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American National Standard

ANSI/AAMI ST67:2003

Sterilization of health care products—Requirements for products labeled “STERILE”

AAMI Association for the Advancement of Medical Instrumentation

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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.

In summary, a standard or recommended practice is truly useful only when it is used in conjunction with other sources of information and policy guidance and in the context of professional experience and judgment.

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American National Standard ANSI/AAMI ST67:2003

Sterilization of medical devices—Requirements for products labeled “STERILE”

Developed by
Association for the Advancement of Medical Instrumentation

Approved 18 December 2003 by
American National Standards Institute, Inc.

Abstract: This standard establishes requirements and guidance for selection of an appropriate sterility assurance level for a terminally sterilized medical device and acceptance criteria for a maximum contamination rate of an aseptically filled product.

Keywords: aseptic processing, sterility assurance level (SAL)

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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 60601-1-2:2001	ANSI/AAMI/IEC 60601-1-2:2001	Identical
IEC 60601-2-04:2002	ANSI/AAMI DF80:2003	Major technical variations
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
IEC TR 60878:2003	ANSI/AAMI/IEC TIR60878:2003	Identical
IEC TR 62296:2003	ANSI/AAMI/IEC TIR62296:2003	Identical
ISO 5840:1996	ANSI/AAMI/ISO 5840:1996	Identical
ISO 7198:1998	ANSI/AAMI/ISO 7198:1998/2001	Identical
ISO 7199:1996	ANSI/AAMI/ISO 7199:1996/(R)2002	Identical
ISO 10993-1:2003	ANSI/AAMI/ISO 10993-1:2003	Identical
ISO 10993-2:1992	ANSI/AAMI/ISO 10993-2:1993/(R)2001	Identical
ISO 10993-3:2003	ANSI/AAMI/ISO 10993-3:2003	Identical
ISO 10993-4:2002	ANSI/AAMI/ISO 10993-4:2002	Identical
ISO 10993-5:1999	ANSI/AAMI/ISO 10993-5:1999	Identical
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ISO 10993-8:2000	ANSI/AAMI/ISO 10993-8:2000	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999	Identical
ISO 10993-10:2002	ANSI/AAMI BE78:2002	Minor technical variations
ISO 10993-11:1993	ANSI/AAMI 10993-11:1993	Minor technical variations
ISO 10993-12:2002	ANSI/AAMI/ISO 10993-12:2002	Identical
ISO 10993-13:1998	ANSI/AAMI/ISO 10993-13:1999	Identical
ISO 10993-14:2001	ANSI/AAMI/ISO 10993-14:2001	Identical
ISO 10993-15:2000	ANSI/AAMI/ISO 10993-15:2000	Identical
ISO 10993-16:1997	ANSI/AAMI/ISO 10993-16:1997/(R)2003	Identical
ISO 10993-17:2002	ANSI/AAMI/ISO 10993-17:2002	Identical

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International designation	U.S. designation	Equivalency
ISO 11134:1994	ANSI/AAMI/ISO 11134:1993	Identical
ISO 11135:1994	ANSI/AAMI/ISO 11135:1994	Identical
ISO 11137:1995 and Amdt 1:2001	ANSI/AAMI/ISO 11137:1994 and A1:2002	Identical
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 TS 11139:2001	ANSI/AAMI/ISO 11139:2002	Identical
ISO 11140-1:1995 and Technical Corrigendum 1:1998	ANSI/AAMI ST60:1996	Major technical variations
ISO 11607:2003	ANSI/AAMI/ISO 11607:2000	Identical
ISO 11737-1:1995	ANSI/AAMI/ISO 11737-1:1995	Identical
ISO 11737-2:1998	ANSI/AAMI/ISO 11737-2:1998	Identical
ISO TR 13409:1996	AAMI/ISO TIR13409:1996	Identical
ISO 13485:2003	ANSI/AAMI/ISO 13485:2003	Identical
ISO 13488:1996	ANSI/AAMI/ISO 13488:1996	Identical
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ISO 14160:1998	ANSI/AAMI/ISO 14160:1998	Identical
ISO 14161: 2000	ANSI/AAMI/ISO 14161:2000	Identical
ISO 14937:2000	ANSI/AAMI/ISO 14937:2000	Identical
ISO 14969:1999	ANSI/AAMI/ISO 14969:1999	Identical
ISO 14971:2000 and A1:2003	ANSI/AAMI/ISO 14971:2000 and A1:2003	Identical
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ISO 15223/A1:2002	ANSI/AAMI/ISO 15223:2000/A1:2001	Identical
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ISO 15674:2001	ANSI/AAMI/ISO 15674:2001	Identical
ISO 15675:2001	ANSI/AAMI/ISO 15675:2001	Identical
ISO TS 15843:2000	ANSI/AAMI/ISO TIR15843:2000	Identical
ISO TR 15844:1998	AAMI/ISO TIR15844:1998	Identical
ISO TR 16142:1999	ANSI/AAMI/ISO TIR16142:2000	Identical
ISO 25539-1:2003	ANSI/AAMI/ISO 25539-1:2003	Identical

