List of Titles

American National Standard

ANSI/AAMI/ISO 14937:2000

Sterilization of health care products—General requirements for characterization of a sterilizing agent and the development, validation, and routine control of a sterilization process for medical devices

AAMI Association for the Advancement of Medical Instrumentation

The Objectives and Uses of AAMI Standards and Recommended Practices

It is most important that the objectives and potential uses of an AAMI product standard or recommended practice are clearly understood. The objectives of AAMI's technical development program derive from AAMI's overall mission: the advancement of medical instrumentation. Essential to such advancement are (1) a continued increase in the safe and effective application of current technologies to patient care, and (2) the encouragement of new technologies. It is AAMI's view that standards and recommended practices can contribute significantly to the advancement of medical instrumentation, provided that they are drafted with attention to these objectives and provided that arbitrary and restrictive uses are avoided.

A voluntary *standard* for a *medical device* recommends to the manufacturer the information that should be provided with or on the product, basic safety and performance criteria that should be considered in qualifying the device for clinical use, and the measurement techniques that can be used to determine whether the device conforms with the safety and performance criteria and/or to compare the performance characteristics of different products. Some standards emphasize the information that should be provided with the device, including performance characteristics, instructions for use, warnings and precautions, and other data considered important in ensuring the safe and effective use of the device in the clinical environment. Recommending the disclosure of performance characteristics often necessitates the development of specialized test methods to facilitate uniformity in reporting; reaching consensus on these tests can represent a considerable part of committee work. When a drafting committee determines that clinical concerns warrant the establishment of *minimum* safety and performance criteria, referee tests must be provided and the reasons for establishing the criteria must be documented in the rationale.

A *recommended practice* provides guidelines for the use, care, and/or processing of a medical device or system. A recommended practice does not address device performance *per se*, but rather procedures and practices that will help ensure that a device is used safely and effectively and that its performance will be maintained.

Although a device standard is primarily directed to the manufacturer, it may also be of value to the potential purchaser or user of the device as a fume of reference for device evaluation. Similarly, even though a recommended practice is usually oriented towards health care professionals, it may be useful to the manufacturer in better understanding the environment in which a medical device will be used. Also, some recommended practices, while not addressing device performance criteria, provide guidelines to industrial personnel on such subjects as sterilization processing, methods of collecting data to establish safety and efficacy, human engineering, and other processing or evaluation techniques; such guidelines may be useful to health care professionals in understanding industrial practices.

In determining whether an AAMI standard or recommended practice is relevant to the specific needs of a potential user of the document, several important concepts must be recognized:

All AAMI standards and recommended practices are *voluntary* (unless, of course, they are adopted by government regulatory or procurement authorities). The application of a standard or recommended practice is solely within the discretion and professional judgment of the user of the document.

Each AAMI standard or recommended practice reflects the collective expertise of a committee of health care professionals and industrial representatives, whose work has been reviewed nationally (and sometimes internationally). As such, the consensus recommendations embodied in a standard or recommended practice are intended to respond to clinical needs and, ultimately, to help ensure patient safety. A standard or recommended practice is limited, however, in the sense that it responds generally to perceived risks and conditions that may not always be relevant to specific situations. A standard or recommended practice is an important *reference* in responsible decision-making, but it should never *replace* responsible decisionmaking.

Despite periodic review and revision (at least once every five years), a standard or recommended practice is necessarily a static document applied to a dynamic technology. Therefore, a standards user must carefully review the reasons why the document was initially developed and the specific rationale for each of its provisions. This review will reveal whether the document remains relevant to the specific needs of the user.

Particular care should be taken in applying a product standard to existing devices and equipment, and in applying a recommended practice to current procedures and practices. While observed or potential risks with existing equipment typically form the basis for the safety and performance criteria defined in a standard, professional judgment must be used in applying these criteria to existing equipment. No single source of information will serve to identify a particular product as "unsafe". A voluntary standard can be used as one resource, but the ultimate decision as to product safety and efficacy must take into account the specifics of its utilization and, of course, cost-benefit considerations. Similarly, a recommended practice should be analyzed in the context of the specific needs and resources of the individual institution or firm. Again, the rationale accompanying each AAMI standard and recommended practice is an excellent guide to the reasoning and data underlying its provision.

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American National Standard ANSI/AAMI/ISO 14937:2000

Sterilization of health care products—General requirements for characterization of a sterilizing agent and the development, validation, and routine control of a sterilization process for medical devices

Approved 13 March 2000 by
Association for the Advancement of Medical Instrumentation

Approved 7 June 2000 by
American National Standards Institute, Inc.

Abstract: Specifies general requirements for the characterization of a sterilizing agent and for the development, validation, and routine control of a sterilization process for medical devices. This standard applies to sterilization processes in which microorganisms are inactivated by physical and/or chemical means. This standard is intended to be applied by process developers, manufacturers of sterilization equipment, manufacturers of products to be sterilized, and the organization with responsibility for sterilizing the product.

Keywords: medical devices, product definition, sterilizing agent, process definition, product release, quality systems

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AAMI Standard

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International standards adopted in the United States may include normative references to other international standards. For each international standard that has been adopted by AAMI (and ANSI), the table below gives the corresponding U.S. designation and level of equivalency to the international standard. (Note: Documents are sorted by International designation.)

Other normatively referenced international standards may be under consideration for U.S. adoption by AAMI, therefore this list should not be considered exhaustive.

International designation	U.S. designation	Equivalency
IEC 60601-2-21:1994 and Amendment 1:1996	ANSI/AAMI/IEC 60601-2-21 & Amendment 1:2000 (consolidated texts)	Identical
IEC 60601-2-24:1998	ANSI/AAMI ID26:1998	Major technical variations
ISO 5840:1996	ANSI/AAMI/ISO 5840:1996	Identical
ISO 7198:1998	ANSI/AAMI VP20:1994	Major technical variations
ISO 7199:1996	ANSI/AAMI/ISO 7199:1996	Identical
ISO 10993-1:1997	ANSI/AAMI/ISO 10993-1:1997	Identical
ISO 10993-2:1992	ANSI/AAMI/ISO 10993-2:1993	Identical
ISO 10993-3:1992	ANSI/AAMI/ISO 10993-3:1993	Identical
ISO 10993-4:1992	ANSI/AAMI/ISO 10993-4:1993	Identical
ISO 10993-5:1999	ANSI/AAMI/ISO 10993-5:1999	Identical
ISO 10993-6:1994	ANSI/AAMI/ISO 10993-6:1995	Identical
ISO 10993-7:1995	ANSI/AAMI/ISO 10993-7:1995	Identical
ISO 10993-8:2000	ANSI/AAMI/ISO 10993-8:2000	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999	Identical
ISO 10993-10:1995	ANSI/AAMI/ISO 10993-10:1995	Identical
ISO 10993-11:1993	ANSI/AAMI 10993-11:1993	Minor technical variations
ISO 10993-12:1996	ANSI/AAMI/ISO/CEN 10993-12:1996	Identical
ISO 10993-13:1998	ANSI/AAMI/ISO 10993-13:1999	Identical
ISO 10993-15:2000	ANSI/AAMI/ISO 10993-15:2000	Identical
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ISO 11135:1994	ANSI/AAMI/ISO 11135:1994	Identical
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ISO 11138-1:1994	ANSI/AAMI ST59:1999	Major technical variations
ISO 11138-2:1994	ANSI/AAMI ST21:1999	Major technical variations
ISO 11138-3:1995	ANSI/AAMI ST19:1999	Major technical variations
ISO 11140-1:1995 and Technical Corrigendum 1:1998	ANSI/AAMI ST60:1996	Major technical variations
ISO 11607:200x [1)]	ANSI/AAMI/ISO 11607:2000	Identical
ISO 11737-1:1995	ANSI/AAMI/ISO 11737-1:1995	Identical
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ISO TR 13409:1996	AAMI/ISO TIR 13409:1996	Identical
ISO 13485:1996	ANSI/AAMI/ISO 13485:1996	Identical
ISO 13488:1996	ANSI/AAMI/ISO 13488:1996	Identical
ISO 14155:1996	ANSI/AAMI/ISO 14155:1996	Identical
ISO 14160:1998	ANSI/AAMI/ISO 14160:1998	Identical
ISO 14161: 2000	ANSI/AAMI/ISO 14161:2000	Identical

[1)] FDIS approved; being prepared for publication.

International designation	U.S. designation	Equivalency
ISO 14937:2000	ANSI/AAMI/ISO 14937:2000	Identical
ISO 14969:1999	ANSI/AAMI/ISO 14969:1999	Identical
ISO 14937:2000	ANSI/AAMI/ISO 14937:2000	Identical
ISO 14971:2000	ANSI/AAMI/ISO 14971:2000	Identical
ISO 15223:2000	ANSI/AAMI/ISO 15223:2000	Identical
ISO 15225:2000	ANSI/AAMI/ISO 15225:2000	Identical
ISO TS 15843:2000	AAMI/ISO TIR15843:2000	Identical
ISO TR 15844:1998	AAMI/ISO TIR15844:1998	Identical
ISO TR 16142:1999	ANSI/AAMI/ISO TIR16142:2000	Identical

Committee representation

Association for the Advancement of Medical Instrumentation

Sterilization Standards Committee

The adoption of ISO 14937:2000 as an American National Standard was initiated by the AAMI General Criteria for Sterilization Processes Working Group of the AAMI Sterilization Standards Committee. The AAMI General Criteria for Sterilization Processes Working Group also functions as a U.S. Technical Advisory Group to the relevant work in the International Organization for Sterilization (ISO). U.S. representatives from the AAMI General Criteria for Sterilization Processes Working Group (U.S. Sub-TAG for ISO/TC 198/WG 11) played an active part in developing the ISO standard.

