated excursions to environmental monitoring control levels that can signal a potential shift in manufacturing state of control.

See ISO 11737-1:2018, Annex A for additional guidance.

Microbiological quality related to microorganism flora on product and in the manufacturing environment is essential for product using bioburden-based radiation sterilization methodologies. The monitoring of microbiological quality can include environmental monitoring, sampling of raw materials and components, additional bioburden estimates, characterization or assessment of frequencies of testing sufficient to ensure microbial quality control.

A.12.1.2.3 No guidance offered.

A.12.1.2.4 When establishing bioburden alert and action levels, consideration should be given to the potential effect on the achievement of the specified SAL.

The adjustment of the verification dose is not appropriate with each bioburden determination; however, for a sustained shift in magnitude of the bioburden, dose re-establishment can be considered.

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 variations in bioburden throughout the year. Product manufactured under controlled conditions will possibly not exhibit variation in bioburden. If control over bioburden in terms of numbers and types of microorganisms can be demonstrated throughout the year, a reduction in the frequency of dose audits can be considered (see A.7.2). This consideration includes those aspects of processing and monitoring specified in 12.1.3. It is noted that all the aspects are considered, but not all of them will necessarily provide definitive outcomes or be of equal importance. The three-month time interval target can vary based on logistics such as availability of parts or production schedules, hence the allowance for an interval not to exceed four months from the previous sampling. Initiation of sampling for dose audits can be different based on manufacturing situations, but initiation can include actions such as placing a work order, pulling samples, instructing a third party to manufacture product, shipping samples to the laboratory, or other conditions.

b) The conservativeness of any method depends on the sterilization dose and the reliability of a dose audit to predict a maximal SAL at a sterilization dose. Higher sterilization doses are more conservative. The reliability of a dose audit increases with the number of samples used. A method is more conservative if the ratio between sterilization dose and verification dose is larger compared to another method. There is inherent conservativeness built into Method 1 and Method VD_{max}^{SD} as product bioburden is challenged against a standard distribution of resistances, with more samples used in Method 1 than in Method VD_{max}^{SD}. Additional conservativeness can be assumed for Method VD_{max}^{SD} in cases where

the sterilization dose substantiated is significantly greater than the Method 1 dose associated with the product average bioburden. Method 2 is based on the radiation resistance of the microorganisms as they occur on the product, and therefore can be more susceptible to changes in that population (see ISO 11137-2 and ISO 13004).

A.12.1.3.2 As experience of product and its manufacture is gained, incremental increases in the interval of time between the performance of sterilization dose audits can occur as follows: initially an interval time of three months, then an interval time of six months and finally an interval time of 12 months.

There can be instances where more than four dose audits are needed before increasing the interval of time between dose audits. The quantity of dose audits needed should be established based on risk and documented in a rationale (e.g. knowledge of product and process bioburden, low sterilization dose, product history, manufacturing and product changes).

It should be recognized that a reduction in the frequency of performance of the sterilization dose audit can result in a reduction in the ability to detect a change in the radiation resistance of the product, 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.12.2 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 OQ status of the irradiator has changed, then PQ should 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, including replacement or design change.

The extent of the OQ depends on the type and degree of the change. Guidance on OQ tests to be performed after a change in a gamma irradiator can be found in ISO/ASTM 51702 and ASTM E3270.

For electron beam and X-ray irradiators, either IQ or OQ, or both, should be performed when changes are made to the irradiator, which can affect dose or distribution. 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 critical processing parameters as defined in ISO/TS 11137-4.

Additionally, for X-ray irradiators, either IQ or OQ, or both, should be performed when changes are made to the X-ray target.

The extent of the OQ depends on the type and extent of the change. For example, an increase of the maximal designed dimensions of the irradiation container requires a complete requalification, whereas replacement of a conveyor part can only require confirmation of the proper functioning of the conveyor. Guidance on OQ testing can be found in ISO/ASTM 51649, ISO/ASTM 51818 and ISO/ASTM 51608. Mathematical models that calculate absorbed dose magnitudes and distributions before and after a change can be used as a tool to help assess the extent of OQ dose mapping required. See ASTM E2232, ISO 11137-3, and ISO/TS 11137-4 for guidance in the use of mathematical models.

A.12.5.2 An assessment of change to product, its packaging system or the presentation of product for sterilization is required to ensure that the existing process specifications are appropriate and that they can still be met by the process. Table A.1 provides guidance on the assessments appropriate for different types of changes.

Table A.1 — Guidance on qualification of changes to product

Product change	Product family	Maximum acceptable dose	PQ	Notes
Change of component origin	✓			A change in component origin absent of other changes can affect product bioburden.
Change of component material	✓	✓	✓	An assessment of PQ is only required if material change results in a significantly different density or product form.
Change of manufacturing location of product or product components	✓			A change in manufacturing location absent of other changes can result in different product bioburden.
Change in packaging design		✓	✓	Any changes to packaging design should also withstand functionality at maximum dose. Packaging changes which result in a different density or loading configuration should be assessed for effect on PQ results and inclusion in processing categories.
Changing in loading configuration			✓	A change to loading configuration can result in a different dose uniformity ratio and relationship of maximum and minimum doses to monitoring.

An assessment of product family inclusion is required for any change that can potentially affect the distribution and numbers and types of bioburden (see A.7.2). Information on the definition and maintenance

of product families for dose setting, dose substantiation and sterilization dose auditing can be found in ISO 11137-2 and ISO 13004. If an assessment of change demonstrates that the product bioburden is more challenging than the bioburden of the product family prior to the change, the sterilization dose can need to be re-established.

An assessment of maximum acceptable dose can be required if a change is made to a material, component or packaging that has not previously been tested to the maximum acceptable dose defined for that product. See A.8.1 and AAMI TIR17 for more guidance on maximum dose establishment.

An assessment of previous PQ dose maps showing maximum and minimum dose locations and their relationship with routine dosimetry, bulk density, and mathematical models as well as repeat PQ dose maps can be performed. From this assessment, a determination of the effect on processing category inclusion where used should be made after any physical changes to the product, packaging or orientation and loading configuration. The assessment should look at the effect of the physical changes on the expected dose magnitude and dose distribution and dose absorption characteristics within the process load. Mathematical models that calculate absorbed dose magnitudes and distributions before and after a change can be used as a tool to help assess the extent of PQ dose mapping required. More guidance on PQ dose mapping and the relationship to process specifications and routine monitoring can be found in ISO/ASTM 52303 and ISO/TS 11137-4. See ASTM E2232, ISO 11137-3, and ISO/TS 11137-4 for guidance in the use of mathematical models.

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