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Committee representation

Association for the Advancement of Medical Instrumentation

AAMI Microbiological Quality (SALs) of Processed Medical Devices Working Group

This standard was developed by the AAMI Microbiological Quality (SALs) of Processed Medical Devices Working Group under the auspices of the AAMI Sterilization Standards Committee. Approval of this standard does not necessarily mean that all working group members voted for its approval.

At the time this document was published, the **AAMI Microbiological Quality (SALs) of Processed Medical Devices Working Group** had the following 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.

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Foreword

This standard was developed by the AAMI Microbiological Quality (SALs) of Processed Medical Devices Working Group under the auspices of the AAMI Sterilization Standards Committee.

The purpose of this standard is to codify current North American sterilization practices and provide a standardized framework for determining appropriate SALs and maximum contamination rates.

As used within the context of this standard, “shall” indicates requirements strictly to be followed in order to conform to the standard; “should” indicates that among several possibilities one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action should be avoided but is not prohibited; “may” is used to indicate that a course of action is permissible within the limits of the standard; and “can” is used as a statement of possibility and capability. “Must” is used only to describe “unavoidable” situations, including those mandated by government regulation.

The concepts incorporated in this standard should be considered flexible and dynamic. AAMI policies and procedures require that AAMI standards and recommended practices be reviewed and, if necessary, revised at least once every five years.

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

NOTE—This foreword does not contain provisions of the AAMI standard *Sterilization of medical devices—Requirements for products labeled “STERILE”* (ANSI/AAMI ST67:2003), but it does provide important information about the development and intended use of the document.

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Introduction

A sterile medical device is one that is free of viable microorganisms. Sterility of a medical device can be achieved through

a) a terminal sterilization process;

b) sterilization of components, followed by sterile filtration of the final liquid formulation and aseptic filling into sterilized containers; or

c) a combination of chemical/physical sterilization and aseptic processing.

Products produced in accordance with manufacturing quality system requirements for medical devices may have microorganisms on them before sterilization. Such products are nonsterile. The purpose of sterilization processing is to inactivate the microbiological contaminants and thereby transform the nonsterile products into sterile products.

The inactivation of a pure culture of microorganisms by a sterilizing agent (e.g., dry heat, moist heat, ethylene oxide, or ionizing radiation) approximates an exponential rate of kill. Thus, there is always a finite probability that a microorganism might survive, regardless of the extent of treatment applied. For a given extent of treatment, the probability of survival is determined by the number and resistance of microorganisms and the environment in which the organisms exist during treatment. The sterility of any one product is defined in terms of the probability of a viable microorganism on the product following sterilization. This probability is typically referred to as a sterility assurance level (SAL).

Some products, such as liquids that cannot withstand the chemical/physical conditions of certain sterilization processes, may be sterilized by filtration. The effectiveness of sterilization by filtration is based on the ability of the filter to remove a known quantity of microorganisms of a known size under the specified filtration conditions. In addition, the subsequent filling and sealing of the sterilized liquid must be conducted aseptically in accordance with quality system requirements to prevent microbial contamination of the sterile product.

Aseptic processing requires the presterilization of all product parts or components that are in direct contact with the aseptically filled product. The products are processed in a controlled environment where microbial counts are maintained at or below defined levels and human intervention is minimized. Manufacturers use validated systems, trained personnel, controlled environments, and well-documented systematic processes to ensure a sterile finished product. One acceptance criterion for validating the sterility of products manufactured by aseptic processing is the maximum contamination rate as determined in microbial growth media fill experiments.

