List of Titles

American National Standard

ANSI/AAMI ST63:2002

Sterilization of health care products—Requirements for the development, validation, and routine control of an industrial sterilization process for medical devices—Dry heat

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.

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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.

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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 ST63:2002

Sterilization of health care products—Requirements for the development, validation, and routine control of an industrial sterilization process for medical devices—Dry heat

Developed by
Association for the Advancement of Medical Instrumentation

Approved 31 October 2002 by
American National Standards Institute, Inc.

Abstract: This standard specifies requirements and guidance for the development, validation, and routine control of dry heat sterilization processes for medical devices. Although the scope of this standard is limited to medical devices, it specifies requirements and provides guidance that may apply to other health care products. This standard does not apply to processes that use infrared or microwaves as the heating medium and does not detail a specified requirement for designation of a medical device as “sterile.”

Keywords: depyrogenation, parametric release, process monitoring, process qualification, routine process control, thermal sterilization, validation

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AAMI Standard

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Glossary of equivalent standards

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 60601-2-21:1994 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/ISO 7198:1998/2001	Identical
ISO 7199:1996	ANSI/AAMI/ISO 7199:1996/(R)2002	Identical
ISO 10993-1:1997	ANSI/AAMI/ISO 10993-1:1997	Identical
ISO 10993-2:1992	ANSI/AAMI/ISO 10993-2:1993/(R)2001	Identical
ISO 10993-3:1992	ANSI/AAMI/ISO 10993-3:1993	Identical
ISO 10993-4:2002	ANSI/AAMI/ISO 10993-4:2002	Identical
ISO 10993-5:1999	ANSI/AAMI/ISO 10993-5:1999	Identical
ISO 10993-6:1994	ANSI/AAMI/ISO 10993-6:1995/(R)2001	Identical
ISO 10993-7:1995	ANSI/AAMI/ISO 10993-7:1995/(R)2001	Identical
ISO 10993-8:2000	ANSI/AAMI/ISO 10993-8:2000	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999	Identical
ISO 10993-10:2002	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
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

International designation	U.S. designation	Equivalency
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 TIR 13409:1996	Identical
ISO 13485:1996	ANSI/AAMI/ISO 13485:1996	Identical
ISO 13488:1996	ANSI/AAMI/ISO 13488:1996	Identical
ISO 14155-1:2003	ANSI/AAMI/ISO 14155-1:2003	Identical
ISO 14155-2:200x*	ANSI/AAMI/ISO 14155-2:2003	Identical
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	ANSI/AAMI/ISO 14971:2000	Identical
ISO 15223:2000	ANSI/AAMI/ISO 15223:2000	Identical
ISO 15223/A1:2002	ANSI/AAMI/ISO 15223:2000/A1:2001	Identical
ISO 15225:2000	ANSI/AAMI/ISO 15225:2000	Identical
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ISO 25539-1:2003	ANSI/AAMI/ISO 25539-1:2003	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

*FDIS approved; final document in production

Committee representation

Association for the Advancement of Medical Instrumentation

AAMI Sterilization Standards Committee

This standard was developed by the AAMI Dry Heat Sterilization Working Group under the auspices of the AAMI Sterilization Standards Committee. Committee approval of this standard does not necessarily imply that all committee and working group members voted for its approval.

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

Acknowledgment

The working group gratefully acknowledges the contributions of working group member and former co-chair James M. Gibson, Jr., of JM Gibson Associates. Mr. Gibson prepared the first comprehensive working draft of the standard and thus advanced the early development of the standard enormously.

Foreword

This standard was developed by the AAMI Dry Heat Sterilization Working Group under the auspices of the AAMI Sterilization Standards Committee. The objective of this standard is to establish requirements and guidance for the development, validation, and routine control of dry heat sterilization processes for medical devices.

This standard is needed to help ensure that medical devices sterilized by dry heat achieve an adequate sterility assurance level, thus minimizing the possibility of a patient infection.

As used within the context of this document, “shall” indicates requirements strictly to be followed in order to conform to the recommended practice; “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 recommended practice; 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.

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 American National Standard *Sterilization of health care products—Requirements for the development, validation, and routine control of an industrial sterilization process for medical devices—Dry heat* (ANSI/AAMI ST63:2002), but it does provide important information about the development and intended use of the document.

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American National Standard ANSI/AAMI ST63:2002

Sterilization of health care products—Requirements for the development, validation, and routine control of an industrial sterilization process for medical devices—Dry heat

1 Scope

1.1 This standard specifies requirements for the development, validation, and routine control of an industrial dry heat sterilization process for medical devices.

NOTE 1—Although the scope of this standard is limited to medical devices, it specifies requirements and provides guidance that may apply to other health care products.

NOTE 2—Although this standard primarily addresses dry heat sterilization, it also covers depyrogenation processes.

NOTE 3—This standard does not apply to processes that use infrared or microwaves as the heating medium.

1.2 This standard does not specify requirements for designation of a medical device as "sterile."

NOTE—See national or regional requirements for designating medical devices as "sterile," e.g., EN 556 or ANSI/AAMI ST67.

1.3 This standard does not describe a quality assurance system for the control of all stages of manufacture.

NOTE—See the standards for quality systems (ANSI/AAMI/ISO 13485 or ANSI/AAMI/ISO 13488) which address the control of all stages of manufacture, including the sterilization process. This standard does not require manufacturers to have a complete quality system during manufacture, but certain elements of such a system are required, and these elements are normatively referenced at appropriate places in the text.

2 Normative references

The following standards contain provisions that, through reference in this standard, constitute provisions of this standard. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this standard are encouraged to investigate the possibility of applying the most recent editions of the standards indicated here. Members of the International Electrotechnical Commission (IEC) and the International Organization for Standardization (ISO) maintain registers of currently valid International Standards.

2.1 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Sterilization of health care products—Biological indicators—Part 1: General*. ANSI/AAMI ST59:1999. Arlington (VA): AAMI, 1999. American National Standard.

2.2 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Sterilization of health care products—Chemical indicators—Part 1: General requirements*. ANSI/AAMI ST60:1996. Arlington (VA): AAMI, 1996. American National Standard.

2.3 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Sterilization of medical devices—Requirements for products labeled "STERILE."* ANSI/AAMI ST67. Arlington (VA): AAMI. American National Standard (in development).

2.4 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Biological evaluation of medical devices—Part 1: Guidance on selection of tests, 2ed*. ANSI/AAMI 10993-1:1997. Arlington (VA): AAMI, 1997. American National Standard.

2.5 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Packaging for terminally sterilized medical devices, 2ed*. ANSI/AAMI/ISO 11607:2000. Arlington (VA): AAMI, 2003. American National Standard.

2.6 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Sterilization of medical devices—Microbiological methods—Part 1: Estimation of population of microorganisms on products.* ANSI/AAMI/ISO 11737-1:1995. Arlington (VA): AAMI, 1995. American National Standard.

2.7 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Sterilization of medical devices—Microbiological methods—Part 2: Tests of sterility performed in the validation of a sterilization process*. ANSI/AAMI/ISO 11737-2:1998. Arlington (VA): AAMI, 1998. American National Standard.

2.8 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Quality systems—Medical devices—Particular requirements for the application of ISO 9001*. ANSI/AAMI/ISO 13485:1996. Arlington (VA): AAMI, 1996. American National Standard.

2.9 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Sterilization of health care products—Biological indicators—Guidance for the selection, use, and interpretation of results*. ANSI/AAMI/ISO 14161:2000. Arlington (VA): AAMI, 2000. American National Standard.

2.10 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Medical devices—Application of risk management to medical devices*. ANSI/AAMI/ISO 14971:2000. Arlington (VA): AAMI, 2000. American National Standard.

2.11 INTERNATIONAL ELECTROTECHNICAL COMMISSION. *Safety requirements for electrical equipment for measurement, control, and laboratory use—Part 1: General requirements*. IEC 61010-1:2001. Geneva: ISO, 2001.

2.12 INTERNATIONAL ELECTROTECHNICAL COMMISSION. *Safety requirements for electrical equipment for measurement, control, and laboratory use—Part 2-043: Particular requirements for dry heat sterilizers using either hot air of hot inert gas for the treatment of medical materials and for laboratory purposes*. IEC 61010-2-043:1997. Geneva: ISO, 1997.

2.13 INTERNATIONAL ORGANIZATION FOR STANDARDIZATION. *Quality systems—Model for quality assurance in design, development, production, installation, and servicing*. ISO 9001:2001. Geneva: ISO, 2001.

2.14 INTERNATIONAL ORGANIZATION FOR STANDARDIZATION. *Quality assurance requirements for measuring equipment—Part 1: Metrological confirmation system for measuring equipment*. ISO 10012-1:1992. Geneva: ISO, 1992.

2.15 UNDERWRITERS LABORATORIES. *Electrical equipment for laboratory use—Part 1: General requirements*. UL 61010A-1:2002. Northbrook (IL): UL, 2002.

2.16 UNITED STATES PHARMACOPEIAL CONVENTION. *United States Pharmacopeia*. USP 24–NF 19. Rockville (MD): United States Pharmacopeial Convention, Inc., 2000.

3 Definitions

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

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

3.3 bioburden estimate: Value established for the bioburden by applying a factor compensating for the efficiency of the defined technique used in the recovery of microorganisms.

3.4 biological indicator (BI): Inoculated carrier, contained within its primary pack ready for use, that provides a defined resistance to the specified sterilization process.

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

3.6 chamber: Enclosed area into which product is placed and in which the sterilization process occurs.

NOTE—For purposes of this standard, “chamber” refers not only to closed batch sterilization systems but also to the tunnels of continuous sterilization systems, even though the latter are open at both ends.

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

3.8 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.

3.9 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.

NOTE—For purposes of this standard, “radiation dose” does not apply.

3.10 depyrogenation: Validated process designed to remove or deactivate endotoxin.

3.11 dry heat sterilization: Sterilization process that uses dry heat as the sterilizing agent.

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

3.13 exposure time: Period for which the process parameters are maintained within their specified tolerances.

3.14 F value: Measure of the microbiological inactivation capability of a heat sterilization process. The F value can be determined by a physical $F_{(phys)}$ or biological $F_{(bio)}$ method. The F value for a specific sterilization temperature and z value is referred to as F_H.

— $F_{(bio)}$: F_H determined by biological methods.

— F_H: For a dry heat sterilization process, the equivalent time, in minutes at 160 °C, that has been delivered to the product by the process and that assumes a z value of 20 °C.

— $F_{(phys)}$: F_H determined by physical methods.

3.15 fault: Process parameter that lies outside of its specified tolerance. Faults can occur in multiples.

3.16 fraction positive: Quotient derived from the number of positive tests of sterility observed and the total number of tests of sterility performed (number of positive tests of sterility plus number of negative tests of sterility).

3.17 health care product: Medical devices, medicinal products (pharmaceuticals and biologicals) and *in vitro* diagnostic medical devices.

3.18 inactivation: Loss of ability of microorganisms to grow and/or multiply.

3.19 inoculated carrier: Supporting material on or in which a defined number of test microorganisms have been deposited.

3.20 installation qualification (IQ): Process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification.

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

a) diagnosis, prevention, monitoring, treatment, or alleviation of disease;

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

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

d) 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.

3.22 microorganism: Entity, encompassing bacteria, fungi, protozoa, and viruses, of microscopic size.

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

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

3.25 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.

3.26 primary package: Element of the packaging system that maintains the sterility of product.

