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Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization

Stérilisation des dispositifs médicaux — Prescriptions pour la validation et le contrôle de routine — Stérilisation par irradiation

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Contents

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Annexes

Foreword

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

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

International Standard ISO 11137 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

Annexes A, B, C and D of this International Standard are for information only.

Introduction

This International Standard describes the requirements for ensuring that the activities associated with the process of radiation sterilization are performed properly. These activities comprise documented work programmes designed to demonstrate that the radiation process, operating within specified limits, will consistently yield products treated with doses that fall between predetermined limits.

The radiation process is a physical one, involving the exposure of a product to ionizing radiation. The product is exposed in specially designed equipment to gamma rays from cobalt 60 (60 Co) radionuclides or cesium 137 (137 Cs) radionuclides, or to an electron or x-ray beam from an electron beam generator. When properly applied, radiation sterilization is a safe and reliable industrial process.

Sterilization is an example of a process for which efficacy cannot be verified by retrospective inspection and testing of the product. It is important to be aware that exposure to a validated and accurately controlled sterilization process is not the only factor associated with ensuring that the product is sterile and suitable for its intended use. Attention has to be given to the microbiological status of raw materials and/or components, the microbiological barrier properties of the packaging, and to the control of the environment in which the product is manufactured, assembled, packaged and stored.

A sterile product is one that is free of viable microorganisms. Items produced under controlled manufacturing conditions can, prior to sterilization, have microorganisms on them, although ordinarily in low numbers. Such products are, by definition, non-sterile. The purpose of sterilization processing is to destroy the microbiological contaminants on these non-sterile products. The destruction of microorganisms by physical and chemical agents follows an exponential law. Accordingly, one can calculate a finite probability of a surviving microorganism regardless of the magnitude of the delivered sterilization dose or treatment. The probability of survival is a function of the number and types (species) of microorganisms present on the product (bioburden), the sterilization process lethality, and, in some instances, the environment in which the organisms exist during treatment. It follows that the sterility of individual items in a population of products sterilized cannot be ensured in the absolute sense. A sterility assurance level (SAL) is derived mathematically and it defines the probability of a viable microorganism on an individual product unit.

The primary manufacturer has ultimate responsability for ensuring that all sterilization operations and quality assurance checks used for the product are appropriate, adequate and correctly performed. However, the irradiator operator is responsible for delivering the required dose within the validated process specifications.

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Sterilization of health care products — Requirements for validation and routine control — Radiation sterilization

1 Scope

This International Standard specifies requirements for validation, process control and routine monitoring in the radiation sterilization of health care products. It applies to continuous and batch type gamma irradiators using the radionuclides 60 Co and 137 Cs, and to irradiators using a beam from an electron or x-ray generator.

Annexes are also included to provide supplementary information.

Facility design, licensing, operator training and factors related to radiation safety are outside the scope of this International Standard. It does not cover the assessment of the suitability of the product for its intended use. The use of biological indicators for validation or process monitoring, or the use of sterility testing for product release, are also not covered, as they are not recommended practices for radiation sterilization.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this International Standard. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this International Standard are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 9001:1994, *Quality systems — Model for quality assurance in design, development, production, installation and servicing.*

ISO 9002:1994, *Quality systems — Model for quality assurance in production, installation and servicing.*

ISO 11737-1:—[1], *Sterilization of medical devices — Microbiological methods — Part 1: Estimation of population of microorganisms on products.*

3 Definitions

For the purposes of this International Standard, the following definitions apply.

3.1 "Health care product" and related terms

3.1.1 batch: Defined quantity of bulk, intermediate or finished product that is intended or purported to be uniform in character and quality, and which has been produced during a defined cycle of manufacture.

3.1.2 health care product: Term encompassing medical devices, medicinal products (pharmaceuticals and biologics) and *in vitro* diagnostics.

3.1.3 primary manufacturer: Company or body responsible for the fabrication, performance and safety of a health care product.

1) To be published.

3.1.4 product category

(1) (for sterilization by exposure to gamma or x-ray radiation) Products of similar bulk density exhibiting a similar pattern of dose distribution.

(2) (for sterilization by exposure to electron radiation) Products of similar maximum surface density exhibiting a similar pattern of dose distribution.