Requirements for quality systems for the design, development, production, supply, installation, and servicing of medical devices are given in the U.S. Food and Drug Administration's (FDA's) Quality System Regulation (21 CFR 820) and the International Organization for Standardization's (ISO's) ISO 13485, adopted in the U.S. by AAMI (current edition ANSI/AAMI/ISO 13485:2003). ANSI/AAMI/ISO 13485 is an application of the ISO 9000 series of quality management system standards. The ISO 9000 series of standards recognizes that there are certain processes used in manufacturing for which the results cannot be fully verified by subsequent inspection and testing of the product. Terminal sterilization, sterile filtration, and aseptic processing are examples of such processes. For this reason, terminal sterilization, sterile filtration, and aseptic processing must be validated before commercial production, and these processes must be monitored routinely. The manufacture of a sterile medical device also requires attention to product and package or container characteristics, facilities, controls, and other aspects of a quality system.

The purpose of this standard is to codify current North American sterilization practices and provide a standardized framework for determining appropriate SALs and maximum contamination rates. The following guidance is provided in the annexes:

a) the background and history of the selection of an appropriate SAL or maximum contamination rate, and

b) examples of medical devices that historically have been terminally sterilized.

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Sterilization of medical devices— Requirements for products labeled “STERILE”

1 Scope

1.1 Inclusions

This standard specifies requirements and provides guidance for selecting an appropriate SAL for a terminally sterilized medical device or a maximum contamination rate for an aseptically processed medical device that is labeled “STERILE.” The requirements and guidance provided in this standard also apply to the selection of an appropriate SAL for a terminally sterilized medical device that is labeled “Sterile Fluid Path.”

1.2 Exclusions

This standard does not address medical devices that are not labeled “STERILE.” For example, nonsterile medical devices that possess antimicrobial properties or contain preservatives for the control of microbial levels are not addressed. This standard also does not address products regulated as drugs or biologics by the FDA.

2 Normative reference

The following normative reference contains provisions that, through reference in the text, constitute provisions of this standard. For any dated reference, subsequent amendments to or revisions of the reference do not apply. However, parties to agreements based on this standard are encouraged to investigate the possibility of applying the most recent editions of the normative reference indicated below.

U.S. FOOD AND DRUG ADMINISTRATION. Quality system regulation. *Code of Federal Regulations*, Title 21, Part 820.

3 Definitions

For the purposes of this standard, the following definitions apply.

3.1 aseptic processing: Use of aseptic techniques for handling and filling product containers and/or devices in a controlled environment in which the air supply, materials, equipment, and personnel are all regulated to control microbial and particulate contamination to acceptable levels.

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

3.3 D value, D_{10} value: Time or radiation dose required to achieve inactivation of 90 % of a population of the test microorganism under stated exposure conditions.

3.4 maximum contamination rate: Mathematical expression of the frequency of the occurrence of a nonsterile unit as determined by media fill simulation of an aseptic process.

NOTE—Maximum contamination rate is normally expressed as a percentage, such as 0.1 % (1/1,000).

3.5 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 a physiological process; or

— 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.

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NOTE—For purposes of this standard, "medical device" includes *in vitro* diagnostic and combination products that have been determined by the FDA to be medical devices.

3.6 product: Raw materials, intermediate products, subassemblies, and health care products.

NOTE—For purposes of this standard, a *product* can be an individual medical device, collection of medical devices, component of a medical device, or sterile fluid pathway of a medical device.

3.7 sterile: Free from viable microorganisms.

3.8 sterile fluid path: Interior surfaces of a medical device that come into contact with a fluid during use of the device and are free from viable microorganisms.

3.9 sterility assurance level (SAL): Probability of a single viable microorganism occurring on a product after sterilization.

NOTE—SAL is normally expressed as 10^{-n}. Historically, 10^{-6} and 10^{-3} SALs have been used for sterilization. The term SAL has a quantitative value, and 10^{-6} is lower than 10^{-3}. When applying this quantitative value to assurance of sterility, one has a greater assurance of sterility with a lower SAL. Therefore, an SAL of 10^{-6} provides a greater assurance of sterility than an SAL of 10^{-3}.