At the time this document was published, the **AAMI Sterilization Standards Committee** had the following members:

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William E. Young

Members:
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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 14937:2000

As indicated in the foreword to the main body of this document (page x), 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, which was developed by ISO Technical Committee 198, *Sterilization of health care products*, to fill a need for general criteria for the characterization of sterilizing agents and the development, validation, and routine control of sterilization processes for which other International Standards do not exist.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 198, administered by the Association for the Advancement of Medical Instrumentation (AAMI).

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 (and ANSI) have adopted other ISO standards. See the Glossary of Equivalent Standards for a list of ISO standards adopted by AAMI which gives the corresponding U.S. designation and the level of equivalency with the ISO standard.

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 come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

NOTE—Beginning with the foreword on page x, this American National Standard is identical to ISO 14937:2000.

Foreword

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

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 3.

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

Attention is drawn to the possibility that some of the elements of this International Standard may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 14937 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products.*

Annexes A, B, C, and D form a normative part of this International Standard. Annexes E and ZA are for information only.

Introduction

A sterile medical device is one which is free of viable microorganisms. When it is necessary to supply a sterile medical device, International Standards specifying requirements for validation and routine control of sterilization processes require that adventitious microbiological contamination of a medical device prior to sterilization be minimized. Even so, medical devices produced under standard manufacturing conditions in accordance with the requirements for quality systems (see, for example, ISO 13485 and ISO 13488) or which have been subjected to a cleaning process as part of their reprocessing in a health care establishment may, prior to sterilization, have microorganisms on them, albeit in low numbers. Such products are non-sterile. The purpose of sterilization is to inactivate the microbiological contaminants and thereby transform the non-sterile products into sterile ones.

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

This International Standard describes requirements which will enable sterilizer manufacturers, medical device manufacturers, and health care facilities to demonstrate that a process intended to sterilize medical devices has appropriate microbicidal activity, and that this activity is both reliable and reproducible, such that the relationship for the inactivation of microorganisms can be extrapolated with reasonable confidence to low levels of probability of there being a viable microorganism present on a product after sterilization processing. This International Standard does not specify the maximal value to be taken by this probability; specification of this probability is a matter for regulatory authorities and may vary from country to country (see, for example, EN 556 and AAMI ST67).

Generic requirements of the quality system for design/development, production, installation, and servicing are given in the ISO 9000 series and particular requirements for quality systems for medical device production in ISO 13485 and ISO 13488. The standards for quality systems recognize that, for certain processes used in manufacturing or reprocessing, the effectiveness of the process cannot be fully verified by subsequent inspection and testing of the product. Sterilization is an example of such a process. For this reason, sterilization processes are validated for use, the performance of the sterilization process monitored routinely, and the equipment maintained.

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

a) for a manufacturing process, the microbiological status of incoming raw materials and/or components;

b) the validation and routine control of the cleaning and disinfection procedures used during reprocessing;

c) the control of the environment in which the product is manufactured, assembled, and packaged, together with control of personnel and their hygiene; and,

d) the manner in which the items are packaged and the conditions under which the sterilized items are stored.

The type of contamination on a product to be sterilized varies, and this impacts upon the effectiveness of a sterilization process. Products that have been used in a health care setting and are being presented for resterilization in accordance with the manufacturer's instructions, should be regarded as a special case. There is the potential for such products to possess a wide range of contaminating microorganisms and residual inorganic and/or organic contamination, in spite of the application of a cleaning process. Hence, particular attention is given to the validation and control of the cleaning and disinfection processes used during reprocessing.

Sterilization technology is at several levels of development and application. There are processes which are developed and have been in use for appreciable periods, and there are processes which are being developed and introduced either for sterilization of specific products or for general application. Furthermore, there may be processes which have yet to be discovered. Experience has identified the requirements which are appropriate for existing sterilization technologies, and these requirements have been specified in International Standards specific to each established process. The intention in developing this International Standard is to use this experience to provide, for suppliers of sterilization technologies, to their users, and to regulatory authorities, a knowledge of the relevant general requirements that will allow development of additional sterilization technologies to continue within a broad

framework until sufficient experience, confidence, and demand exist to justify the preparation of a specific International Standard.

This International Standard has three distinct applications:

— for manufacturers of health care products who wish to apply to their products a sterilization process for which a specific International Standard does not exist;

— for manufacturers and users of sterilization systems in health care settings for which a specific International Standard does not exist; and,

— to provide a framework for the preparation or revision of standards for specific sterilization processes.

The responsibility for carrying out the activities required by this International Standard will vary from case to case. This International Standard requires that the responsibilities of the various parties be defined (see 4.2) but does not specify to whom the responsibilities are allocated. Annex E provides guidance on allocation of responsibility.

Sterilization of health care products—General requirements for characterization of a sterilizing agent and the development, validation, and routine control of a sterilization process for medical devices

1 Scope

1.1 This International Standard specifies general requirements for the characterization of a sterilizing agent, and for the development, validation, and routine control of a sterilization process for medical devices.

1.2 This International Standard applies to sterilization processes in which microorganisms are inactivated by physical and/or chemical means.

1.3 This International Standard does not apply to processes that rely solely on physical removal of microorganisms (for example, filtration).

1.4 This International Standard does not describe detailed test procedures for assessing microbial inactivation.

1.5 This International Standard is intended to be applied by process developers, manufacturers of sterilization equipment, manufacturers of medical devices to be sterilized, and the organization with responsibility for sterilizing the medical device.

1.6 This International Standard does not supersede or modify published International Standards for particular sterilization processes.

NOTES—

1 Although the scope of this International Standard is limited to medical devices, the principles described may also be applied to other health care products.

2 Sterilization processes validated and controlled in accordance with the requirements of this International Standard should not be assumed to be effective in inactivating the causative agents of spongiform encephalopathies such as scrapie, bovine spongiform encephalopathy, and Creutzfeld-Jakob disease. Specific recommendations have been produced in particular countries for the processing of materials potentially contaminated with these agents.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this International Standard. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this International Standard are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

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

ISO 10993-1, *Biological evaluation of medical devices—Part 1: Evaluation and testing.*

ISO 10993-17, *Biological evaluation of medical devices—Part 17: Establishment of allowable limits for leachable substances using health-based risk assessment.*

ISO 11138-1, *Sterilization of health care products—Biological indicators—Part 1: General.*

ISO 11140-1, *Sterilization of health care products—Chemical indicators—Part 1: General requirements.*

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

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

ISO 13485, *Quality systems—Medical devices—Particular requirements for the application of ISO 9001.*

ISO 13488, *Quality systems—Medical devices—Particular requirements for the application of ISO 9002.*

IEC 61010-1, *Safety requirements for electrical equipment for measurement, control and laboratory use—Part 1: General requirements.*

3 Terms and definitions

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

3.1 bioburden: Population of viable microorganisms on a product and/or a package.

3.2 biological indicator: Microbiological test system providing a defined resistance to a specified sterilization process.

3.3 change control: Formal assessment and determination of the appropriateness of a proposed alteration to product or procedure.

3.4 chemical indicator: System that reveals a change in one or more predefined process variables based on a chemical or physical change resulting from exposure to a process.

3.5 development: Act of elaborating a specification in preparation for validation.

3.6 establish: Determine by theoretical evaluation and confirm by experimentation.

3.7 fault: One or more of the process parameters which lies outside of its/their specified tolerance(s).

3.8 health care product: Medical device, medicinal product (pharmaceuticals and biologics) or *in vitro* diagnostic medical device.

3.9 installation qualification (IQ): Obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification.

3.10 material safety data sheet: Document specifying the properties of a material, its potential hazardous effects for humans and the environment, and the precautions necessary to handle and dispose of the material safely.

3.11 medical device: Any instrument, apparatus, appliance material, or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

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

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

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

— control of conception;

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

3.12 operational qualification (OQ): Process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures.

3.13 parametric release: Declaration that a product is sterile, based on the records demonstrating that the process parameters were delivered within specified tolerances.

3.14 performance qualification (PQ): Process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification.

3.15 process challenge device: Item designed to simulate product to be sterilized and to constitute a defined challenge to the sterilization process, and used to assess the effective performance of the process.

3.16 process parameter: Specified value for a process variable.

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

3.17 process variable: Condition associated with a sterilization process, changes in which alter microbicidal effectiveness.

NOTE—Process variables may include, for example, time, temperature, pressure, concentration, humidity, wavelength.

3.18 recognized culture collection: International depository authority under the Budapest Treaty on 'The International Recognition of the Deposit of Microorganisms for the Purpose of Patent and Regulation.'

3.19 reference microorganism: Microbial strain obtained from a recognized culture collection.

3.20 requalification: Repetition of part of validation for the purpose of confirming the continued acceptability of a specified process.

3.21 services: Supplies from an external source, necessary for the correct functioning of sterilizing equipment.

NOTE—Examples of services are electricity, water, compressed air, and drainage.

3.22 specify: Stipulate in detail within an approved document.

3.23 sterile: Free from viable microorganisms.

3.24 sterility: State of being free from viable microorganisms.

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

3.26 sterilization load: Product to be, or that has been, sterilized together using a given sterilization process.

3.27 sterilization process: Series of actions or operations to achieve the specified requirements for sterility.

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

3.28 sterilizing agent: Physical or chemical entity, or combination of entities, that have sufficient microbicidal activity to achieve sterility under defined conditions.

3.29 survivor curve: Graphical representation of the inactivation of a population of microorganisms with increasing exposure to a microbicidal agent under stated conditions.

3.30 test for sterility: Test defined in an official Pharmacopoeia for product release following exposure to a sterilization process.

3.31 test of sterility: Test performed as part of development, validation, or requalification to establish the presence or absence of viable microorganisms on product units, or portions thereof.

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

4 Quality system elements

4.1 General

The purpose of the quality system is to define and document procedures, the implementation of which control all stages of development, application and use of the sterilization process. It is not a requirement of this International Standard to have a complete quality system during design/development and production, but certain elements of a quality system are required and these are normatively referenced at appropriate places in the text. Attention is drawn to ISO 9001 and ISO 13485 which describe a quality system. This International Standard does not require third party assessment of the specified quality system elements.

