List of Titles

American National Standard

ANSI/AAMI/ISO 11137:1994

Sterilization of health care products—Requirements for validation and routine control—Radiation sterilization, 3ed.

AAMI Association for the Advancement of Medical Instrumentation

List of Titles

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American National Standard, Sterilization of health care products— Requirements for validation and routine control—Radiation sterilization

(ANSI/AAMI/ISO 11137—1994)

Approved 25 May 1994 by
Association for the Advancement of Medical Instrumentation

Approved 11 July 1994 by
American National Standards Institute, Inc.

Association for the Advancement of Medical Instrumentation

The adoption of this International Standard as an American National Standard was approved by the AAMI Radiation Sterilization Working Group, under the auspices of the AAMI Sterilization Standards Committee. Committee approval of the recommended practice does not necessarily imply that all committee, subcommittee, and working group members voted for its approval.

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NOTE—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

Background of ANSI/AAMI adoption of ISO 11137

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

The International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard.

ISO 11137 was developed by ISO Technical Committee 198 to fill a need for an international standard for

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radiation sterilization of health care products. TC 198 approved the standard in 1994 and it was published by ISO in 1995. U.S. participation in ISO/TC 198 is organized through the U.S. Technical Advisory Group for ISO/TC 198, administered by the Association for the Advancement of Medical Instrumentation (AAMI). The United States made a considerable contribution to this standard.

This International Standard is based on a draft standard prepared by the European Standardization Committee (CEN) and also reflects the requirements of the previous editions of the American National Standards, *Guideline for Electron Beam Radiation Sterilization of Medical Devices* (ANSI/AAMI ST31-1990) and *Guideline for Gamma Radiation Sterilization* (ANSI/AAMI ST32-1991).

AAMI and ANSI procedures require that standards be reviewed and, if necessary, revised every five years to reflect technological advances that may have occurred since publication. AAMI encourages its committees to harmonize their work with international standards as much as possible. As part of their review of ANSI/AAMI ST31 and ST32, the AAMI Radiation Sterilization Working Group examined this corresponding international standard to determine to what extent the documents could be harmonized. During this review, the Working Group decided to adopt ISO 11137 verbatim as the ANSI/AAMI revision of ST31 and ST32.

The Working Group will also be reviewing ISO TR 13409-1, *Sterilization of health care products—Substantiation of 25 kGy for radiation sterilization of small or infrequent production batches*, for adoption with U.S. modifications. This document will provide a method of substantiating the suitability of 25 kGy as a sterilization dose which may be used for radiation sterilization of products which are manufactured in small quantities (that is less than 1,000 product units) either as a single batch or for production of a number of small batches. This method originated in the U.S. and was first published in ANSI/AAMI ST32.

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data comes to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201.

NOTE—Beginning with the ISO foreword on page vii, this American National Standard is identical to ISO 11137:1994.

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 annex D of this International Standard are for information only.

Introduction

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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 programs 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 responsibility 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.

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

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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.

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

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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 = 3.7×10^{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.

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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.

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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

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Responsibility 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 these 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 program.

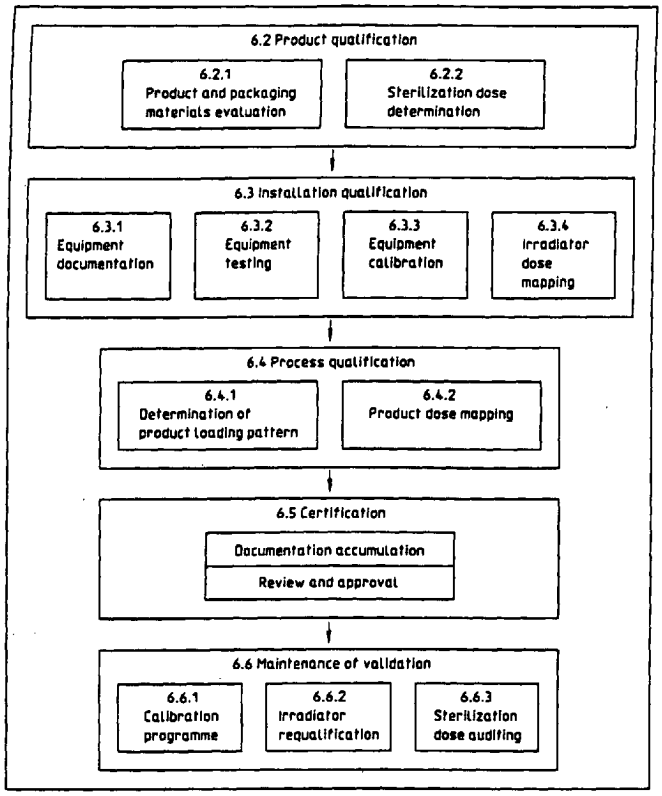

Figure 1—Elements of typical validation program

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 program to demonstrate the quality, safety and performance of the product throughout its shelf life shall be performed.

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

Typically, in designing a test program, 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 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.

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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 program 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; and

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 program shall be implemented to assure 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

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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 homogenous 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

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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 exercises.

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 or 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 program

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 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);

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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 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 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.

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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 interruption 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 differentiating irradiated products from non-irradiated products.

7.4.3.1 Monitoring location

Dosimetry monitoring locations shall be determined from current dose mapping data for the product (see annex C). Descriptions of these locations shall become part of the current processing specifications to help ensure proper placement of dosimeters. Dosimeters shall be placed at a location having a known dose relationship to the minimum and maximum doses.

7.4.3.2 Monitoring frequency

The process shall be monitored by placement of dosimeters at specified intervals sufficient to verify that the dose absorbed by product falls within specified limits.

For gamma irradiators, at least one irradiation container with a dosimeter shall be in the irradiator at all times. When more than one pathway is used, each pathway shall be monitored with at least one dosimeter in the irradiator at all times.

For electron beam and x-ray irradiators, the processing shall be monitored with dosimeters at specified intervals with sufficient frequency to ensure that the sterilization dose is delivered to all products throughout the irradiation process.

7.4.3.3 Analysis

Following irradiation, the dosimeters shall be read and results recorded. All routine dosimetry data shall be analyzed and measurements of dose shall be compared to the doses stipulated in the process specification.

Any dosimetric reading (that is, from a single dosimeter or the average of multiple dosimeters) indicating a dose outside the specified limits shall be investigated. If multiple dosimeters are used in each monitoring location and a single dosimeter reading exceeds the precision of the dosimetry system, it shall also be investigated. The processed product associated with this reading shall not be released until the investigation is satisfactorily completed, and evidence indicating that the product is acceptable for release is documented.

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7.5 Process documentation

For each product, the following information shall be recorded and reviewed by authorized individuals and maintained in the process documentation:

a) incoming count of product by product code and manufacturing batch number (if used);

b) product loading pattern;

c) dosimeter placement and retrieval;

d) sterilization batch number;

e) specified sterilization dose and allowed maximum dose;

f) process parameters:

— setting of cycle timer and/or conveyor speed (gamma),

— beam characteristics and conveyor speed set points (electron beam and x-ray);

g) verification count of product loaded into the irradiation container;

h) sterilization date(s);

i) verification count of product unloaded from the irradiation container;

j) dosimeter readings and analysis;

k) verification count of outgoing product;

l) process records:

— of the conveyor operation and source position (gamma),

— of the beam characteristics and conveyor speed (electron beam and x-ray);

m) for those irradiators offering a choice of internal conveyor paths, documentation of which path was used for the product;

n) process interruptions and action taken;

o) process deviations and actions taken.

7.6 Sterilization acceptance

When records are available to demonstrate that the sterilization process complies with the requirements in this International Standard, the sterilization process is accepted.

NOTE 16 Additional records of manufacture and inspection of product will be required as specified in a quality system/quality control plan (see ISO 9001/ISO 9002) in order for the product to be released as sterile and distributed.

Finished product sterility testing is not a requirement of this International Standard.

8 Management and control

Control of the radiation sterilization process shall be fully documented and managed in accordance with ISO 9001 and/or ISO 9002, whichever is applicable.

Control can only be achieved if procedures for validation and processing are standardized and documented, and these documents are in turn controlled. For example, internal audits to ensure the efficiency of these

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procedures are essential, and corrective action and records of results for future review are important.

Annex A
(informative)

Device and packaging materials qualification

This annex gives guidance only for the qualification of medical devices and is particularly relevant to medical devices fabricated from synthetic polymeric materials. For other health care products, the effects of exposure to radiation on properties other than those outlined in this annex will need to be addressed.

Prior to selecting the radiation sterilization process for a medical device, it is important to consider the effect that radiation will have on the stability of the materials that make up the devices or device components. While some materials such as polystyrene are inherently less affected by radiation than others such as polytetrafluoroethylene (PTFE) or polyoxymethylene, the radiation stability of any device will be a function both of the materials and the design (table A.1). Therefore, a program to demonstrate functional stability of the device throughout its shelf life should be carried out.

Testing should include any specific property essential to the intended function of the device, such as strength, clarity, color, biocompatibility and package integrity. The test program should encompass all variations in manufacturing processes, tolerances, radiation doses, radiation source, raw materials and storage conditions. Based upon the above considerations, the maximum dose for each device shall be specified.

Table A.1—General guidelines for selection of radiation-stable materials

There are several rules that apply toward selecting or designing radiation-stable materials. A general rule, however, is that all plastics can be classified as materials whose molecules either a) predominantly degrade with irradiation or b) predominantly crosslink with irradiation. Materials that crosslink with irradiation tend to have higher radiation stability. The physical properties of some materials are affected differently by the mode of radiation. More specific guidelines are:

1. Aromatic materials are more stable than aliphatic materials.
2. Phenolic antioxidants contained in most plastics are a cause of discoloration. The use of non-phenolic additives may eliminate the problem.
3. Most polypropylenes and polytetrafluoroethylene are unstable with irradiation. Polyvinylchloride and polypropylene should be especially stabilized to improve radiation compatibility.
4. Polymer processing conditions and materials that lead to embrittlement of medical devices should be carefully evaluated for radiation sterilization (for example, the use of plastic regrind or nucleated polymers; the use of high temperatures during moulding; the creation of high levels of crystallinity in semi-crystalline polymers in slow cooling and autoclaves).
5. High levels of antioxidants help radiation stability. In general, the level of antioxidant should be doubled if the device is going to be radiation-sterilized.
6. For semi-crystalline polymers, processing conditions that lead to low degrees of crystallinity will improve stability.
7. The elastic modulus of plastics is not significantly affected with a sterilizing dose of irradiation.
8. Carefully evaluate the use of low molecular mass polymers.
9. Within a given polymer class, the lower the density the greater the radiation stability.

The effects of radiation dose on materials might not be immediately apparent. Therefore, the test program may include accelerated aging at extreme conditions for initial indication of material suitability, as well as ambient real-time aging. The accelerated testing may include doses above those required simply to achieve sterilization, combined with storage at extreme environmental conditions. However, in most cases, ambient, real-time and non-irradiated control samples should be part of the test program.

A typical testing protocol can require devices or material samples to be exposed to radiation at various dose

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levels between 10 kGy and 100 kGy. The irradiation of test samples should be in accordance with C.1.5.4.

Although there is no substitute for long-term shelf stability studies, an accelerated aging study can be used for screening of materials. In this case, the same test protocol for material testing is employed, but the temperature is held at 60°C. In the absence of a more accurate relationship, seven days at 60°C may be considered equivalent to 180 days of aging at ambient conditions. A suggested time interval for accelerated testing is one week to 30 days. At ambient conditions, the suggested time intervals are 0, 3, 6, 9 and 12 months [2]. In all cases, non-irradiated material should be maintained as a control for the intended life of the device.

There are many tests employed in materials evaluation: a selection of these is listed in table A.2. Once a material is selected on the basis of these tests, final qualification to demonstrate functional stability of the device should be carried out on fully processed components, complete devices and packages, as appropriate. If testing of individual device components is done, a demonstration that the components are compatible with each other in a complete device should be part of the testing.

Table A.2—Physical and functional test methods for plastics material evaluation

Test method	**Test reference**
Test for embrittlement:	
1. Tensile properties	
a) Tensile strength	ISO/R 527:1966
b) Ultimate elongation	ISO/R 527:1966
c) Modulus of elasticity	ISO/R 527:1966
d) Work	ISO/R 527:1966
2. Flexural properties	
a) Flange bending test	"Stability of Irradiated Polypropylene. 1. Mechanical
	Properties", Williams, Dunn, Sugg, Stannet, Advances in
	Chemistry Series, No. 169, Stabilization and Degradation of
	Polymers, Eds. Allara, Hawkins, pp. 142-150, 1978.
b) Flexbar test	ISO 178:1975
3. Impact resistance	1985 ASTM Standards, Vol. 08.01-Plastics, D-1822-84
4. Hardness	
a) Shore	ISO 868:1985
b) Rockwell	1985 ASTM Standards, Vol. 08.01-Plastics, D-785-65
5. Compressive strength	ISO 604:1973
6. Burst strength	1985 ASTM Standards, Vol. 08.01-Plastics (Tubing), D-1180-57
7. Tear strength	1985 ASTM Standards, Vol. 08.01-Plastics, D-1004-66, and ISO 6383/1-1983
Test for discoloration:	
1. Yellowness index	1985 ASTM Standards, Vol. 08.02-Plastics, D-1925-70
2. Optical spectrometry	1985 ASTM Standards, Vol. 08.02-Plastics, D-1746-70
NOTE Source: International Atomic Energy Agency. *Guidelines for industrial radiation sterilization of disposable medical products, Co-60 gamma irradiation*. TEC DOC-539. Vienna IAEA, 1990.	

In addition to the physical and mechanical qualification testing, some materials might need to undergo biocompatibility testing. Changes in the chemical structure of the polymer and/or its additives, as well as gaseous byproducts liberated during irradiation, can alter the material's biocompatibility for medical device applications. This testing should also demonstrate biocompatibility throughout the intended life of the device. ISO 10993-1 [1] gives a description of basic biological screening testing that may be used for predicting the safety of irradiated materials for use in medical devices. Specific tests might be required depending upon the end use of the device.

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In summary, careful adherence to the guidelines in this International Standard will help the primary manufacturer to avoid problems encountered with radiation sterilization of medical devices. It is the responsibility of the device designer and primary manufacturer to ensure the suitability of the material, design and packaging for irradiation. The irradiator operator can only, if requested, advise in general terms and perform test irradiations. Primary manufacturers of medical devices are also responsible for ensuring that they are informed by suppliers of materials and components of any changes in the formulation and/or manufacturing process that could affect radiation stability.

Table A.3 lists some typical materials with good radiation stability. Table A.4 gives general guidelines to radiation stable materials.

Table A.3—Examples of radiation-stable materials (in sterilizing dose range)

The following generic materials, which are readily available, are naturally
radiation-stable, and can be used in most sterile device applications:

- Acrylonitrile/Butadiene; Styrene (ABS)
- Polystyrene
- Polystyrene-Acrylonitrile (SAN)
- Polyethylene (all densities and UHMW)
- Polyamides
- Polysulfones
- Polyimides
- Polyurethane
- Polyphenylene sulfide
- Polyesters
- Poly(ethylene-vinyl acetate)
- Poly(ethylene-acrylate)
- Phenolics
- Epoxies
- Natural rubber
- Silicone
- Most synthetic elastomers (except Butyl or Polyacrylic).