3.1.5 product unit: Health care product, collection of products or components within a primary package.

3.2 "Irradiator" and related terms

3.2.1 batch (type) irradiator: Irradiator in which the irradiation containers are introduced or removed whilst the radioactive source is in the storage position.

3.2.2 bulk density: Mass of product and all associated packaging in the irradiation container divided by the volume determined by the dimensions of the outermost packaging.

3.2.3 continuous (type) irradiator: Irradiator which can be loaded and unloaded with product whilst the source is in the processing mode.

3.2.4 irradiation container: Carrier, cart, tray or other container in which products are transported through the irradiator.

3.2.5 irradiator: Assembly that permits safe and reliable sterilization processing, including the source of radiation, conveyor and source mechanisms, safety devices and shield.

3.2.6 irradiator operator: Company or body responsible for delivery of a specified dose to health care products.

3.2.7 surface density: Density of a columnar section through the product within its outermost packaging or through the irradiation container, in the direction of the electron beam, expressed as a ratio against the surface area of the section at a position where the ratio takes its highest value.

NOTE 1 The unit for surface density is g/cm^2 (ISO 31-3:1992, item 3-6).

3.2.8 timer setting: Interval of time selected for the irradiation container to spend at each position within the irradiator. It controls the duration of radiation exposure.

3.3 Radiation sources and related terms

3.3.1 average beam current: Time-averaged current produced by an electron beam generator.

3.3.2 bremsstrahlung: Broad spectrum electromagnetic radiation emitted when an energetic electron is influenced by a strong magnetic or electric field, such as that in the vicinity of an atomic nucleus.

NOTE 2 Practically, bremsstrahlung is produced when an electron beam strikes any material (converter). The bremsstrahlung spectrum depends on the electron energy, the converter material and its thickness, and contains all energies up to the maximum energy of the incident electrons.

3.3.3 converter: Target for high-energy electron beams, generally of high atomic number, in which x-rays (bremsstrahlung) are produced by radiative energy losses of the incident electrons.

3.3.4 electron beam: Continuous or pulsed stream of high energy electrons.

3.3.5 electron energy: Kinetic energy of the electrons in the electron beam.

3.3.6 gamma ray: Short wavelength electromagnetic radiation (photons) emitted from radioactive substances in the process of nuclear transition.

NOTES

3 This is a commonly used name.

4 For irradiation of health care products, gamma rays are generally high-energy penetrating photons as emitted from 60 Co or 137 Cs radionuclide sources.

3.3.7 source activity: Quantity of the radionuclide 60 Co or 137 Cs measured in becquerels or curies (1 curie = $3{,}7 \times 10^{10}$ becquerels, where 1 becquerel = 1 disintegration per second).

3.3.8 x-rays: Short wavelength electromagnetic radiation emitted by high-energy electrons when they are accelerated, decelerated or deflected by strong electric or magnetic fields.

NOTES

5 This is a commonly used name.

6 The term generally includes both bremsstrahlung produced when an energetic electron is decelerated in the vicinity of an atomic nucleus and the characteristic monoenergetic radiation emitted when atomic electrons make transitions to more tightly bound states. In this International Standard, the definition for bremsstrahlung applies.

3.4 Terms related to dose measurement

3.4.1 absorbed dose: Quantity of radiation energy imparted per unit mass of matter. The unit of absorbed dose is the gray (Gy) where 1 gray is equivalent to absorption of 1 joule per kilogram (= 100 rads).

3.4.2 dose: (See absorbed dose.)

3.4.3 dosimeter: Device or system having a reproducible, measurable response to radiation, which can be used to measure the absorbed dose in a given material.

3.4.4 dosimetry: Measurement of absorbed dose by the use of dosimeters.

3.4.5 dosimetry system: System used for determining absorbed dose, consisting of dosimeters, measuring instrumentation and procedures for the system's use.

3.4.6 primary standard dosimeter: Dosimeter, of the highest metrological quality, established and maintained as an absorbed dose standard by a national or international standards organization.

3.4.7 reference standard dosimeter: Dosimeter, of high metrological quality, used as a standard to provide measurements traceable to and consistent with measurements made using primary standard dosimeters.

3.4.8 routine dosimeter: Dosimeter calibrated against a primary, reference or transfer standard dosimeter and used for routine dosimetry measurement.