4.2 Assignment of responsibilities

4.2.1 The responsibility for performing each element of the procedures in this International Standard shall be defined and documented. Responsibility for each element may vary from case to case and this International Standard does not allocate responsibility for each element to particular parties.

The elements are: quality system; sterilizing agent characterization; process/equipment characterization; product definition; process definition; validation; routine monitoring and control; product release from sterilization; and maintaining process effectiveness.

NOTE—These elements are illustrated in Table E.1.

4.2.2 Responsibilities shall be further assigned to qualified personnel as specified in ISO 13485 or ISO 13488.

NOTE—4.1.1, 4.1.2.2, and 4.18 of ISO 13485:1996 and ISO 13488:1996 detail requirements for management responsibility, personnel, and training.

4.3 Documentation and records

4.3.1 Documented procedures for each phase of the development, validation, routine monitoring and control, and product release from sterilization shall be prepared and implemented.

4.3.2 Documentation and records required by this International Standard shall be reviewed and approved by designated personnel (see 4.1.2). A system shall be prepared, documented, and maintained to control all procedures and records required by this International Standard. This system shall comply with ISO 13485 or ISO 13488.

4.3.3 Records of development, validation, routine monitoring and control, and product release from sterilization activities shall be retained.

4.3.4 The records required by this International Standard shall be retained in accordance with ISO 13485 or ISO 13488.

NOTE—4.4.6 of ISO 13485:1996 and ISO 13488:1996 detail requirements for retention of records.

4.4 Design control

Characterization of the sterilizing agent and sterilization process shall be undertaken in accordance with a documented plan. At defined stages, design reviews shall be planned, conducted, and documented.

NOTE—4.4.6 of ISO 13485:1996 details requirements for design reviews.

4.5 Calibration

A documented system, complying with ISO 13485, ISO 13488, or ISO 10012-1, shall be established and maintained for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this International Standard.

5 Sterilizing agent characterization

5.1 General

The purpose of this activity is to define the sterilizing agent, demonstrate its microbicidal effectiveness, identify the factors which influence microbicidal effectiveness, assess the effects that exposure to the sterilizing agent have on materials, and identify requirements for safety of personnel and protection of the environment. This activity may be undertaken in a test or prototype system; the final equipment specification (see 6.3) should be relatable to the experimental studies undertaken using any such test or prototype equipment.

5.2 Sterilizing agent

A specification for the sterilizing agent shall be generated and documented. This shall include, if appropriate, conditions for storage to maintain the sterilizing agent within its specification for the duration of any stated shelf life.

5.3 Microbicidal effectiveness

5.3.1 Microbicidal effectiveness studies shall

a) demonstrate the lethal action of the sterilizing agent against a representative range of microorganisms selected in accordance with annex A;

b) establish an empirical mathematical relationship defining the microbial inactivation kinetics of identified resistant microorganisms, and confirm that the probability of a microorganism surviving exposure to a defined treatment can be validly predicted;

c) select reference microorganism(s), based on the microbial inactivation kinetics, which have known high resistance(s) to the sterilizing agent for use in establishing the sterilization process;

d) identify the process variables which affect the lethal action of the sterilizing agent and the interactions of these process variables in relation to this lethal action;

e) assess those factors that can adversely affect the delivery and/or distribution of the sterilizing agent;

NOTE—Such factors may include, for example, the environment, packaging configuration(s), geometry, materials and residues from manufacturing, cleaning, and/or disinfection.

f) assess those factors that can adversely influence the effectiveness of the sterilizing agent based upon physical and/or chemical interactions;

NOTE—Such factors may include, for example, interactions with materials and residues from manufacturing, cleaning, and/or disinfection.

g) identify a means for terminating the activity of the sterilizing agent, if applicable.

5.3.2 The test method(s), acceptance criteria, test results, and justification for the choice of test microorganisms shall be documented.

5.4 Material effects

5.4.1 The effects of exposure to the sterilizing agent on the physical and/or chemical properties of materials and on their biological safety shall be assessed. The materials should be selected on the basis of the likely usage of the sterilizing agent.

5.4.2 The effects of repeated exposure to the sterilizing agent on properties of materials using the combination of process parameters likely to maximize material effects shall be studied.

5.4.3 The materials tested and the outcomes of all tests shall be documented, together with the criteria against which the properties of materials were assessed before and after exposure to the sterilizing agent.

5.5 Safety and the environment

5.5.1 Either a material safety data sheet or analogous safety information shall be prepared and documented for the sterilizing agent, its precursors (if any), and any by-products of the sterilizing agent. This material safety data sheet may be provided by a supplier for a chemical agent or be prepared as a prelude to experimental studies on the sterilizing agent.

5.5.2 The potential impact on the environment of any substance which could be released, either deliberately or accidentally, during or following use of the sterilizing agent, shall be assessed and measures for its control determined. This assessment, including the potential impact (if any) and the measures for control (if identified), shall be documented.

NOTE—ISO 14001 provides a specification for an environmental management system. ISO 14040 provides guidance on designing a life cycle assessment study.

6 Process and equipment characterization

6.1 General

The purpose of this activity is to define the entire sterilization process and the equipment necessary to deliver the sterilization process safely and reproducibly.

6.2 Process characterization

6.2.1 The process parameters, together with their tolerances, shall be established and documented. These tolerances shall be based upon knowledge of the combination of process parameters yielding the minimum acceptable microbicidal effectiveness and shall yield acceptable product.

NOTE—The establishment of the process parameters comprises the definition of process variables, including those that are excluded or minimized in ensuring the effectiveness of the sterilization process.

6.2.2 Means of monitoring and controlling the process variables shall be determined.

6.2.3 Any treatment of product that is required prior to exposure to the sterilization process to ensure the effectiveness of the process shall be defined and documented.

6.2.4 Any treatment of product that is required following exposure to the sterilizing agent to ensure the safety of the product shall be defined as part of the sterilization process and documented.

6.3 Equipment characterization

6.3.1 The specification for equipment to deliver the process within the tolerances stipulated for the process parameters and in a safe manner shall be established and documented.

6.3.2 The specification shall include but is not limited to

a) physical description of the equipment, together with any necessary ancillary items, including materials of construction;

b) specification of the sterilizing agent and the means by which it is provided, including any additives or precursors necessary for its delivery;

c) description of instrumentation for monitoring and controlling the sterilization process, including sensor characteristics and locations, indicating and recording instruments;

d) fault recognized by the sterilizing equipment;

e) safety features, including those for personnel and environmental protection;

f) installation requirements, including for the control of emissions, if applicable.

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

NOTE—Attention is drawn to ISO 9000-3.

6.3.4 Means shall be provided to ensure that a failure in a control function does not lead to a failure in recording of process parameters such that an ineffective process appears effective. This may be achieved either by the use of independent systems for control and monitoring, or a cross-check between control and monitoring which identifies any discrepancies and indicates a fault.

7 Product definition

7.1 The purpose of this activity is to define the product to be sterilized, including the microbiological quality of the product prior to sterilization and the manner in which product is packaged and presented for sterilization.

7.2 Product to be sterilized, including the packaging materials to be used and the manner in which product is to be presented to the sterilizing agent, shall be defined and documented.

Meeting this requirement could necessitate that appropriate information be provided to the organization undertaking the sterilization process by the manufacturer of the medical device and the manufacturer of the sterilization equipment.

7.3 A system shall be defined, documented, and maintained to ensure that the condition of the product presented for sterilization, including microbiological, organic, and inorganic contamination levels, is controlled and does not compromise the effectiveness of the sterilization process.

7.4 The effectiveness of the system defined in accordance with 7.3 shall be demonstrated. For medical devices to be supplied for single use, this demonstration shall include estimation of bioburden in accordance with ISO 11737-1. For medical devices to be reprocessed, this demonstration shall include assessment of the effectiveness of the specified cleaning and, if applicable, disinfecting process.

The intention is that bioburden be stable and low, given the nature of the raw materials, product, and manufacturing or reprocessing procedures prior to sterilization. This can be achieved by employing a quality system complying with ISO 13485 or ISO 13488 throughout the manufacture of the medical device, or by employing a defined and controlled cleaning process of demonstrated effectiveness, together with a disinfection process (if specified) prior to sterilization, and thereafter preventing recontamination of the medical device.

NOTE—International Standards for equipment to be used in cleaning and disinfecting medical devices prior to sterilization are in the course of preparation. These International Standards will include methods to demonstrate the effectiveness of a cleaning and disinfecting process.

8 Process definition

8.1 The purpose of this activity is to obtain a detailed specification for the sterilization process to be applied to defined product (see clause 7), without compromising the safety, quality, and performance of that product.

8.2 The sterilization process applicable for defined product shall be established. This shall be achieved by

a) if practical, demonstrating the attainment of the process parameters by measurements; and

b) delivering the sterilizing agent under conditions so designed to represent increments of treatments that deliver less lethality than the intended sterilization process using one of the approaches outlined in annexes B, C or D to this standard.

8.3 If biological indicators are used as part of the establishment of the sterilization process, these shall

a) comply with ISO 11138-1 and any subsequent parts of ISO 11138 which are applicable to the sterilization process;

b) be shown to be resistant to the sterilizing agent relative to the bioburden of product to be sterilized; and

c) be placed at positions in product where it has been determined that sterilizing conditions are most difficult to achieve.

8.4 If chemical indicators are used as part of the establishment of the sterilization process, these shall comply with ISO 11140-1 and any subsequent parts of ISO 11140 which are applicable to the process and shall be placed at positions in product where it has been determined that sterilizing conditions are most difficult to achieve.

8.5 If tests of sterility are performed during the establishment of the sterilization process, such tests shall comply with ISO 11737-2.

8.6 The biological safety of product following exposure to the sterilization process shall be established in accordance with ISO 10993-1.

8.7 A health-based risk assessment shall be conducted in accordance with ISO 10993-17 to identify and document limits for process residuals in product.