Table A.4—General guide to radiation stability of materials

Materials	Radiation stability	Comments
Thermoplastics:		
Polystyrene	Excellent	
Polyethylene	Excellent	
Polyamides	Excellent	
Polyimides	Excellent	
Polysulfone	Excellent	Natural material is yellow.
Polyphenylene sulfide	Excellent	
Polyvinylchloride (PVC)	Good	Yellows — antioxidants and stabilizers prevent yellowing. High molecular weight organotin stabilizers improve radiation stability.
Polyvinylchloride-Polyvinylacetate	Good	Less resistant than PVC
Polyvinylidene chloride	Good	Less resistant than PVC
Polyvinyl Formal	Good	Less resistant than PVC

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Polyvinylbutyral	Good	Less resistant than PVC
Styrene/Acrylonitrile (SAN)	Good	
Polycarbonate	Good	Yellows — mechanical properties not greatly affected.
Polypropylene	Poor	Must be stabilized — physical properties greatly reduced when irradiated.
Fluropolymers - Polytetrafluroethylene (PTFE) Polychlorotrifluoroethylene (PCTFE) Polyvinyl fluoride Polyvinylidene fluoride Ethylene-Tetrafluroethylene (ETFE) Fluorinated ethylene propylene (FEP)	Poor	When irradiated, PTFE and PCTFE are significantly damaged. The others show better stability.
Cellulosics - Esters Cellulose	Poor	Esters degrade less than does cellulose.
Polyacetals	Poor	Irradiation causes embrittlement — color changes have been noted (yellow to green).
Thermosets:		
Phenolics	Good	Very good with the addition of mineral fillers.
Epoxies	Good	Very good with the use of aromatic curing agents.
Polyesters	Good	Very good with the addition of mineral or glass fibers.
Allyl diglycol carbonate (Polyester)	Excellent	Maintains its excellent optical properties after irradiation.
Polyurethanes Aliphatic	Excellent	
Aromatic	Good	Darkening can occur. Possible breakdown products could be derived.
Elastomers:		
Urethane	Excellent	
EPDM	Excellent	
Natural Rubber	Good	
Nitrile	Good	Discolors.
Polychloroprene (neoprene)	Good	Discolors — the addition of aromatic plasticizers renders the material more stable to irradiation.
Silicone	Good	Phenyl-methyl silicones are more stable than are methyl silicones.
Styrene-butadiene	Good	
Polyacrylic	Poor	
Chlorosulfonated polyethylene	Poor	
NOTE Partial source: IAEA, 1990.		

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Annex B
(informative)

Dose setting methods for radiation sterilization

NOTE 17 While the dose setting methods described in this annex meet the requirements of this International Standard (see 6.2.2), other methods that also meet the requirements may be used. For this reason, the annex is considered "informative" and use of the terms "shall," "should," etc. should be considered within the context of this annex only. That is, if the decision is made to use one of the annex B dose setting methods, then the method should be followed in adherence with the requirements ("shall") and recommendations ("should") as set forth in this annex.

B.1 Introduction

The basis of the dose determination methods described in this annex owe much to the ideas first propounded by Tallentire (Tallentire, 1973; Tallentire, Dwyer and Ley, 1971; Tallentire and Khan, 1978). Subsequently, standardized incremental dose protocols were developed (Davis *et al*, 1981; Davis, Strawderman and Whitby, 1984) which formed the basis of the dose-setting procedures put forward in the AAMI recommended practice for sterilization by gamma radiation (AAMI 1984, 1992).

The dose setting methods and audit procedures use data derived from the inactivation of the microbial population in its natural state. These methods are based on a probability model for inactivation of microbial populations. The probability model, as applied to bioburden made up of a mixture of various microbial species, assumes each species has its own unique D_{10} value. In the model, the probability that a particular item will be sterile after exposure to a given dose of irradiation is defined in terms of the initial number of organisms on the item prior to irradiation and their D_{10} values.

The methods involve sterility testing of product, or portions of product, that have received lower doses of radiation than the sterilization dose. Once the sterilization dose has been established, audits should be performed to reaffirm that the sterilization dose provides the specified sterility assurance level.

B.2 Definitions

See 3.8 in the body of this International Standard.

B.3 Selection and testing of product for dose setting

B.3.1 Selection

The method of selecting product units for subsequent testing can influence the test result observed. It is preferred to select product units at random. The product units may be chosen from routine production of a batch which is representative of processing procedures and conditions, in which case product units produced at different times during the manufacture of a single batch should be included. If a number of batches are manufactured concurrently, product units may be selected from each batch. Product units for testing may be selected from items rejected during the manufacturing process provided that they have been subjected to the same processing and conditions as the remainder of the batch.

B.3.1.1 Sample item portion (SIP)

Whenever practicable, an entire product unit should be used for testing, but it is recognized that this is not always possible. In such situations, a selected portion of a product unit (sample item portion, SIP), which is convenient to handle during testing, may be substituted. The SIP should be as large a portion of the product unit as it is possible to manipulate readily in the laboratory. If a product unit or SIP cannot be tested in available laboratory glassware, it may be divided into two or more containers and these containers scored

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together as one unit; if one container yields a positive result, the entire unit is considered positive. SIP can be calculated on the basis of length, mass, volume or surface area of the product unit to be tested (see table B.23 for examples).

The SIP has to represent validly the microbial challenge presented to the sterilization process and the diverse elements of complex product units. The microbial challenge in or on a product unit shall be represented adequately by the SIP selected. The distribution of bioburden on the product unit shall be considered and, if it can be demonstrated that the bioburden is evenly distributed, the SIP may be selected from any location of the product unit. In the absence of such a demonstration, the SIP shall be constituted from a portion (or portions) of a product unit selected at random.

The preparation and packaging of an SIP shall be conducted under conditions chosen to minimize alterations of the bioburden. Environmentally controlled conditions should be used for preparation of SIPs and, whenever possible, packaging materials should be equivalent to those used for the finished product.

The adequacy of a selected SIP shall be demonstrated. The bioburden of the SIP shall be such that sterility testing of 20 non-irradiated samples yields a minimum of 17 positive sterility tests (i.e. 85% positives). If this criterion is not achieved, a larger SIP is required.

NOTE 18 If the entire product unit is tested, no minimum number of positives is specified for non-irradiated samples.

If the product unit has a label claim of sterility of the fluid path only, testing the fluid path should be considered the entire product unit (i.e. SIP = 1).

B.3.1.2 Sample item portion for kits

A kit is considered to be a product unit containing more than one health care product; these may be a) multiple units of identical health care products, or b) a variety of procedure-related health care products.

a) Kits containing multiples of the same health care product. The SIP for such kits shall be based upon a single health care product and not the summation of all the products in the kit. For example, for a kit containing five syringes, one syringe tested in its entirety would equal an SIP of 1.0.

b) Kits containing different health care products. The SIP for such kits shall be based upon each type of health care product and a separate SIP established for each product in the kit. For example, for a kit containing two gowns, two towels, two pairs of gloves and a drape, an individual SIP will need to be determined for each type of health care product independent of the other products in the kit.

B.3.2 Microbiological testing

Bioburden and sterility tests conducted as part of the dose setting experiments shall be conducted using acceptable laboratory practices and in accordance with ISO 11737-1 and ISO 11737-2.

NOTE 19 See note 13.

The methods described hereafter use a single culture medium for sterility testing. The use of this medium assumes that it will be optimal for the culture of aerobic and facultative anaerobic organisms which may appear as survivors. When this assumption is not valid, the complete dose setting method shall be conducted using other appropriate media and incubation conditions.

NOTE 20 Soybean Casein Digest Broth, with an incubation temperature of (30 ± 2)°C and an incubation period of 14 days, is generally recommended when a single medium is used.

B.3.3 Product irradiation

The irradiation of product, or SIPs, should be in compliance with annex C, subclause C.1.5.4.

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It is preferred that the product is irradiated in its original form and package. However, to minimize and/or simplify the manipulations during testing and reduce the possibility of false positive test results, it may be decided to disassemble the product and repackage prior to sterilization.

NOTE 21 Manipulations prior to irradiation may not always be acceptable. In certain instances, such manipulations may change the response of the microorganisms to irradiation, for example, manipulations may alter the chemical environment in the vicinity of the microorganisms, typical oxygen tension.

Materials used for repackaging products or SIPs for irradiation shall be capable of withstanding the radiation doses to be delivered and the post-irradiation handling in order to minimize the likelihood of contamination.

B.3.4 Dose setting methods

B.3.4.1 Method 1: Dose setting using bioburden information

B.3.4.1.1 Rationale

This method of choosing a sterilization dose depends upon experimental verification that the response to radiation of the product microflora is greater than that of a microbial population having a standard resistance.

A rationalized choice has been made for the standard distribution of resistances (D_{10} values) (see table B.24), and, using computational methods, the individual doses required to achieve values of SAL of 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6} have been calculated for levels of bioburden on product prior to irradiation (average bioburden). The calculated values of dose for given average bioburdens are tabulated in table B.1.

In practice, an estimate is made of the average bioburden. The dose that gives an SAL of 10^{-2} for product units having this bioburden is read from table B.1. This dose is designated the verification dose, and it represents the dose that will reduce the microbial population of standard resistances to a level that gives a one in 100 chance of occurrence of a non-sterile product unit. A sample of 100 product units or portion thereof (SIP) is then exposed to the selected verification dose and each product unit is tested individually for sterility. If there are not more than two positive tests out of the 100 tests, table B.1 is again entered at the estimated level of bioburden to provide the sterilization dose for any desired SAL.

B.3.4.1.2 Procedure for Method 1

If dose setting Method 1 is used, the five stages below shall be followed.

NOTE 22 Worked examples appear in clause B.4.

B.3.4.1.2.1 Stage 1: Select SAL and obtain samples of product units

Record the sterility assurance level (SAL) to be used. Then take a random sample of at least 10 product units from a minimum of three production batches immediately prior to the sterilization phase of production. The number of product units that is sampled shall be sufficient to represent validly the bioburden on the product to be sterilized.

NOTE 23 A sample may be the whole product unit or a portion of the product unit (sample item portion [SIP]).

B.3.4.1.2.2 Stage 2: Determine average bioburden

Using methods such as those contained in ISO 11737-1, determine

a) the average bioburden per product unit (SIP) for all product unit samples (overall average bioburden); and

b) the average bioburden per product unit (SIP) for each of the three batches (batch average 1, 2 and 3).

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Compare the three batch averages to the overall average bioburden. Determine whether any one of the batch averages is two or more times greater than the overall average bioburden.

Table B.1—Radiation dose (kGy) required to achieve a given SAL for different bioburdens having standard distribution of resistances

(Tabulated values are used in Stages 3, 4, and 5 of Method 1 of dose setting)

Average	Sterility Assurance Level					Average	Sterility Assurance Level				
bioburden	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	bioburden	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}
0.063	1.0	2.6	4.8	7.4	10.4	28.00	6.4	9.3	12.4	15.8	19.3
0.075	1.1	2.7	5.0	7.6	10.6	30.48	6.5	9.4	12.6	15.9	19.4
0.088	1.2	2.8	5.1	7.8	10.8	33.16	6.6	9.5	12.7	16.0	19.5
0.10	1.3	3.0	5.3	8.0	11.0	36.06	6.7	9.7	12.8	16.1	19.6
0.12	14	3.1	5.5	8.2	11.3	39.20	6.8	9.8	12.9	16.2	19.8
0.14	1.5	3.3	5.7	8.4	11.5	42.60	6.9	9.9	13.0	16.4	19.9
0.17	1.6	3.5	5.9	8.6	11.7	46.28	7.0	10.0	13.2	16.5	20.0
0.19	1.7	3.6	6.0	8.8	11.9	50.25	7.1	10.1	13.3	16.6	20.2
0.22	1.8	3.7	6.2	9.0	12.1	54.55	7.2	10.2	13.4	16.8	20.3
0.26	1.9	3.9	6.4	9.2	12.3	59.20	7.3	10.3	13.5	16.9	20.4
0.29	2.0	4.0	6.5	9.4	12.5	64.22	7.4	10.4	13.6	17.0	20.5
0.34	2.1	4.1	6.7	9.6	12.7	69.65	7.5	10.5	13.7	17.1	20.7
0.39	2.2	4.3	6.8	9.8	12.9	75.51	7.6	10.6	13.9	17.3	20.8
0.44	2.3	4.4	7.0	9.9	13.1	81.83	7.7	10.7	14.0	17.4	20.9
0.50	2.4	4.5	7.1	10.1	13.3	88.67	7.8	10.9	14.1	17.5	21.0
0.57	2.5	4.7	7.3	10.3	13.5	96.04	7.9	11.0	14.2	17.6	21.2
0.65	2.6	4.8	7.5	10.4	13.6	104.0	8.0	11.1	14.3	17.7	21.3
0.73	2.7	4.9	7.6	10.6	13.8	112.6	8.1	11.2	14.4	17.9	21.4
0.83	2.8	5.1	7.8	10.8	14.0	121.9	8.2	11.3	14.5	18.0	21.5
0.93	2.9	5.2	8.0	10.9	14.2	131.9	8.3	11.4	14.7	18.1	21.7
1.05	3.0	5.3	8.1	11.1	14.3	142.6	8.4	11.5	14.8	18.2	21.8
1.17	3.1	5.4	8.2	11.2	14.5	154.3	8.5	11.6	14.9	18.3	21.9
1.32	3.2	5.6	8.3	11.4	14.7	166.8	8.6	11.7	15.0	18.5	22.0
1.47	3.3	5.7	8.5	11.5	14.8	180.3	8.7	11.8	15.1	18.6	22.2
1.64	3.4	5.8	8.6	11.7	15.0	194.8	8.8	11.9	15.2	18.7	22.3
1.83	3.5	6.0	8.8	11.9	15.1	210.5	8.9	12.0	15.3	18.8	22.4
2.04	3.6	6.1	8.9	12.0	15.3	227.4	9.0	12.2	15.5	18.9	22.5
2.27	3.7	6.2	9.0	12.2	15.5	245.6	9.1	12.3	15.6	19.0	22.7
2.51	3.8	6.3	9.2	12.3	15.6	265.2	9.2	12.4	15.7	19.2	22.8
2.79	3.9	6.4	9.3	12.4	15.8	286.3	9.3	12.5	15.8	19.3	22.9
3.09	4.0	6.6	9.4	12.6	15.9	309.0	9.4	12.6	15.9	19.4	23.0
3.42	4.1	6.7	9.6	12.7	16.1	333.4	9.5	12.7	16.0	19.5	23.1
3.77	4.2	6.8	9.7	12.9	16.2	359.7	9.6	12.8	16.1	19.6	23.3
4.17	4.3	6.9	9.9	13.0	16.4	388.0	9.7	12.9	16.2	19.8	23.4
4.60	4.4	7.0	10.0	13.1	16.5	418.4	9.8	13.0	16.4	19.9	23.5
5.06	4.5	7.1	10.1	13.3	16.6	451.1	9.9	13.1	16.5	20.0	23.6
5.57	4.6	7.3	10.2	13.4	16.8	486.3	10.0	13.2	16.6	20.1	23.7
6.13	4.7	7.4	10.4	13.6	16.9	524.2	10.1	13.3	16.7	20.2	23.9
6.74	4.8	7.5	10.5	13.7	17.1	564.9	10.2	13.4	16.8	20.3	24.0
7.40	4.9	7.6	10.6	13.8	17.2	606.6	10.3	13.5	16.9	20.5	24.1
8.12	5.0	7.7	10.7	14.0	17.4	655.6	10.4	13.7	17.0	20.6	24.2
8.91	5.1	7.9	10.9	14.1	17.5	706.2	10.5	13.8	17.1	20.7	24.3
9.76	5.2	8.0	11.0	14.2	17.6	760.5	10.6	13.9	17.3	20.8	24.5
10.69	5.3	8.1	11.1	14.4	17.8	818.8	10.7	14.0	17.4	20.9	24.6
11.70	5.4	8.2	11.2	14.5	17.9	881.4	10.8	14.1	17.5	21.0	24.7
12.80	5.5	8.3	11.4	14.6	18.1	948.7	10.9	14.2	17.6	21.1	24.8
13.99	5.6	8.4	11.5	14.7	18.2	1,021	11.0	14.3	17.7	21.3	24.9
15.28	5.7	8.5	11.6	14.9	18.3	1,099	11.1	14.4	17.8	21.4	25.1
16.69	5.8	8.6	11.7	15.0	18.5	1,182	11.2	14.5	17.9	21.5	25.2
18.21	5.9	8.8	11.8	15.1	18.6	1,271	11.3	14.6	18.0	21.6	25.3