3.27 process challenge device (PCD): 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.

NOTE 1—The item is so constituted that a biological indicator can be placed in the position that is most difficult for the sterilant to reach.

NOTE 2—The design of the PCD depends on the type of goods to be sterilized and the sterilization procedure.

NOTE 3—The biological indicator should not interfere with the function of the PCD.

NOTE 4—In some PCDs, an inoculated carrier may be used in place of a biological indicator.

3.28 process parameter: Specified value for a process variable.

NOTE—Specifications for a sterilization process include the process parameters and their tolerances.

3.29 process variable: Condition within a sterilization process, changes in which alter microbicidal effectiveness.

3.30 product: Raw materials, intermediate products, subassemblies, and finished medical devices.

3.31 product unit: Health care product or collection of products or components contained within a primary package.

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

3.33 spore log reduction (SLR): Lethality observed in a full or fractional sterilization cycle.

NOTE—SLR can be calculated as the log of the initial population minus the log of the final population, as below:

$$SLR = \log N_o - \log N_f$$

where:

N_f = final population

and

N_o = initial population

3.34 sterile: Free from viable microorganisms.

3.35 sterility: State of being free from viable microorganisms.

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

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

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

NOTE—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.

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

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

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

3.40 sterilization system: Chambers and ancillary equipment associated with delivering the sterilization process.

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

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

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

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

3.45 z value: Number of degrees of temperature (Fahrenheit or Celsius) required to obtain a 1-logarithm (to the base 10) change in the D value. The z value of a microorganism is a measure of how heat resistance changes with changes in temperature.

4 Quality systems

NOTE—The purpose of the quality system is to define and document procedures, the implementation of which controls all stages of development, application, use, and control of dry heat sterilization processes. This standard does not require that the manufacturer have a complete quality system during design/development and production; however, certain elements of a quality system are required, and these are normatively referenced at appropriate places in the text.

4.1 Assignment of personnel responsibilities

4.1.1 The responsibility for performing each element of this standard shall be defined and documented.

4.1.2 Responsibilities shall be assigned to qualified personnel, as specified in ANSI/AAMI/ISO 13485. Qualified personnel shall have oversight for the selection and purchase of the sterilization equipment. Qualified personnel shall be responsible for developing all policies, procedures, and documentation of sterilization activities throughout the facility. The format for policies, procedures, and documentation shall be compatible with recognized standards (e.g., ISO 9001 and ANSI/AAMI/ISO 13485). Qualified personnel shall be responsible for the training and in-service education of the staff operating the sterilization equipment, and for documenting their competency. Qualified personnel shall be responsible for the program of process audits.

4.1.3 The manufacturer shall provide manuals and instructions for the use of the equipment.

4.2 Documentation and records

Documentation and records shall include the equipment specification, validation results (installation, operational, and performance), cycle parameters, load configuration, staff training documentation, process audit results, and a description of any corrective actions required (see ISO 9001). All records of maintenance, calibration, and repairs of sterilization equipment shall be retained for the life of the equipment. All cycles shall be documented and records maintained.

4.3 Design control

The sterilization process is a critically important step in the manufacture of sterile medical devices; therefore, it is subject to the designed control requirements as outlined in 21 CFR 820.30 of the Quality System Regulation. The sterilization process should be addressed at each phase of the design control process to ensure that an effective and reproducible cycle is routinely used for processing a particular device or device family. All design control activities, including the design and development of sterilization cycles, shall be documented.

4.4 Calibration

Procedures shall be established, documented, and maintained for the calibration of the controlling, indicating, and recording instruments used for validation and routine control of the sterilization process. Scheduled recalibration shall be performed and documented to ensure that the equipment is operating within the established specifications. See also 12.2.

5 Sterilizing agent characterization

5.1 Sterilizing agent

The sterilizing agent is dry heat at elevated temperatures. A specification for the dry heat temperature for a specific sterilization process shall be generated and documented.

5.2 Microbicidal effectiveness

5.2.1 The effectiveness of dry heat for sterilization of a particular product shall be demonstrated.

NOTE—The microbicidal effectiveness of dry heat has been demonstrated, and references are available to show its ability to kill a large variety of microorganisms (Pflug and Holcomb, 1991).

5.2.2 When biological indicators (BIs) are used for process development or validation, their appropriateness (resistance to the dry heat process relative to the resistance of the bioburden on the product to be sterilized) shall be documented.

5.2.3 The death of microorganisms from dry heat has been demonstrated to follow first-order kinetics. Lethal rates (L) at any temperature can be calculated from the equation:

$$L = 10^{(T-Tr)/z}$$

where:

T = temperature at time t;

Tr = reference temperature (see A.5); and

z = temperature increment required to change the D value by a factor of 10.

NOTE—A z value of 20 °C can be assumed.

5.2.4 The process variables in dry heat sterilization are product temperature and exposure time. The product, its packaging (when used), and the loading of the sterilization system shall allow the penetration of the heating medium to ensure that heating is as uniform as possible.

5.3 Material effects

5.3.1 The material effects from dry heat are caused by exposure to heat for the required time. Materials for dry heat sterilization shall be evaluated for

a) changes in physical properties, such as softening, cracking, deformation, or shape changes;

b) changes in chemical properties, such as decomposition, generation of gases, polymerization, or formation of toxic compounds;

c) differences in expansion rates, which could cause damage to mated parts; and

d) material functionality or product performance.

5.3.2 Where applicable, the effects of repeated sterilization processes shall be evaluated and documented.

5.4 Safety and environment

5.4.1 The safety hazards of dry heat processes are associated with the potential exposure of personnel to hot surfaces and products. Equipment and procedures shall be designed to ensure that the temperature of all handwheels, handles, or similar devices that the operator will use during normal operation of the sterilizer comply with UL 61010A-1.

5.4.2 The use of dry heat processes has no direct environmental impact.

6 Process and equipment characteristics

6.1 General

The dry heat sterilization process and dry heat sterilization system shall be defined to ensure that the sterilization process can be delivered safely and reproducibly.

6.2 Process monitoring

6.2.1 Process parameters

The process parameters identified for process control during dry heat sterilization are temperature and time. In continuous dry heat sterilization systems, process control is additionally required for the conveyor speed and other mechanisms that control the temperature/time exposure.

6.2.2 Tolerance of the parameters

6.2.2.1 The minimum temperature for sterilization or depyrogenation shall be determined during process development or validation studies. The maximum temperature, exposure time, and number of allowable resterilizations shall be determined from an evaluation of product stability, the materials of construction, and manufacturers' data, or from development or validation studies.

NOTE—Some materials that are typically dry heat sterilized (e.g., glass, metals) have a great tolerance for the temperatures used for the dry heat process. Process tolerances for these types of products can, therefore, have a wide range.

6.2.2.2 Dry heat sterilization or depyrogenation processes shall be validated and controlled within the maximum and minimum parameters determined. See also sections 9 and 10, respectively.

6.2.3 Process monitoring locations

The process shall be monitored from representative locations within the chamber, which have been determined during validation studies. The process shall be monitored for time, temperature, and, where applicable, airflow and conveyor speed. See also section 10.

6.3 Documentation of equipment

6.3.1 Identification

Each sterilization system shall have one or more information plates, permanently fastened and marked, that provide the following information in the language agreed to by the user:

a) name and address of the manufacturer;

b) serial number or other system identification;

c) chamber design maximum working temperature;

d) stamp of inspection authority and vessel identification mark; and

e) date of primary construction of the vessel.

6.3.2 Safety

Compliance of the sterilization system with the safety requirements specified in IEC 61010-1, IEC 61010-2-043, and any other standards or regulatory requirements applicable in the country of use shall be documented.

6.3.3 Manuals and instructions

At a minimum, the following information shall be available for each identified sterilization system in the language agreed to by the user:

a) installation instructions that are sufficiently detailed to ensure the safe and effective operation of the equipment;

b) a list of materials of construction exposed to the sterilizing agent or in contact with the product;

c) instructions for safe and effective operation, including recommendations for vessel temperature limits as well as safety precautions;

d) instructions and recommended schedules for routine preventive maintenance;

e) a repair manual that includes a list of recommended replacement parts;

f) sterilization system drawings sufficient to define configuration and hardware, ductwork and control-system schematic drawings, drawings showing recommended installation, and a parts list defining all significant system components; and

g) process-control logic and/or software documentation necessary to operate and maintain the equipment control system. Any software supplied shall be accompanied by proof of validation of its release and revision level.

6.3.4 Additional information

The specifications for a sterilization system to be used for dry heat sterilization, including its installation and installation tests, shall be documented.

6.4 Sterilization system performance, utilities, components, accessories, and controls

6.4.1 Performance

Sterilization systems used to process health care products by dry heat shall be designed in accordance with regulations or standards for sterilization equipment performance applying in the country of use.

6.4.2 Utilities

6.4.2.1 Air

The purity of the air or other gases used in the sterilization chamber shall be such that the safety of the product is not impaired and shall be of sufficient quality for its intended use.

6.4.2.2 Electrical power

The electrical supply shall meet the manufacturer's requirements.

6.4.3 Components

The materials and components used in the construction of the sterilization system shall be selected to minimize the potential for microbiological or chemical contamination.

6.4.4 Accessories

The system to support the product in the chamber shall be designed to allow uniform heat penetration, heat transfer, or both. The carrier system shall also maintain the integrity of the load. The exhaust, cooling, and (if applicable) filtration systems shall meet the design specifications. Appropriate filtration systems shall be used if the chamber interfaces with a controlled environment or is in a controlled environment. The efficiency of HEPA filters, when used, shall be monitored. If the sterilization system is equipped with an air circulation system, the system shall be designed to minimize the potential for impeding circulation.

6.4.5 Control and recording systems

6.4.5.1 The following process parameters shall be automatically controlled and recorded:

a) temperature;

b) time;

c) rate of change of temperature, if required for product integrity;

d) speed of the conveyor system, if used; and

e) chamber pressure and airflow, if applicable.

6.4.5.2 The recorder and process control systems shall either be independent or be designed in a manner that will cause a warning to occur should the difference between a controlled and a recorded variable exceed specified limits.

6.4.6 Control programs

Programs used to execute and control the sterilization process, whether microprocessor based or electro-mechanically based, shall be validated. The documented control program shall be evaluated according to procedures designed to demonstrate the correctness of the program logic in both process-simulated conditions and actual sterilization system use. Any subsequent changes shall be similarly documented, evaluated to assess whether requalification is required, and approved by the user.

6.5 Performance of instruments

6.5.1 Instrument accuracy

6.5.1.1 Accuracy of instruments used for validation shall be adequate to demonstrate that processing specifications are met.

6.5.1.2 Temperature and airflow and, where applicable, pressure sensors shall be selected, installed, and used in a manner that will ensure that the stated accuracy is maintained.

6.5.2 Calibration standards

The accuracy of the standards used to calibrate process measurement instruments shall be specified, and calibration shall be traceable to a national reference standard and, where applicable, as specified in ISO 10012-1.

6.5.3 Calibration program

An effective procedure shall be established, documented, and maintained for calibrating all controlling, indicating, and recording instruments used for validation and routine control of the sterilization cycle. When applicable, the procedure shall comply with the requirements of ISO 9001.

6.6 Maintenance

An effective system shall be established, documented, and maintained for the preventive maintenance of all equipment used for performance of the sterilization cycle and any other associated processes. When applicable, the system shall comply with the requirements of ISO 9001. See also section 12.