8.8 If necessary, means shall be established to reduce level(s) of process residual(s) in product below that (those) identified in accordance with 8.7.

8.9 It shall be demonstrated that the product meets its specified requirements for safety, quality, and performance following application of the specified sterilization process.

8.10 The specification for the sterilization process shall be documented.

9 Validation

9.1 General

The purpose of validation is to demonstrate that the sterilization process established in process definition (see clause 8) can be delivered effectively and reproducibly to the sterilization load. Validation consists of a number of identified stages: installation qualification, operational qualification, and performance qualification.

Installation qualification is undertaken to demonstrate that the sterilization equipment and any ancillary items have been supplied and installed in accordance with their specification.

Operational qualification is carried out either with unloaded equipment or using appropriate test material to demonstrate the capability of the equipment to deliver the sterilization process that has been defined (see clause 8).

Performance qualification is the stage of validation that uses product to demonstrate that equipment consistently operates in accordance with predetermined criteria and the process produces product that is sterile and meets the specified requirements.

9.2 Installation qualification

9.2.1 Equipment

9.2.1.1 The complete specification of all equipment used to deliver the sterilizing agent, including any ancillary items, shall be established and documented.

9.2.1.2 Sterilization equipment shall comply with IEC 61010-1 and any subsequent parts of IEC 61010 that are applicable to the sterilization equipment.

9.2.1.3 The operating procedures for the equipment shall be established and documented. These operating procedures shall include, but are not limited to,

a) step-by-step operating instructions;

b) fault conditions, the manner in which they are indicated, and actions to be taken;

c) instructions for maintenance and calibration; and

d) details of contacts for technical support.

9.2.2 Installation

9.2.2.1 A specification shall be documented for the location in which the equipment is to be installed, including any services required. Any special precautions and provisions shall be identified (for example, safety equipment).

9.2.2.2 Instructions for installation shall be documented and shall include instructions pertinent to the health and safety of personnel.

9.2.2.3 Prior to installation qualification, the calibration status of all instrumentation (including any test instruments) used for monitoring, controlling, indicating, or recording shall be confirmed (see 4.4).

9.2.2.4 It shall be demonstrated that the equipment and any ancillary items, as installed, operate as intended.

9.2.2.5 If applicable, conditions for the safe storage of the sterilizing agent to ensure that its quality and composition remain within specification shall be established and documented.

9.3 Operational qualification

9.3.1 Prior to operational qualification, the calibration status of all instrumentation (including any test instruments) used for monitoring, controlling, indicating, or recording shall be confirmed (see 4.4).

9.3.2 Operational qualification shall demonstrate that the installed equipment is capable of delivering the specified process (see 8.10) within defined tolerances.

9.4 Performance qualification

9.4.1 The manner of presenting the product for sterilization, including the orientation of product, shall be established and documented.

9.4.2 Product used for performance qualification shall be packaged identically to that to be sterilized routinely.

9.4.3 Data shall be generated to demonstrate the attainment of the defined physical and/or chemical conditions, within specified tolerances, throughout the sterilization load. The relationship(s) between the conditions occurring at positions used routinely to monitor the sterilization process and those conditions occurring throughout the sterilization load shall be established. This is achieved by determining the attainment of the specified condition(s) at predetermined positions throughout the sterilization load.

9.4.4 Microbiological performance qualification studies shall comprise delivery of the sterilizing agent under conditions designed so that the extent of treatment is reduced relative to that in the sterilization process. Extrapolation of the outcomes of such reduced treatment(s) shall predict that, on application of the sterilization process, the specified requirements for sterility will be met. The approaches to process definition described in annexes B, C, or D may also be employed in microbiological performance qualification studies.

9.4.5 Biological indicators employed during microbiological performance qualification shall comply with 8.3.

9.4.6 If test(s) of sterility are performed on product subjected to conditions as specified in 9.4.4, such tests shall be performed in accordance with ISO 11737-2.

9.4.7 If chemical indicators are used in performance qualification, they shall comply with 8.4.

9.4.8 Performance qualification shall include a series of at least three consecutive exposures of product to the sterilization process, within defined tolerances, in order to demonstrate the reproducibility of the process. Any exposures outside of defined tolerances during performance qualification shall be reviewed, and corrective measures determined and instituted before initiating a new series of exposures.

If failure can be attributed to factors not relevant to the effectiveness of the process being validated, this test may be documented as unrelated to performance of the process without requiring three further consecutive successful runs.

EXAMPLES—This type of failure may include, but is not limited to, power failures, loss of services, or failure of external monitoring equipment.

9.4.9 The levels of any process residues following exposure to the upper tolerances of the process parameters shall be demonstrated as being below the specified limits identified in the health-based risk assessment (see 8.7).

9.4.10 It shall be confirmed that the product meets its specified requirements for safety, quality, and performance following application of the defined process at the upper tolerances of the process parameters.

9.5 Review and approval of validation

9.5.1 The purpose of this activity is to undertake and document a review of the validation data to confirm the acceptability of the sterilization process and to approve the process specification.

9.5.2 Information gathered or produced during installation qualification, operational qualification, and performance qualification shall be documented and reviewed for acceptability (see also 4.2 and 4.3). The results of this review shall be documented.

9.5.3 A complete process specification, including the process parameters and their tolerances, shall be confirmed. This process specification shall also include the criteria for designating an individual sterilization process used for a particular sterilization load as conforming.

10 Routine monitoring and control

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

10.2 There shall be evidence through measurements, supplemented as necessary by biological indicators or chemical indicators, that the sterilization process was delivered within the defined tolerances (see also 9.4.3).

10.3 Data shall be recorded to demonstrate the attainment of process parameters.

10.4 All records shall be retained in accordance with 4.3.4.

10.5 If biological indicators are used in routine monitoring, they shall comply with 8.3 a) and b).

10.6 If chemical indicators are used in routine monitoring, they shall comply with ISO 11140-1 and any subsequent parts of ISO 11140 that are applicable to the process.

11 Product release from sterilization

11.1 A documented procedure(s) for product release from sterilization shall be defined and implemented. This procedure(s) shall define the criteria (see 9.5.3) for designating a sterilization process as conforming to its specification.

11.2 If biological indicators or chemical indicators are used to monitor the sterilization process (see 10.5 and 10.6), the results from exposure of these indicators shall be included within the criteria for product release from sterilization.

11.3 If the criteria specified in 11.1 are not met, product shall be considered as non-conforming and handled in accordance with documented procedures (see 4.3).

12 Maintaining process effectiveness

12.1 General

12.1.1 The continued effectiveness of the system for ensuring the condition of the product presented for sterilization (see 7.3) shall be demonstrated. This may include, for example, routine monitoring of product bioburden and/or monitoring the effectiveness of the cleaning process.

12.1.2 The accuracy and reliability of the instrumentation used to control and monitor the sterilization process shall be verified periodically in accordance with 4.5.

12.2 Maintenance of equipment

12.2.1 Preventative maintenance shall be planned and performed in accordance with documented procedures. The procedure for each planned maintenance task and the frequency at which it is to be carried out shall be specified and documented.

12.2.2 Equipment shall not be used to process product until all specified maintenance tasks have been satisfactorily completed and recorded.

12.2.3 Records of maintenance shall be retained.

12.2.4 The maintenance scheme, maintenance procedures and maintenance records shall be reviewed periodically by a designated person. The results of the review shall be documented.

12.3 Requalification

12.3.1 Requalification of a sterilization process carried out with specified equipment shall be performed at defined intervals.

12.3.2 Requalification report(s) shall be documented and retained in accordance with 4.3.3.

12.3.3 Requalification data shall be reviewed against specified acceptance criteria in accordance with documented procedures. Records of reviews of requalification data and corrective actions taken in the event that the specified acceptance criteria are not met shall be retained (see 4.3.3 and 4.3.4).

12.4 Assessment of change

A change to equipment, product, packaging, or presentation of product for sterilization or a modification to the sterilizing agent and/or its presentation shall be assessed for impact on the effectiveness of the sterilization process. The extent of qualification that is necessary shall be determined. The outcome of the assessment, including the rationale for decisions reached, shall be documented.

The magnitude of the change is considered in determining the extent to which installation qualification, operational qualification, or performance qualification is undertaken.

Annex A
(normative)

Factors to be considered in selection of microorganisms for demonstrating microbicidal effectiveness

A.1 General

This annex presents the factors to be considered in selecting microorganisms used in demonstrating the microbicidal effectiveness of a sterilizing agent. Table A.1 gives examples of microorganisms that may be included in such studies. Table A.1 is not exhaustive and, for a new sterilization process, it should not be assumed that the microorganisms listed in Table A.1 will be the most resistant.

A.2 Data

The data obtained in the demonstration of microbicidal effectiveness should establish whether a bacterial spore can be employed as a representative model of high resistance during process characterization studies.

A.3 Selection of microorganisms

The selection of species of microorganisms to be used in demonstrating the microbicidal effectiveness of a sterilizing agent shall take account of all of the following factors:

a) known high resistance to the sterilizing agent or an expectation of a high resistance from information in scientific literature or a knowledge of the mode of action of the sterilizing agent;

b) known resistance to well-characterized sterilization processes;

c) representative species of aerobic and anaerobic Gram positive and Gram negative bacteria, bacterial spores, mycobacteria, fungi including spore forms and yeasts, parasites, and viruses;

d) species that might be present as a result of the materials of construction of the product or the environment in which it is manufactured;

e) species that have been isolated during estimations of bioburden undertaken on typical product to be processed.

NOTES—

1 The information obtained in A.3 b) is to provide a comparison with other sterilization processes and to ensure that well-characterized microorganisms are included in the studies.

2 Inactivation of viruses and parasites [see A.3 c)] is a particular consideration in processes used to sterilize products containing material of animal origin (see also EN 1244-3), as well as in resterilizing medical devices in health care facilities.

3 In considering the information from A.3 e), it should be noted that the resistance of microorganisms isolated from product can be modified by recultivation.