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19.87	6.0	8.9	'12.0	15.3	18.7	1,387	11.4	14.7	18.2	21.8	25.4
21.66	6.1	9.0	12.1	15.4	18.8	1,470	11.5	14.8	18.3	21.9	25.5
23.61	6.2	9.1	12.2	15.5	19.0	1,581	11.6	14.9	18.4	22.0	25.7
25.72	6.3	9.2	12.3	15.6	19.1	1,699	11.7	15.0	18.5	22.1	25.8
1,827	11.8	15.1	18.6	22.2	25.9	75,463	17.2	20.8	24.5	28.2	32.0
1,963	11.9	15.2	18.7	22.3	26.0	80,629	17.3	20.9	24.6	28.3	32.1
2,109	12.0	15.3	18.8	22.4	26.1	86,142	17.4	21.0	24.7	28.4	32.3
2,266	12.1	15.5	18.9	22.6	26.2	92,025	17.5	21.1	24.8	28.5	32.4
2,435	12.2	15.6	19.0	22.7	26.4	98,302	17.6	21.2	24.9	28.6	32.5
2,615	12.3	15.7	19.1	22.8	26.5	105,000	17.7	21.3	25.0	28.8	32.6
2,808	12.4	15.8	19.3	22.9	26.6	112,140	17.8	21.4	25.1	28.9	32.7
3,016	12.5	15.9	19.4	23.0	26.7	119,760	17.9	21.5	25.2	29.0	32.8
3,238	12.6	16.0	19.5	23.1	26.8	127,890	18.0	21.6	25.3	29.1	32.9
3,476	12.7	16.1	19.6	23.2	26.9	136,560	18.1	21.7	25.4	29.2	33.0
3,731	12.8	16.2	19.7	23.3	27.1	145,810	18.2	21.8	25.5	29.3	33.1
4,004	12.9	16.3	19.8	23.4	27.2	155,670	18.3	21.9	25.6	29.4	33.3
4,297	13.0	16.4	19.9	23.6	27.3	166, 190	18.4	22.0	25.7	29.5	33.4
4,611	13.1	16.5	20.0	23.7	27.4	177,410	18.5	22.1	25.8	29.6	33.5
4,946	13.2	16.6	20.1	23.8	27.5	189,360	18.6	22.2	25.9	29.7	33.6
5,306	13.3	16.7	20.2	23.9	27.6	202,110	18.7	22.3	26.1	29.8	33.7
5,691	13.4	16.8	20.4	24.0	27.7	215,710	18.8	22.5	26.2	29.9	33.8
6,104	13.5	16.9	20.5	24.1	27.9	230,200	18.9	22.6	26.3	30.1	33.9
6,545	13.6	17.0	20.6	24.2	28.0	245,650	19.0	22.7	26.4	30.2	34.0
7,018	13.7	17.1	20.7	24.3	28.1	262,110	19.1	22.8	26.5	30.3	34.1
7,524	13.8	17.2	20.8	24.5	28.2	279,660	19.2	22.9	26.6	30.4	34.2
8,065	13.9	17.4	20.9	24.6	28.3	298,370	19.3	23.0	26.7	30.5	34.3
8,645	14.0	17.5	21.0	24.7	28.4	318,310	19.4	23.1	26.8	30.6	34.5
9,265	14.1	17.6	21.1	24.8	28.6	339,560	19.5	23.2	26.9	30.7	34.6
9,928	14.2	17.7	21.2	24.9	28.7	362,200	19.6	23.3	27.0	30.8	34.7
10,638	14.3	17.8	21.3	25.1	28.8	386,320	19.7	23.4	27.1	30.9	34.8
11,397	14.4	17.9	21.4	25.2	28.9	412,030	19.8	23.5	27.2	31.0	34.9
12,209	14.5	18.0	21.6	25.3	29.0	439,420	19.9	23.6	27.3	31.1	35.0
13,078	14.6	18.1	21.7	25.4	29.1	468,600	20.0	23.7	27.4	31.2	35.1
14,006	14.7	18.2	21.8	25.5	29.2	499,690	20.1	23.8	27.5	31.3	35.2
15,000	14.8	18.3	21.9	25.6	29.3	532,810	20.2	23.9	27.6	31.5	35.3
16,062	14.9	18.4	22.0	25.7	29.5	568,080	20.3	24.0	27.7	31.6	35.4.
17,197	15.0	18.5	22.1	25.8	29.6	605,660	20.4	24.1	27.8	31.7	35.5
18,411	15.1	18.6	22.2	25.9	29.7	645,680	20.5	24.2	28.0	31.8	35.7
19,709	15.2	18.7	22.3	26.0	29.8	688,310	20.6	24.3	28.1	31.9	35.8
21,096	15.3	18.8	22.4	26.1	29.9	733,710	20.7	24.4	28.2	32.0	35.9
22,578	15.4	18.9	22.5	26.2	30.0	782,060	20.8	24.5	28.3	32.1	36.0
24,162	15.5	19.0	22.6	26.3	30.1	833,540	20.9	24.6	28.4	32.2	36.1
25,885	15.6	19.1	22.7	26.4	30.3	888,370	21.0	24.7	28.5	32.3	36.2
27,664	15.7	19.2	22.8	26.6	30.4	946,746	21.1	24.8	28.6	32.4	36.3
29,596	15.8	19.3	23.0	26.7	30.5	1,008,900	21.2	24.9	28.7	32.5	36.4
31,661	15.9	19.4	23.1	26.8	30.6						
33,867	16.0	19.5	23.2	26.9	30.7						
36,222	16.1	19.7	23.3	27.0	30.8						
39,739	16.2	19.8	23.4	27.1	31.0						
41,426	16.3	19.9	23.5	27.2	31.1						
44,296	16.4	20.0	23.6	27.3	31.2						
47,360	16.5	20.1	23.7	27.4	31.3						
50,632	16.6	20.2	23.8	27.6	31.4						
54,126	16.7	20.3	23.9	27.7	31.5						
57,855	16.8	20.4	24.0	27.8	31.6						
61,836	16.9	20.5	24.1	27.9	31.7						
66,086	17.0	20.6	24.2	28.0	31.8						
70,622	17.1	20.7	24.3	28.1	31.9						

NOTE The presence in table B. 1 of high bioburden levels is not intended to imply that such levels are the norm.

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B.3.4.1.2.3 Stage 3: Establish verification dose

To establish the verification dose, use one of the following (as determined in stage 2 above):

— highest batch average, if one or more batch average ≥ overall average bioburden × 2; or

— overall average bioburden, if each of the batch averages < overall average bioburden × 2.

Using table B.1, determine the verification dose based on the average bioburden (overall average bioburden or highest batch average). If the average bioburden is not given in the table, use the closest average bioburden number greater than the actual average bioburden.

NOTE 24 Table B.1 is designed to test for the resistance of the average bioburden of the sample to the sterilization process at a SAL of 10^{-2}. A sample may be the whole product unit or a portion of the product unit (SIP). If a portion of the product is tested, the bioburden for the portion of the sample (SIP bioburden) should be used to determine the verification dose.

B.3.4.1.2.4 Stage 4: Perform verification dose experiment

To perform the experiment, select 100 product unit samples from a single batch of product.

The 100 product units for the performance of stage 4 may be selected from either one of the batches for which a bioburden estimation was obtained in stage 2 or a fourth batch manufactured under conditions which are representative of normal production. The ability of the health care product to support microbial growth should be taken into account in selecting the batch to be used.

Irradiate the samples at the verification dose derived from table B.1 in stage 3 above.

The actual dose may vary from the verification dose by + 10%. If the delivered dose is less than 90% of the calculated verification dose, the test may be repeated.

NOTE 25 Use of the verification dose experiment without bioburden estimation is not valid.

Individually test the irradiated product units (SIPs) for sterility. Sterility test the samples in Soybean Casein Digest Broth, incubated at (30 ± 2)°C for 14 days (in accordance with ISO 11737-2). Record the number of positive sterility tests.

NOTE 26 Other media and incubation conditions may be employed as appropriate (see B.3.2).

Statistical verification is accepted if there are no more than two positive sterility tests from the 100 tests carried out.

NOTE 27 The rationale for allowing two positives is based upon the statistical probability that, when the average bioburden is used to predict the dose at which one of 100 samples is expected to be non-sterile, there is an 0.92 probability that zero, one or two positives may occur (table B.25).

If there are more than two positive sterility tests, and this cannot be ascribed to incorrect performance of the estimation of bioburden, the sterility testing, or the delivery of the verification dose (e.g. the delivered dose was less than 90% of the calculated verification dose), this method of dose setting is not valid and an alternative method involving measurement of the resistance to radiation of contaminating microorganisms as they occur naturally should be used (e.g. Method 2).

B.3.4.1.2.5 Stage 5: Establish sterilization dose

If the verification procedure is passed (that is, statistical verification is accepted), table B.1 is used to obtain the sterilization dose for the product unit by finding the closest bioburden number on the table that is equal to or greater than the average bioburden for the product unit, and then reading off the dose necessary to achieve the desired SAL.

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NOTE 28 The bioburden number used to obtain the sterilization dose is the average bioburden for the entire product unit (SIP = 1.0). If a portion of the product was tested (in stage 2) to determine the bioburden (SIP bioburden), the SIP bioburden should be divided by the SIP to determine the average bioburden for the entire product unit.

B.3.4.1.3 Method 1 audit

The established sterilization dose shall be based either on the most recent dose experiment or on an augmented dose action indicated by previous dose audit (B.3.5.3). To determine the continued validity of a dose, the audit shall be performed every three months in accordance with B.3.5.

B.3.4.2 Method 2: Dose setting using fraction positive information from incremental dosing to determine extrapolation factor

NOTES

29 In the following procedures and examples, notation is lower case when it refers to results derived from product samples of a single batch, and upper case when it refers to a summary of all three batches.

30 Calculations for A kGy, DS kGy, and sterilization dose are not the same for Methods 2A and 2B: therefore close attention should be paid to the use of the correct calculations.

31 Method 2B requires that the entire product unit (SIP = 1.0) be used, while Method 2A may be used for either an entire product unit or a portion of product unit (SIP ≤ 1.0).

B.3.4.2.1 Rationale

With Method 2, information is obtained about the resistance to radiation of microorganisms as they occur on product. The method uses the results of sterility tests conducted on samples of product that have been exposed to a series of incremental doses to estimate the dose at which one in 100 product units is expected to be non-sterile (that is, a SAL of 10^{-2}). The microorganisms surviving exposure to such a dose should have a more homogeneous D_{10} value than the initial bioburden. From the incremental dose experiment, an estimate is made of this D_{10} value, and this estimate is used for extrapolation to SALs below 10^{-2} in order to determine the sterilization dose.

The validity of the calculated sterilization dose generally depends upon the validity of the extrapolation beyond the verification dose. In extensive tests of the experimental protocol employing computer simulation of inactivation of microorganisms on items, the validity of this extrapolation has been established for microbial populations for which distributions of resistance have been measured.

An elaboration on the rationale outlined above, and the results from the computer simulation, are contained in Davis, Strawderman and Whitby (1984).

The following text describes two procedures:

a) Method 2A for products with bioburdens as would be expected from normal manufacturing processes.

b) Method 2B for products with a consistent and very low bioburden.

B.3.4.2.2 Procedure for Method 2A ("normal" product)

For dose setting Method 2A, the four stages below shall be followed.

NOTE 32 Worked examples appear in clause B.4.

B.3.4.2.2.1 Stage 1: Select SAL and obtain samples of product units

Record the sterility assurance level (SAL) to be used. Take random samples of at least 280 product units

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from each of three independent production batches immediately prior to the sterilization phase of production. The conditions for the selection of SIP given in B.3.1.1 shall be met.

NOTE 33 A sample may be the whole product unit or a portion of the product unit (sample item portion [SIP]).

B.3.4.2.2.2 Stage 2: Perform incremental dose experiment

Irradiate 20 product units, or portions thereof, from each of the three batches at one of a series of not less than nine doses, increasing in nominal increments of 2 kGy. The doses shall be delivered independently and may vary at random from the nominal dose by ± 1.0 kGy or ± 10%, whichever is greater. If the delivered dose is less than the stipulated range, the incremental dose may be repeated. Individually monitor each of the doses delivered to product units with dosimeters.

Individually test the irradiated product units, or portions thereof, for sterility using Soybean Casein Digest Broth and incubating at (30 ± 2)°C for 14 days (in accordance with ISO 11737-2). Record the number of positive and negative sterility tests.

NOTE 34 Other media and incubation conditions may be employed as appropriate (see B.3.2).

From this experiment, the following values are obtained.

B.3.4.2.2.2.1 A kGy and First Fraction Positive (FFP) kGy

For each of the three batches, determine the lowest dose from the incremental dose series where at least one of the 20 tests is negative. Designate these doses ffp kGy and find the median value. Determine A kGy by recording its value from table B.2 using the number of positive sterility tests at the median ffp kGy dose.

NOTE 35 A kGy is a proportional part of the preceding dose increment which is subtracted from the median ffp kGy dose to convert it to the dose at which 19 positive sterility tests are expected to occur.

The formula for calculating A kGy (Method 2A) is

(B.1)

$$A\ kGy = (2\ kGy)\ \frac{(\log_{10}(\log_e 20) - \log_{10}[\log_e(20/n)])}{(\log_{10}(\log_e 20) - \log_{10}[\log_e(20/19)])}$$

where n is the number of tests that are negative.

Calculate FFP kGy from (Eq.B.2):

(B.2)

$$FFP\ kGy = median\ ffp\ dose - A\ kGY$$

NOTE 36 FFP kGy is an estimate of the dose at which only one sample of 20 irradiated samples will be sterile.