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

NOTE 1—In a sterilization process, the nature of microbial inactivation is described by an exponential function. Therefore, the presence of a viable microorganism on any individual item can be expressed in terms of probability. While this probability may be reduced to a very low number, it can never be reduced to zero. (See sterility assurance level (SAL).)

NOTE 2—In a sterile fill process, sterility is achieved by microbial removal under aseptic conditions using a mechanical process (e.g., filtration). The efficacy of this process can be expressed as a maximum contamination rate.

3.11 terminal sterilization: Validated process whereby product within its primary package is sterilized.

4 Determination of an appropriate SAL or maximum contamination rate for a medical device to be labeled "STERILE"

4.1 General

An SAL of 10^{-6} has been used for terminal sterilization of certain medical devices. An SAL of 10^{-3} has been used for certain medical devices, depending on their intended use or their inability to withstand a terminal sterilization process that provides an SAL of 10^{-6}. (See Annex A.) The choice of a sterilization process and SAL shall be addressed during the development of the product and process design requirements in conformance with a quality system (e.g., see 21 CFR 820.30). The appropriate validation method shall be selected in order to demonstrate that the sterilization process will routinely achieve the chosen SAL.

Historically, a maximum contamination rate of no more than 0.1 % (1:1,000) has been used as an acceptance criterion in the validation of aseptic processing. (See 4.3 and Annex A.)

This standard specifies requirements and offers guidance (as given in the annexes) for the selection of an appropriate SAL or maximum contamination rate for medical devices. Both terminal sterilization and aseptic processing are acceptable processes for the production of a sterile product when the processes are appropriately validated and correctly applied.

The selection of an SAL for those products that are terminally sterilized is discussed in 4.2. The selection of a maximum contamination rate for those products that are aseptically processed is discussed in 4.3.

4.2 Selection of an SAL for a terminal sterilization process

4.2.1 General

For medical devices to be terminally sterilized, the SAL shall be selected on the basis of the criteria given in 4.2.2, 4.2.3, or 4.2.4. (See Figure 1.)

4.2.2 Selection based on intended use of the medical device

NOTE—Examples of products that historically have been terminally sterilized and the SALs that historically have been selected for the products are provided in Annex B.

The SAL selected for a terminally sterilized device shall be dependent on the intended use of the product:

a) a 10^{-6} SAL, or an SAL providing a greater assurance of sterility (i.e., 10^{-7}, 10^{-8}, etc.), shall be used for

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- products intended to come into contact with breached skin or compromised tissue (i.e., tissue that has lost natural barrier integrity or is damaged or injured);
- invasive products that enter normally sterile tissue;
- products with claims of sterile fluid pathways; and
- surgically implanted devices.

NOTE—4.2.4 describes instances in which other SALs may be acceptable.

b) a 10^{-3} SAL, or an SAL providing a greater assurance of sterility (i.e., 10^{-4}, 10^{-5}, etc.), shall be used for

- products not intended to come into contact with breached skin or compromised tissue; and
- topical products that contact intact skin or mucous membranes.

4.2.3 Selection based on sterilization process and/or validation method

NOTE—Examples of products that historically have been terminally sterilized and the SALs that historically have been selected for the products are provided in Annex B.

The extent of treatment with a sterilizing agent that is determined as being required to achieve a particular SAL may be related to the validation method used (for example, in general, a bioburden-based validation method will give a shorter extent of treatment to achieve a particular SAL than a biological indicator–bioburden or "overkill" method). Validation methods for each of the sterilization processes are detailed in ANSI/AAMI/ISO 11134, ANSI/AAMI/ISO 11135, ANSI/AAMI/ISO 11137, and ANSI/AAMI ST63.

For those products that require a 10^{-6} SAL and are incapable of withstanding the sterilization process chosen, alternative sterilization processes and/or validation methods should be investigated before selecting an alternative SAL (e.g., 10^{-5}, 10^{-4}, or 10^{-3}). (See also 4.2.4.) For example, if the manufacturer has chosen to validate a moist heat sterilization process using an overkill method and the product cannot withstand the process, alternative sterilization processes (e.g., ethylene oxide or radiation) or validation methods (e.g., biological indicator–bioburden or bioburden) should be investigated.