3.4.9 transfer standard dosimeter: Dosimeter, often a reference standard dosimeter, intended for transport between different locations for use as an intermediary to compare absorbed dose measurements.

3.5 "Validation" and related terms

3.5.1 calibration: Comparison of a measurement system or device of unknown accuracy to a measurement system or device of a known accuracy (traceable to national standards) to detect, correlate, report or eliminate by adjustment any variation from the required performance limits of the unverified measurement system or device.

3.5.2 installation qualification: Obtaining and documenting evidence that equipment has been provided and installed in accordance with its specifications and that it functions within predetermined limits when operated in accordance with the operational instructions.

3.5.3 national standard: Standard recognized by an official national decision as the basis for fixing the value, in a country, of all other standards of the quantity concerned.

3.5.4 process qualification: Obtaining and documenting evidence that the sterilization process will produce acceptable health care products.

3.5.5 product qualification: Obtaining and documenting evidence that the health care product will be acceptable for its intended use after exposure to radiation.

3.5.6 validation: Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

3.6 "Sterile" and related terms

3.6.1 sterile: Free from viable microorganisms.

NOTE 7 In practice no such absolute statement regarding the absence of microorganisms can be proven (see sterilization).

3.6.2 sterility assurance level (SAL): Probability of a viable microorganism being present on a product unit after sterilization.

NOTE 8 SAL is normally expressed as 10^{-n}.

3.6.3 sterilization: Validated process used to render a product free from viable microorganisms.

NOTE 9 In a sterilization process, the nature of microbial death is described by an exponential function. Therefore, the presence of microorganisms on any individual item can be expressed in terms of probability. While the probability may be reduced to a very low number, it can never be reduced to zero. The probability can be expressed as a sterility assurance level (SAL).

3.6.4 sterilization dose: Minimum absorbed dose required to achieve the specified sterility assurance level.

3.7 Terms related to dose setting

3.7.1 bioburden: Population of viable microorganisms on a product.

NOTE 10 In the context of irradiation sterilization, bioburden is determined immediately prior to sterilization.

3.7.2 fraction positive: Quotient with the number of positive sterility tests in the numerator and the number of samples in the denominator.

3.7.3 incremental dose: Dose within a series applied to a number of product units or portions thereof and used in dose setting methods to establish or confirm the sterilization dose.

3.7.4 radiation stability: Ability of a health care product to remain acceptable for intended use throughout its shelf life after exposure to the maximum radiation dose.

3.7.5 sterilization dose audit: Action taken to detect whether or not a change in sterilization dose is needed.

3.8 Terms related to annex B

3.8.1 sterility testing: Test performed to determine if viable microorganisms are present.

3.8.2 positive sterility test: Sterility test samples which exhibit detectable microbial growth after incubation.

3.8.3 negative sterility test: Sterility test samples which do not exhibit detectable microbial growth after incubation.

3.8.4 false positive: Test result where turbidity is interpreted as growth arising from the sample tested, when the growth resulted from extraneous microbial contamination or the turbidity arose from an interaction between the sample and the test medium.

3.8.5 false negative: Test result interpreted as no growth, either where growth was present but not detected, or where viable microorganisms failed to grow.

3.8.6 aerobic organism: Microorganism that utilizes oxygen as the final electron acceptor during metabolism.

3.8.7 anaerobic organism

(1) Microorganism that does not utilize oxygen as the final electron acceptor during metabolism.

(2) Microorganism that will only grow in the absence of oxygen.

3.8.8 facultative organism: Microorganism capable of both aerobic and anaerobic metabolism.

3.8.9 sample item portion (SIP): Defined portion of a health care product unit that is tested.

3.8.10 verification dose (D kGy):** A dose of radiation estimated to produce an SAL of 10^{-2} for a product unit or portion thereof, and used in dose setting methods to establish or confirm the sterilization dose.

3.8.11 D_{10} kGy: Radiation dose required to kill 90 % of a homogeneous microbial population where it is assumed that the death of microbes follows first order kinetics.

4 Documentation

In order to ensure reproducibility, the validation and processing procedures and all other elements which will influence the sterilization process shall be fully documented. This documentation shall be implemented and maintained in accordance with ISO 9001 and/or ISO 9002, whichever is applicable.