B.3.4.2.2.2.2 D* kGy

For each of the three batches, determine d* kGy by either

a) finding the lowest dose of two consecutive doses at which all tests are negative, followed by no more than one further positive test in any of the remaining tests in the incremental dose series; or

b) finding the lowest dose at which one positive in 20 tests occurs, immediately preceded and followed by incremental doses at which all tests are negative.

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Additionally, in each of the three incremental dose experiments, there may be no more than one further positive sterility test at incremental doses above d* kGy.

Designate D* kGy as follows:

a) if the highest batch d* kGy exceeds the median batch d* kGy by less than 5 kGy, the median batch d* kGy becomes D* kGy; or,

b) if the highest batch d* kGy exceeds the median batch d* kGy by 5 kGy or more, the highest batch d* kGy becomes D* kGy.

NOTE 37 D* kGy is the initial estimate of the dose required to achieve an SAL of 10^{-2}.

B.3.4.2.2.2.3 CD* batch

Establish the batch for which d* kGy equals D* kGy and designate this as CD* batch. If more than one batch has a d* kGy equal to D* kGy, one of these batches is chosen at random as CD* batch.

B.3.4.2.2.3 Stage 3: Perform verification dose experiment

Irradiate 100 product units, or portions thereof, from CD* batch at a dose of D* kGy. Monitor the dose delivered with dosimeters and designate the delivered dose as DD* kGy. The actual dose may vary from the D* kGy dose by + 1.0 kGy or + 10%, whichever is greater. If the delivered dose is less than 90% of the D* kGy dose, the verification dose experiment may be repeated.

Individually test the irradiated product units, or portions thereof, for sterility using Soybean Casein Digest Broth and incubating at (30 ± 2)°C for 14 days (in accordance with ISO 11737-2). Record the number of positive sterility tests in this experiment.

Table B.2—Values of A kGy for different numbers of positive sterility tests at median ffp kGy (Method 2A)

Number of positive sterility tests at median ffp kGy	A kGy	Number of positive sterility tests at median ffp kGy	A kGy
19	0.00	9	0.79
18	0.13	8	0.87
17	0.22	7	0.95
16	0.31	6	1.05
15	0.38	5	1.15
14	0.45	4	1.28
13	0.52	3	1.43
12	0.58	2	1.65
11	0.65	1	2.00
10	0.72	0	2.00

NOTES

38 Other media and incubation conditions may be employed as appropriate (see B.3.2).

39 This experiment is done to confirm the estimate of the dose at which one of the 100 product units, or portions thereof, is expected to be non-sterile (First No Positives, FNP kGy).

From this experiment, the following values are obtained:

a) DD* kGy, the actual dose delivered;

b) CD*, the number of positive sterility tests;

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c) First No Positives (FNP) kGy:

— if CD* is 2 or less, FNP kGy is equal to DD* kGy,

— if CD* is greater than 2 and less than 10, FNP kGy is equal to DD* + 2.0 kGy,

— if CD* is greater than 9 and less than 16, FNP kGy is equal to DD* + 4.0 kGy,

— if CD* is greater than 15, D* kGy should be redetermined (stage 2).

B.3.4.2.2.4 Stage 4: Establish sterilization dose

From FFP kGy and FNP kGy, determine DS kGy using (Eq.B.3) or (Eq.B.4) depending on the value of the difference between FNP and FFP kGy.

When (FNP-FFP) kGy is less than 10 kGy (Method 2A)

(B.3)

$$DS\ kGy = 2 + 0.2\ (FNP\text{-}FFP)\ kGy$$

NOTE 40 When using (Eq.B.3), if (FNP-FFP) kGy is less than zero, set (FNP-FFP) = 0.

When (FNP-FFP) kGy is 10 kGy or greater (Method 2A)

(B.4)

$$DS\ kGy = 0.4\ (FNP\text{-}FFP)\ kGy$$

Establish D** kGy for Method 2A using (Eq.B.5).

D** kGy formula for Method 2A

(B.5)

$$D^{**}\ kGy = DD^{*}\ kGy = [\log(CD^{*})]\ (DS)\ kGy$$

NOTE 41 If CD* equals zero, set [log (CD*)] = 0.

Calculate the sterilization dose for Method 2A using (Eq.B.6)

Sterilization dose (Method 2A)

(B.6)

$$sterilization\ dose = D^{**}\ kGy + [-\log(SAL) - \log(SIP) - 2]\ (DS)\ kGy$$

where

D** kGy is the estimate of the dose that will provide a 10^{-2} SAL for the test samples;

SAL is the preselected sterility assurance level for the product;

SIP is the portion of product unit (sample item portion) used for determining D** kGy and DS kGy;

DS kGy is an estimate of the dose required to inactivate 90% of the organisms surviving D** kGy.

NOTES

42 Dose calculations should be made with data that are reported to one place of decimals. The sterilization dose may be rounded (using standard rounding procedures) to one place of decimals.

43 The term log(SIP) in Eq.B.6 provides the appropriate correction factor if the entire product unit is not sterility-tested.

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B.3.4.2.3 Method 2A audit

The sterilization dose shall be based either on the most recent dose experiment carried out to establish sterilization dose or on an augmented dose indicated by a dose audit.

To determine the continued validity of the sterilization dose, a dose audit shall be performed in accordance with section B.3.5.

B.3.4.2.4 Procedure for Method 2B (product with consistent and very low bioburden)

For the use of Method 2B to be valid, three requirements shall be satisfied:

a) The whole product unit is utilized (SIP = 1.0).

b) The number of sterility test positives after irradiation with any of the incremental doses does not exceed 14 out of 20 in any production batch.

c) FNP kGy does not exceed 5.5 kGy.

For dose setting Method 2B, the four stages below shall be followed.

NOTE 44 Worked examples appear in clause B.4.

B.3.4.2.4.1 Stage 1: Select SAL and obtain samples of product units

Record the sterility assurance level (SAL) to be used. Take random samples of at least 260 product units from each of three independent production batches immediately prior to the sterilization phase of production.

For Method 2B, the whole product unit (SIP = 1.0) is used for bioburden and sterility test purposes. If the whole product unit (SIP = 1.0) cannot be placed into a single test container, multiple test containers may be used and scored as a single sample.

B.3.4.2.4.2 Stage 2: Perform incremental dose experiment

Irradiate 20 product units from each of the three batches at one of a series of not less than eight doses, increasing in nominal increments of 1 kGy. The doses shall be delivered independently and may vary at random from the nominal dose by ± 0.5 kGy or + 10%, whichever is greater, with the exception that at 1.0 kGy the dose may vary by only ± 0.2 kGy. If the delivered dose is less than the stipulated range, the incremental dose may be repeated. Individually monitor each of the doses delivered to product units with dosimeters.

Individually test the irradiated product units for sterility using Soybean Casein Digest Broth and incubating at (30 ± 2)°C for 14 days (in accordance with ISO 11737-2). Record the number of positive and negative sterility tests.

NOTE 45 Other media and incubation conditions may be employed as appropriate (see B.3.2).

For Method 2B, the number of sterility test positives after irradiation with any dose should not exceed 14 out of 20 in any production batch. If more than 14 positives are observed, then another dose setting method should be used (e.g. Method 2A). From this experiment, the following values are obtained.

B.3.4.2.4.2.1 A kGy and First Fraction Positive (FFP) kGy

From the incremental dose series for each of the three batches, identify the lowest doses where at least one of the 20 tests is negative, designate these doses ffp kGy, and find the median value. Determine A kGy by reading its value from table B.3 from the number of positive sterility tests at the median ffp kGy.

NOTE 46 A kGy is a proportional part of the preceding dose increment which is subtracted from the median

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dose to convert it to the dose at which 19 positive sterility tests are expected to occur.

The formula for calculating A kGy (Method 2B) is

(B.7)

$$A\ kGy = (2\ kGy)\ \frac{(\log_{10}(\log_e 20) = \log_{10}[\log_e(20/n)])}{(\log_{10}(\log_e 20) = \log_{10}[\log_e(20/19)])}$$

where *n* is the number of tests that are negative.

Calculate FFP kGy (Method 2B) from (Eq.B.8)

(B.8)

$$FFP\ kGy = medium\ ffp\ dose - A\ kGy$$

NOTE 47 FFP kGy is an estimate of the dose at which only one sample of 20 irradiated samples will be sterile.

B.3.4.2.4.2.2 D* kGy

For each of the three batches, determine d* kGy by either

a) finding the lowest dose of two consecutive doses at which all tests are negative, followed by no more than one further positive test in any of the remaining tests in the incremental dose series; or

b) finding the lowest dose at which one positive in 20 tests occurs, immediately preceded and followed by incremental doses at which all tests are negative.

Additionally, in each of the three incremental dose experiments, there may be no more than one further positive sterility test at incremental doses above d* kGy.

Designate D* kGy as follows:

a) if the highest batch d* kGy exceeds the median batch d* kGy by less than 5 kGy, the median batch d* kGy becomes D* kGy;

b) if the highest batch d* kGy exceeds the median batch d* kGy by 5 kGy or more, the highest batch d* kGy becomes D* kGy.

NOTE 48 d* kGy is the initial estimate of the dose required to achieve a SAL of 10^{-2}.

B.3.4.2.4.2.3 CD* batch

Establish the batch for which d* kGy equals D* kGy and designate this as CD* batch. If more than one batch has a d* kGy equal to D* kGy, one of these batches is chosen at random as CD* batch.

B.3.4.2.4.3 Stage 3: Perform verification dose experiment

Irradiate 100 product units from CD* batch at a dose of D* kGy. Monitor the dose delivered with dosimeters and designate the delivered dose as DD* kGy. The actual dose may vary from the D* kGy dose by + 1,0 kGy or + 10%, whichever is greater. If the delivered dose is less than 90% of the D* kGy dose, the verification dose experiment may be repeated.

Individually test the irradiated product units for sterility using Soybean Casein Digest Broth and incubating at (30 ± 2)°C for 14 days (in accordance with ISO 11737-2). Record the number of positive sterility tests in this experiment.

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Table B.3—Values of A kGy for different numbers of positive sterility tests at median ffp kGy (Method 2B)

Number of positive sterility tests at median ffp kGy	A kGy	Number of positive sterility tests at median ffp kGy	A kGy
14	0.22	6	0.52
13	0.26	5	0.58
12	0.29	4	0.64
11	0.32	3	0.72
10	0.36	2	0.82
9	0.40	1	1.00
8	0.44	0	1.00
7	0.48		

NOTES

49 Other media and incubation conditions may be employed as appropriate (see B.3.2).

50 This experiment is done to confirm the estimate of the dose at which one of the 100 product units is expected to be non-sterile (First No Positives, FNP kGy).

From this experiment, the following values are obtained:

a) DD* kGy, the actual dose delivered;

b) CD*, the number of positive sterility tests;

c) First No Positives (FNP) kGy (For Method 2B, FNP may not exceed 5.5 kGy. If FNP exceeds 5.5 kGy, then another dose setting method should be used (e.g. Method 2A):

— if CD* is 2 or less, FNP kGy is equal to DD* kGy,

— if CD* is greater than 2 and less than 10, FNP kGy is equal to DD* + 2.0 kGy,

— if CD* is greater than 9 and less than 16, FNP kGy is equal to DD* + 4.0 kGy,

— if CD* is greater than 15, D* kGy should be redetermined (stage 2).

B.3.4.2.4.4 Stage 4: Establish sterilization dose

From FFP kGy and FNP kGy, determine DS kGy (Method 2B) using (Eq.B.9).

(B.9)

$$DS\ kGy = 1.6 + 0.2\ (FNP\text{-}FFP)\ kGy$$

NOTE 51 When using (Eq.B.9), if (FNP-FFP) kGy is less than zero, set (FNP-FFP) = 0.

Establish D** kGy for Method 2B using (Eq.B.10).

Formula for D** kGy Method 2B (same as equation B.5):

(B.10)

$$D^{**}\ kGy = DD^{*}\ kGy = [\log(CD^{*})]\ (DS)\ kGy$$

NOTE 52 If CD* equals zero, set [log(CD*)] = 0.

Calculate the sterilization dose for Method 2B using (Eq.B.11).

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(B.11)

$$sterilization\ dose = D^{**}\ kGy + [-\log(SAL) - 2]\ (DS)\ kGy$$

where

D** kGy is the estimate of the dose that will provide a 10^{-2} SAL for the test samples;

SAL is the preselected sterility assurance level for the product;

DS kGy is an estimate of the dose required to inactivate 90% of the organisms surviving the 10^{-2} verification dose (D** kGy).

NOTE 53 Dose calculations should be made with data that are reported to one place of decimals. The sterilization dose may be rounded (using standard rounding procedures) to one place of decimals.

B.3.4.2.5 Method 2B audit

The sterilization dose shall be based either on the most recent experiment carried out to establish sterilization dose or on an augmented dose indicated by dose audit (B.3.5.3). To determine the continued validity of the sterilization dose, a dose audit shall be performed in accordance with B.3.5.

B.3.5 Sterilization dose auditing

B.3.5.1 Purpose and frequency

Once the sterilization dose has been established, periodic audit is required to reaffirm the sterilization dose. For products in regular production, audit is performed at three month intervals to detect changes in the bioburden that could require an increase in the sterilization dose.

Auditing is achieved by irradiation of 100 product units, or portions thereof, at the dose used to establish the 10^{-2} SAL (the verification dose, or D** kGy), testing each irradiated product individually for sterility and determining the number of positive sterility tests. Based upon the results of auditing, the sterilization dose is accepted, augmented or reestablished.

B.3.5.2 Procedure

Audits shall be conducted as follows.

a) A random sample of 110 product units is taken from a randomly selected production batch immediately prior to the sterilization phase of production.

b) Utilizing the same SIP and bioburden test methods as used in the original dose setting experiment, determine the bioburden on each of 10 product units or portions of product unit.

c) Again utilizing the same SIP, irradiate the remaining 100 product units or portions thereof at the verification dose (for Method 2, D** kGy) found in the original dose setting experiment.

If the verification dose has been augmented during a previous audit, the augmented verification dose should be used.

The actual dose may vary from the verification dose (for Method 2, D** kGy) by + 10%. If the delivered dose is less than 90% of the calculated verification dose, the test may be repeated.

d) Perform sterility testing using the media and incubation conditions employed in the original dose setting experiment.

B.3.5.3 Interpretation and action

A review of environmental and manufacturing controls, together with estimates of bioburden, should be

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conducted in conjunction with audit results. If the review indicates lack of control, appropriate action should be taken.

a) If two or fewer positives are obtained, the original sterilization dose is acceptable. No action required.

b) If three or four positives are obtained, the original sterilization dose might not be acceptable. Therefore, the sterilization dose shall be augmented immediately. (Refer to B.3.5.4.1 or B.3.5.4.2 as appropriate.)

Thereafter, a retest at the original verification dose may be performed to determine if augmentation of the sterilization dose must continue.

1) If, on retest, two or fewer positives are obtained, and the review of environmental and manufacturing controls, and product unit bioburden indicates no values outside established specifications, use of the original sterilization dose may be resumed.

2) If, on retest, three to four positives are obtained, follow audit actions prescribed for five to six positives [B.3.5.3c)].