7 Product definition

7.1 Introduction

7.1.1 The purpose of product definition 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 to be packaged and presented for sterilization.

7.1.2 Dry heat sterilization is used in a number of applications and can be either a batch or a continuous process. These applications include

a) terminal sterilization of single-use and multiple-use devices;

b) sterilization of components for aseptic filling operations; and

c) depyrogenation (which often results in sterilization) of devices.

7.1.3 The diverse applications for dry heat sterilization necessitate various product, packaging, and bioburden requirements.

7.2 Product considerations

The product shall be designed to comply with its specifications and requirements for safety and efficacy following exposure to the maximum sterilization process conditions and maximum number of sterilization cycles specified for the product. Any treatment required before resterilization shall also be validated as part of the resterilization procedure. The product shall be designed and materials shall be selected to be compatible with environmental changes occurring in the sterilization chamber during the sterilization cycle. Compatibility with dry heat shall be documented.

7.3 Packaging considerations

7.3.1 The packaging materials and procedures shall be specified.

7.3.2 Packaging materials shall be selected to be compatible with the sterilization conditions in the sterilization chamber throughout the cycle.

7.3.3 When handled according to instructions, packaging shall protect the product from physical damage and maintain the sterility of the product until it is used.

7.3.4 Packaging materials shall comply with ANSI/AAMI/ISO 11607.

7.3.5 For terminally sterilized devices, the packaging shall consist of at least a primary package.

7.3.6 The primary package and, if present at the time of sterilization, the secondary package shall comply with each of their specifications following sterilization.

7.4 Bioburden

7.4.1 For terminally sterilized products, the bioburden shall be established and documented. The method used to determine the bioburden shall be validated and comply with ANSI/AAMI/ISO 11737-1.

7.4.2 For resterilization of reusable products, the cleaning procedure shall be validated, documented, and periodically evaluated.

7.4.3 For sterilization processes based on bioburden, there shall be a bioburden program that determines the numbers and resistance of the bioburden before sterilization. The frequency of bioburden testing shall ensure that significant changes in bioburden have not occurred.

7.4.4 The bioburden program shall demonstrate that the product bioburden is in control as specified.

8 Process definition

8.1 Introduction

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

8.2 Selection of the sterilization process

Selection of the sterilization process to be used depends on the product configuration and the ability of the product and package to withstand temperature and dehydration without compromising the safety, quality, and performance of the product.

8.3 Sterilization process development

8.3.1 Process variables

The variables that significantly affect the sterilization of products are temperature and exposure time. The minimum chamber temperature used in cycle development shall be specified as the minimum temperature tolerance for process validation. The maximum temperature shall be identified on the basis of its ability to maintain product and package functionality and stability and shall be specified as the maximum temperature tolerance for process validation. The temperature range identified for routine sterilization parameters shall be within the minimum and maximum temperature used for process validation. During the performance qualification, the product temperature shall be measured and compared with the chamber control temperature to verify that the specified product temperature can be reproduced during the exposure phase of the cycle.

8.3.2 Sterility assurance level

The development process shall set the exposure/time requirements necessary to provide the desired sterility assurance level (SAL). For guidance on selecting the SAL, see ANSI/AAMI ST67.

8.3.3 Cycle development

Before the introduction of a new or altered product, the sterilization loading pattern for that product shall be defined for the sterilization process. The sterilization cycle developed shall be reproducible for routine processing. The BI or other process challenge device (PCD) shall be appropriate for the sterilization process and meet the requirements of ANSI/AAMI/ISO 14161.

Cycle development is performed by running successive exposure times and determining the extent of lethality to the microbial challenge. Three basic methods may be used to develop an effective dry heat sterilization cycle: overkill (8.3.3.1), combined BI/bioburden (8.3.3.2), and absolute bioburden (8.3.3.3).

NOTE—It is not necessary to use the following methods when validating a depyrogenation process. See 8.7.

8.3.3.1 Overkill method

The overkill approach is based on the use of a resistant BI with a known population to demonstrate a specific spore log reduction (SLR).

8.3.3.2 Combined biological indicator/bioburden method

The combined BI/bioburden approach is based on the use of a resistant BI or other PCD with a population that is equal to or greater than that of the natural product bioburden. This method is appropriate when sufficient bioburden data is available from the bioburden monitoring program to demonstrate that a BI or other PCD with a population of less than 10^6 can be used.

8.3.3.3 Absolute bioburden method

The absolute bioburden approach is based solely on the naturally occurring product bioburden. Representative product samples that are indicative of the highest levels of bioburden and most resistant organisms are subjected to incremental dwell periods. Following exposure, a test of sterility shall be performed according to ISO 11737-2.

8.4 Process challenge devices

Process challenge devices may be used to evaluate the delivered lethality of the selected process parameters for the product and package during validation. They may also be used to monitor the routine process, either inside or outside of the load. PCDs shall be placed in representative positions throughout the densest sterilization load, ensuring that the slowest-to-heat portion of the sterilization system is represented by the PCD.

8.5 Sterility testing

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

8.6 Biocompatibility

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

8.6.2 A health-based risk assessment shall be conducted in accordance with ANSI/AAMI/ISO 14971 to identify and document limits for by-products associated with the process.

8.7 Depyrogenation

8.7.1 The effectiveness of a depyrogenation process for a particular product shall be validated. The requirements for validating a depyrogenation process shall be similar to those applicable to microbiological validation (see section 9) and include an installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). The validation shall include demonstration of process reproducibility and process effectiveness at minimum process conditions.

NOTE—Dry heat processes are often used for depyrogenation of equipment, components, and medical products, and their effectiveness has been demonstrated. The key process parameters for depyrogenation are time and temperature. Because the conditions for depyrogenation are typically more severe than those required for sterilization, products that have been validated for depyrogenation are generally considered sterile without additional validation.

8.7.2 The appropriateness of the level of the endotoxin challenge used for development or validation of the depyrogenation process shall be demonstrated.

9 Sterilization process validation

9.1 General

The validation program shall be performed using an approved protocol that conforms to the requirements outlined in ISO 9001. An IQ, OQ, and PQ shall be performed for each sterilization system upon installation. The calibration of process parameter measurement systems used for validation shall be demonstrated to be accurate throughout the entire validation program. New products and new sterilization equipment or process conditions shall be validated or evaluated for adoption into or equivalency with an existing process (see A.9.6). Validation activities shall be assigned to a designated person experienced in this task.

9.2 Installation qualification

The IQ demonstrates that the equipment has been installed according to the manufacturer's specifications, and shall include demonstration and documentation of

a) the equipment design features (i.e., materials of construction, cleanability);

b) compliance with equipment construction specifications after installation;

c) conformance of the quality and capacity of the utilities;

d) supplier information, prints, drawings, and manuals;

e) software;

f) calibration, preventive maintenance program, and cleaning schedule; and

g) compliance with performance specification.

9.3 Operational qualification

The OQ demonstrates that the equipment operates according to design specifications for performance, control system function, computer system qualification, and data collection systems associated with the equipment. Before OQ, all instrumentation used for monitoring, controlling, indicating, and recording shall be calibrated. Operational qualification is performed in an empty chamber. The OQ shall include demonstration and documentation

a) that the controls such as alarms, set-point controllers, safety devices, monitoring systems, and door interlocks perform as designed;

b) that preprogrammed cycles run as specified;

c) that the uniformity of physical parameters (i.e., temperature, airflow, pressure) is within the specified limits throughout the chamber;

d) of the relationship between set control parameters and actual parameters measured in the chamber; and

e) of operational procedures for the equipment.

9.4 Performance qualification

9.4.1 Performance qualification—Physical

Physical PQ shall be performed when new or altered products, packaging, loading patterns, equipment, or process parameters are introduced, unless equivalence to a previously validated product, packaging, or loading pattern combination has been demonstrated. The demonstration of equivalence shall be documented. The physical PQ shall demonstrate that the sterilization process is reproducible over the range of conditions proposed for routine processing. The physical PQ shall demonstrate and include

a) the relationship of the control set point and parameters to the actual parameters measured in the load;

b) the consistent achievement and uniformity of lethal conditions in the load, correlated to the routine process monitoring system;

c) the acceptable maximum and minimum loading configurations;

d) the acceptable minimum product temperature before processing, unless the process is controlled using load temperature;

e) the acceptable product mix in the load;

f) the representativeness of simulated product loads in relation to actual products;

g) if applicable, the return of qualification loads to specified conditions before reuse;

h) the conformance of product and packaging to applicable specifications after the sterilization process and, where applicable, after resterilization; and

i) the consistency with which the sterilization process conforms to specifications established during process development.

Product used for physical PQ shall be packaged in the same manner as it will be routinely presented for sterilization. The number of temperature sensors and cycles required for PQ or performance requalification shall be specified and sufficient to cover the temperature range in the load during routine processing. The results of the physical PQ shall be documented.

9.4.2 Performance qualification—Microbiological

Microbiological PQ shall be performed when new or altered products, packaging, loading patterns, equipment, or process parameters are introduced, unless equivalence to a previously validated product, packaging, or loading pattern combination has been demonstrated. This demonstration of equivalence shall be documented.

The microbiological PQ shall demonstrate that the sterilization process consistently achieves the specified SAL over the range of conditions proposed for routine processing. The microbiological PQ shall demonstrate and include

a) the appropriateness of the BI or other PCD and its relationship to the presterilization microbial load (bioburden);

b) the acceptable maximum bioburden level on the product before sterilization;

c) the relationship of the delivered physical parameters to microbiological lethality;

d) the inactivation of PCDs under conditions selected to deliver less lethality than the conditions used for routine processing;

e) the achievement of expected lethality throughout the entire load; and

f) the consistency with which the sterilization process achieves the specified SAL after routine processing at the specified parameters.

Product used for microbiological PQ shall be packaged in the same manner as it will be routinely presented for sterilization. The number of BIs or PCDs and number of cycles required for PQ or performance requalification shall be specified and sufficient to cover the expected range of conditions in the load during routine processing, including any known cold spots as determined during physical PQ. The results of the microbiological PQ shall be documented.

9.5 Parametric release

For parametric release, the microbiological qualification shall, in addition to the requirements of 9.4, include a determination of the lethality of the cycle by either survivor-curve construction or the fraction-negative method. See A.9.5 and also, for further information on methodology, ANSI/AAMI/ISO 11135, ANSI/AAMI/ISO 14161, ANSI/AAMI ST59, ANSI/AAMI/ISO 14937, AAMI TIR16, Pflug (1990), and Block (2001).

If a circulation system is used, a monitoring system to verify that the system is operating within specification is required to ensure uniformity in the chamber and document system failure.

9.6 Other sterilization systems

Other sterilization systems that deliver the same process parameters to the product and have undergone full physical PQ demonstrating equivalency (see A.9.6) shall be validated either

a) in the same manner as the original sterilization system; or

b) by means of a reduced microbiological PQ (i.e., a PQ using fewer cycles than were used in the PQ of the original sterilization system) that demonstrates the delivery of the required level of microbiological lethality.

9.7 Validation report

When the validation is complete, all data shall be formally reviewed, approved, and certified by designated persons. The validation report shall be retained as specified in ISO 9001.