5 Personnel

Reponsibility for the validation and routine control for sterilization by irradiation shall be assigned to qualified personnel in accordance with subclauses 4.1.2.2 and 4.18 of ISO 9001:1994 and/or subclauses 4.1.2 and 4.17 of ISO 9002:1994, whichever is applicable.

6 Sterilization process validation

6.1 General

Validation of the sterilization process shall include the following elements:

a) product qualification undertaken in an irradiator that has been subjected to installation qualification;

b) installation qualification;

c) process qualification using a specified product, or simulated product, in qualified equipment;

d) an administrative certification procedure to review and approve documentation of a), b) and c);

e) activities performed to support maintenance of validation.

Figure 1 shows a typical validation programme.

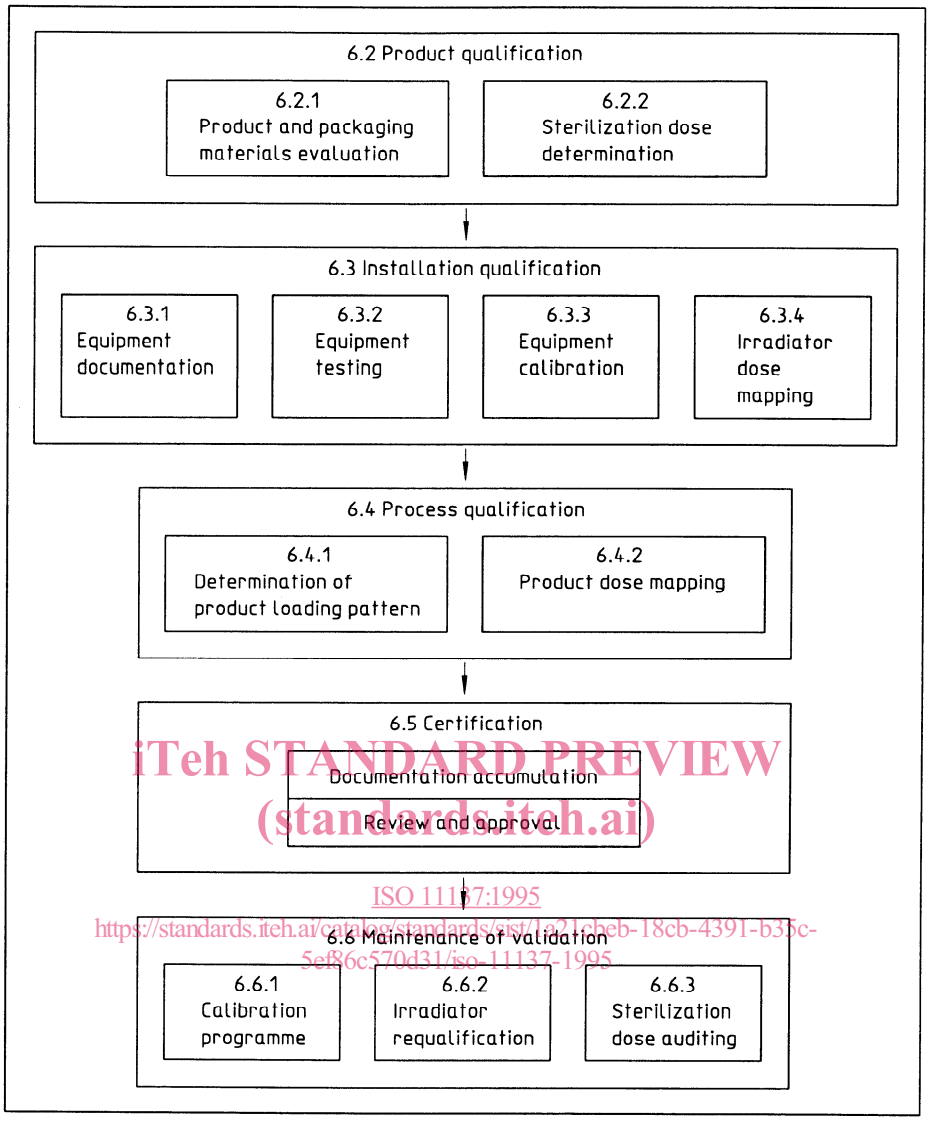

Figure 1 — Elements of typical validation programme

6.2 Product qualification

6.2.1 Product and packaging materials evaluation

Prior to using radiation sterilization for a health care product, the effect that radiation will have on the materials that make up the products (or product components) and packaging shall be considered. A programme to demonstrate the quality, safety and performance of the product throughout its shelf life shall be performed.