Table A.1—Examples of potential test microorganisms

Bacterial spores	*Bacillus subtilis* var. *niger* *Bacillus stearothermophilus* *Clostridium sporogenes*
Vegetative bacteria	*Staphylococcus aureus* *Salmonella choleraesuis* *Pseudomonas aeruginosa*
Fungi	*Trichophyton mentagrophytes* (with conidia) *Candida* spp.
Mycobacteria	*Mycobacterium terrae*
Nonlipid viruses	Hepatitis A Parvovirus Poliovirus type 1 (attenuated)
Lipid viruses	*Herpes simplex*
Parasites	*Cryptosporidium parvum*

NOTES—

1 This table is not intended to be a comprehensive list of microorganisms that have to be evaluated and should not be assumed to cover all the factors specified above for any particular sterilization process. This table is informative only.

2 Viral culture may use any suitable cell line which is traceable and for which the number of passage(s) is known.

Annex B
(normative)

Approach 1—Process definition based on inactivation of the microbial population in its natural state

B.1 General

Methods 1 and 2 in annex B of ISO 11137:1995 + Corrigendum 1:1997 are examples of process definition based on inactivation of the microbial population in its natural state.

This approach has been described as a “bioburden-based method.”

B.2 Sampling

Product selected for studies on process definition shall be representative of routine production.

B.3 Procedure

Expose product to the sterilizing agent in predetermined increment(s) of the anticipated sterilization process. Establish the required accuracy and precision of increments, and control and monitor the delivery of the sterilizing agent to meet defined limits.

Following exposure to the sterilizing agent, subject product individually to the test of sterility in accordance with ISO 11737-2.

To define the sterilizing process, use knowledge of the relationship between the proportion of products exhibiting no growth in tests of sterility and the extent of exposure to the sterilizing agent.

B.4 Follow-up

Confirm the continued appropriateness of the sterilization process at defined intervals using product representative of routine production.

Annex C
(normative)

Approach 2—Process definition based on inactivation of reference microorganisms and knowledge of bioburden on product items to be sterilized

C.1 General

This approach has been referred to as the “combined biological indicator/bioburden method.” Guidance on this approach can be found in ISO 14161.

C.2 Procedure

Establish the location within the product at which sterility is most difficult to achieve.

Create a challenge to the sterilization process, comprising a known number of microorganisms with known resistance to the sterilizing agent, by one of the following approaches:

a) placing biological indicators within the product at position(s) where sterilizing conditions are most difficult to achieve;

b) inoculating the position(s) within product where sterilizing conditions are most difficult to achieve with reference organisms.

If the product is inoculated in this manner, it can be considered to be a biological indicator. Subclause 8.3 requires this packaged, inoculated product to meet the requirements of ISO 11138.

Package the challenge, created in accordance with the list above, in the same manner as products produced routinely and included within the sterilization load.

Expose the sterilization load to the sterilizing agent under conditions selected to deliver less lethality than those conditions to be used routinely, such that not all the reference microorganisms have been inactivated.

Determine the number of microorganisms surviving, either by direct enumeration or estimated by a most probable number technique.

Calculate the rate of inactivation of the reference microorganisms.

From a knowledge of the bioburden (established in accordance with 7.4) and the rate of inactivation of the reference microorganisms, determine the extent of treatment required to achieve the specified requirements for sterility.

Annex D
(normative)

Approach 3—Conservative process definition based on inactivation of reference microorganisms

D.1 General

This approach to process definition has been widely employed, particularly for products to be re-processed in health care establishments. Qualifying a sterilization process for such products employs an approach different from that adopted with virgin product. This is because the challenge to the sterilization process is difficult to define and preprocessing treatments such as cleaning are difficult to validate and control. Therefore, sterilization processes applied in these situations are often conservative and employ a treatment that may exceed that required to achieve the specified requirements for sterility. This approach has been referred to as the "overkill approach." Guidance on this approach can be found in ISO 14161.

D.2 Procedure

D.2.1 Determine the position(s) within product where it is most difficult to achieve sterilizing conditions.

Create a challenge to the sterilization process containing a known number of microorganisms with defined resistance to the sterilizing agent by one of the following approaches:

a) placing biological indicators within the product at position(s) where sterilizing conditions are most difficult to achieve;

b) inoculating the position(s) within product where sterilizing conditions are most difficult to achieve with reference organisms.

If the product is inoculated in this manner, it can be considered to be a biological indicator. Subclause 8.3 requires this packaged, inoculated product to meet the requirements of ISO 11138.

Package the challenge, created in accordance with the list above, in the same manner as products produced routinely and included within the sterilization load.

D.2.2 Expose the sterilization load to the sterilizing agent under conditions designed to deliver a reduced level of treatment.

D.2.3 Identify the extent of treatment that inactivates 10^6 microorganisms.

NOTE—With an initial challenge of 10^6 viable microorganisms, this extent of treatment can be identified conservatively as the treatment after which no surviving microorganisms are recovered.

D.2.4 Repeat exposure to the level of treatment identified in D.2.3 on at least two further occasions.

D.2.5 If the inactivation of 10^6 microorganisms has been confirmed following D.2.4, determine the extent of treatment for the sterilization process by extrapolation to a predicted probability of a surviving microorganism of 10^{-6} or better, taking into account the nature of the inactivation kinetics of the sterilizing agent and the number and resistance of the microorganisms on the biological indicator.

This approach is best suited to sterilization processes which demonstrate linear inactivation kinetics. In such cases the extent of treatment can be defined conservatively as twice that employed in D.2.4. For sterilization processes that do not demonstrate linear inactivation kinetics, the exact nature of the inactivation kinetics shall be established in order to derive a relationship to use for the extrapolation.

NOTE—A knowledge of the inactivation kinetics can be obtained as in 5.3 b), and may be modified by the influence of product.

Annex E
(informative)

Guidance on application of this International Standard

E.1 General

The guidance given in this annex is not intended as a checklist for assessing compliance with this International Standard. This guidance is intended to assist in obtaining a uniform understanding and implementation of this standard, by providing explanations and acceptable methods for achieving compliance with specified requirements. It highlights important aspects and provides examples. Methods other than those given in the guidance may be used, providing their performance achieves compliance with this International Standard.

E.2 Quality system elements

E.2.1 Assignment of responsibilities

E.2.1.1 General

The development, validation, and routine control of a sterilization process is likely to involve a number of separate parties, each of whom is responsible for certain elements. This International Standard does not require particular elements to be carried out by defined parties but does require that the party accepting particular responsibilities is defined and that this definition of responsibilities is documented. This documented definition of responsibilities should be within the quality management system(s) of the identified parties and may form part of a contractual relationship.

Table E.1 illustrates the elements of this International Standard and, for illustration only, names parties that may be responsible for identified activities. It should be noted that

a) the elements listed may not be sequential, as the design and testing program may be iterative in part; and,

b) responsibilities for the elements may vary from case to case.

The organization accepting responsibilities for defined elements is required to assign these elements to appropriately trained and qualified personnel (see E.2.2).

In order to illustrate the variety of possible allocations of responsibility, three sample scenarios are presented. These scenarios are not intended to be all-inclusive.

E.2.1.2 Health care facility

In this scenario, the user of the sterilization process is a health care facility. Three parties are involved in complying with this International Standard: the health care facility, the sterilizer manufacturer, and the medical device manufacturer. The assignment of responsibilities, and the means used to undertake these responsibilities, might be as follows.

a) Quality system

   Each party has its own quality system. The limits of responsibility of each party are laid down in formal contracts.

b) Sterilizing agent characterization

   The health care facility has agreed to a contract to purchase a sterilization system from a sterilizer manufacturer; this sterilizer manufacturer accepts responsibility for sterilizing agent characterization and has the resultant data on file. The health care facility has access to these data and, prior to making the decision to purchase, has reviewed the manufacturer's data and the data available in the published scientific literature.

c) Process/equipment characterization

   The sterilizer manufacturer has undertaken the process/equipment characterization, developed the equipment specification and has the necessary regulatory approval to place the product onto the market. The health care facility reviews the equipment specification to confirm that it has the services and infrastructure necessary to operate the sterilizing equipment.

d) Product definition

The health care facility has identified the medical devices that it intends to reprocess. The instructions for reprocessing these medical devices provided by the manufacturer include instructions for cleaning and disinfection and confirm that the proposed method for sterilization is appropriate. The medical device manufacturer has undertaken process definition studies in collaboration with the sterilizer manufacturer in order to substantiate the reprocessing instructions provided. The health care facility reviews its data on the effectiveness of its cleaning processes and confirms they are adequate for the particular device(s) and sterilization process.

e) Process definition

The sterilizer manufacturer and the medical device manufacturer have collaborated to define the sterilization process for these particular medical devices and have included the relevant instructions within each of their instructions for use. The necessary regulatory approvals have been obtained. The health care facility reviews the documentation and confirms that it has the capability to follow these instructions.

f) Validation

The health care facility agrees, by contract with the sterilizer manufacturer, to undertake installation qualification and operational qualification, in accordance with documented procedures. The health care facility undertakes performance qualification and then reviews and approves the validation exercise.

g) Routine monitoring and control

The health care facility undertakes the routine control and monitoring in accordance with its documented procedures.

h) Product release from sterilization

The health care facility undertakes the product release from sterilization in accordance with its documented procedures.

i) Maintaining process effectiveness

The health care facility accepts responsibility for maintaining process effectiveness. It agrees by contract with the sterilizer manufacturer to undertake planned preventative maintenance and calibration. It defines procedures for requalification. The health care facility defines procedures for the periodic reassessment of the effectiveness of its cleaning and disinfection processes.