The validation report shall contain or reference the specific validated product and the documented specification for the dry heat sterilization process. The validation report shall also include the value and tolerances for

a) the minimum temperature of product permitted to enter the sterilization chamber (unless the process is controlled by load temperature);

b) the loading pattern and separation of product within the sterilization chamber;

c) the time to reach exposure temperature within the chamber;

d) the temperature of the sterilization load, including heat-up and cool-down times if F_H is to be used to release loads;

e) the chamber temperature, including heat-up and cool-down times if F_H is to be used to release loads;

f) the exposure time or conveyor speed;

g) the circulation (airflow) rate, if applicable; and

h) a comparison of load to chamber F_H if F_H is to be used to release loads.

The validation report shall also include evidence that the circulation system (if used) was operational during the sterilization cycle.

10 Routine monitoring and control

10.1 Process control systems

10.1.1 When process development studies and the validation program are complete, procedures for the routine monitoring of the sterilization cycle shall be developed and documented to ensure product sterility and efficacy. The type(s) of load(s) to be sterilized and the load configuration shall be specified.

10.1.2 The control system for production sterilization systems shall reproduce within specified limits the parameters developed and validated for the specific product. All process parameters used for release of the product shall be recorded throughout the cycle. Sufficient redundancy and/or sensor failure detectors are necessary to ensure accurate measurement and recording. It is essential that all control systems be validated and locking-out devices or administrative systems be in place to prevent unauthorized changes to process set points and ensure selection of the correct cycle (see 12.4). It is also important to establish systems to ensure correct loading of the sterilization system as per validation.

10.1.3 Before a sterilization system is used for production, the maintenance and calibration programs shall be established and the schedules maintained to ensure that the parameters of the sterilization cycle are within limits equivalent or correlated to those determined during performance qualification. Maintenance activities, including the date and identification of the individual(s) who performed the maintenance activities, shall be documented. The accuracy and reliability of instruments used to monitor each production cycle shall be periodically checked for compliance with their specifications.

10.2 Process recording systems

10.2.1 For each cycle, a record shall be made of the following, at a minimum:

a) date;

b) sterilization system identification;

c) cycle identification;

d) operator identification and signature;

e) product temperature before entering the chamber (unless the process is controlled by load temperature);

f) for batch sterilization systems, the time required for heat-up and cool-down in the chamber if F_H is used to release loads;

g) chamber temperature throughout the cycle;

NOTE—It is recommended that there be a minimum of two independent temperature sensors.

h) exposure time or conveyor speed;

i) calculation of F_H if used for release of loads; and

j) evidence that the circulation system (if used) was operational during the sterilization cycle.

Table 1 summarizes the key control variables determined during cycle development, OQ, and PQ (see 9.7) and identifies the parameters that shall be monitored during routine processing.

Table 1—Monitoring of key process control variables

Key process variables	Required during validation	Required during processing for routine or parametric release
Program logic verification (if applicable)	Yes	No
Load identification	Yes	Yes
Load configuration	Yes	Yes
Load temperature before entering chamber (unless process is controlled by load temperature)	Yes	Yes
Sterilizer temperature come-up time	Yes	If F_H is used for release
Load temperature come-up time	Yes	No
Airflow setting (if applicable)	Yes	Yes
Airflow (feet per minute) (if applicable)	Yes	No
Fan revolutions per minute (if applicable)	Yes	No
Conveyor speed (if applicable)	Yes	Yes
Exposure temperature	Yes	Yes
Temperature distribution	Yes	No
Exposure time	Yes	Yes
Exposure pressure (if applicable)	Yes	Yes
Sterilizer cool-down time	Yes	If F_H is used for release
Load cool-down time	Yes	No
Accumulated F_H of the chamber (if applicable)	Yes	Yes
Accumulated F_H of the load (if applicable)	Yes	No

10.2.2 All records shall be retained as specified in ISO 9001.

10.2.3 If a physical cycle variable is outside of the documented tolerances, product shall be considered nonconforming and shall be handled in accordance with ISO 9001.

10.3 Microbiological testing

If used for routine monitoring, the BI or other PCD shall be consistent with that used during cycle development and validation studies. Guidance on BIs can be found in ANSI/AAMI/ISO 14161.

NOTE—Typically, fewer BIs are used for routine monitoring than for validation.

11 Product release

11.1 For release of the product, the process parameters monitored during routine sterilization shall be within the validated limits. A system to differentiate between processed and unprocessed items shall be used. Only authorized persons shall release product after sterilization.

11.2 Where reliable process measurement and control can be documented for the entire manufacturing process and correlated with sterility assurance, items may be considered for release in accordance with delivered process parameters. Additionally, the data from all microbial challenges, if used, shall be acceptable.

11.3 Records to demonstrate that the product has been sterilized in accordance with all specifications shall be produced and maintained as specified in ISO 9001.

12 Maintaining process effectiveness

12.1 Maintenance

12.1.1 A preventive maintenance program shall be established with scheduled maintenance intervals as recommended by the sterilization system manufacturer, instrument manufacturer, and/or filter manufacturer.

12.1.2 Preventive maintenance shall be performed in accordance with documented procedures. The procedure for each maintenance task and the frequency with which it is to be performed shall be documented in sufficient detail that a knowledgeable person could perform it in a satisfactory manner.

12.1.3 A preventive maintenance log shall be maintained for each individual sterilization system. The designated person shall summarize all scheduled and nonscheduled maintenance that was performed and sign and date the entry.

12.1.4 The maintenance log shall be periodically reviewed to determine

a) any necessary changes to preventive maintenance procedures or frequency;

b) the need for additional training of maintenance personnel; and

c) the completeness of preventive maintenance documentation.

12.1.5 A sterilization system shall not be used to process health care products until scheduled and unscheduled maintenance tasks have been satisfactorily performed and properly recorded.

12.1.6 Evidence shall be documented to demonstrate that persons carrying out maintenance have successfully completed training in the skills necessary to maintain the specified sterilization systems.

12.2 Calibration

12.2.1 A documented calibration program shall be established to ensure accurate measurement of process control parameters. Written calibration procedures shall specify the method to be used and accuracy to which the instruments should be calibrated, as well as the accuracy and precision of the standards used to calibrate the instrument.

12.2.2 Naturally derived standards (e.g., boiling water, melting ice) or primary and secondary standards that are traceable to appropriate national standards shall be used to calibrate instrumentation.

12.3 Requalification

12.3.1 Requalification shall be performed whenever a major repair of or change to the sterilization system has occurred that could affect the efficacy of the process. The process shall also be reviewed at least annually, and the extent of required requalification shall be determined and documented. At a minimum, the correlation between the physical and microbiological data shall be reconfirmed at least annually.

12.3.2 Procedures for review, requalification, and implementation of changes to the process, sterilization system (hardware and software), product, or packaging shall be documented. The responsibility for determining the need for and extent of repetition of the original validation studies shall be assigned to trained personnel.

12.3.3 Modifications to equipment or control systems shall be evaluated to confirm that the process conditions delivered to the product load are comparable to those originally qualified.

12.3.4 For batch sterilization systems, operational requalification of the sterilization system shall consist of at least one empty-chamber temperature distribution run. For continuous sterilization systems, operational requalification shall consist of at least one run to monitor heating-zone temperatures and airflow rates.

12.3.5 The microbiological review shall include, but not be limited to, verification that

a) no changes to the product design, manufacturing and packaging materials, PCDs, suppliers, manufacturing area or facility, or manufacturing process have occurred that could affect product sterility;

b) product bioburden has not significantly changed, nor has there been a change in the bioburden characterization that could invalidate the delivered SAL;

c) the sterilization process has remained reproducible since the last validation;

d) no changes to the sterilization process have occurred that could affect product sterility; and

e) biological environmental monitoring indicates no significant shifts in either the type of microbiological flora or counts.

12.4 Change control

A change control system shall be used to prevent unauthorized changes to the sterilization system, control system, or products being sterilized. Documented procedures shall be in place to ensure that no changes occur in equipment, process, or materials that could affect the sterilization process. If such changes do occur as a planned event, the effect of the change on the process shall be evaluated, as well as the need for requalification of the current process or development of a new process. Process failures that cannot be attributed to lack of adherence to process specifications shall be examined to determine the need for requalification. The change control system shall establish when OQ or PQ testing should be repeated.

Annex A
(informative)

Guidance on application of this standard

A.1 Scope

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

A.2 Normative references

No further guidance is required.

A.3 Definitions

No further guidance is required.

A.4 Quality systems

A.4.1 Assignment of personnel responsibilities

The development, validation, and routine control of a sterilization process is likely to involve a number of separate parties, each of whom will be responsible for certain elements. This standard does not require particular elements to be carried out by defined parties, but it does require that the party accepting particular responsibilities be identified and the definition of responsibilities be documented. This documented definition of responsibilities may form part of a contractual relationship.

To illustrate the variety of possible allocations of responsibilities, this section presents two example scenarios. These scenarios are not intended to be all-inclusive.

Medical device manufacturer using in-house facilities. In this scenario, the user of the sterilization process is a manufacturer of single-use medical devices that is installing in-house facilities for sterilization. The parties involved are the medical device manufacturer and sterilizer manufacturer. The allocation of responsibilities may 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 characterization of the sterilizing agent (i.e., dry heat at elevated temperatures) 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 that is capable of being programmed to deliver a predefined process. The medical device manufacturer may provide specific equipment specifications.

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 devices to be sterilized. The medical device manufacturer undertakes the biological safety assessments and product compatibility studies. These studies may be 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.** The medical device manufacturer carries out routine control and monitoring in accordance with documented procedures.

h) **Product release from sterilization.** The medical device manufacturer carries out product release in accordance with documented procedures.

i) **Maintaining process effectiveness.** The medical device manufacturer maintains process effectiveness in accordance with documented procedures.

Medical device manufacturer using a sterilization subcontractor. In this scenario, the user of the sterilization process is a manufacturer of single-use medical devices that 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, sterilization subcontractor, and contract laboratory. The allocation of responsibilities may 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 undertakes the sterilizing agent characterization and makes the data available to the medical device manufacturer. Alternatively, the sterilization subcontractor licenses the sterilization process from a separate organization that has characterized and developed the sterilization process. The process developer undertakes the sterilizing agent characterization and makes the resultant data available to the sterilization subcontractor and medical device manufacturer.

c) **Process/equipment characterization.** The sterilization subcontractor develops an equipment specification, including a control system for the equipment that is capable of being programmed to deliver a predefined process. The sterilizer manufacturer is contracted to manufacture and install the specific equipment.

d) **Product definition.** The medical device manufacturer is responsible for specifying the product and its manufacture.

e) **Process definition.** The medical device manufacturer defines a process for the particular medical devices 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 sterilization subcontractor undertakes installation qualification and operational qualification in accordance with documented procedures. The medical device manufacturer is responsible for 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 exercises.

g) **Routine control and monitoring.** Routine control and monitoring are carried out by the sterilization subcontractor in accordance with documented procedures agreed upon by the medical device manufacturer.

h) **Product release from sterilization.** The medical device manufacturer carries out product release in accordance with documented procedures, on the basis of records provided by the sterilization subcontractor and 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 before sterilization and takes responsibility for requalification; the sterilization subcontractor carries out any necessary repetition of part or all of installation qualification or operational qualification.

The level of qualification, training, and experience personnel at various levels require will depend on 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, microbiological and physical performance qualification, routine sterilizer operation, calibration, process design, and equipment specification.

A.4.2 Documentation and records

No further guidance is required.

A.4.3 Design control

No further guidance is required.

A.4.4 Calibration

No further guidance is required.