This testing shall include any specific property essential to the intended function of the product.

Typically, in designing a test programme, the following should be addressed: variations in manufacturing processes, tolerances, radiation doses, radiation source, raw materials and storage conditions.

A maximum acceptable dose shall be established for each product and packaging.

NOTE 11 Guidance on the qualification of product and packaging materials appears in annex A.

6.2.2 Sterilization dose selection

6.2.2.1 A knowledge of the number and resistance to radiation of the natural microbial population as it occurs on or in the product shall be obtained and used for determination of the sterilization dose. The dose

shall be capable of achieving the preselected sterility assurance level (SAL).

One of two approaches shall be taken in selecting the sterilization dose:

a) selection of sterilization dose using either

   1) bioburden information, or

   2) information obtained by incremental dosing.

   NOTE 12 Examples of these dose setting methods are methods 1 and 2, respectively, in annex B.

b) selection of a sterilization dose of 25 kGy following substantiation of the appropriateness of this dose.

6.2.2.2 Basic technical requirements to generate the information required for selection of sterilization dose using bioburden or fraction positive information, and to substantiate the selection of 25 kGy, shall be

a) access to competent microbiological laboratory services;

b) microbiological testing performed in accordance with ISO 11737-1 and the future ISO 11737-2;

   NOTE 13 These International Standards are currently in the course of preparation. Until they are published, information on microbiological testing can be found in *Microbiological methods for gamma irradiation sterilization of medical devices.* Technical information report AAMI TIR8, Arlington, Va, Association for the Advancement of Medical Instrumentation, 1991.

c) access to

   — a 60 Co or 137 Cs radiation source, or

   — an electron beam or x-ray irradiator operated at an energy level and dose rate similar to those used in processing,

   capable of delivering accurate and precise doses ranging from 1 kGy upward.

6.2.3 Transfer of sterilization dose

When product is transferred between two radiation facilities, use by the second facility of the same sterilization dose that was selected in accordance with 6.2.1 and 6.2.2 for use at the first facility shall be considered only with the following data.

For transfer between an electron beam or x-ray facility and any other radiation facility (electron beam → electron beam; x-ray → x-ray; electron beam ↔ x-ray; electron beam ↔ gamma; x-ray ↔ gamma) data shall be available to show that, using the same sterilization dose, microbial inactivation is not affected by differences between the two facilities in source characteristics, particularly radiation energy and the rate at which dose is delivered, or by differences in dose distribution through the product.

For transfer between two gamma radiation facilities, data shall be available to show that, using the same sterilization dose, microbial inactivation is not affected by differences between the two gamma radiation facilities in dose distribution through the product.

6.3 Installation qualification

An installation qualification programme shall be established, documented and implemented.

6.3.1 Equipment documentation

Documentation shall exist describing the irradiator and its operation. Such documentation shall be retained for the life of the irradiator and include

a) the irradiator specifications and characteristics;

b) a description of the location of the irradiator within the operator's premises in relation to the means provided for the segregation of non-irradiated products from irradiated products;

c) a description of the construction and the operation of any associated conveyor system;

d) the dimensions and the description of the materials and the construction of the irradiation containers;

e) a description of the manner of operating the irradiator and any associated conveyor system;

f) for gamma facilities, dated certificates of source activity and location of individual source capsules within the source frame;

g) any modification made to the irradiator.

Other documentation shall exist describing the instrumentation used to control, monitor, and record critical process parameters during irradiation. Such documentation shall be retained in accordance with

the requirements of ISO 9001 and/or ISO 9002, whichever is applicable.

For gamma facilities, the critical process parameters shall include timer setting, exposure time or conveyor speed during irradiation, and dose measurements.

For electron beam and x-ray facilities, the critical process parameters shall include electron beam characteristics (average electron beam current, electron energy, scan width), conveyor speed, conveyor speed feedback circuitry and/or control feedback circuitry, and dose measurements.