4.2.4 Selection based upon the product's inability to withstand a terminal sterilization process that achieves a 10^{-6} SAL

NOTE—Examples of products that historically have been terminally sterilized and the SALs that historically have been selected for the products are provided in Annex B.

If, based on its intended use, a product would be required to achieve a 10^{-6} SAL, but the product is incapable of withstanding the process, the selection of an SAL other than 10^{-6} may be necessary. A different SAL may be selected when all of the following apply:

a) the product cannot be designed to allow a sterilization process that achieves an SAL of 10^{-6} without adversely affecting its essential safety and function;

b) the product offers unique or superior benefits for patient diagnosis, treatment, or care; and

c) no alternative product is available that can be sterilized with a process that achieves a 10^{-6} SAL.

In these instances, the product is sterilized by means of a validated sterilization process in which the theoretical probability of a viable microorganism being present on the product after sterilization is an SAL of 10^{-5}, 10^{-4}, or 10^{-3}. The most rigorous SAL shall be selected (i.e., a 10^{-5} SAL shall be chosen before a 10^{-4} SAL, and a 10^{-4} SAL shall be chosen before a 10^{-3} SAL), based upon the ability of the product to function after sterilization.

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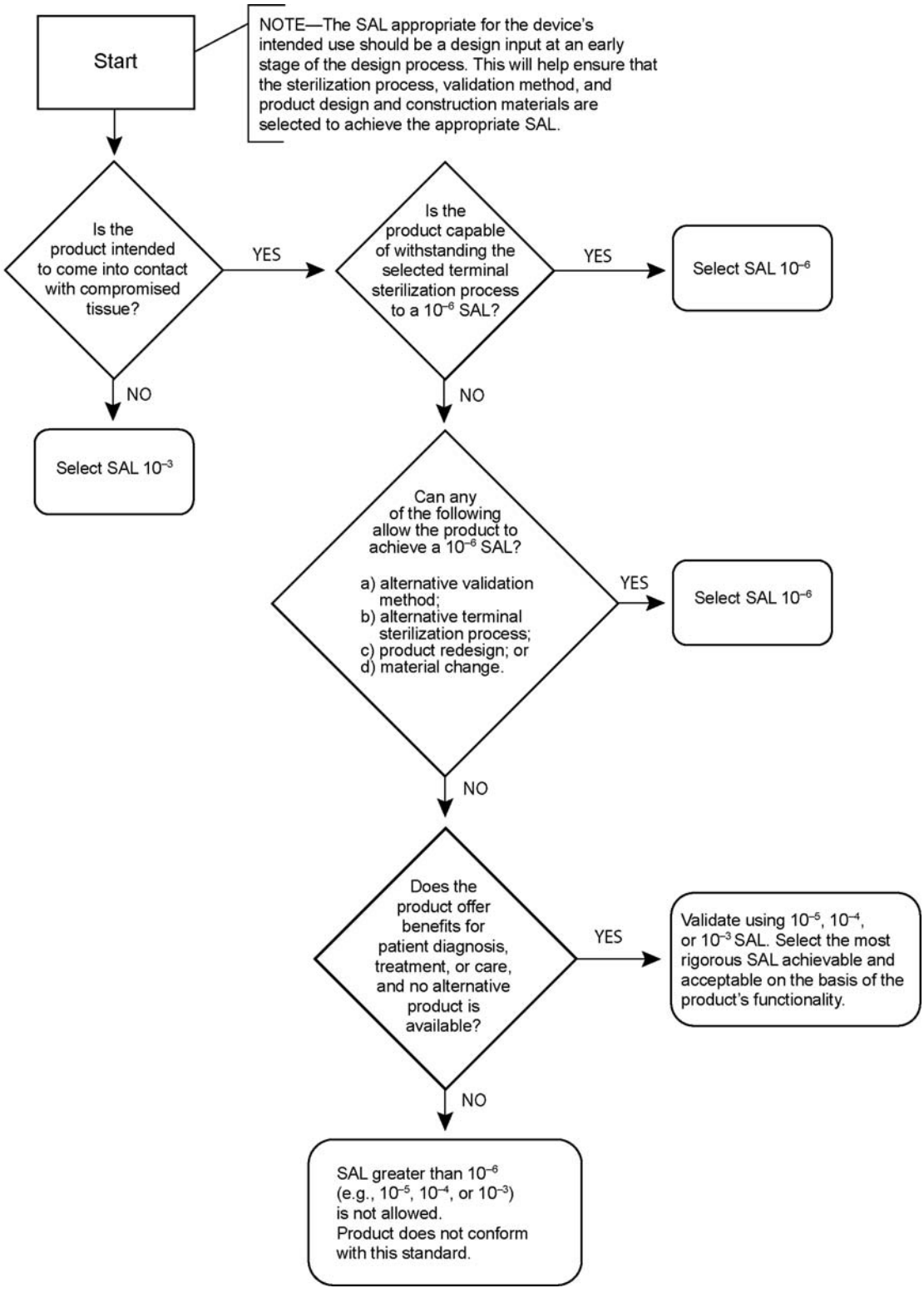