3) If, on retest, five or more positives are obtained, follow audit actions prescribed for seven or more positives [B.3.5.3d)].

If augmentation of the sterilization dose was continued, the next quarterly audit shall be conducted using a revised verification dose. If augmentation of the sterilization dose was not continued, the next quarterly audit shall be conducted using the original verification dose.

A repeat of the sterilization dose audit is not permitted unless there is documented evidence that the audit was compromised by an unacceptable procedure or low dosing (e.g. the delivered dose was less than 90% of the verification dose).

c) If five or six positives are obtained, the original sterilization dose is not adequate. Therefore, the sterilization dose shall be augmented immediately (refer to B.3.5.4.1 or B.3.5.4.2 as appropriate) and a retest is not allowed. The sterilization dose shall be reestablished.

The next quarterly audit shall be performed utilizing the revised verification dose or, when the sterilization dose has been reestablished, the new verification dose.

A repeat of the sterilization dose audit is not permitted unless there is documented evidence that the audit was compromised by an unacceptable procedure or low dosing (e.g. the delivered dose was less than 90% of the verification dose).

d) If seven or more positives are obtained and there has been no significant increase in the bioburden estimate, the radiation resistance of the bioburden has probably changed by an amount which invalidates the use of the assumed resistance. In these circumstances, the sterilization dose cannot be augmented and shall be reestablished.

A repeat of the sterilization dose audit is not permitted unless there is documented evidence that the audit was compromised by an unacceptable procedure or low dosing (e.g. the delivered dose was less than 90% of the verification dose).

B.3.5.4 Dose augmentation

B.3.5.4.1 Method 1

Revision of the verification dose and augmentation of the sterilization dose are carried out as follows.

a) If during the audit procedure either

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1) three or four positives occur, or

2) five or six positives occur and the bioburden shows an increase,

change the verification and sterilization doses to the greater values derived from the following:

— utilizing the average bioburden estimate obtained on audit, determine new verification and sterilization doses from table B.1.

— multiplying the average bioburden estimated when establishing the original sterilization dose by a factor of 10 and utilizing this revised estimate of bioburden, obtain new verification and sterilization doses from table B.1.

b) If five or six positives occur during the audit and the bioburden estimates show no increase, the radiation resistance may have changed by an amount which invalidates the use of the assumed resistance; in these circumstances the sterilization dose cannot be augmented. Sterilization at the original sterilization dose shall not be allowed and the sterilization dose shall be reestablished.

B.3.5.4.2 Method 2 dose augmentation

Revision of the verification dose and augmentation of the sterilization dose are carried out as follows:

a) If during the audit procedure either

1) three or four positives occur, or

2) five or six positives occur and the bioburden shows an increase,

calculate the revision of the verification dose and augmentation of the sterilization dose using the following equations:

Revision of verification dose for Methods 2A and 2B

(B.12)

$$D{**}\ kGy = DD{*}\ kGy + [\log(CD{*})]\ (DS)\ kGy$$

where

CD* is the number of positive sterility tests from exposure to the audit dose, and DS kGy is calculated using (Eq.B.3), (Eq.B.4), or (Eq.B.9) as appropriate.

NOTE 54 FNP kGy is based on the audit CD*. FFP kGy is from the original dose setting experiment.

Augmented sterilization dose formula for Method 2A

(B.13)

$$\text{sterilization dose} = D{**}\ kGy + (-\log(SAL) - \log(SIP) - 2)\ (DS)\ kGy$$

Augmented sterilization dose formula for Method 2B

(B.14)

$$\text{sterilization dose} = D{**}\ kGy + [-\log(SAL) - 2]\ (DS)\ kGy$$

b) If five or six positives occur during the audit and the bioburden estimates show no increase, the radiation resistance may have changed by an amount which invalidates the use of the assumed resistance. Therefore, a revised verification dose or an augmented sterilization dose cannot be calculated. Sterilization at the original sterilization dose shall not be allowed and the sterilization dose shall be

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reestablished.

B.3.5.5 Biological indicators and sterility testing

The use of biological indicators (BI's) for validation and process monitoring, or the use of sterility testing for release of product, are not recommended practice for radiation sterilization.

There are many organisms that have been found to have a higher resistance to radiation than the typical biological indicator of spores of *Bacillus pumilus*. These organisms can naturally have a higher resistance to radiation, or when irradiated under certain circumstances (for example, anaerobic conditions, encapsulation) can become more resistant to radiation. A listing of the resistances of many organisms can be found in Block (1983). In addition, industrial experience has indicated that the radiation resistance of products with naturally occurring bioburden exceeds the resistance of the spores of *Bacillus pumilus* in many instances. Therefore, unless the resistance of the product is proven to be less than the resistance of the BI's, the use of BI's is not recommended for validation or process monitoring.

It is not feasible to use sterility testing of product to substantiate a sterility assurance level (SAL) of less than 10^{-2} (i.e. 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6}) because of the high number of test samples that would be required to substantiate the SAL. For example, in order to prove an SAL of 10^{-6}, one million items would need to be sterility tested after exposure to the sterilization process. This is impractical since typically the sterility test false positive level that can be achieved is 1/1000 or 0.1%. Therefore, the use of product sterility testing is not recommended for process monitoring/release of product.

B.4 Worked examples

B.4.1 Method 1 examples

Two worked examples are given for Method 1. The first is for a product unit that was too large to be tested easily, so a portion of the product (SIP < 1) was used, and with an end use requiring a sterility assurance level of 10^{-6}. The second is for a product unit that could be tested for resistance group verification using the whole unit (SIP = 1), and with an end use requiring a sterility assurance level of 10^{-3}. This second example continues through the audit and augmentation of sterilization dose (table B.6).

Method 1 audit

The audit procedure for Method 1 is the same regardless of whether an SIP of 1, or an SIP less than 1 is used. The following example is a continuation of the table B.5 example, where a sterilization dose was determined for a product unit with an end use requiring an SAL of 10^{-3} and, during stage 2 of that original validation, an average bioburden of 382 was observed; during stage 3, a verification dose of 9.7 kGy was established; and in stage 5, a sterilization dose of 12.9 kGy was established. Table B.6 is an example of the first quarterly audit after the sterilization dose was established.

B.4.2 Method 2 examples

Two worked examples are given for Method 2A, one for a product unit that could be tested using the whole unit (SIP = 1), and a second for a product unit that had to be tested using a portion of product (SIP < 1). One worked example is given for Method 2B, which has as one of its requirements that the whole product unit be used. An example of the audit and augmentation of sterilization dose is also provided for Method 2 in table B.22.

NOTE 55 In the following examples, notation is lower case when it refers to results derived from product samples of a single batch, and upper case when it refers to a summary of all three batches.

B.4.2.1 Worked example for Method 2A (SIP = 1)

B.4.2.1.1 Stage 1: Select SAL and obtain samples of product units

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The product unit end use required an SAL of 10^{-6}. The whole product unit was able to be used for sterility testing (SIP = 1), and 280 random samples were chosen from each of three batches.

Table B.4—Determination of sterilization dose (Method 1, SIP < 1)

Term	Value	Comment
Stage 1		
SAL	10^{-6}	For the example, the product unit end use required an SAL of 10^{-6}
SIP	0.05	As the product unit was too large to be sterility tested easily, a 1/20 portion was selected for resistance group verification
Stage 2		
SIP bioburden	59	SIP bioburden results of 50, 62 and 65 were observed from the three batches tested, for an average SIP bioburden of 59. None of the individual SIP bioburden results was twice the average bioburden of 59, therefore 59 was used to establish the verification dose.
Average bioburden	1180	The bioburden for the product units was calculated as follows: 50/0.05 = 1000 62/0.05 = 1240 65/0.05 = 1300 The average bioburden is therefore 1180. None of the individual batch bioburden results was twice the average bioburden of 1180, therefore if the verification test results are acceptable, the average bioburden of 1180 will be used to establish the sterilization dose.
Stage 3		
Verification dose	7.3 kGy	The verification dose for an SIP bioburden of 59 is found in table B.1 (As a bioburden of 59 is not listed in the table, the next larger bioburden of 59.2 is used.)
Stage 4		
Sterility results	2 positives at 6.8 kGy	The actual dose was within the specified dose range (i.e. less than 8.0 kGy) and the sterility test results were acceptable (i.e.≤ 2 positives); therefore, verification is accepted.
Stage 5		
Sterilization dose for 10^{-6} SAL	25.2 kGy	The 10-6 SAL sterilization dose for an average product bioburden of 1180 is 25.2 kGy, from table B.1 (As a bioburden of 1180 is not listed in the table, the next larger bioburden of 1182 is used.)

The allocation of product units within the incremental dose experiment is shown in table B.7.

B.4.2.1.2 Stage 2: Perform incremental dose experiment

Table B.8 provides an example of data from an incremental dose series, and table B.9 shows the calculations.

B.4.2.1.3 Stage 3: Perform verification dose experiment

Table B.10 shows the values that were derived from the stage 3 experiment.

B.4.2.1.4 Stage 4: Establish sterilization dose

The calculations to establish the sterilization dose appear in table B.11.

B.4.2.2 Worked example for Method 2A (SIP < 1)

B.4.2.2.1 Stage 1: Select SAL and obtain samples of product units

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The product unit end use requires an SAL of 10^{-3}. The product unit was too large to be tested easily, so a portion of the product (SIP < 1) was used, and 300 random samples were chosen from each of three batches.

The allocation of product units within the incremental dose experiment is shown in table B.12.

Table B.5—Determination of sterilization dose (Method 1, SIP = 1)

Term	Value	Comment
Stage 1		
SAL	10^{-3}	For the example, the product unit end use required an SAL of 10^{-3}.
SIP	1.00	The entire product unit was used for resistance group verification.
Stage 2		
SIP bioburden	382	SIP bioburden results of 360, 402 and 384 were observed from the three batches tested, for an average SIP bioburden of 382. None of the individual SIP bioburden results was twice the average bioburden of 382, therefore 382 was used to establish the verification dose.
Average bioburden .	382	The entire SIP was used (SIP = 1.00), therefore no further calculations are required to determine the average bioburden for the product unit. None of the individual batch bioburden results was twice the average bioburden of 382, therefore the average bioburden of 382 will be used to establish the sterilization dose.
Stage 3		
Verification dose	9.7 kGy	The verification dose for an SIP bioburden of 382 is found in table B.1. (As a bioburden of 382 is not listed in the table, the next larger bioburden of 388 is used.)
Stage 4		
Sterility results	1 positive at 10.1 kGy	The actual dose was within the specified dose range (i.e. less than 10.7 kGy) and the sterility test results were acceptable (i.e. ≤ 2 positives); therefore, verification is accepted.
Stage 5		
Sterilization dose for 10^{-3} SAL	12.9 kGy	The 10^{-3} SAL sterilization dose for an average product bioburden of 382 is 12.9 kGy, from table B. 1. (As a bioburden of 382 is not listed in the table, the next larger bioburden of 388 is used.)

B.4.2.2.2 Stage 2: Perform incremental dose experiment

Table B.13 provides an example of data from an incremental dose series, and table B.14 shows the calculations.

B.4.2.2.3 Stage 3: Perform verification dose experiment

Table B.15 shows the values that were derived from the stage 3 experiment.

B.4.2.2.4 Stage 4: Establish sterilization dose

The calculations to establish the sterilization dose appear in table B.16.

B.4.2.3 Worked example for Method 2B

B.4.2.3.1 Stage 1: Select SAL and obtain samples of product units

The product unit end use required an SAL of 10^{-6}. The whole product unit was used. During stage 1,260 random samples were chosen from each of three batches.

The allocation of product units within the incremental dose experiment is shown in table B.17.

B.4.2.3.2 Stage 2: Perform incremental dose experiment

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Table B.18 provides an example of data from an incremental dose series, and table B.19 shows the calculations.

B.4.2.3.3 Stage 3: Perform verification dose experiment

Table B.20 shows the values that were derived from the stage 3 experiment.

B.4.2.3.4 Stage 4: Establish sterilization dose

The calculations to establish the sterilization dose appear in table B.21.

Table B.6—Revision of verification dose and augmentation of sterilization dose (Method 1)

Term	Value	Comment
A quarterly audit was performed and four positives were observed after exposure to a dose of 9.5 kGy: therefore the revision of the verification and augmentation of the sterilization doses needs to be determined. (Note that the audit dose was within ± 1.0 kGy of the stage 3 verification dose.)		
SAL	10^{-3}	For the example, the product unit end use requires an SAL of 10^{-3}.
Average bioburden	652	The average bioburden for the product units tested during the quarterly audit was 652 (SIP = 1.0).
Original average bioburden	382	The average bioburden for the product units tested during the original validation was 382 (SIP = 1.0).
Revised verification dose	12.9 kGy	As the average bioburden observed during the quarterly audit was less than one logarithm greater than the average bioburden obtained during validation, the bioburden used for revision is one logarithm greater than the average bioburden obtained during validation. Therefore, the revised dose based upon a bioburden of 3820, and from table B.1, is 12.9 kGy. (As a bioburden of 3820 is not listed in the table, the next larger bioburden of 4004 is used.)
Augmented sterilization dose	16.3 kGy	As the audit average bioburden was less than one logarithm greater than the average bioburden obtained during validation, the bioburden used for augmentation is one logarithm greater than the average bioburden obtained during validation. The augmented dose is based upon a bioburden of 3820, and from table B. 1, is 16.3 kGy. (As a bioburden of 3820 is not listed in the table, the next larger bioburden of 4004 is used.)

Table B.7—Number of samples for evaluations at various incremental kGy doses (Method 2A, stage I [SIP = 1])

	Incremental doses kGy									Hold samples for stage 3 experiment	Total samples required
	2	4	6	8	10	12	14	16	18		
Batch 1	20	20	20	20	20	20	20	20	20	100	280
Batch 2	20	20	20	20	20	20	20	20	20	100	280
Batch 3	20	20	20	20	20	20	20	20	20	100	280

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Table B.8—Example of data from incremental radiation dose sterility test series (number of positive tests from 20 devices). (Method 2A, stage 2 [SIP = 1])

	Target DOSE (kGy)	2	4	6	8	10	12	14	16	18
Batch 1	Delivered dose (kGy)	2.2	5.0	5.3	9.0	9.2	11.6	15.0	16.2	19.3
	Number positive	20	5	2	0	0	0	0	0	0
Batch 2	Delivered dose (kGy)	2.6	3.2	6.6	8.0	9.7	13.0	13.8	15.8	17.9
	Number positive	11	7	0	0	1	0	0	0	0
Batch 3	Delivered dose (kGy)	2.3	4.2	5.9	7.5	10.7	11.4	13.7	17.5	17.1
	Number positive	18	7	2	2	0	0	0	0	0

NOTE Doses were delivered independently and are less than +1.0 kGy or +10% of the target dose, whichever is greater.