6.3.2 Equipment testing

Process equipment, including the radiation source, conveyor mechanisms, safety devices and ancillary systems, shall be tested to verify satisfactory operation within the design specifications. The test method(s) and results shall be documented.

6.3.3 Equipment calibration

A documented calibration programme shall be implemented to ensure that the equipment and dosimetry systems are calibrated (traceable to national standards) and maintained within specified accuracy limits, in accordance with ISO 9001.

For gamma irradiators, this includes calibration of the irradiator cycle timers or conveyor speed, weighing equipment and the dosimetry system.

For electron beam and x-ray irradiators, this includes calibration of the characteristics of the electron beam, the speed of the equipment moving the irradiation container, weighing equipment and the dosimetry system.

Dosimeters with a known level of accuracy and precision shall be used for the validation and routine control of radiation sterilization. Proper dosimetric measurement procedures, with appropriate statistical controls and documentation, shall be employed.

NOTE 14 Variables that may affect measurements of dose are discussed in annex C.

6.3.4 Irradiator dose mapping

Dose mapping shall be carried out to characterize the irradiator with respect to the magnitude, distribution and reproducibility of dose delivery.

For gamma and x-ray irradiators, dose mapping shall be carried out using irradiation containers filled to their design limits with material of homogeneous density within the limits of the bulk density range for which the irradiator is to be used. Such containers shall be used to determine the absorbed dose at multiple internal locations. If there is more than one product path through the irradiator, dose mapping shall be carried out for each path to be used.

For electron beam irradiators, dose mapping shall be carried out using material of homogeneous density. Dose mapping shall characterize the dose distribution over the volume used for the irradiation of material that is transported through the radiation field. It shall also establish the relationship of the dose and dose distribution to the operating parameters of the electron beam system over the operational limits encountered in the irradiation of products. If there is more than one product path through the irradiator, dose mapping shall be carried out for each path to be used.

All records, including records of irradiator operating conditions, results and conclusions from the dose mapping, shall be retained and reviewed in accordance with ISO 9001 and/or ISO 9002, whichever is applicable.

6.4 Process qualification

6.4.1 Determination of product loading pattern

A loading pattern shall be established for each product type. The specification for this loading pattern shall document the following.

6.4.1.1 Gamma and x-ray facilities

a) a description of the packaged product, including dimensions and density, and acceptable variations in this parameter and when applicable, the orientation of the product within the package;

b) a description of the product loading pattern within the irradiation container;

c) a description of the irradiation container and its dimensions.

6.4.1.2 Electron beam facilities

a) a description of the packaged product, including orientation of the product with respect to the conveyor flow and electron beam, unit count within the package, package dimensions and

mass, the orientation of product within the package, and acceptable variations in these parameters;

b) a description of the product loading pattern within the irradiation container;

c) a description of the irradiation container and its dimensions.

6.4.2 Product dose mapping

The dose mapping study shall be performed to identify the zones of minimum and maximum dose, within the product load with the specified loading pattern, and to assess the reproducibility of the process. This information shall then be used in selecting the dose monitoring locations for routine processing.

Dose mapping shall be carried out for representative irradiation containers sufficient in number to determine the variability of absorbed dose between representative containers, particularly at the expected maximum and minimum dose zones and the routine monitoring position.

Dose mapping exercises shall be carried out at the limits of the density ranges of product categories to be processed irrespective of dose. Product loading patterns and the pathway used for processing shall be included in such excercises.

Facilities that process only product loads that exhibit the same dose distribution characteristics as those used in the qualification dose mapping(s) have met the product dose mapping requirements for process validation. If the bulk density of loading pattern dimensions of a product load have not been sufficiently characterized in current dose mapping data, additional dose mapping shall be performed.

All records, including those of irradiation parameters, results, and conclusions from the dose mapping, shall be retained in accordance with ISO 9001 and/or ISO 9002, whichever is applicable.

6.5 Certification

Information gathered or produced while conducting product qualification, installation qualification, and process qualification shall be documented and reviewed for acceptability by a designated individual or group and retained in accordance with ISO 9001 and/or ISO 9002, whichever is applicable.

6.6 Maintenance of validation

6.6.1 Calibration programme

Recalibration of equipment and dosimetry systems (see 6.3.3) shall be carried out at regular intervals, established on the basis of stability, purpose and usage in accordance with ISO 9001 and/or ISO 9002, whichever is applicable.