Figure 1—Decision tree for selection of SAL for medical devices to be terminally sterilized (section 4.2)

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4.3 Maximum contamination rate for validation of aseptic processing

Manufacturers using an aseptic technique should aim to achieve a contamination rate of zero. The specification of a maximum contamination rate depends on the rate that can be achieved by the particular aseptic processing technology (the process capability) and the limitations of available validation techniques. The maximum contamination rate shall be no more than 0.1 %. Acceptance limits allow a maximum of 0/3,000 or 1/4,750 positive products, which provides 95 % confidence of obtaining a 0.1 % contamination rate. (See also FDA, 1991; FDA, 1994; ISO 13408; ISO 14644; and ISO 14698.)

Examples of aseptically filled products that have been produced using a maximum contamination rate of no more than 0.1 % include

a) biotechnology products,

b) *in vitro* diagnostics,

c) prefilled syringes,

d) radiopharmaceuticals,

e) respiratory therapy devices,

f) clinical laboratory devices, and

g) lens care solutions.

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Annex A
(informative)

Background and historical application of sterility assurance levels and maximum contamination rates

A.1 Sterility assurance levels (SALs)

The effectiveness of a validated sterilization process can be determined by measuring the kinetics of microbial inactivation. It is from the exponential value of inactivation kinetics that the concept of the SAL is derived. The value of SAL is expressed as a negative power to the base 10. Historically, there have been several definitions of SAL. The definition chosen for this standard is that used by the International Organization for Standardization (ISO).

SALs were first developed by the food canning industry. Since it was impossible to establish sterility by sampling cans of product after moist heat sterilization, a safety factor was established that incorporated the kinetics of inactivation of *Clostridium botulinum* spores so that the moist heat cycle would have the equivalent of a 12-log spore reduction (i.e., 12 D value).

In the mid-1960s, the National Aeronautics and Space Administration (NASA) used the dry heat sterilization process for the Viking Planetary Space Probe. For this process, NASA specified that the probability of landing a microorganism on Mars would be 10^{-4} or less. Also in the 1960s, the Swedish public health authorities required a stated SAL of 10^{-6} (or an SAL providing a greater assurance of sterility) for medical devices labeled “STERILE.”

In 1979, the Canadian Health Protection Branch proposed a Microbiological Survival Index (MSI), which was defined as the reciprocal of the logarithm for the probability of a survivor from a sterilization process. The Canadian Health Protection Branch proposed labeling sterile medical products with the MSI numbers corresponding to SALs of 10^{-3} (MSI-3) and 10^{-6} (MSI-6). Such labeling met with strong opposition from both industry and medical care professionals because of an anticipated market battle over labeling claims that had no corresponding clinical benefit to the patient. However, the North American medical device industry and the Bureau of Medical Devices of the U.S. Food and Drug Administration (FDA) supported the use of two SALs which would be based on the assessment of the capabilities of the microbial inactivation potential of a sterilization process and on the intended use of the medical device (Bruch, 1981). Implicit in the meaning of SAL is not just the concept of sterility and the probability of an item being contaminated, but also the elements of good manufacturing practices (GMPs) and process validation. An SAL is a measurement or estimate of lethality of the entire sterilization process (Favero, 1993).