E.2.1.3 Medical device manufacturer using in-house facilities

In this scenario, the user of the sterilization process is a manufacturer of single-use medical devices who is installing in-house facilities for sterilization. The parties involved are the medical device manufacturer and the sterilizer manufacturer. The allocation of responsibilities might be as follows.

a) Quality system

Each party has its own quality system. The limits of responsibility of each party are laid down in formal contracts.

b) Sterilizing agent characterization

The sterilizer manufacturer has undertaken the sterilizing agent characterization and made the data available to the medical device manufacturer.

c) Process/equipment characterization

The sterilizer manufacturer has developed an equipment specification, including a control system for the equipment, which is capable of being programmed to deliver a predefined process.

d) Product definition

The medical device manufacturer is responsible for the specification of the product and its manufacture.

e) Process definition

The medical device manufacturer defines a process for the particular medical device(s) to be sterilized. The medical device manufacturer undertakes the biological safety assessments and product compatibility studies. These studies are conducted using experimental sterilization equipment.

f) Validation

The medical device manufacturer undertakes validation using the sterilization equipment to be used routinely, confirming that it is capable of delivering the defined sterilization process.

g) Routine control and monitoring

This is carried out by the medical device manufacturer in accordance with documented procedures.

h) Product release from sterilization

This is carried out by the medical device manufacturer in accordance with documented procedures.

i) Maintaining process effectiveness

This is carried out by the medical device manufacturer in accordance with documented procedures.

E.2.1.4 Medical device manufacturer using a sterilization subcontractor

In this scenario, the user of the sterilization process is a manufacturer of single-use medical devices who is using a sterilization subcontractor to deliver the sterilization process. Additionally, the medical device manufacturer is using a contract laboratory to undertake defined testing as part of the product release procedures. The parties involved are the medical device manufacturer, the sterilization subcontractor, and the contract laboratory. The allocation of responsibilities might be as follows:

a) Quality system

Each party has its own quality system. The limits of responsibility of each party are laid down in formal contracts.

b) Sterilizing agent characterization

The sterilization subcontractor has licensed the sterilization process from a separate organization who characterized and developed the sterilization process. The process developer has undertaken the sterilizing agent characterization and made the resultant data available to the sterilization subcontractor and the medical device manufacturer.

c) Process/equipment characterization

The sterilization subcontractor has developed an equipment specification, including a control system for the equipment, which is capable of being programmed to deliver a predefined process. A sterilizer manufacturer has been contracted to manufacture and install the specified equipment.

d) Product definition

The medical device manufacturer is responsible for the specification of the product and its manufacture.

e) Process definition

The medical device manufacturer defines a process for the particular medical device(s) to be sterilized. The medical device manufacturer undertakes the biological safety assessments and product compatibility studies. In this case, these studies are conducted using experimental sterilization equipment.

f) Validation

The sterilization subcontractor undertakes installation qualification and operational qualification in accordance with documented procedures. The medical device manufacturer then undertakes performance qualification using the installed sterilization equipment, confirming that the equipment is capable of delivering the defined sterilization process. The medical device manufacturer reviews and approves the validation exercise.

g) Routine control and monitoring

This is carried out by the sterilization subcontractor and the contract laboratory in accordance with documented procedures agreed with the medical device manufacturer.

h) Product release from sterilization

This is carried out by the medical device manufacturer in accordance with documented procedures, on the basis of records provided by the sterilization subcontractor and the contract laboratory.

i) Maintaining process effectiveness

The sterilization subcontractor carries out equipment maintenance and calibration in accordance with documented procedures. The medical device manufacturer maintains the quality of product prior to sterilization and takes responsibility for requalification; the sterilization subcontractor carries out any necessary repetition of part or all of installation qualification or operational qualification.

E.2.2 Personnel

The level of qualification, training, and experience required by personnel at various levels will depend upon the activities being performed. General guidance on training as part of the overall system of quality assurance is given in ISO 9004.

Particular qualifications and training are appropriate for personnel with the following responsibilities: microbiological testing; chemical analysis and formulation; installation of equipment; equipment maintenance; physical performance qualification; routine sterilizer operation; calibration; process design; equipment specification.

E.3 Sterilizing agent characterization

E.3.1 Neutralization

Before commencing any investigation of microbial inactivation, it is necessary to ensure that the results of the investigation are not influenced adversely by microbicidal or microbiostatic effects due to carry-over of the sterilizing agent or its residual derivatives into the recovery system; such effects can be reduced by

a) dilution of the sterilizing agent;

b) removal of the sterilizing agent by filtration; or

c) inactivation of the sterilizing agent by reaction with a neutralizing agent.

If a secondary host such as cell culture is used as the detection system for the survival of test organisms, the absence of carry-over effects on the cell culture system itself should also be demonstrated. Cytotoxity controls also should be included to determine the effect of the sterilizing agent on the cell culture system used for detection of test organisms. In addition, challenge of the defined cell culture system previously exposed to the residual levels of sterilizing agent and its derivatives, if any, with a low level (approximately 10) of microorganisms will show that the enumeration assay is functional.

The choice of neutralizing system is influenced by the nature of the sterilizing agent. The effectiveness of the chosen system should be demonstrated prior to the commencement of inactivation studies.

E.3.2 Studies of microbial inactivation

E.3.2.1 General

Many chemicals and processes can be shown to have antimicrobial activity. Not all, however, meet the criteria for a sterilizing agent. The intent and approach of the microbial inactivation studies are to

— provide definition of the sterilizing agent and the associated process and equipment sufficient to establish and maintain reproducible conditions for microbial inactivation studies. This activity should be documented;

— develop and validate methods for the growth of microorganisms and their inoculation onto carriers for exposure to the sterilizing agent. These procedures include recovery and enumeration of microorganisms from the carriers, and estimation of the fraction of exposed carriers rendered sterile. The necessity for neutralization of residues of the sterilizing agent should be considered (see E.3.1);

— define the microbicidal activity of the sterilizing agent against different types of microorganisms;

— identify a highly resistant microorganism(s) appropriate for detailed microbial inactivation studies;

— with the highly resistant microorganism(s), characterize the microbicidal activity of the sterilizing agent in regard to concentration/potency, exposure time/dose, and/or other variables that could affect the microbicidal activity;

— using the inactivation data obtained with the highly resistant microorganism(s), define the kinetics of microbial inactivation and demonstrate that the attainment of a probability of a microorganism surviving a defined treatment can be calculated. Confirm that the lethal action can be extrapolated validly to predict the probability of a microorganism surviving exposure to a defined treatment.

E.3.2.2 Sterilizing agent and associated equipment

E.3.2.2.1 Studies on sterilizing agent characterization may be performed with laboratory, prototype, or routine production-type equipment. For each situation, sufficient definition of the sterilizing agent and the associated process(es) and equipment is required in order to ensure reproducible conditions for microbial inactivation studies.

E.3.2.2.2 Consideration should be given to reproducible set-up and operation of equipment and the monitoring and control of variables that can affect the outcome of the microbial inactivation studies. Operational aspects of inactivation studies vary according to the complexity of the overall system. For example, inactivation studies with a liquid chemical sterilizing agent performed in a "test tube" will be, by nature, much less complex than those with a gas plasma agent.

E.3.2.2.3 Regardless of the complexity of the process, the set-up for each study should be documented; any changes to the set-up and their impact on the outcome of microbial inactivation studies should be assessed and documented. Operation of the equipment and the performance of studies should preferably be conducted in accordance with a previously written procedure. Data defining the conditions of exposure to the sterilizing agent should be documented together with the microbiological and any other test measurements.

E.3.2.3 Development of microbiological methods and their validation

E.3.2.3.1 Microbial inactivation studies require the use of test methods validated for the specific sterilizing agent. During the design and validation of the test methods, particular attention should be paid to test conditions that result in spurious data arising from, for example, inadequate recovery conditions, the occurrence of microbiostasis, and false positives. Residual microorganism inactivation due to delay in testing arising, for example, from transport of test material to a contract laboratory should also be considered. Development of the test methods and/or their performance may be carried out in-house or in a contract laboratory.

E.3.2.3.2 Selection of test microorganisms for microbial inactivation studies should be justified. Methods to be validated may include

a) growth, maintenance, and enumeration of the selected test organism;

b) inoculation of samples of the selected microorganisms onto carriers for exposure to the sterilizing agent;

   Microorganisms inoculated onto carriers should be prepared in a defined and reproducible manner. The effects of drying of the inoculum and storage of the carriers (under defined conditions) upon organism viability and resistance to the sterilizing agent should be considered. The carriers should neither inhibit nor potentiate the action of the agent upon the inoculated microorganisms.

c) quantitative assessment of inactivation of microorganisms on carriers exposed to a sterilizing agent and recovery of microorganisms from carriers following exposure to a sterilizing agent.

   Demonstration of the lethal action of the sterilizing agent, over a range sufficient to define the microbial inactivation kinetics, requires an adequate number of viable microorganisms to be initially present on and recoverable from carriers. In studies requiring quantitative enumeration of surviving organisms from carriers exposed to graded treatments of the sterilizing agent, the numbers of microorganisms recovered from exposed carriers are compared to those recovered from the unexposed controls to construct survivor curves relating log survival to extent of treatment.

NOTE—Microbial inactivation and failure to recover viable test microorganisms from the surface of an inoculated carrier exposed to the sterilizing agent might not be distinguishable. In this context, use of tracer agents (such as radiolabeled microorganisms) could be useful.

E.3.2.4 Microbial inactivation studies

E.3.2.4.1 Studies of microbial inactivation are both qualitative and quantitative in nature. The qualitative studies test the activity of the candidate sterilizing agent against a range of microorganisms. The purpose of these studies is two-fold:

a) to demonstrate that a range of different types of microorganisms are sensitive, to some degree, to the action of the sterilizing agent;

b) to identify one or more highly resistant microorganisms for more quantitative inactivation studies.

E.3.2.4.2 If, during these studies, bacterial spores are found to be essentially insensitive to the action of the candidate sterilizing agent, its use for sterilization applications is not permissible although other antimicrobial uses may exist (e.g., low-level disinfection).