Table B.9—Stage 2 calculations (Method 2A, SIP = 1)

Term	Value	Comment
Batch 1 ffp Batch 2 ffp Batch 3 ffp	5.0 kGy 2.6 kGy 2.3 kGy	A batch ffp is the first incremental dose where at least one of the 20 product units is sterile (i.e. test is negative).
A	0.65 kGy	Find the minimum number of positive sterility tests at the median ffp dose and use Table B.2 to determine A kGy. For the example, the number of positives at median ffp (2.6 kGy) was 11; so A is 0.65 kGy.
FFP	1.95 kGy	FFP kGy is the median of the three batch ffp's minus A kGy. For the example, FFP = 2.6 kGy - 0.65 kGy = 1.95 kGy.
Batch 1 d* Batch 2 d* Batch 3 d*	9.0 kGy 6.6 kGy 10.7 kGy	The 10^{-2} SAL estimate, or d* kGy for a batch is the minimum dose of a) or b), where a) is the minimum of the first incremental dose where two consecutive 0/20 positives occur, followed by a total number of positives less than 2; b) is the first incremental dose at which 1/20 positives occur, immediately preceded and followed by 0/20 positives, followed by a total number of positives less than 2.
D*	9.0 kGy	D* kGy is the median of the three batch d*'s, except when any batch has a d* which exceeds the median d* by 5.0 kGy or more. If the exception is observed, D* kGy is taken to be the maximum of the batch d*'s.
CD* batch	Batch 1	The CD* batch is the batch which has d* equal to D*. If more than one d* is equal to D*, choose one at random as the CD* batch.

Table B.10—Stage 3 calculations (Method 2A, SIP = 1)

Term	Value	Comment
D*	9.0 kGy	From stage 2 experiment.
DD*	8.0 kGy	DD* kGy is the actual dose delivered in the stage 3 experiment. The DD* dose is acceptable if it is less than + 1.0 kGy or + 10% of D* kGy, whichever is greater.
CD*	2	CD* is the number of positive sterility tests of 100 observed in the stage 3 experiment.
FNP	8.0 kGy	If CD* is 2 positives or less, FNP is equal to DD* kGy. If CD* is greater than 2 and less than 10 positives, FNP is equal to DD* + 2.0 kGy. If CD* is greater than 9 and less than 16 positives, FNP is equal to DD* + 4.0 kGy. If CD* is greater than 15 positives, D* should be redetermined.

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Table B.11—Stage 4 calculations (Method 2A, SIP = 1)

Term	Value	Comment
CD*	2	From stage 3 experiment.
DD*	8.0 kGy	From stage 3 experiment.
FNP	8.0 kGy	From stage 3 experiment.
FFP	1.95 kGy	From stage 2 experiment.
FNP-FFP	6.05 kGy	For the example, FNP-FFP = 8.0 kGy - 1.95 kGy = 6.05 kGy NOTE — If FNP-FFP is less than zero, set (FNP-FFP) = 0.
DS	3.21 kGy	When FNP-FFP is less than 10, DS = 2 kGy + 0.2 (FNP-FFP) kGy. When FNP-FFP is 10 or greater, DS = 0.4 (FNP-FFP) kGy. For the example, DS kGy = 2 kGy + 0.2 (6.05) kGy = 3.21 kGy
Verification dose (D**)	9.0 kGy	D** kGy = DD* kGy + [log(CD*)](DS)kGy NOTE — If CD* equals zero, set [log (CD*)] = 0. For the example: D** = 8.0 kGy + [log(2)] x (3.21) kGy = 8.0 kGy + (0.3010)(3.21) kGy = 8.97 kGy = 9.0 kGy
SAL	10^{-6}	From stage 1 decision.
SIP	1.0	From stage 1 decision.
Sterilization dose for 10^{-6} SAL	21.8 kGy	Sterilization dose = D** kGy + [-log(SAL) -log(SIP) -2](DS) kGy For the example: Sterilization dose = 9.0 kGy + (6 - 0 - 2) x (3.21) kGy = 9.0 kGy + (4)x(3.21) kGy = 21.84 kGy = 21.8 kGy

Table B.12—Number of samples for evaluations at various incremental kGy doses (Method 2A, stage I [SIP < 1])

	Incremental doses kGy										Hold samples for stage 3 experiment	Total sample required
	0	2	4	6	8	10	12	14	16	18		
Batch 1	20	20	20	20	20	20	20	20	20	20	100	300
Batch 2	20	20	20	20	20	20	20	20	20	20	100	300
Batch 3	20	20	20	20	20	20	20	20	20	20	100	300

Table B.13—Example of data from incremental radiation dose sterility test series (number of positive tests from 20 devices) (Method 2A, stage 2 [SIP < 1])

	Target DOSE (kGy)	0	2	4	6	8	10	12	14	16	18
Batch 1	Delivered dose (kGy)	0.0	1.8	3.7	6.3	7.8	10.9	12.8	14.2	15.2	18.0
	Number positive	20	17	1	0	0	0	0	0	0	0
Batch 2	Delivered dose (kGy)	0.0	1.5	3.9	5.7	8.5	9.9	11.3	14.5	17.3	18.4
	Number positive	20	20	3	0	0	0	0	0	0	0
Batch 3	Delivered dose (kGy)	0.0	2.5	3.5	6.1	7.3	10.2	12.4	12.7	14.8	17.7
	Number positive	20	9	4	0	0	0	0	0	0	0

NOTES
1 When non-irradiated SIP samples (target dose = 0 kGy) were sterility tested, at least 17 positives were observed for each batch.
2 Doses were delivered independently and are less than + 1.0 kGy or + 10%, whichever is greater, of the target dose.

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Table B.14—Stage 2 calculations (Method 2A, SIP < 1)

Term	Value	Comment
Batch 1 ffp Batch 2 ffp Batch 3 ffp	1.8 kGy 3.9 kGy 2.5 kGy	A batch ffp is the first incremental dose where at least one of the 20 product units is sterile (i.e. test is negative).
A	0.79 kGy	Find the minimum number of positive sterility tests at the median ffp dose and use table B.2 to determine A kGy. For the example, the number of positives at median ffp (2.5 kGy) was 9; hence, A is 0.79 kGy.
FFP	1.71 kGy	FFP kGy is the median of the three batch ffp's minus A kGy. For the example, FFP = 2.5 kGy - 0.79 kGy = 1.71 kGy.
Batch 1 d* Batch 2 d* Batch 3 d*	6.3 kGy 5.7 kGy 6.1 kGy	The 10^{-2} SAL estimate, or d* kGy for a batch is the minimum dose of a) or b), where a) is the minimum of the first incremental dose where two consecutive 0/20 positives occur, followed by a total number of positives less than 2, b) is the first incremental dose at which 1/20 positives occur, immediately preceded and followed by 0/20 positives, followed by a total number of positives less than 2.
D*	6, 1 kGy	D* kGy is the median of the three batch d*'s, except when any batch has a d* which exceeds the median d* by 5.0 kGy or more. If the exception is observed, D* kGy is taken to be the maximum of the batch d*'s.
CD* batch	Batch 3	The CD* batch is the batch which has d* equal to D*. If more than one d* is equal to D*, choose one of these batches at random as the CD* batch.

Table B.15—Stage 3 calculations (Method 2A, SIP < 1)

Term	Value	Comment
D*	6.1 kGy	From stage 2 experiment.
DD*	5.5 kGy	DD* kGy is the actual dose delivered in the stage 3 experiment. The DD* dose is acceptable if it was less than + 1.0 kGy or + 10% of D* kGy, whichever is greater.
CD*	2	CD* is the number of positive sterility tests of 100 observed in the stage 3 experiment.
FNP	5.5 kGy	If CD* is two positives or less, FNP is equal to DD* kGy. If CD* is greater than 2 and less than 10 positives, FNP is equal to DD* + 2.0 kGy. If CD* is greater than 9 and less than 16 positives, FNP is equal to DD* + 4.0 kGy. If CD* is greater than 15 positives, D* should be redetermined.

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Table B.16—Stage 4 calculations (Method 2A, SIP < 1)

Term	Value	Comment
CD*	2	From stage 3 experiment.
DD*	5.5 kGy	From stage 3 experiment.
FNP	5.5 kGy	From stage 3 experiment.
FFP	1.71 kGy	From stage 2 experiment.
FNP-FFP	3.79 kGy	For the example, FNP-FFP = 5.5 kGy - 1.71 kGy = 3.79 kGy NOTE — If FNP-FFP is less than zero, set (FNP-FFP) = 0.
DS	2.76 kGy	When FNP-FFP is less than 10, DS = 2 kGy + 0.2 (FNP-FFP) kGy. When FNP-FFP is 10 or greater, DS = 0.4 (FNP-FFP) kGy. For the example, DS kGy = 2 kGy + 0.2(3.79) kGy = 2.76 kGy
Verification dose (D**)	6.3 kGy	D** kGy = DD* kGy + [log(CD*)](DS)kGy NOTE — If CD* equals zero, set [log (CD*)] = 0. For the example: D** = 5.5 kGy + [log(2)] × (2.76) kGy = 5.5 kGy + (0.3010)(2.76) kGy = 6.33 kGy = 6.3 kGy
SAL	10^{-3}	From stage 1 decision.
SIP	0.05	From stage 1 decision.
Sterilization dose for 10^{-3} SAL	12.7 kGy	Sterilization dose = D** kGy + [-log(SAL) -log(SIP) -2](DS)kGy For the example: Sterilization dose = 6.3 kGy + (3 + 1.301 - 2) × (2.76) kGy = 6.3 kGy + (2,301) × (2.76) kGy = 12.65 kGy = 12.7 kGy

Table B.17—Number of samples for evaluations at various incremental kGy doses (Method 2B, stage 1)

	Incremental doses kGy								Hold samples for stage 3 experiment	Total samples required
	1	2	3	4	5	6	7	8		
Batch 1	20	20	20	20	20	20	20	20	100	260
Batch 2	20	20	20	20	20	20	20	20	100	260
Batch 3	20	20	20	20	20	20	20	20	100	260

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Table B.18—Example of incremental radiation dose sterility test series (number of positive tests from 20 devices). (Method 2B, stage 2])

	Target DOSE (kGy)	1	2	3	4	5	6	7	8
Batch 1	Delivered dose (kGy)	1.1	2.4	3.3	4.4	4.6	6.4	73	7.8
	Number positive	13	2	0	0	0	0	0	0
Batch 2	Delivered dose (kGy)	1.1	1.5	2.6	3.8	5.2	5.9	7.2	8.3
	Number positive	8	7	1	0	0	0	0	0
Batch 3	Delivered dose (kGy)	1.0	2.2	2.6	3.7	5.2	6.1	7.7	8.8
	Number positive	12	4	0	1	0	0	0	0

NOTES
1 Doses were delivered independently and are within ± 0.5 kGy or ± 10% of the target dose, whichever is greater; the first incremental dose needs to be 1 kGy ±0.2 kGy.
2 None of the incremental dose sterility tests exceeded 14 positives out of 20 tested.

Table B.19—Stage 2 calculations (Method 2)

Term	Value	Comment
Batch 1 ffp Batch 2 ffp Batch 3 ffp	1.1 kGy 1.1 kGy 1.0 kGy	A batch ffp is the first incremental dose where at least one of the 20 product unit samples is sterile (i.e. test is negative).
A	0.44 kGy	Find the minimum number of positive sterility tests at the median ffp dose and use table B.3 to determine A kGy. For the example, the minimum number of positives at median ffp (1.1 kGy) was 8; hence, A is 0.44 kGy.
FFP	0.66 kGy	FFP kGy is the median of the three batch ffp's minus A kGy. For the example, FFP = 1.10 kGy - 0.44 kGy = 0.66 kGy.
Batch 1 d* Batch 2 d* Batch 3 d*	3.3 kGy 3.8 kGy 3.7 kGy	The 10^{-2} SAL estimate, or d* kGy for a batch is the minimum dose of a) or b), where a) is the minimum of the first incremental dose where two consecutive 0/20 positives occur, followed by a total number of positives less than 2, b) is the first incremental dose at which 1/20 positives occur, immediately preceded and followed by 0/20 positives, followed by a total number of positives less than 2.
D*	3.7 kGy	D* kGy is the median of the three batch d*'s.
CD* batch	Batch 3	The CD* is the batch which has d* equal to D*. If more than one d* is equal to D*, choose one of these batches at random as the CD* batch.

Table B.20—Stage 3 calculations (Method 2B)

Term	Value	Comment
D*	3.7 kGy	From stage 2 experiment.
DD*	3.4 kGy	DD* kGy is the actual dose delivered in the stage 3 experiment. The DD* dose is acceptable if it is less than + 0.1 kGy or + 10% of D* kGy, whichever is greater.
CD*	3	CD* is the number of positive sterility tests of 100 observed in the stage 3 experiment.
FNP	5.4 kGy	If CD* is 2 positives or less, FNP is equal to DD* kGy. If CD* is greater than 2 and less than 10 positives, FNP is equal to DD* + 2.0 kGy. If CD* is greater than 9 and less than 16 positives, FNP is equal to DD* + 4.0 kGy. If CD* is greater than 15 positives, D* should be redetermined. NOTE — FNP may not exceed 5.5 kGy.

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Table B.21—Stage 4 calculations (Method 2B)

Term	Value	Comment
CD*	3	From stage 3 experiment.
DD*	3.4 kGy	From stage 3 experiment.
FNP	5.4 kGy	From stage 3 experiment.
FFP	0.66 kGy	From stage 2 experiment.
FNP-FFP	4.74 kGy	For the example: FNP-FFP = 5.4 kGy - 0.66 kGy = 4.74 kGy NOTE — If FNP-FFP is less than zero, set (FNP-FFP) = 0.
DS	2.55 kGy	When requirements R2 and R3 are satisfied, DS = 1.6 kGy + 0.2 (FNP-FFP) kGy. When requirements R2 and R3 are not satisfied, use Method in B.3.4.2.2 for DS. For the example: DS kGy = 1.6 kGy + 0.2 (4.74) kGy = 2.55 kGy
Verification dose (D**)	4.6 kGy	D** kGy = DD* kGy + [log(CD*)](DS)kGy NOTE — If CD* equals zero, set [log (CD*)] = 0. For the example, D** = 3.4 kGy + [log(3)] × (2.55) kGy = 3.4 kGy + (0.4771) × (2.55) kGy = 4.62 kGy = 4.6 kGy
SAL	10^{-6}	From stage 1 decision.
SIP	1.0	Stage 1 requirement.
Sterilization dose for 10^{-6} SAL	14.8 kGy	Sterilization dose = D** kGy + [-log(SAL) -2](DS) kGy For the example: Sterilization dose = 4.6 kGy + (6 - 2) × (2.55) kGy = 4.6 kGy + (4) × (2.55) kGy = 14.8 kGy

Method 2 audit

The audit procedures for Method 2A (SIP = 1), Method 2A (SIP < 1), and Method 2B are the same up to the stage where the revised verification dose and the augmented sterilization dose are determined (see B.3.5.4.1 and B.3.5.4.2). The example provided in table B.22 is for a product unit that, using Method 2A, was initially established to require a sterilization dose of 17.8 kGy. The entire product (SIP = 1) was used during the original validation; in stage 1, an SAL of 10^{-6} was selected, and during stage 2 an FFP of 1.95 kGy was observed; during stage 3, a verification dose of 6.2 kGy was established.