Research has shown that factors other than SAL influence the outcome of patient infection and the use of sterile medical devices. These factors include (a) device material, (b) improper handling of the device once sterile packaging is opened, (c) extent of patient and device exposure time during surgery or other procedures, (d) number and types of microorganisms contacted, and (e) immune status of the patient (Elek and Conen, 1957; Ritter et al., 1976; Moylan et al., 1987; Greene, 1993; Merritt et al., 1999). So far, there has never been a relationship established between the particular SAL of a medical device and hospital-acquired (nosocomial) infections. Factors associated with nosocomial infections have been studied, and it has been documented that the microorganisms associated with those infections may originate from (a) microbial flora of the patients themselves, (b) other patients, visitors, and health care personnel, or (c) the hospital environment.

SAL is the probability of a survivor per item determined from first-order death rate kinetics data after exposure to the sterilant used for the sterilization process. The required SAL is assured by such factors as the sterilization cycle development, calibration of equipment, validation of the sterilization process, standard loads with known zones of minimum lethality, process monitoring and control, product and process change control, and GMPs such as control of microbial contamination on products before the sterilization process. Implicit in an SAL, then, is not just the probability of an item being nonsterile, but also all of the elements of GMPs and process validation.

In the 1990s, the European Committee for Standardization (CEN) established the standard *Sterilization of medical devices—Requirements for medical devices to be labeled sterile* (EN 556). CEN determined that it would not be acceptable to ascribe two different interpretations (i.e., 10^{-3} and 10^{-6} SALs) to the term “STERILE.” An SAL of 10^{-6} was chosen for EN 556, with the provision that a greater probability of non-sterility could be permitted under special circumstances. However, that edition of EN 556 applied only to terminally sterilized medical devices and did not address aseptically processed products labeled “STERILE.”

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A.2 Maximum contamination rates for aseptically processed products

Aseptic processing does not inactivate microorganisms, as in the case of terminal sterilization, but prevents the introduction of microorganisms during manufacture. The ISO standard *Aseptic processing of health care products* (ISO 13408) describes control and validation for aseptic manufacturing processes. The standard details such topics as monitoring the environment, qualification of personnel, validation of cleaning, validation of sterilization of components, and the media fill program. The media fill program is considered a process simulation test and demonstrates the contamination rate of a particular aseptic process or part thereof.

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Annex B
(informative)

Examples of terminally sterilized products and the selected sterility assurance level

Table B.1—Sterility assurance levels for terminally sterilized products*

10^{-3}	10^{-6} (or SAL providing greater assurance of sterility (e.g., 10^{-7}, 10^{-8}))
a) Products not intended to come into contact with breached skin or compromised tissue, such as: 1) Collection or transfer devices: — Blood collection tubes for *in vitro* diagnostic tests — Culture media devices — Serological pipettes — Specimen containers 2) Topical devices: — ECG electrodes — Drainage bags — Grounding pads — Surgical drapes and gowns 3) Mucosal contacting devices: — Tongue depressors — Examination gloves — Urinary catheters b) Products that cannot withstand a 10^{-6} SAL process: 1) Porcine heart valves 2) Wound dressings of a biological nature	a) Products intended to come into contact with breached skin or compromised tissue, such as: 1) Wound dressings 2) Cardiac catheters 3) Cauterizing devices 4) Scalpels and other surgical instruments 5) Surgeons' gloves 6) Syringes 7) Hypodermic needles 8) Parenteral solutions 9) Peritoneal dialysis solutions 10) Prefilled syringes 11) Laparotomy sponges 12) Incise drapes b) Invasive products that enter normally sterile tissue c) Products with claims of sterile fluid pathways: 1) Fluid pathways of IV sets 2) Fluid pathways of syringes 3) Blood collection containers or bags d) Surgically implanted devices: 1) Reconstructive devices (e.g., hip, knee, elbow) 2) Implantable devices (e.g., pacemakers) 3) Trauma devices (e.g., nails, screws, plates, pins, wires) 4) Sutures 5) Intraocular lenses e) Components used in aseptic processing

* Depending on its intended use and material composition, the same product may be listed in both columns and require different SALs.

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Annex C
(informative)

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