A.5 Sterilizing agent characterization

Dry heat is a relatively slow-acting sterilizing agent, generally requiring higher temperatures than other modes of sterilization. However, one of the distinct advantages of dry heat is its penetrating power. It will penetrate a variety of materials, including oils, petrolatum jelly, and closed containers that are not permeable to steam.

The rate of microbiological destruction associated with devices and components sterilized by dry heat can be influenced by the temperature, uniformity of the heating medium during sterilization, permeability of the packaging material to the heating medium, accessibility of the device or component fluid pathway to the heating medium, and physiological state of the bioburden associated with the product.

Dry heat sterilization of sealed containers with liquid and gas phases can require external pressures higher than those provided for heating alone. If the contained liquid is water (or a solution with similar physical properties), the vapor pressure produced by heating cannot, during the heat-up and exposure phases, exceed the pressure of the heating media. However, additional pressure is produced by heating of the vapor space (e.g., air) and expansion of the liquid, which compresses the vapor. It may be necessary to add external pressure higher than ambient to compensate for these heat-up and exposure phases and for the interior temperature and vapor pressure being higher than the cooling media.

Mathematical techniques and graphing methods have been developed by which the process lethality (often expressed as $F_{(phys)}$) can be calculated from product temperature data. The calculation of an F value derived from physical process parameters is explained in such publications as Parenteral Drug Association (1981), Stumbo (1973), and Pflug (1973). Definitions of *D value*, *F value*, $F_{(bio)}$, F_H *value*, $F_{(phys)}$, and *z value* are given in section 3 of this standard. Both the reference temperature and z value are needed to calculate the F value.

The larger the D value, the more resistant the microorganism is to thermal destruction. The value can be derived by plotting the logarithm (log) of the number of microbiological survivors against sterilization exposure time; the time corresponding to a 1-log reduction in numbers can then be directly measured.

The use of F_H to express cycle lethality assumes a reference temperature. The standard reference temperature for dry heat is 160 °C, with a z value of 20 °C. (It should be noted, however, that with the variety of temperatures used in dry heat processes, any reference temperature can be selected.) Product temperature data accumulated during the entire process (heating, exposure, cooling) is converted to the equivalent lethality at 160 °C and mathematically or graphically integrated to derive a physical lethality value expressed as the equivalent minutes of exposure at 160 °C. For example, each minute at 140 °C has a lethal rate equivalent to 0.1 minute at 160 °C if z = 20 °C. Some software programs can calculate the process F value continuously during the sterilization cycle using input from one or more temperature sensors in the product. Specific techniques to calculate F_H are described in the references included with this standard (see annex B) and in other literature.

Preliminary studies should be conducted to select the locations for monitoring temperatures to calculate F_H so that the F values used in process development represent the greatest challenge to the system. These studies should include temperature distribution studies in the loaded sterilization system to find slow-to-heat regions in the chamber sterilizing zone, determine whether they are reproducible, and find the lowest-temperature regions in the sterilizing zone during exposure. These studies should demonstrate that the temperature sensor is in the product's low-temperature zone, or a documented technical rationale should be given for the selected location of the temperature sensor. If the size of the package or container or the volume of fill is small, consideration should be given to the possible effects of heat conduction along the probe and into the product, and to the need to insert the probe to the proper depth in order to minimize stem conduction errors. Small-gauge sensor wire can be used to minimize this heating effect.

Accurate estimation of a process $F_{(phys)}$ value requires that the temperature measurement system be properly calibrated. Correction factors must be applied to individual readings before calculating cycle lethality. The validity of the $F_{(phys)}$ value is based on the assumption that the resistant species in the product bioburden have a z value of approximately 20 °C. The relationship between the $F_{(phys)}$ value and the $F_{(bio)}$ value of organisms in the product/ sterilization environment (D and z values) should be determined. Validation depends on first-order death kinetics.

Lethality using physical process data should be determined in conjunction with appropriate microbiological studies. Whereas the $F_{(phys)}$ is determined by temperature probes and the resulting physical data, the $F_{(bio)}$ is determined by the PCD and the resulting biological data (D values and z values). By using the biological data together with the $F_{(phys)}$, one can predict the effectiveness of a sterilization cycle.

A.6 Process and equipment characteristics

A.6.1 General

Dry heat sterilization systems fall into two general categories: batch and continuous (continuous systems are often referred to as “tunnel” or “conveyor” sterilization systems). Continuous sterilization systems are often used for the sterilization or depyrogenation of containers for aseptic fill. In these cases, no packaging is used, and the product is sterilized in an aseptic environment and delivered into an aseptic area. (Batch dry heat sterilization systems can also be used for this function.)

Dry heat sterilization and depyrogenation generally take place at a temperature of 160 °C or higher, although sterilization processes at significantly lower temperatures have been developed and validated.

The high temperature of typical dry heat processes limits the materials that can be used for the product and packaging. Conversely, the relative insensitivity of the materials used can allow wide tolerances in process parameters, as compared with other sterilization processes.

A.6.2 Process monitoring

A.6.2.1 Process parameters

No additional guidance is offered.

A.6.2.2 Tolerance of the parameters

The tolerance of the process parameters is determined by the control capability of the sterilization system and material being sterilized. Many products that are dry heat sterilized are made of glass and metal. These types of products can withstand high temperatures and, thus, will permit larger temperature and heating-time tolerances. In these situations, temperature ranges of greater than 5 °C are not unusual. For continuous dry heat sterilizers, the time at temperature is determined by conveyor speed. While conveyor speeds are adjustable, once set they maintain speeds with close tolerances, provided that the mechanical and control systems function properly. Any tolerances in the conveyor speed should be included in the minimum time required for sterilization or depyrogenation.

In batch dry heat sterilizers, the time is generally the parameter that can best be controlled. Typical time tolerances are generally acceptable. If F_H is used to calculate the sterilization time, the temperature ramp-up and ramp-down rates must be controlled and monitored.

The gaseous heating mediums used in dry heat sterilization have a low heat capacity. The temperature distribution in a chamber will contribute to the process tolerances. The distribution is influenced by

a) loading;

b) airflow rate and distribution (e.g., dampers);

c) blower speed;

d) operation of the heating elements; and

e) for continuous sterilization systems, the temperature of adjacent zones (or ambient temperature at the entrance to and exit from the tunnel).

Loading should be consistent with that used during the validation. The mechanical elements associated with the sterilization system are generally not adjusted for a particular cycle. Proper performance of these elements (e.g., blower, dampers, heaters) should be ensured.

A.6.2.3 Process monitoring locations

Locations of temperature monitoring devices are determined during the process validation. The location should be at the worst-case site (lowest-temperature and/or slowest-to-heat zone) in the load (or chamber). A convenient location that can be related to this zone may also be used. The latter is determined during the validation. If a convenient location is used, the sterilization (or depyrogenation) time is set to ensure that the worst-case location receives the required time at temperature.

It is typical to measure chamber temperatures rather than load temperatures. In continuous systems, it may be impossible to measure load temperatures. At least two temperature measurement devices are recommended for routine production cycles; these devices can be placed together in the selected location. If the two devices are separately positioned, the allowable difference between the devices should be determined.

When required, the speed of a conveyor should be monitored at the conveyor surface or a location as close as possible to the conveyor surface. Such monitoring will detect any problems that develop with the drive mechanism. However, the drive mechanism can be evaluated and alternate speed sites determined as acceptable (i.e., shaft rotation) if it can be ensured that such alternate sites represent the conveyor speed.

If the pressure in the sterilization chamber is controlled, the site for pressure monitoring should represent the worst-case location for gas leakage out of the chamber. For example, if the chamber is pressurized to maintain an aseptic environment and it is not hermetically sealed, the pressure monitor should be placed at the openings to the external environment.

A.6.3 Documentation of equipment

A.6.3.1 Identification

No additional guidance is offered.

A.6.3.2 Safety

Written instructions should be available to alert the user to potential hazards associated with equipment use.

The equipment, including the chamber, should comply with IEC 61010-1 and IEC 61010-2-043 and, where appropriate, with national safety regulations applying in the country of intended use.

For batch sterilization systems, means should be provided to ensure that the system cannot be accidentally operated unless the chamber doors are closed, sealed, and locked. The sterilization system should be provided with means to prevent the door from being unsealed if the chamber is heated or pressurized. Unless a fault condition is indicated, the sterilization system doors should be able to be unsealed, unlocked, and opened only at the end of a sterilization cycle. The sterilization system should also be provided with means to return the chamber to atmospheric conditions and open the loading doors if a breakdown of the automatic cycle occurs.

If a loading, unloading, or maintenance operation requires entrance into the sterilization system (whether batch or continuous), a lockout procedure and equipment should be provided to ensure that the sterilization system cannot be started while it is being worked on, except by the personnel conducting the work.

Unloading procedures should be developed to prevent damage to the package and danger to personnel from hot materials. Sterilizer loads should be removed from the chamber and allowed to cool further before handling. This equilibrium should take place in an area free of drafts and with restricted traffic patterns.

A.6.3.3 Manuals and instructions

Information should be supplied to enable proper installation, operation, and routine maintenance of the sterilization system.

The installation instructions should include a description of

a) the overall dimensions and masses of the sterilization system;

b) the type of electrical supply, voltage, frequency, and power;

c) the flow and pressure for air supplies;

d) the emitted sound intensity for operator safety; and

e) the cooling system, if applicable.

The instructions for safe and effective system operation should include a description of

a) the range of application, type of load, and kind of packaging;

b) the chamber capacity;

c) the available sterilizing cycles;

d) the controls and indicating devices;

e) safety devices;

f) the exhaust system, if applicable;

g) safety instructions; and

h) what to do in the event of a malfunction.

The maintenance and repair instructions should include

a) maintenance procedures;

b) the recommended maintenance interval or timetable;

c) electrical diagrams and circuits;

d) hydraulic plans and circuits;

e) a spare-parts list; and

f) safety procedures.

The process-control logic and/or software documentation necessary to operate and maintain the equipment control system (or any other software supplied) should be provided and accompanied by proof of validation. This validation may be performed by either an independent party or, where applicable, the manufacturer of the software in accordance with the requirements of the appropriate parts of the ISO 9000 series.

A.6.3.4 Additional information

A series of checks and tests should be performed after the sterilization system is installed in the location of intended use. The manufacturer, supplier, and purchaser should agree on who is responsible for performing these checks and tests.

A.6.4 Sterilization system performance, utilities, components, accessories, and controls

A.6.4.1 Performance

The performance of the sterilization system should be checked through a test program that complies with appropriate national regulations or standards. See A.9.2, A.9.3, and A.9.4.

A.6.4.2 Utilities

A.6.4.2.1 Air

The sterilization system should be designed to operate with an air or other gaseous heating medium supply which is free of liquid water, filtered to 5 micrometers (μm), and contains not more than 0.5 milligrams (mg) of oil per cubic meter of free air. If an aseptic environment is required in the chamber, the heating medium should be passed through a microbiologically retentive HEPA filter that retains at least 99.5 % of particles greater than 0.3 μm.

For sealed products, it may not be necessary for air admitted to the chamber to be microbiologically filtered. Under conditions of high heat, however, permeable packaging can allow microbiological penetration that would not occur under normal conditions. Also, normally sealed packaging can breathe if heat-induced expansion of components or internal gases, followed by cooling, occurs.