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Table B.22—Revision of verification dose and augmentation of sterilization dose (Method 2)

Term	Value	Comment
An audit was conducted and six positives were observed after exposure to a dose of 6.5 kGy. The original doses were established using Method 2A. Revision of the verification and augmentation of the sterilization doses were calculated following the equations of B.3.4.2.2.		
SAL	10^{-6}	For the example, the device end use required an SAL of 10^{-6}.
SIP	1.0	The whole device was tested and therefore the SIP = 1.0.
FNP	8.5 kGy	If the audit obtained three to six positives, FNP is equal to the audit dose + 2.0 kGy.
FFP	1.95 kGy	FFP kGy is the median of the three batch ffp's minus A kGy (determined during the original dose setting experiments).
FNP-FFP	6.55 kGy	FNP - FFP = 8.5 kGy - 1.95 kGy = 6.55 kGy
DS	3.31 kGy	When FNP-FFP is less than 10, DS = 2 kGy + 0.2 (FNP-FFP) kGy. When FNP-FFP is 10 or greater, DS = 0.4 (FNP-FFP) kGy. For the example, DS kGy = 2.0 kGy + 0.2 (6.55) kGy = 3.31 kGy
Revised verification dose (D**)	9.1 kGy	D** = audit dose + [log(audit positives)] (DS) kGy For the example: D** = 6.5 kGy + [log(6)] (3.31) kGy = 6.5 kGy + (0.778) (3.31) kGy = 9.08 kGy = 9.1 kGy
Augmented sterilization dose for 10^{-6} SAL	22.3 kGy	Method 2A is utilized, therefore the augmented sterilization dose is calculated as follows: Sterilization dose = D** + [-log(SAL)-2] (DS) kGy For the example: Sterilization dose = 9.1 kGy + (6 - 2) (3.31) kGy = 9.1 kGy + 13.24 kGy = 22.34 kGy = 22.3 kGy

B.5 Illustrations

Table B.23—Examples of SIP calculation

Basis for SIP calculation	Product examples
Surface area	Implants (non-absorbable)
Mass Powders	Gowns Implants (absorbable)
Length	Tubing (consistent diameter)
Volume	Water cup
Fluid path	IV catheter

Table B.24—Reference microbial resistance distribution used in Method I (Whitby and Gelda, 1979

D_{10} kGy	1.0	1.5	2.0	2.5	2.8	3.1	3.4	3.7	4.0	4.2
Frequency	0.65487	0.22493	0.06302	0.03179	0.01213	0.00786	0.00350	0.00111	0.00072	0.00007

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Table B.25—Expected frequency of positives from 100 tests at 10^{-2} SAL

Number positives	0	1	2	3	4	5	6	7	8
Probability	0.366	0.370	0.185	0.061	0.015	0.003	0.0005	0.00006	0.000007

Annex C
(informative)

Dosimeters, dosimetry and associated equipment

C.1 Dosimetry

This annex provides information for selecting and using dosimetry systems used to measure absorbed dose in irradiators. The types of dosimetry systems that may be employed on a routine basis as a means of quality assurance in commercial radiation sterilization processing of health care products are discussed. The absorbed dose range covered is from 1.0 kGy to 100 kGy (0.1 Mrad to 10 Mrad). Standard practices and methods for specific dosimetry systems are covered in other standards (see, for example, ASTM 1989, 1991a, 1992, 1993a, 1993b, 1993c, 1993d, 1993e).

C.1.1 Dosimeter classification

Dosimeters may be divided into various classes according to their relative quality and areas of application. Three types of dosimeters are used as standards—primary, reference and transfer. Routine dosimeters are used for routine measurement.

Primary standard dosimeters are the highest quality dosimeters and are usually established and maintained by national standards laboratories. The two most commonly used primary standard dosimeters are ionization chambers [International Commission of Radiation Units and Measurements (ICRU) 1969, 1970] and calorimeters (ICRU 1982, 1984; Laughlin and Genna 1966). Reference or transfer standard dosimeters are used to calibrate radiation sources and routine dosimeters. The reference standard dosimeters most widely used are the ferrous sulphate (Fricke) and dichromate aqueous solutions for gamma and x-ray applications, and the calorimeter for electron beam applications.

Listed in table C.1 are examples of reference standard dosimeters, most of which may also serve as transfer standard dosimeters. Electron energy application ranges are listed in table C.2.

Routine dosimeters are used for monitoring and for quality assurance in routine medical product radiation processing. Examples of routine dosimeters are listed in table C.3. Electron energy application ranges are listed in table C.4.

The absorbed dose in an irradiated health care product is generally specified in terms of the dose absorbed in water because most nonmetallic health care products are nearly water-equivalent in terms of radiation absorption properties. A detailed discussion on the determination of absorbed dose in other materials is given in ASTM (1988d), Attix (1986), and McLaughlin *et al* (1989a).

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Table C.1—Examples of reference standard dosimeters

Dosimeter	Readout system	Approximate absorbed dose range Gy	Reference
Calorimeter	Thermometer	10 to 10^5	Laughlin and Genna (1966); Miller and Kovacs (1990)
Alanine	Electron spin resonance spectrometer	1 to 10^5	Regulla, *et al*. (1982, 1985)
Ceric-cerous sulfate solution	Ultraviolet spectrophotometer or potentiometer	10^3 to 10^5	Matthews (1982), Bjergbakke (1970a)
Ethanol-chlorobenzene solution	Colorimetry titrator or high frequency oscillometer	10^2 to 10^5	Razem, *et al*. (1985); Kovacs, *et al*. (1985)
Ferrous-sulfate (Fricke) solution	Ultraviolet spectrophotometer	10 to 4 x 10^2	Ellis (1977); Sehested (1970)
Dichromate solution	Ultraviolet spectrophotometer	10^3 to 5 x 10^4	Sharpe, *et al*. (1985)

NOTE Most of the examples of reference standard dosimeters given may also serve as transfer standard dosimeters.

Table C.2—Electron energy application range of reference standard dosimeters

Dosimeters	Energy Range MeV			
	0.1 to 0.3	0.3 to 1.0	1.0 to 5.0	5.0 to 15.0
Calorimeters	X	X	X	X
Alanine	?	?	X	X
Ceric-cerous sulphate solution	NA	NA	?	X
Ethanol-chlorobenzene solution	NA	NA	?	X
Ferrous-sulphate (Fricke) solution .	NA	NA	?	X
Dichromate solution	NA	NA	?	X

Symbols:

NA = Current system(s) not appropriate for this range.
? = Current system(s) possibly could be modified for use in this range.
X = Current system(s) are appropriate for this range.

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Table C.3—Examples of routine dosimeters

Dosimeter	Readout system	Approximate absorbed dose range Gy	Reference
Dyed polymethyl-methacrylate	Visible spectrophotometer	10^3 to 5×10^4	Barrett (1982); Whittaker, *et al.* (1985); Glover, *et al.* (1985)
Clear polymethyl-methacrylate	Ultraviolet spectrophotometer	10^3 to 10^5	Barrett (1982); Chadwick (1977)
Cellulose triacetate	Ultraviolet spectrophotometer	10^4 to 4×10^5	Tamura, *et al.* (1981); Tanaka, *et al.* (1984)
Ceric-cerous sulphate solution	Potentiometer or ultraviolet spectrophotometer	10^3 to 10^5	Matthews (1982); Bjergbakke (1970a)
Radiochromic dye film, solution, optical wave-guide	Visible spectrophotometer or optical densitometer	1 to 10^5	Miller, *et al.* (1981); Liu, *et al.* (1985); McLaughlin, *et al.* (1989b); Farahani, *et al.* (1990)
Ferrous-cupric solution	Ultraviolet spectrophotometer	10^3 to 3×10^4	McLaughlin, *et al.* (1981); Bjergbakke (1970b)

C.1.2 Selection of dosimetry systems

Some considerations for selecting a suitable dosimetry system are as follows:

a) suitability of the dosimeter for the absorbed dose range of interest and for use with a specific product;

b) adequate stability and reproducibility of the system;

c) ease of system calibration;

d) system calibration traceable to and consistent with national standards;

e) ability to control or correct system response for systematic errors, such as those related to temperature and humidity;

f) ease and simplicity of use;

g) whether the time and labor required for dosimeter response development, readout, and interpretation are within acceptable limits for production;

h) ruggedness of the system (such as resistance to damage during handling and use in routine processing environment);

i) whether the variance of the dosimetry system response data is within established limits about a fitted calibration curve over the absorbed dose range of interest. Suitable regression analysis methods should be used to fit the curve and could include linear, polynomial or exponential functions;

j) dependence of dosimeter response and dosimeter readout equipment on environmental conditions (such as temperature, humidity, light) before, during, and after both calibration and use;

k) dependence of dosimeter response on absorbed dose rate and/or fractionated delivery of absorbed dose, both in calibration and in-process use;

l) stability of dosimeter response both before and after irradiation;

m) variation of dosimeter response within a batch or between batches;

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n) effects of differences in radiation energy spectra between calibration and product irradiation fields.

Advantages and disadvantages of current dosimetry systems are shown in table C.5.

Table C.4—Electron energy application range for routine dosimeters

Dosimeters	Energy Range MeV			
	0.1 to 0.3	0.3 to 1.0	1.0 to 5.0	5.0 to 15.0
Dyed polymethylmethacrylate	NA	NA	?	X
Clear polymethylmethacrylate	NA	NA	?	X
Cellulose triacetate film	X	X	X	X
Ceric-cerous sulphate solution	NA	NA	?	X
Radiochromic film	X	X	X	X
Radiochromic solution	NA	NA	X	X
Ferrous-cupric solution	NA	NA	?	X

Symbols:

NA = Current system(s) not appropriate for this range.
? = Current system(s) possibly could be modified for use in this range.
X = Current system(s) are appropriate for this range.

C.1.3 Dosimetry system calibration

A formal calibration program shall be implemented to ensure that dosimeters and associated measurement and test equipment are calibrated and maintained within specified accuracy limits that are deemed sufficient for the individual measurement task.

The dosimetry system shall be calibrated at intervals to ensure that the accuracy of the absorbed dose measurement is maintained within required limits. Calibration of the entire system shall include irradiation of dosimeters to known dose levels followed by readout on the measuring devices to be used at the irradiation facility. The system calibration shall have documented traceability to national standards. Traceability should also apply to each type of measuring instrumentation listed below. This is to ensure that measurement accuracy is maintained within specified limits. See ASTM 1991b, and McLaughlin *et al* 1989a for additional guidance.

C.1.3.1 Dosimeters

Each batch of dosimeters shall be calibrated by the irradiation of representative samples of dosimeters to known absorbed doses of radiation. This may be accomplished by irradiation of the dosimeters at a standards or reference laboratory. Alternative methods are to irradiate the dosimeters in the user's facility together with reference standard dosimeters issued by a standards or reference laboratory, or to use a radiation field where calibration is traceable to a standards laboratory.

Dosimeter calibration procedures usually require the development of a calibration curve relating dosimeter response values to absorbed dose. In practice, this curve is reduced to an equation relating response to dose, from which appropriate tabulated values can be derived.

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Table C.5—Advantages and disadvantages of dosimetry systems

Dosimetry system	Advantages	Disadvantages
Calorimeter	High accuracy and precision. Direct measurement of absorbed dose.	Dependence on spatial distribution of absorbed dose in absorber. Limited sensitivity. Must be effectively adiabatic system for extended exposure periods.
Ferrous-sulphate (Fricke) solution	High accuracy and precision. Well-established radiation chemical yield and molar linear absorption coefficient. Little dose-rate dependence. Small known temperature dependence. Stability for long periods before and after irradiation.	Sensitivity to impurity of water and reagents. Limited absorbed dose range well below sterilizing doses. Dissolved oxygen dependence. Require ultra-clean fragile glass containers. Batch-to-batch variations. Each batch must be calibrated.
Ceric sulphate solution	High accuracy and precision. Little dose-rate dependence. No dissolved oxygen dependence. Variability of dose range to well above sterilizing doses by choice of initial ceric ion concentration. Small known temperature dependence. Stability for long periods before and after irradiation.	Sensitivity to purity of water and reagents. Low-energy spectral dependence. Necessity to dilute solution prior to reading with spectrophotometer, requiring operator skill. Sensitivity of diluted solution to light. Requires ultra-clean fragile glass containers.
Ceric cerous sulphate solution	High accuracy and precision. Little dose-rate dependence. No dissolved oxygen dependence. Variability of dose range to well above sterilizing doses by choice of initial ceric ion concentration. Small known temperature dependence. Stability for long periods before and after irradiation. Can be read on either a spectrophotometer or potentiometer. Potentiometric measurement does not require dilution prior to reading. Less sensitive to organic impurities than ceric sulphate.	Sensitivity to purity of water and reagents. Low-energy spectral dependence. Requires ultra-clean fragile glass containers.
Ethanol chlorobenzene solution	High accuracy and precision. Little dose-rate dependence. No temperature or humidity dependence.	Requires careful combinations of solvents and concentrations. Requires fragile glass containers. Some types of readout require special analytical

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	Stability for long periods before and after irradiation. Variability of dose range to well above and below sterilizing doses by choice of chloro-benzene concentration.	equipment.
Dichromate solution	High accuracy and precision. No measurable dose-rate dependence. Variability of dose range to well above and below sterilizing doses by choice of combination of dichromate concentration. Small known temperature dependence. Stability for long periods before and after irradiation.	Sensitivity to purity of water and reagents. Sensitivity of solutions to extended exposure to light. Requires ultra-clean fragile glass containers.
Radiochromic solution	High accuracy and precision. Little dose-rate dependence. Known temperature dependence. Stability for long periods before and after irradiation. Relatively insensitive to impurities.	Requires careful combinations of solvents and concentrations. Limited absorbed dose range somewhat below sterilizing doses. Sensitive to UV (requires amber glass or opaque containers).
Alanine	High accuracy and precision; covers wide dose ranges. No measurable dose-rate dependence, Small known temperature dependence. Little humidity dependence. Stability for long periods before and after irradiation.	Not yet commercially available in large quantities. Requires expensive readout equipment not readily available. Batch-to-batch variations. Each batch must be calibrated.
Polymethyl methacrylate (dyed or clear)	Saturates somewhat above sterilization doses. Commercially available. Little temperature dependence (at < 40°C).	Some post-irradiation instability of absorbance values. Thickness must be measured carefully. Batch-to-batch variations. Each batch must be calibrated. Slight dose-rate dependence. Humidity and temperature effects during storage and irradiation.
Radiochromic dye film	Saturates well above sterilizing doses. Covers wide dose ranges. Little or no oxygen dependence. Provides high-resolution dose mapping. No dose-rate dependence at sterilization dose ranges, except at very low dose rates (or long exposure times).	Sensitivity to UV (requires packaging). Thickness of some types must be measured carefully. Some types show errors if used at low relative humidities (< 35 %) or at high relative humidities (> 65 %). Temperature effects during irradiation for some types.

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	Little temperature dependence (at < 40°C) for most types. Commercially available.	Batch-to-batch variations. Each batch must be calibrated. Dose-rate dependence at doses > 35 kGy.
Cellulose triacetate film	Only slight dose-rate dependence. Commercially available. Provides high-resolution dose mapping.	Post-irradiation instability of absorbance values. Thickness of some batches must be measured carefully. May show errors if used at low relative humidities (< 20%) or at high relative humidities (> 90%). Batch-to-batch variations. Each batch must be calibrated. Limited to sterilization dose range and above.