E.3.2.4.3 The quantitative microbial inactivation studies demonstrate that the sterilizing agent, when applied in a defined manner, can reliably yield a calculable probability of a surviving microorganism. These studies generally involve the use of graded exposure to or contact with the sterilizing agent to generate survival data defining the inactivation of the previously identified highly resistant microorganism(s). To define the upper section of the microbial survival curve, direct enumeration methods are generally used. For the section of the curve where there is a low probability of survivors occurring, fraction negative data are employed. In the construction of such survival curves, the practical lower limit of estimation of average numbers of surviving microorganisms is 0.01. The extent of treatment to provide a probability of a surviving microorganism lower than this limit is inferred by extrapolation. In situations where the survival curve is log-linear, i.e.. a plot on semi-log paper yields a straight line, this extrapolation is readily performed. A curve that is concave in relation to the *x*-axis can yield a somewhat conservative estimate of the extent of treatment. Caution has to be used if the microbial inactivation studies indicate a result that is best approximated by a survivor curve that is convex in relation to the *x*-axis.

E.3.2.4.4 Further information can be found in the references cited in the Bibliography.

E.4 Product definition

E.4.1 General

This clause describes product considerations that are addressed when evaluating a sterilization process. These considerations ensure that the sterilization process will result in a safe and functional product. Certain process conditions can adversely affect the integrity of medical devices and packages. Some packaging materials and devices could impede the sterilization process. Therefore, the effects of the sterilization process on materials and design characteristics and on packaging configurations and materials are evaluated. This evaluation is usually conducted during product development.

E.4.2 Design considerations for medical devices intended for sterilization

E.4.2.1 Product function

Product can be subjected to various environmental stresses during sterilization, such as vacuum and pressure changes, elevated temperature, and changes in relative humidity. Product also could react with the sterilizing agent and/or any diluent(s). The product design has to ensure that functionality and safety are not compromised by exposure to the anticipated range of sterilization conditions. Typically, the maximum conditions would represent the most severe challenge to the product including the package. If applicable, the effects of multiple exposures to the sterilization process are evaluated.

E.4.2.2 Design tolerances and configuration

Design tolerances and configuration are important in ensuring effective delivery of the sterilizing agent and its distribution. If fitments are intended to maintain sterility, they are designed to avoid inadvertent contamination of surfaces intended to be sterile.

E.4.2.3 Materials composition

It is important to select materials that exhibit adequate resistance during sterilization to chemical and physical changes caused by the sterilizing agent and/or any diluents over the anticipated range of sterilization conditions. Properties of materials required to satisfy requirements for product performance, such as physical strength, permeability, physical dimensions, and resilience, are evaluated after sterilization to ensure that the materials are still acceptable for use. Degradation effects due to exposure to the sterilization process, such as crazing, embrittlement, and phase separation, should be determined, and resistant materials specified. Materials should also allow sufficient sterilizing agent, transmission, or permeation to ensure that target surfaces and materials are sterilized. The materials should allow aeration (if applicable) within a reasonable time and retain biocompatibility. Methods for determining residuals of the sterilizing agent should be selected and validated during product development. If applicable, the effects of exposure to multiple sterilization processes are evaluated.

E.4.3 Packaging considerations

E.4.3.1 General

The major function of a package for a sterilized medical device is to ensure that the product remains sterile until used. During sterilization, the package is intended to withstand the process conditions without a negative effect on overall product quality (e.g., generation of particulates).

Packaging considerations are addressed in more detail in ISO 11607.

E.4.3.2 Primary packaging

When selecting a primary package for a product that is to be sterilized, certain major design and manufacturing factors are considered with respect to the particular sterilization process. If penetration is required, the permeability of the package to the particular sterilizing environment is of utmost importance. For nonpermeable packaging (e.g., vials, ampoules, flexible pouches), the material and design permit adequate transfer of the sterilizing agent to the product. If air removal is part of the sterilization process, the package also permits air evacuation without damage or rupture. It is recommended that preliminary evaluation of the maintenance of primary package integrity be conducted before final selection of a sterilization cycle. Those portions of the primary package or product components intended to maintain product sterility (e.g., closures) should be demonstrated to maintain their integrity during and following exposure to the sterilization process.

E.4.3.3 Secondary packaging

The ability of the secondary packaging to protect the product during customary handling and distribution should be demonstrated. If the secondary packaging is to be exposed to the sterilization process evidence, is generated to show that the secondary packaging can withstand the process without losing its ability to protect the product . Additionally, the effect of the materials from which the secondary packaging is made on the attainment of sterilizing conditions during the process is established, together with the effect of resterilization (if applicable) on the secondary packaging.

E.5 Process definition

E.5.1 General

Process definition is undertaken to define the process parameters for a sterilization process, which will achieve the specified requirements for sterility for a defined product without adversely affecting product performance. Therefore process definition includes at least two bodies of work: one directed at assessing the impact (if any) of a range of candidate values for the process variables on the product and packaging and the other directed at defining the process parameters which will achieve the specified requirements for sterility for the product.

E.5.2 Influence on product and packaging

As sterilization does not typically improve product performance, a careful selection of values and tolerances for each process variable should be undertaken during process definition. In general, those variables which, when increased, significantly improve sterilization effectiveness without adversely affecting product performance should be maximized during this stage. Conversely, those variables which, when increased, adversely impact product performance without significantly improving sterilization effectiveness should be minimized during this stage. In addition, if there is a threshold value observed during these studies above which significant adverse effects on product or packaging are observed, it should be documented.

E.5.3 Determination of process effectiveness

E.5.3.1 General

The sterilization process will be defined based on the inactivation of microorganisms. These microorganisms could be either the natural contamination on the product or reference microorganisms that present at least as great a challenge as does the bioburden on the product. There are, however, a number of stages in the determination of process effectiveness that should be performed in order to have confidence in the selection of the process parameters. If biological indicators are to be used, the stages include the selection of the biological indicator, the determination of the most difficult to sterilize location, the assessment of lethality at this location, and the evaluation of the influence of packaging and load configuration.

E.5.3.2 Selection of biological indicator

A review of the data obtained from the microbial inactivation studies performed in E.3.2.4 should be conducted to select a biological indicator. The biological indicator should have a relatively high resistance to the sterilization process when compared to other microorganisms evaluated. In addition, the challenge presented by the biological indicator should be compared to that of the product bioburden and, if the challenge is greater than that of the product

bioburden, it can be considered as appropriate for process definition and subsequent validation studies. While it is not necessary to determine the D-value for each bioburden isolate, it is important to assess the more resistant portion of the bioburden population. Relative inactivation can be assessed via graded exposures to the sterilizing agent.

E.5.3.3 Placement of the biological indicator

Once the biological indicator has been selected, an appropriate location within the product has to be established. This location can be established based on an expert understanding of the process and a documented rationale for why a given location will be the last to fully achieve the sterilizing conditions. If this cannot be done with certainty, then a number of locations that are likely to be difficult to sterilize should be evaluated. A biological indicator should be placed at each of these locations within product and the product exposed to a fraction of the sterilization process. The location which consistently yields the greatest number of survivors should be chosen.

E.5.3.4 Selecting the process parameters

From the range of values for the process variables studied in E.5.2, a single value with its tolerance should be defined for all but one of the process variables. Typically the process variable that is not defined is time. A series of studies is performed to generate a survivor curve which is extrapolated to enable the process to be fully defined. The form of the survivor curve can be different than that observed during earlier characterization studies. For instance, the survivor curve observed during characterization may have been a straight line. This might be expected when the process parameters are fully achieved at process start, and fully depleted at the end of the process. When measuring inactivation at the most difficult to sterilize location, however, the process parameters may not be fully achieved at process start or fully depleted at the end of the process. This is certainly the case for processes which involve heating or gas penetration. In such cases, the effectiveness of the sterilizing agent will increase with time, and the survivor curve will be concave with respect to the *x*-axis. However, at no time should the inactivation rate be greater than that observed in the characterization studies. Conversely, if the process parameters decay with time, the microbicidal effects of the sterilizing agent will deteriorate, and the survivor curve will be convex in respect of the *x*-axis. In this case, there is greater risk in predicting end points, and it is recommended that other values for the process variables be evaluated.

E.5.3.5 Evaluating the influence of packaging and load configuration

While it is desirable to evaluate all primary and secondary packaging in the process definition studies, this may not always be possible. In most cases, the primary packaging can and should be used in the process definition studies, as it could impact the rate of achievement of the sterilizing conditions. If experimental sterilization equipment is used to perform these studies, it may not be possible to accommodate the secondary and/or tertiary packaging that might also influence the attainment of sterilizing conditions. Furthermore, the effectiveness of the process can be affected by the load configuration, mass, density, etc. For these reasons, it is desirable to perform the process definition studies where possible in equipment that will accommodate the sterilization load. While the impact of the sterilization load will be assessed during validation, it is recommended that it be evaluated as early in development as practical.

E.5.3.6 Process residues

If the health-based risk assessment conducted in accordance with 8.7 identifies residues of the sterilizing agent for which acceptable limits have to be set, the process definition should aim to minimize the presence of such residues on or in product while meeting the specified requirements for sterility. Additionally, a post-treatment may have to be defined to reduce further the level of residues to meet any specified limits. If a post-treatment is required, it is defined and validated as part of the sterilization process.

E.6 Validation

E.6.1 General

A validation study has at least the three main elements described in E.6.2 to E.6.4.

E.6.2 Installation qualification (IQ)

For new equipment, IQ begins with establishing and documenting the design, purchase, and installation requirements. IQ should be based on written requirements which ensure that the established construction and installation requirements are assessed as soon as installation permits and that these requirements are met. IQ should be documented, and the documentation should include drawings and details of all the construction materials, the dimensions and tolerances of the chamber in which the load will be placed (if applicable), support services, and power supplies.

IQ should be certified prior to operational qualification of the equipment.

E.6.3 Operational qualification (OQ)

Operational qualification consists of documented testing of the equipment over its defined and installed operating range to verify consistent operation. OQ should be documented and certified prior to performance qualification of the process. The documentation should include details of alarm systems, monitoring systems with response tolerance and accuracy requirements, the operational limits of all critical process variables, and safety checks.