6.6.2 Irradiator requalification

A change in the irradiator which affects dose distribution shall require a repeat of part or all of the installation qualification procedure (see 6.3).

6.6.3 Sterilization dose auditing

An audit shall be performed at a defined and documented frequency. To determine the continued validity of the sterilization dose, the audit shall be performed following any change that could significantly affect the level or nature of the bioburden. In the absence of any such change, the audit shall be performed, at a minimum, every three months.

7 Routine process control

Process control includes control and monitoring of process equipment, handling of product prior to, during and after irradiation, routine and preventive maintenance, production dose monitoring, process continuity and documentation.

7.1 Process specification

A process specification shall be established for each product or product category. The process specification shall include a description of

a) the product or products covered by the specification;

b) the maximum dose allowed and the sterilization dose (see 6.2);

c) the product loading pattern and the relationship between dose at the monitoring position and the dose at the maximum and minimum dose positions (see 6.4.1);

d) the routine dosimeter monitoring position(s) (see annex C);

e) for gamma sterilization, the relationship between product density, dose and source strength;

f) for electron beam and x-ray sterilization, the relationship between beam characteristics, conveyor speed, product configuration and dose.

On occasion, products require multiple exposures to the irradiation field, some of which involve reorientation of product; these requirements shall be included in the specification.

7.2 Product handling

Documentation shall be established and maintained describing the handling of product before, during and after radiation sterilization. Product shall be handled and stored in a way that ensures that its efficacy and microbial condition are not compromised. A system of product count shall be maintained throughout the product receipt, loading, unloading, post-irradiation handling and release.

7.2.1 Product shipment and receipt

To ensure product accountability, the processing records for the product that is to be sterilized shall include a count of product upon receipt. Any discrepancy between the number received and the number on the shipping or transfer documents shall be resolved before processing.

7.2.2 Pre- and post-irradiation product storage

Pre- and post-irradiated products shall be stored in a segregated area. If separate areas are not exclusively designated for storage of non-sterile products, and for storage of sterile products, respectively, or if the product storage area(s) are remote from the irradiator loading and unloading areas, individual pallets or products shall be identified as to their status.

7.3 Routine and preventive maintenance

Routine and preventive maintenance procedures (normally recommended by the equipment supplier) shall be documented and implemented, and preventive maintenance shall be recorded in accordance with ISO 9001 and/or ISO 9002, whichever is applicable.

7.4 Product irradiation

7.4.1 Process control

The irradiator shall be operated and maintained in accordance with documented procedures designed to ensure that the established and documented process specifications are met.

7.4.1.1 Gamma irradiators

a) Control. For a given product or product category, the timer setting and/or the conveyor speed shall be controlled and adjusted for source decay. The cycle timer shall have a backup to monitor any variations from the preset time interval. The source shall be controlled to ensure that it is in the correct irradiation position.

b) Monitoring. The source position, timer setting, and movement of irradiation container shall be monitored.

c) Product loading. Product shall be loaded into the irradiation container in accordance with the designated product loading pattern.

7.4.1.2 Electron beam and x-ray irradiators

a) Control. The electron beam characteristics and conveyor speed shall be automatically controlled.

b) Monitoring. The electron beam characteristics and conveyor speed shall be monitored to detect process deviations.

c) Product loading. Product shall be loaded into the irradiation container in accordance with the designated product loading pattern.

7.4.2 Process interruption

Where process interrruption occurs during sterilization and delays the completion of sterilization beyond the specified time, its effect on the microbiological quality of the product shall be investigated and appropriate action taken.

For products capable of supporting microbial growth, process specification shall include the maximum interval of time that may elapse between completion of manufacture and completion of sterilization processing, and the conditions of storage and transportation to be applied during this time interval, including irradiation.

NOTE 15 For products not capable of supporting microbial growth, the effect of radiation dose on microorganisms is cumulative, thus the interruption of the process in the irradiator does not generally necessitate action.

7.4.3 Dose monitoring

Dosimeters shall be used to monitor routinely the irradiation process. Radiation sensitive visual indicators shall not be used as proof of satisfactory radiation processing or as the sole means of