A.6.4.2.2 Electrical power

The purchase specification for the sterilization system should include the characteristics of the electrical power that is available at the installation site. The sterilization system should be designed to operate when the main voltage is maintained within ± 10 % of the nominal supply voltage. The sterilization system should be designed to operate with an electrical supply provided with means to simultaneously isolate all poles from the main supply and fuse each pole separately. The electrical installation should comply with the *National Electrical Code* (NEC) and any applicable local codes.

A.6.4.3 Components

The materials used in the sterilization system should resist the adverse effects of heat, and should not lead to deterioration of the quality of the heating medium or release any substances known to be toxic in quantities that could create a health hazard. Ductwork and other surfaces that personnel could touch that have a temperature higher than 70 °C should be thermally insulated. Connections should be provided so that temperature or other monitoring sensors can be inserted for testing temperature distribution and product heat penetration. Components that must be replaced (e.g., HEPA or other filters) should be conveniently located, and the sterilization system should be installed in a manner that allows easy access.

A.6.4.4 Accessories

Trays, racks, carts, and, where applicable, conveyors should be designed to allow uniform contact of all products with the heating medium. They should ensure that the product and package are not damaged or their sterility compromised. They should also be designed to hold the product securely and prevent movement of the product resulting from gas flow or movement of a conveyor.

Filters, if they are used, should be appropriate for the intended use. They should be tested or replaced periodically. If HEPA filters are used, they should be tested at least every six months and certified.

Hot exhaust gases should be safely vented.

A.6.4.5 Control and recording systems

The sterilization cycle should be controlled by an automatic program control that has one or more preset sterilization cycles. Provisions may be made to adjust the stage parameters of the preset sterilization cycles. Access to the control device should be restricted through the use of a special key, code, or tool.

For maintenance or test purposes and in case of emergency, means should be provided to permit manual progression of the program. During the manual process, any safety devices should not be circumvented.

The recorder may be either analog or digital and should produce permanent, legible records of the values of the specified process parameters throughout the sterilization cycle. The rate of change of temperature and pressure can be derived from the time, temperature, and pressure recordings, rather than from a distinct recording.

A.6.4.6 Control programs

The sterilization system manufacturer is responsible for the quality of any of the software provided. For proprietary reasons, the sterilization system manufacturer may decide not to disclose the software source list. In this case, the manufacturer should supply the user with a validation statement that includes a reference indicating on which points and to which standards the validation was performed. The logic of electromechanical or other means of control should also be validated. The device manufacturer is responsible for all validations in support of all changes.

A.6.5 Performance of instruments

A.6.5.1 Instrument accuracy

The temperature control device should

a) be either digital or analog;

b) have an accuracy of ± 1 % or better over the operating range;

NOTE—The accuracy should be sufficient to demonstrate compliance with specifications.

c) be adjusted to ± 0.5 °C at the sterilization temperature;

d) have broken-sensor protection; and

e) be adjustable *in situ* by the use of a key, code, or tool without dismantling the instrument.

The pressure control device should

a) be either digital or analog;

b) have an accuracy of ± 1.6 % or better over the scale range of 0 bar to 3 bar;

c) have broken-sensor protection; and

d) be adjustable *in situ* by the use of a key, code, or tool without dismantling the instrument.

The time control device should have an accuracy of ± 1 % or better for time periods longer than 5 minutes and have an accuracy of ± 2.5 % or better for time periods of up to 5 minutes.

Where possible, systematic errors should be quantified and corrected by applying the appropriate correction factors.

A.6.5.2 Calibration standards

Calibration standards should be traceable to the National Institute for Standards and Technology (NIST) or another nationally recognized laboratory. If a third party is used for calibration, the sterilization system user should audit the third party for compliance to traceability.

A.6.5.3 Calibration program

The sterilization system reference instruments should enable detection of control-instrument drift or changes in performance. Both measurement systems should be under the same calibration program. The performance of the reference measuring instrument should equal or exceed that of the control system. Typically, the reference instruments are expected to be at least three times as accurate as the control instruments. The maximum allowable deviation between the two measurement systems should be established in the system design, process development, or equipment qualification phase. The measurement system should be recalibrated if the deviation between the two measurements exceeds the specified limit.

A documented calibration program should be established to ensure that accurate and valid measurements are obtained. The calibration program should address standards requirements, use written calibration procedures, and specify the accuracy and precision of the instruments. Instruments should be calibrated in accordance with the manufacturer's instructions, and calibration should include a value within 2 °C of the sterilization temperature. The frequency of routine calibration depends on the monitoring system being used and the degree of risk deemed acceptable in the event of loss of calibration. For a validation program, calibration should be performed, at a minimum, before the validation program is initiated and when it is concluded.

The organization providing calibration services should be evaluated to determine whether personnel are competent and capable of performing calibration to the degree of accuracy required.

Calibration records or third-party calibration facilities should be audited at least annually as part of the requalification program. The review of calibration records should aim to identify whether

a) there are emerging defects;

b) changes are required in the calibration program;

c) changes have occurred to any calibration procedure;

d) additional training is required by calibration personnel;

e) records have been completed satisfactorily, signed, and dated; and

f) adequate traceability is being maintained.

A.6.6 Maintenance

A maintenance scheme should be developed from the schedules provided by the sterilization system manufacturer, instrument manufacturers, and equipment manufacturers; from the generic tasks and tests carried out in the plant; and as a result of experience. The maintenance scheme and frequency with which each task is carried out should be based on the recommendations given by the manufacturer and persons with specialized experience. In addition, usage, risk to safety, and the need to maximize utilization should be considered.

The procedure for each maintenance task should be based on the manufacturer's instructions.

The designated person should sign and date all entries relating to maintenance, both scheduled and unscheduled, stating that all of the necessary work and tests have been completed and are satisfactory. Recurring faults should be identified, and corrective action taken.

The review of maintenance records should aim to identify whether

a) there are emerging defects;

b) changes are required in the maintenance scheme;

c) changes have occurred to any maintenance procedure;

d) additional training is required by maintenance persons; and

e) records have been completed satisfactorily, signed, and dated.

A.7 Product definition

A.7.1 Introduction

No further guidance is required.

A.7.2 Product considerations

When dry heat is to be used to sterilize health care products, the product should

a) be able to withstand high temperatures;

b) facilitate contact between the sterilant and all surfaces to be sterilized; and

c) remain sterile when properly stored.

These points should be considered when the product is designed. Simple design changes that do not affect product performance could possibly prevent sterilization and validation problems. Any change in design should not be implemented before the factors mentioned above are considered and, if necessary, validated.

It is essential to select materials capable of withstanding the temperature stresses inherent in dry heat sterilization. For some materials, it is also essential that the material be readily permeable to air or other gaseous heating medium. Procedures should be specified and followed to ensure that the materials used in routine production are equivalent to those used in validation studies. Improving one quality can lead to a negative effect on another quality; therefore, any change could require requalification of the current process or new process development and validation.

A.7.3 Packaging considerations

The same considerations associated with product design and selection of materials apply to packaging. Also, to allow proper transportation and handling of the sterile product, the packaging should be designed to accommodate shelf-life requirements. The product and its packaging should withstand the rates of temperature change and the maximum temperature occurring during the sterilization cycle.

For terminally sterilized devices, packaging design should consist of not less than two layers, which may include

a) **primary packaging** containing the product or, where only the inside of the product is considered sterile, the product itself (e.g., the fluid path of tubing);

NOTE 1—Fittings and closures intended to keep the inside of the product sterile are designed and validated to at least the same standards as the primary packaging materials.

NOTE 2—The primary packaging may consist of more than one layer to ensure that after the outer layer has been removed and the product has been presented to the user, particulate and biological carryover is at a minimum.

b) **secondary packaging** containing one or more primary packages intended to facilitate proper storage and internal transport by the user; and/or

c) **transport packaging** protecting the product and the primary and secondary packaging during external transport.

For sterile products, the total packaging configuration should perform the functions of a primary package, secondary package, and transport package as described above. For sterile-fluid-path products, the packaging should perform at least the functions of a secondary package and transport package. Also, all packaging configurations should be strong enough to protect the product during intended handling and shipping.

During sterilization, the product will be contained in at least the primary packaging, but sterilizing products in the secondary or transport packaging is not uncommon.

In general, the properties needed for a good packaging design for sterilization contradict those needed for optimum protection of the product. A compromise may be made in either the selection of packaging materials or the level to which the product is packed before and during sterilization.

In contract sterilization, temporary second and third packaging layers should be considered for use during transport before sterilization.

Materials used for packaging should be compatible with the contained product. When selection procedures for packaging materials are developed, consideration should also be given to

a) resistance to tearing;

b) facility of aseptic presentation;

c) the need to minimize levels of toxic ingredients, nonfast dyes, and lint to the extent possible without compromising the quality of the product; and

d) the need to avoid generating any gases that could restrict the transmission of heat.

Small packages or containers are recommended, and product density should be kept as low as possible. It is recommended that, when oil or powder is sterilized, the volume should not exceed one ounce and the depth should not exceed one-quarter inch. Instruments are not required to be in an open position because the heat is transferred throughout the instrument by conduction.

For further information on packaging material requirements, see ANSI/AAMI/ISO 11607.

A.7.4 Bioburden

No further guidance is offered.

A.8 Process definition

A.8.1 Introduction

Process definition is undertaken to define the process parameters for a dry heat sterilization process that 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 effect (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 that will achieve the specified requirements for product sterility.

A.8.2 Selection of the sterilization process

Selection of the duration and temperature of the sterilization cycle to be used depends on the product configuration and the ability of the product and package to withstand temperatures and total heat input. Dry heat processes should be developed with the narrowest practical range of temperatures in the sterilization chamber. Cycle development studies may be performed in a research chamber if process equivalency with the production chamber is demonstrated.

A.8.3 Sterilization process development

Development of a dry heat sterilization cycle for health care products must take into account the sensitivity of the process to significant variations in load configuration, load initial temperature, and the specific heat of the load components. Factors that can influence dry heat sterilization of health care products are listed in Table A.1.

Table A.1—Factors that can influence dry heat sterilization of health care products

Variables	Factors	Considerations
Packaging	Density per unit volume	Heat penetration
	Hermetic seals	Seal strengths
	Porosity	Maintenance of sterility
	Labeling	Retention of product labels during process
Device or component	Composition	Heat tolerance
	Complexity	Design
		Thermal degradation
		Maintenance of sterility potential
		Loss of function
Sterilizer	Sterilizer load density (e.g., fully loaded or partially loaded sterilizer)	Rate of heat penetration in the load
		Rate of poststerilization cooling

Factors such as entrapment of microorganisms in the product, product contact with contaminated liquids during manufacturing, and use of materials that could support microbiological growth should be considered when developing a dry heat sterilization cycle. Recovery of heat-treated spores can also vary with time between treatment and culturing, and with culturing conditions. Therefore, such conditions should be carefully controlled and documented.

"Overkill" methods traditionally have been used to establish industrial dry heat sterilization cycles. This approach is based on the premise that the sterilization process will inactivate a high microbiological challenge (e.g., between 10^3 and 10^6) that is not necessarily related to the presterilization bioburden. This method is called "overkill" because the cycle conditions established to kill the microbiological challenge, with an additional safety factor, should be much more severe than those required to inactivate the product bioburden.

The D value of the microbiological challenge and product bioburden microorganisms can vary in different environments and at different sites. Thus, the initial count or challenge concentration is selected on the basis of the resistance of the spore population under the conditions of use.