A documented dosimetry calibration procedure shall specify details of the calibration process and calibration quality requirements.

In cases where the response characteristics of the dosimeter differ when irradiated under widely differing environmental conditions, such as dose rate, humidity, or temperature, either appropriate corrections should be applied or the dosimeter should be calibrated under conditions approximating those of intended use.

C.1.3.2 Absorbance-measuring instrumentation

A spectrophotometer or optical densitometer may be used to measure the absorbance of dosimeters at specified wavelengths. Calibration of these instruments shall be performed independently of the other components of the dosimetry system at established intervals using standards traceable to national standards, and the calibration interval shall be identified in the documented procedure.

C.1.3.3 Thickness-measuring instrumentation

Thickness-measuring instrumentation shall be calibrated and maintained within specified accuracy and precision limits. Calibration of these instruments shall be performed independently of the other components of the dosimetry system at established intervals using standards traceable to national standards and the calibration interval shall be identified in the documented procedure.

C.1.3.4 Other measuring instrumentation

Measuring instrumentation not previously mentioned that is used for analysis of dosimeters (such as ceric-cerous, alanine and other dosimeters), as well as environmental measuring instruments, shall be calibrated at established intervals. Calibration of these instruments shall be performed independently of the other components of the dosimetry system at established intervals using standards traceable to national standards, and the calibration interval shall be identified in the documented procedure.

C.1.4 Uncertainty of absorbed dose measurements

Dosimetry systems shall have the ability to provide a measure of absorbed dose within specified limits. Significant sources of error that may contribute to the total measurement uncertainty include dosimeter characteristics, calibration, absorbance measurement and thickness measurement. The use of dosimeters should take associated uncertainties into account.

C.1.4.1 Dosimeter characteristics

The following dosimeter characteristics can affect the uncertainty of absorbed dose determination.

C.1.4.1.1 Sensitivity to temperature

The response of a given dosimeter may vary with the temperature before, during or after irradiation, or during the period between irradiation and analysis. Therefore, it is important to understand and characterize the temperature dependence of the dosimeter being used and apply appropriate correction factors.

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C.1.4.1.2 Sensitivity to humidity

It is important to understand the effect of humidity variations on the dosimeter being used and to protect the dosimeters from adverse humidity conditions before, during and after irradiation. If dosimeters are in hermetically sealed packages to control the water content, the package integrity should be confirmed.

C.1.4.1.3 Dose rate dependence

If the response of the dosimeter being used is significantly affected by dose rate or fractionated irradiation, the user shall apply the appropriate correction factor.

C.1.4.1.4 Instability

Some dosimeters exhibit instability after being irradiated: for example, the absorbance after irradiation will change with time. The measurement uncertainty caused by this characteristic may be minimized by adhering to specific measurement procedures that specify the appropriate time limits for the measurement of absorbance of irradiated dosimeters.

C.1.4.1.5 Geometry

In the case of electrons, the thickness, size, and orientation of dosimeters can introduce uncertainties in calibration accuracy and in the dose assessment and dose mapping of products. The following recommendations apply.

a) The electron range in the region of interest shall be greater than the dosimeter thickness.

b) Response with the dosimeter should be uniform over the area of analysis.

c) In the case of dosimeter calibration with electron beams, thin dosimeters should be oriented approximately perpendicular to the general beam direction so that the dose is uniform over the area of the dosimeter. Moreover, care shall be taken to ensure that the electron scattering environment is controlled when comparing dosimeter responses. In general, such measurements should be made with the dosimeters positioned in an absorber at the depth of the maximum of dose build-up for the nominal energy. This serves both to reduce sensitivity to geometry and to attenuate the low-energy portion of the spectrum reducing spurious response differences.

Caution should be exercised to ensure that any electric charge accumulated in the measurement assembly is drained before handling. Arcing can generate a response in the dosimeter.

C.1.4.1.6 Energy spectrum

The response of some dosimeters to electrons, x-rays, and gamma rays over typical energies used for sterilization, in particular those dosimeters whose atomic composition is greatly different from water, may exhibit an energy dependence; that is, a response that varies with energy relative to the response of water or relative to response of other dosimeters.

For electrons, this effect is mainly due to differences between the electron mass collision stopping powers of the dosimeters and the stopping power of water. The ratios of stopping powers for most dosimetry systems to stopping powers of water is constant within about 5% over the electron energy range 0.1 MeV to 10 MeV. Therefore, energy dependence of dosimeter response to electrons in sterilization is usually not a problem.

C.1.4.1.7 Reproducibility

Dosimeters normally exhibit random variability in individual responses for any single dose value. The effect of this variability may be reduced by using several dosimeters for each measured dose value, and using the mean of the individual dosimeter responses to determine the dose value. Reproducibility is a measure of the variability and can be estimated by calculating the sample standard deviation (s_{n-1}) and the coefficient of

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variation (C.V.) for each dose value as follows:

Sample standard deviation

(C.1) $$s_{n-1} = \sqrt{\frac{\Sigma (x_i - \bar{x})^2}{n-1}}$$

Coefficient of variation

(C.2) $$percent\ C.V. = \frac{s_{n-1}}{\bar{x}} (100)$$

In both (Eq.C.1) and (Eq.C.2)

x_i is the individual dosimeter response;

$\bar{x}$ is the mean response of a group of dosimeters;

i = 1, ..., *n*;

n is the number of dosimeters in group.

NOTE 56 In general, C.V. values for routine dosimeters are 2% or less.

C.1.4.2 Dosimeter calibration uncertainty

The calibration certificate issued by standards laboratories performing dosimeter calibrations shall include a statement of the estimated total uncertainty.

C.1.4.3 Absorbance measurement uncertainty

Measurement uncertainties associated with absorbance measurement of dosimeters shall be considered. These include

a) accuracy of wavelength;

b) accuracy of absorbance measurement;

c) light scattering due to scratches and irregularities of dosimeter surface area.

C.1.4.4 Dosimeter thickness measurement uncertainty

Measurement uncertainties associated with dosimeter thickness shall be considered. These can be attributed to

a) accuracy of the measuring instrument;

b) instrument/dosimeter alignment (cosine error);

c) force applied to plastic dosimeter;

d) accuracy of the thickness standard;

e) surface irregularity of the dosimeter.

C.1.4.5 Overall dosimeter uncertainty

All sources of uncertainty for a particular dosimetry system shall be combined to provide an overall uncertainty statement at a specific confidence level.

C.1.5 Dosimeter applications

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C.1.5.1 Irradiator dose mapping

The material used for irradiator dose mapping should have a bulk density within the limits of the bulk density range for which the irradiator is intended to be used and should fill the irradiation container to its designed volume limits.

Dosimeters should be distributed throughout each selected irradiation container. The number and positioning of the dosimeters will determine the spatial resolution of the dose mapping study. If several dosimeters are used at a single site, their effect upon each other shall be considered.

After the irradiation, the dosimeters are retrieved and read, and the results analyzed. The zones of minimum and maximum dose, max./min. dose ratio and processing rate shall be determined and documented. The irradiator shall be monitored for unusual events (such as machine malfunction) that might affect the dose distribution or its measurement and thus invalidate the dose mapping.

For gamma and x-ray facilities, to determine the reproducibility of dose delivery, dose measurements should be made in several irradiation containers. The dose-mapping containers should be surrounded during irradiation by a sufficient number of irradiation containers holding material of equivalent density and dimensions of the product to be irradiated to simulate a fully loaded system.

For electron beam and x-ray facilities, if the linear or scanned dimensions of the beam are varied for different products, then baseline dose distributions for these different conditions shall also be established. For systems that employ proportional control over beam current or beam current density, or conveyor speed, the dose distribution in product which is in front of the beam during system start-up and shut-down shall be evaluated.

Depth-dose measurements are performed to correlate the electron beam energy readout with the penetration of the electron beam. Penetration measurements shall be made on the beam centerline at a specified distance from the vacuum window. These measurements are made by placing dosimeters between layers of a material such as polystyrene, aluminum or graphite. For a variable energy and/or variable current machine, multiple dose distribution measurements should be made to cover the range of operating conditions.

Dosimetry is also used in qualifying a facility to verify the dose and penetration of the electron or x-ray beam during start-up and shut-down of systems. For facilities that employ proportional control, dosimeters are also used to verify that the dose increases or decreases as anticipated when beam current, conveyor speed or beam current density are changed.

C.1.5.2 Product dose mapping

The dose mapping study is performed to identify the zones of minimum and maximum dose within the product load and to assess the reproducibility of the process. This information is then used in selecting the monitoring locations for routine processing.

Dosimeters are distributed throughout selected product loads. The quantity and positioning of the dosimeters will determine the spatial resolution of the dose mapping study. A three-dimensional grid defined within the product load is useful in maintaining consistent dosimeter placement.

The placement of dosimeters in the dose distribution mapping study should be guided by the current qualification dose mapping data for the product bulk density previously characterized. Dosimeters should be concentrated in probable areas of minimum and maximum dose within the product load, with fewer dosimeters used in areas likely to be intermediate in absorbed dose. If the minimum or maximum dose locations are expected to lie within the boundaries of product containers, it may be necessary to place dosimeters inside representative containers.

Regions of high density or voids within the loaded irradiation container can require detailed dose mapping

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within the regions of interest.

For electron beams, electrons have both mass and charge, and therefore lose energy in materials more readily than do photons (for example gamma rays or X rays). This results in steeper dose gradients with electron beams than are observed with gamma radiation from isotopic sources. The dose at any point within a product unit is sensitive to product density, composition and geometry. Because of this, dosimeters placed in similar locations over a series of irradiations may produce a range of absorbed dose measurements. Meaningful evaluations of the doses absorbed at specific locations within a product unit carrier should therefore include statements of mean and standard error along with appropriate confidence intervals.

The number and spatial resolution of dose mapping measurements conducted on each product shall be sufficient to allow the location of dose extremes (that is, high- and low-dose zones) to be reliably determined. Product dose mapping shall be repeated whenever there are significant changes in

a) the irradiator,

b) the scan width or beam energy, or

c) the attributes of the product unit affecting absorbed dose.

In cases where the product configuration can be varied with respect to the beam direction, dose measurements shall be taken to ensure that alignment of dense objects will not compromise the validity of the process. As electron beams are relatively directional, the dose to an internal surface of the product unit is dependent on the orientation of that surface to the beam. To properly determine internal doses, care shall be taken to ensure that the dosimeters are placed flush to the surfaces being monitored.

C.1.5.3 Routine dosimetry

In conjunction with a well-documented manufacturing program, a routine dosimetry program will provide documentation that the dose delivered to the product meets specifications and release criteria.

C.1.5.3.1 Monitoring location

Dosimetry monitoring locations are determined from current dose mapping data for the product. The locations shall become part of the current processing specifications to help ensure proper placement of routine dosimeters. Dosimeters should be placed in the minimum dose zone and, if required, also in the maximum dose zone.

C.1.5.3.1.1 Alternate monitoring location

Routine processes may be monitored at points of convenience within zones having a known relationship to the minimum dose zone. In a similar manner, the maximum dose may be computed from the process minimum dose using the dose uniformity ratio (maximum/minimum) determined in the dose mapping study.

C.1.5.3.1.2 Equivalent positions

The proper monitoring position may be selected from among locations that show equivalent readings for the minimum or maximum dose zone. Determination of equivalency should be documented.

C.1.5.3.2 Monitoring frequency

For gamma irradiation, at least one dosimeter should be in the irradiator at all times.

For electron beam and x-ray irradiation, dosimeters should be placed at the beginning, middle, and end of each processing run that utilizes the same parameters.

NOTE 57 Proper characterization of the range of absorbed dose can require more dosimeters than indicated above, due to product inconsistencies or variations in processing conditions.

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C.1.5.3.3 Target dose concept

It is advisable to set the radiation processing parameters, or cycle time, such that a target dose greater than the required minimum is delivered. This provides assurance that the measured minimum will equal or exceed the minimum required dose, by accounting for the uncertainties of the dosimetry system and the variability among irradiation containers.

C.1.5.4 Test sample irradiation

C.1.5.4.1 Dosimetry system selection

The dosimetry system used in routine production may be used to monitor test sample irradiations if the dose range and precision are acceptable.

C.1.5.4.2 Control of dose uniformity

Test methods for dose setting often require the uniformity ratio (maximum/minimum) of the delivered dose to be as low as 1.10 to 1. To meet such tolerances, it is often necessary to limit sample size and to use special processing methods.

NOTE 58 Dose setting Method 2B (see annex B, B.3.4.2.4) requires the uniformity ratio of the delivered dose to be as low as 1.05 to 1.

The size of the sample package should be kept as small as practical. Exact size limits will depend upon the bulk density of the sample as well as the specific capabilities of the irradiation facility. Large groups of samples to be processed at the same dose level may be divided into subgroups for irradiation. Report the overall minimum and maximum doses as the dose limits for the entire group.

The need to limit sample size and use special processing methods to achieve a uniformity ratio (maximum/minimum) suitable for dose setting test methods should be considered. Special methods of processing can be used to improve dose uniformity.

For gamma and x-ray facilities, these include performance of the irradiation in low-dose-rate zones as well as the use of rotation schemes (for example, two-sided, four-sided, turn-table rotations).

For electron beam facilities, these include the irradiation of product samples outside the normal case carton configuration (for example, two-sided irradiation of a single layer of product).

C.1.5.4.3 Dosimeter placement

Dosimeters should be placed to measure the minimum and maximum dose that is absorbed by the test sample. The specific number and placement of dosimeters that are required will be dictated by the sample configuration and the irradiation scheme employed.

C.2 Equipment control

C.2.1 Irradiator control

Irradiator control, monitoring and recording should capture all operating characteristics which are known to affect delivered dose.

C.2.1.1 Gamma irradiator

In a facility, the source configuration and distance to the product are fixed. Thus, at any given time the operator can vary only the exposure time to account for the composition and density of materials in the irradiator (with a view to achieving specified dose). Therefore, the exposure time shall be continuously controlled and appropriately monitored, and recorded with sufficient information linking the record with specific product batches. The records of processes performed shall be retained.

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The form of control, monitoring and recording will vary with irradiator type but shall capture all operating characteristics which are known to affect delivered dose. There shall be positive indication that the source is in its correct operating position during processing and that the conveyor inside the cell is operating correctly. Primary devices that cause the source to move automatically to the storage position should be installed. These include devices that detect power loss, conveyor failure, loss of pressure, source rack fault, high temperatures or master timer failure.

C.2.1.2 Electron beam and x-ray irradiator

The equipment parameters should be monitored and compared to specifications on time scales sufficiently short to detect process deviations. Since the absorbed dose distribution in a product depends on the effective beam energy, the number of incident electrons per specific unit area of product (for electron beam) or of the converter (for x-ray) and the conveyor speeds, the values of these critical parameters should be carefully monitored and controlled in order to ensure reliable and consistent delivery of the specified sterilization dose.

In general, any reliable system that completely monitors and controls the critical parameters described above, and that can be unambiguously correlated with them, may be used for routine process control. Back-up monitoring systems are recommended where applicable.

Because of the variety of existing types of accelerators and the possibility of new designs yet to be developed, it is neither feasible nor appropriate for this International Standard to state specific methods of controlling these parameters for all possible cases.

Annex D
(informative)

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