E.6.4 Performance qualification (PQ)

PQ consists of documented trials and testing to establish confidence that the finished product produced by the specified process in the specified equipment meets all the requirements for safety, quality, and performance. Changing process variables that can affect quality should form part of this testing. Changes should simulate those that may be encountered in routine production including “worst case” conditions to ensure that results are reproducible.

E.7 Routine monitoring and control

Routine monitoring and control of sterilization processes is based primarily on measurements of the conditions delivered during the sterilization process. Supplementation of these measurements by the use of biological indicators or chemical indicators may be required.

Procedures for routine monitoring and control are required to ensure that the process parameters of the sterilization cycle are within limits equivalent during performance qualification. These procedures should include the tests and checks, and the frequency with which these tests and checks should be performed. In addition, routine monitoring positions for taking direct measurements are defined as are the locations where any biological indicators or chemical indicators are to be placed. The appropriateness of routine monitoring positions and any process challenge devices that are used are demonstrated during performance qualification.

If product test samples are required, these should be properly identified and placed among other products in a routine sterilization load.

E.8 Product release from sterilization

E.8.1 General

Failure to meet the physical specification or failure of the indicator to meet its specified requirements should lead to the sterilization load being placed in quarantine and the cause of failure investigated. The investigation should be documented.

If the process parameters are outside their specified tolerances, product should not be released. Product should be evaluated in accordance with non-conforming product procedures. The decision reached as to the disposition of the product is documented.

The suitability of the product and packaging for resterilization and the effect of repeated exposures to the sterilization process on product functionality should be included in the validation exercises. If product is sterilized again because the initial exposure to the sterilization process was outside of its specification, records of the initial sterilization process should be included or referenced in the sterilization file.

E.8.2 Product release using biological indicators

If biological indicators are to be used in product release, records of the physical sterilization process parameters and results of indicator testing are reviewed to demonstrate the effective delivery of the sterilization process.

Guidance on the selection, use, and interpretation of results of biological indicators is contained in ISO 14161.

E.8.3 Parametric release

If a sterilization cycle operating within specified tolerances has been demonstrated to be both effective and reproducible, confirmation that the process parameters were within specification limits is taken as evidence of the reliability of the cycle. Parametric release is the declaration of adequacy of sterilization of product based on the direct measurement and evaluation of physical parameters within the chamber and the sterilization load. No other sample or indicator testing is required for parametric release.

Parametric release is considered a design aspect of a sterilization process that can be fully characterized. The appropriateness of parametric release should be demonstrated during the development and validation of the sterilization process. For parametric release to be effective, all process parameters have to be identified and their values known. Therefore, parametric release should be supported by extensive experience of the sterilization process. Typically, parametric release is justified for a defined sterilization process and defined product rather than for generic application.

E.8.4 Test for sterility

Various pharmacopoeias specify tests for sterility that can be applied to a sample withdrawn from a batch of product that has been exposed to a sterilization process. The value of conducting such tests for sterility is limited because of the insensitivity of the method. This International Standard does not require the conduct of a test for sterility. However, should a manufacturer specify such testing as part of the criteria for product release from sterilization (see 11.1), product is treated as nonconforming and handled accordingly if the test criteria are not satisfied.

E.9 Maintaining process effectiveness

E.9.1 Change control

A change control system should be employed that establishes when operational or performance qualification testing should be repeated. Qualification is recommended if significant changes are made in the sterilization equipment (hardware or software), process, product, or packaging that could influence sterilization effectiveness. The following are examples (not necessarily all-inclusive) of changes that could necessitate performance qualification unless data are available to establish equivalency prior to and after such changes.

a) Product tolerance: a change in the product material, assembly, construction, or design tolerances that could affect attainment of sterilizing conditions;

b) Product design: significant change in product design including product materials composition or thickness that could influence the effectiveness of the sterilization process;

c) Packaging: a change in packaging design that could significantly affect physical properties of the package and attainment of sterilizing conditions;

d) Equipment: changes that could affect the ability to maintain specified process parameters or a modification to the sterilizing agent and/or its presentation;

e) Process: alterations in the process that could substantially change the manner in which process parameters are achieved and controlled (e.g., changes in process control software);

f) Product loading or density: changes in the previously validated loading configurations that could affect sterilizing agent penetration into the load.

E.9.2 Requalification

E.9.2.1 To guard against unreported or inadvertent changes, consideration should be given to periodic repetition of all or part of installation, operational, and performance qualification. The interval between periodic requalifications should be determined by the nature of the sterilization process and by the amount of process data documented. The interval may be varied taking into account historical data that demonstrate process reproducibility and conformance with established specifications for process parameters. The decision to perform requalification may be event-related or time-related.

E.9.2.2 Typically, requalification would be performed for the reference load or for a sample product type. However, if requalification detected a process change, performance qualification may need to be performed again.

E.9.2.3 Previous validation and requalification results should be considered in establishing the requalification protocol. Single requalification cycles are typically performed. Data from requalification should be compared with records of the original validation (and any subsequent requalification) to confirm that the original performance has been retained. This comparison is facilitated by a common format for validation and requalification reports.

Table E.1—Elements of sterilizing agent characterization, and sterilization process development, validation, and routine control

ELEMENTS	PURPOSE	COMPONENTS	RESPONSIBLE PARTY
QUALITY SYSTEM	To provide a structure to control all stages of the sterilization process	- Personnel and training - Documentation - Records - Review procedures - Corrective action	All parties with respect to the elements undertaken
STERILIZING AGENT CHARACTERIZATION	To define the sterilizing agent and its microbicidal effectiveness	- Agent definition - Microbicidal effectiveness - Material effects - Safety and environment	Developer of the sterilizing agent and/or sterilization process
PROCESS/ EQUIPMENT CHARACTERIZATION	To define the overall sterilization process and the equipment necessary to carry it out	- Process description - Equipment specification - Ancillary equipment and service definition	Sterilizer manufacturer, in collaboration with the developer of the sterilization process, if appropriate
PRODUCT DEFINITION	To define the product to be sterilized	- Product specification - Packaging materials - Product quality prior to sterilization	Manufacturer of product to be sterilized (and sterilizer manufacturer, depending on claims made for sterilizing equipment)
PROCESS DEFINITION	To define the sterilization process in order to achieve sterility for identified product while maintaining safety performance of the product	- Development - Biological safety - Process residuals - Product compatibility - Limits on resterilization	Manufacturer of product to be sterilized, in collaboration with the sterilizer manufacturer and, if appropriate, the health care facility
VALIDATION	To demonstrate that the defined sterilization process can be delivered effectively and reproducibly to the sterilization load	- Installation qualification - Operational qualification - Performance qualification - Review and approval of validation	Organization with responsibility for sterilizing the product (either product manufacturer or health care facility), in collaboration with the sterilizer manufacturer, if appropriate Product manufacturer or health care facility, in collaboration with the organization sterilizing the products, if appropriate
ROUTINE MONITORING AND CONTROL	To demonstrate that the validated sterilization process has been delivered within defined tolerances to all products within a sterilization load	- Sterilization load configuration - Process monitoring - Record generation - Record retention	Product manufacturer or health care facility
PRODUCT RELEASE FROM STERILIZATION	To review records of routine control procedures and determining the disposition of a particular sterilization load	- Record review - Indicator testing (if any) - Product disposition - Corrective action (if any)	Product manufacturer or health care facility
MAINTAINING PROCESS EFFECTIVENESS	To ensure the continued acceptability of the validated sterilization process	- Product quality prior to sterilization - Calibration - Equipment maintenance	Product manufacturer or health care facility, together with organization sterilizing the product, if appropriate

Annex ZA
(informative)

Corresponding International and European Standards

At the time of publication of this International Standard, the following EN documents were equivalent to the normative International Standards referenced in the text. CEN maintains a register of currently valid European standards.

ISO/IEC Publication	EN
ISO 13485	EN ISO 13485 or EN 46001
ISO 13488	EN ISO 13488 or EN 46002
ISO 10012-1	EN ISO 10012-1
ISO 10993-1	EN ISO 10993-1
ISO 10993-17 (in preparation)	EN ISO 10993-17 (in preparation)
ISO 11138-1	EN 866-1
ISO 11140-1	EN 867-1
ISO 11737-1	EN 1174-1, -2, -3
ISO 11737-2	EN ISO 11732-2
IEC 61010-1	EN 61010-1

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General Bibliography

[1] EN 556, *Sterilization of medical devices—Requirements for terminally-sterilized medical devices to be labeled "Sterile."*

[2] AAMI ST67,[1)] *Sterilization of medical devices—Requirements for products labeled 'STERILE.'*

[3] ISO 9000-3, *Quality management and quality assurance standards—Part 3: Guidelines for the application of ISO 9001:1994 to the development, supply and maintenance of computer software*.

[4] ISO 9001, *Quality systems—Model for quality assurance in design, development, production, installation and servicing*.

[5] ISO 9002, *Quality systems—Model for quality assurance in production installation and servicing*.

[6] ISO 9004, *Quality management systems—Guidelines for performance improvements*.

[7] ISO 11134, *Sterilization of health care products—Requirements for validation and routine control—Industrial moist heat sterilization*.

[8] ISO 11135, *Medical devices—Validation and routine control of ethylene oxide sterilization*.

[9] ISO 11137, *Sterilization of health care products—Requirements for validation and routine control—Radiation sterilization*.

[1)] To be published.

[10] ISO 13683, *Sterilization of health care products—Requirements for validation and routine control of moist heat sterilization in health care facilities*.

[11] ISO 14160, *Sterilization of single-use medical devices incorporating materials of animal origin—Validation and routine control of the sterilization by liquid chemical sterilants*.

[12] ISO 14161, *Sterilization of health care products—Biological indicators—Guidance for the selection, use and interpretation of results*.

[13] ISO 11607, *Packaging for terminally sterilized medical devices*.

[14] ISO 14001, *Environmental management systems—Specification with guidance for use*.

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