When the overkill method is used, the potential thermal degradation of the product and its package or container should be considered. Increased chemical and physical degradation, increased formation of particulates, and limited product shelf life may result from excessive thermal exposure.

The manufacturer should obtain data for the typical bioburden loading associated with the product. That data need not be as extensive nor obtained as frequently as when bioburden cycle development methods are used.

In the **combined biological indicator/bioburden method**, the microbiological sterilization challenge of the product could necessitate inactivation of the initial inoculum concentration to an established logarithmic level. The relative resistance and population of the initial challenge inoculum of the microbiological challenge microorganism should be compared with the mean number and thermal resistance of the bioburden typically associated with the product. The comparison should demonstrate that inactivation of a predetermined level of microbiological challenge ensures that the desired probability of a bioburden survivor is achieved. This method is considered to be based on bioburden; therefore, the bioburden should be enumerated and the resistance determined as in the absolute bioburden method.

The **absolute bioburden method** involves screening product for thermally resistant microorganisms—for example, by using a bioburden isolate (recovered for purposes of challenging product sterilization) that is representative of the most resistant bioburden population. The isolate may be propagated, inoculated on or into the product, and used in product sterilization challenge studies to directly demonstrate the desired probability of survival for the product

bioburden. Typical bioburden counts used in the calculation are based on the mean bioburden count plus three times the standard deviation.

Bioburden resistance can be determined by exposing product samples containing the bioburden to fractional exposure time increments at proposed cycle conditions and then conducting sterility tests to determine the number of survivors or fractional positives present at various durations of exposure (Halvorson and Ziegler, 1932; Pflug and Holcomb, 1991). Alternatively, isolation and propagation, followed by inoculation onto the product or an appropriate carrier, may be used to determine the resistance of bioburden organisms; however, propagation can change the resistance of the bioburden. The resistance of other microbiological challenge systems that could be used for routine biological monitoring should also be determined.

A cycle based on bioburden requires frequent bioburden screening to determine bioburden counts and species associated with the products. The frequency of bioburden screening depends on the quality and variability of the historical data, the kinds of products being sterilized, the manufacturing process, and the type of sterilization process. Representative products from each manufacturing facility should be sampled during routine production. A bioburden monitoring program should be designed to evaluate any changes in product components and manufacturing, the environment, or production processes that could significantly affect bioburden. If a change in the manufacturing environment occurs, additional bioburden monitoring should be considered.

The microbiological challenge resistance may be evaluated at fractional exposure times to determine the degree of lethality as a function of proposed process parameters. The degree of lethality can be measured either by recovering and counting surviving microorganisms to develop a death-rate curve, or performing an end-point analysis where sterility test methods are used. In the latter case, exposure times are selected so that the shortest exposure results in growth of all test samples, the longest exposure results in no growth, and the intermediate exposures result in growth of some of the samples.

Biological indicators have been widely used to evaluate the lethality of the various combinations of process parameters, products, and packaging. A microbiological challenge system of known resistance directly measures the achieved lethality at certain product sites as a result of the variable employed.

The microorganisms used for production of BIs are generally more resistant to sterilization than typical bioburden. However, as part of cycle development, studies should be conducted to demonstrate this resistance. Procedures that can be applied include (1) isolation, propagation, and resistance evaluation of recovered bioburden organisms, or (2) exposure of product with typical bioburden to short cycles, together with product sterility testing. The number and resistance of isolates can be used to calculate the lethality of the sterilization process relative to the bioburden. However, the propagation of bioburden organisms can change their resistance. If short exposure cycles are used, they should be selected to allow extrapolation of the results.

A.8.4 Process challenge devices

Process challenge devices usually consist of a known spore population of *Bacillus atrophaeus* or another strain of microorganism known to have a resistance to dry heat that has been demonstrated to be equivalent to or greater than that of var. *B. atrophaeus*. There are several types of PCDs, including but not limited to the following.

a) **Inoculated product.** The actual product may be inoculated directly or indirectly with spores of a known population and resistance, as described in A.8.3. Direct inoculation is accomplished by applying a liquid suspension on the product. Indirect inoculation is accomplished by placing an inoculated carrier in or on the product or in the package.

   NOTE—Direct inoculation of a product can result in variable resistance of the inoculum because of the occlusion of the spores on or in the product, surface phenomena, and/or other environmental factors. Therefore, it is important to validate this practice to ensure that the resistance of the inoculated simulated product is reasonably correlated to the natural product. The inoculum recovery must also be validated. See Gillis and Schmidt (1983), West (1977), and ANSI/AAMI/ISO 11737-1 for additional information.

b) **Inoculated simulated product.** A simulated product consists of portions of a device or a combination of components known to represent the greatest challenge to the process while still adequately representing all products in a product family. The simulated product may be inoculated by direct or indirect means, as described in A.8.4(a).

c) **Inoculated carrier.** A carrier such as a paper strip, disc, or other substrate may be inoculated with spores of a known population and resistance. In order to use the inoculated carrier for cycle development, the resistance of the inoculated carrier should be correlated with the resistance of the inoculated product, simulated product, or natural product.

d) **Natural product.** A product with naturally occurring bioburden may be used as the microbiological challenge system for the absolute bioburden method of cycle development. When a natural product is used,

there should be a bioburden monitoring program that complies with ANSI/AAMI/ISO 11737-1 and determines the numbers, distribution, and resistance of the bioburden before sterilization.

There are no national or international standards for reference organisms (i.e., BI organisms) for dry heat sterilization. However, further guidance on paper-strip BIs can be found in USP (2003), and an international standard for dry heat BIs is under development by the International Organization for Standardization.

Products may be grouped into families for selection of the sterilization cycle, for validation activities, and for routine control of dry heat sterilization. Product families should be established on the basis of the product bioburden, complexity of the product and packaging, and configuration and density of the sterilization load. The general approach is to classify individual products and packages by their similarities and then evaluate which conditions within a given classification provide the greatest challenge. A family of products may be represented by the master product, an equivalent product, or a simulated product. The studies or rationale used to place a product in a particular product classification should be documented.

The master product may represent the product family if assessment indicates that one member of the product family presents a challenge to the sterilization process that is greater than all of the other family members. In some situations, there may be several products in the family that could be considered the master product. In such circumstances, any one of these products may be selected as the master product to represent the family.

A group of equivalent products may represent the product family if assessment indicates that members of a product family are considered equivalent. Selection of the equivalent product should be either at random or in accordance with a planned schedule to include the equivalent family members. The manufacturing volume and availability of the product should be considered in selecting the product to represent the family.

A simulated product may represent a product family if it constitutes a challenge to the sterilization process that is equivalent to or greater than the challenge associated with the products in the family. A simulated product is not intended for clinical use; it is fabricated solely for the development of the sterilization cycle, validation, and routine production sterilization. A simulated product may be one that

a) is similar to the actual product in terms of materials, size, complexity, and packaging, and is subjected to similar manufacturing processes (for example, a piece of the material used for implants that goes through the entire manufacturing process);

b) is a packaged combination of components from products in the family that would not typically be combined for use (for example, a tubing set containing multiple filters, clamps, and stopcocks that are components of other products in the product family); or

c) has similar heat transfer characteristics.

The individual with responsibility for sterilization should participate in periodic reviews of the product families and assessing the impact of any modifications to the product or process. The outcome of such assessments and reviews should be documented.

A formal review should be performed at a specified frequency (at least annually) to ensure that all product families and products used to represent each family remain valid.

A.8.5 Sterility testing

No further guidance is offered.

A.8.6 Biocompatibility

No further guidance is offered.

A.8.7 Depyrogenation

Thermal destruction by dry heat (convection, conduction, or radiant heat ovens) is the most common and effective way to destroy pyrogenic material of bacterial origin (endotoxin). Dry heat depyrogenation is the method of choice for heat-resistant materials such as glassware, metal equipment, and instruments, as well as heat-stable chemicals, waxes, and oils.

The standard method of depyrogenation, as described in many reference texts and compendia, is exposure at not less than 250 °C for more than 30 minutes (USP 2003; Sweet and Huxsoll, 1985). Temperatures in excess of 180 °C for not less than 3 hours have also been shown to effectively destroy bacterial endotoxin. Lower dry heat temperatures (i.e., 175 °C or less) are relatively insufficient to destroy at least 2 log units of pyrogen (Akers, et al., 1982; Ludwig and Avis, 1989). For example, at 170 °C, a 3-log to 5-log reduction in endotoxin was shown to require processing times greater than 1,000 minutes.

Validation should be completed by demonstrating a 3 log reduction in endotoxin. One or more challenge articles should be treated with 1,000 or more USP endotoxin units (EU). A positive control, not exposed to thermal destruction, and the exposed challenge articles should-be measured for endotoxin. The endotoxin assay should be the Limulus Amebocyte Lysate (LAL) test.

NOTE—If a lower level of EU reduction is validated, a program should be in place for routine monitoring of endotoxin levels on articles before processing to ensure that they do not exceed the validated level.

When depyrogenation cycle validation is being conducted, the nature of the endotoxin should be considered. Different rates of endotoxin destruction have been found. Commercial endotoxin preparations formulated without fillers (i.e., lactose, polyethylene glycol) have been shown to be most resistant to dry heat exposure and, therefore, are regarded as worst case challenges (Ludwig and Avis, 1990). Destruction of endotoxin does not follow the simple logarithmic decline exhibited in sterilization studies on homogeneous spore suspensions. The inactivation kinetics of endotoxin from *E. coli*, *S. typhosa*, *Serratia marcescens*, and *Pseudomonas aeruginosa* have been demonstrated to be a nonlinear, second-order process (Tsuji and Harrison, 1978). Ensuring reliable endotoxin recovery from the challenge articles is crucial in endotoxin inactivation or removal studies (Avis, et al., 1987; Ludwig and Avis, 1989).

So that depyrogenation is ensured, it is important that every article in the oven be exposed to at least the stated temperature for not less than the stated time. Consequently, an extended exposure time may be required for the entire oven load to reach temperature.

A.9 Sterilization process validation

A.9.1 General

The validation program is performed to evaluate the reliability of a sterilization or depyrogenation process. (Further references to “sterilization” will include depyrogenation where applicable.) Therefore, the validation protocol should be explicit in what, when, and how to measure. A major part of the protocol will also need to address the interpretation of the results. True objective validation is possible only if the requirements on which the sterilization process will be judged are determined and established before the validation. Compliance with a quality system such as ISO 9001 will ensure clear and objective validation.

Careful attention should be given to ensuring that physical parameters throughout the entire sterilization cycle (not just the exposure phase) are comparable to those set during cycle development. The conditioning (heat-up) phase could deliver significant lethality to the load.

The analysis of the data obtained during validation will demonstrate that a given sterilization cycle in an identified sterilization system will or will not render a specified load sterile. Therefore, validation is not related just to the sterilization system but also to such factors as the load and its configuration.

The homogeneity of the load and the loading pattern largely determine the number of temperature sensors needed. Using mixed loads could require an increase in the number of sensors being used. At least one sensor should be placed next to the monitoring and control sensors. Sensors may also be placed in the free chamber space.

A good interpretation of the results is possible only if the criteria have been set before validation is performed. Adapting the requirements to the validation results contradicts any quality system or principle. If the sterilization process is not within the preset limits, experience and expertise are necessary to interpret the results and identify the problems causing noncompliance.

The installation qualification, operational qualification, and performance qualification are part of the design control process and should be conducted using approved protocols.

The reliability of the validation results depends on the accuracy and reproducibility of the process parameters delivered and measured. Calibration in conjunction with validation should ensure the accuracy, precision, and sensitivity of the measuring equipment that is used in validation, as well as the equipment that delivers, senses, records, or otherwise controls the specified process parameters. Specifications associated with calibration for validation should include detection values and tolerance limits for accuracy and precision. The validation program should include provisions for addressing out-of-calibration conditions that might be encountered. Calibration standards should be traceable to a national or international standard.

Validation may be scheduled as measurement sessions (or runs) among production runs of already validated loads. However, the interruption of validation sessions for scheduling purposes does not preclude the necessity to demonstrate process reproducibility throughout multiple consecutive validation runs. Thus, a new series of validation runs should be initiated following the investigation and correction of any failed validation run. However, such new series need not be initiated where a validation run has been disqualified because of an unforeseen failure of something peripheral to the system being validated. Peripheral failures include, for example, power failures, loss of services, and failure of external monitoring equipment. A peripheral failure would be documented as a

disqualification and not as a failed validation test if the factor responsible for the failure is truly unrelated to the control or performance of the process or equipment being validated. Normally, a disqualified run would simply be rescheduled.

A.9.2 Installation qualification

The installation qualification plan should include procedures that will ensure that the sterilization system and its connected service utilities comply with the specifications, and the sterilizer is safe and fit for use.

Upon completion of the IQ, “as built” drawings should be prepared, because the actual installation may not be the same as that planned in the design or installation drawings.

A.9.3 Operational qualification

The operational qualification plan should include a study that demonstrates that the sterilization system will perform the required process without product. Any carts, trays, or racks used to hold the product should be in the chamber.

Temperature sensors should be distributed throughout the volume occupied by the load. Locations should include

a) expected hot zones (e.g., near heating medium inlets);

b) expected cold zones (e.g., near doors or locations farthest from heating medium inlets);

c) areas next to fixed chamber temperature sensors; and

d) the top, geometric center, and bottom of the load volume, distributed uniformly.

For small batch sterilizers, a minimum of three temperature sensors, or one temperature sensor per cubic foot, should be used, up to 10 cubic feet of chamber volume. A minimum of 10 temperature sensors should be used for chamber volumes of 10 cubic feet or more. The number of sensors should be based on the temperature range found and the specification required. The smaller the temperature range in the chamber, the fewer temperature sensors will be needed. Temperature should be monitored throughout the entire cycle using the longest anticipated exposure time.

For continuous (tunnel) sterilization systems, the temperature across the conveyor belt and temperature of the belt should be monitored. Sensors should be fastened to the belt to include the edges of the product area and the center. If the sterilization system is set with different temperature zones, each zone should be monitored. The monitoring location should be above the maximum product height. If the temperature sensors are rotated (i.e., the zones are not monitored simultaneously), a reference position is needed to compare temperatures from different zones. If the sterilizer is not zoned, the temperatures should be monitored in the heat-up (entrance) area, exposure area, and cool-down (exit) area. Locations should include the area above the maximum height of the product and across the width occupied by the product. Locations next to control probes should also be included. A minimum of 10 temperature locations should be monitored. In larger chambers, a minimum of five temperature locations per 2.8 cubic meters (100 cubic feet) of product volume should be monitored. Temperature should be measured at equilibrium operating conditions for the maximum exposure time. It could be necessary to bring a continuous sterilization system to operating temperature before conducting heat mapping.

If pressurization of the chamber or tunnel is required, measurements should be conducted in areas where the gaseous heating medium is expected to leak out. In tunnel units, these areas are typically the exit and entrance locations.

Additional process parameters that should be measured during validation include

a) heating medium flow rates and uniformity;

b) amperage draw of electrical heater(s); and

c) conveyor speed, if applicable.

A.9.4 Performance qualification (PQ)

The performance qualification is performed to demonstrate the ability of the process to attain defined physical conditions, within specified tolerances, throughout the load. Different loads and modifications of loads should be evaluated to determine the acceptable range of product and packaging types and densities that can be sterilized by a specific process. It may be that certain loads and loading patterns will not be sterilizable in dry heat sterilization processes. The PQ includes a physical qualification and microbiological qualification.

A.9.4.1 Performance qualification—Physical

Temperature profiles of the sterilization load should be determined for each representative loading pattern. The number of temperature sensors recommended for the empty chamber during the operational qualification should provide an adequate profile of the load. Product should be at or below the minimum specified temperature (see 9.4.1) before it is introduced into the sterilization chamber, unless the process is controlled using load temperature. Temperature sensors should be distributed throughout the volume occupied by the load, with particular attention to any suspected hot and cold spots or zones.

Simultaneous internal (penetration) and external (distribution) temperature monitoring may be conducted during the physical PQ. This monitoring might indicate the presence of unforeseen problems that could occur in loaded versus empty chambers; in this case, twice the number of temperature sensors recommended above should be used.

It should be confirmed that the product meets its specified requirements for safety, quality, and performance after application of the sterilization process at the upper tolerances of the process parameters.

A.9.4.2 Performance qualification—Microbiological

The microbiological qualification should include a minimum of three fractional cycles that demonstrate reproducible kill from cycle to cycle and uniform kill throughout the chamber or tunnel using a full chamber load of worst-case product. The cycles should provide less lethality than the production process, which can be accomplished by reducing the exposure time, temperature, or both.

The type of BI or PCD is determined by the type of microbiological validation that has been selected (8.3 and 8.4). If an external or different microbiological monitor is to be used in routine production, it should be included in the microbiological qualification.

Biological indicators or other PCDs should be placed in the load on the basis of data acquired during the physical performance qualification (A.9.4.1).

The number of BI or PCD locations should be based on the temperature range found and the specification required. The smaller the temperature range in the chamber, the fewer BI or PCD locations will be needed. For small batch sterilizers (those having a chamber volume less than or equal to 10 cubic feet), a minimum of 10 BI or PCD locations should be used. For larger batch sterilizers (those having a chamber volume more than 10 cubic feet), a minimum of 20 BI or PCD locations should be used. Each of the temperature sensors should be placed next to a BI or PCD location.

For continuous (tunnel) sterilization systems, the microbiological kill across the conveyor belt should be determined. Biological indicators or other PCDs should be placed in the product on the belt to include the edges of the product area and the center. In addition, BIs or PCDs should be included at the beginning, middle, and end of each processing run. Biological indicators or other PCDs should be placed in the worst-case product, which is generally the largest. A minimum of 10 BIs or other PCDs should be passed through the tunnel during each of three runs with the tunnel at equilibrium conditions. The runs should be conducted on three different days with the tunnel shut down between each run. It may be necessary to bring a continuous sterilization system to operating temperature before the microbiological qualification is conducted. The microbiological monitoring should be conducted at a fractional exposure time, which is established by adjusting the conveyor speed. Each of the temperature sensors should be placed next to a BI or PCD location. Because it is not practical to continuously monitor the load temperature throughout the entire processing run for continuous (tunnel) sterilization systems, the load temperatures should be monitored, at minimum, at the beginning, middle, and end of each processing run.

For validation of depyrogenation processes, a standard endotoxin challenge is used in place of BIs or other PCDs. The number and placement should follow the guidance above. A 3-log reduction of a standard endotoxin challenge is typical; however, a lower level of reduction can be validated, provided that a program is in place to ensure that pyrogen levels are controlled to the validated limits.

The reproducibility of the production cycle is demonstrated by conducting a minimum of three cycles at nominal process parameters, using the worst-case full chamber load for each cycle. At least one minimum load cycle should be run to confirm that the parameters at minimum loading are consistent with the maximum loading. If mixed product loads are to be processed, sufficient cycles should be run to demonstrate that the mix of products results in consistent process parameters.

A.9.5 Parametric release

A.9.5.1 General

Parametric release is the release of product as sterile on the basis of documented attainment of validated process parameters rather than microbiological testing. Additionally, for parametric release, load density and loading

configuration should be documented and verified as elements of product release. For continuous (tunnel) sterilization systems, the belt speed should also be monitored for parametric release. Routine cycle temperature should be monitored for parametric release at additional locations or redundant locations in the chamber. The number of temperature sensors should be the same as previously described (A.9.3).

A complete validation, as outlined in 9.2, 9.3, and 9.4, demonstrates the process uniformity and reproducibility necessary to consistently achieve the specified SAL during routine processing. However, the validation alone does not provide sufficient information about the dynamics of lethality to assess the margin of safety and provide the confidence necessary for parametric release.

The microbiological performance qualification should be performed by determining the process lethality (F_H value) of the cycle, either by the survivor-curve method (A.9.5.2) or fraction-negative method (A.9.5.3).

Chamber temperature sensors should be duplicated to ensure data in the event of a sensor failure. Chamber or tunnel loading should be carefully controlled to ensure that the validated load configuration is used.

Before parametric release is implemented, microbiological release should be used for a sufficient time period to ensure the adequacy of quality assurance programs in conjunction with the reliability of the sterilization process.

A.9.5.2 Survivor-curve method

A survivor curve is constructed by counts of exposed BIs or PCDs. At least five data points, using graded exposure times with all other process parameters constant, should be included. The starting population (N_o) of the BI system can be used as the initial time increment. Using uniform time increments will make calculating the D value simpler. A minimum of five samples per data point is recommended. See also the references provided in 9.5.

NOTE—For tunnel or large-chamber-size batch sterilization systems, the survivor curve may be generated in a smaller batch system to permit more accurate time and temperature data to be achieved. In this case, the results are then transferred to the production chamber. The minimum accumulated F_H, a point on the survivor curve, or a point in the quantal region can then be used to duplicate the lethality in the production chamber. The lethal end-point time should be confirmed with validation cycles in the production chamber.

A.9.5.3 Fraction-negative method

In the fraction-negative method, BIs or PCDs are exposed to graded time increments with all other process parameters constant. This method requires that the starting population (N_o) of the BI system be known. One set of samples should show all positive results. A minimum of four data points should show a fraction of the samples growing (quantal region). A minimum of two data points at the same time interval should show no growth. This method evaluates the potential for “tailing” or erratic microbiological kill. A minimum of 10 samples is recommended for each data point. It should be noted that the number of samples is determined by the desired accuracy of the data point. See also AAMI TIR16 and the references provided in 9.5.

A.9.6 Other sterilization systems

A.9.6.1 General

The introduction of a new sterilization system is an important change, even if the new system replaces a similar sterilizer or is one of a number of sterilizers of the same type. In some cases, data from one sterilizer can be used to demonstrate the proper functioning of another sterilizer.

Process equivalency can be established when sterilization equipment is located either in the same facility or at a different facility. The recommendations for establishing a process equivalency program are

a) full validation of the sterilization process in at least one existing system according to the requirements of this standard; and

b) performance of the installation qualification and operational qualification studies that demonstrate and document that all equipment has been installed in accordance with engineering specification requirements and operates in accordance with those requirements.

A.9.6.2 Determination of process equivalency

The equivalency of a specific sterilization process can be established by comparing the data obtained when the sterilization process is run in the candidate sterilization process equipment with the data obtained when the same sterilization process is run in the existing equipment. This comparison should include an evaluation of the equipment’s ability to deliver the desired specifications reproducibly to a worst-case product load. The specifications should be those that were previously validated in the performance qualification of the sterilization process in the existing equipment. The candidate sterilization process equipment should also be compared with the existing

equipment to determine how significant the differences are. The IQ and OQ for all candidate equipment should be reviewed to ensure that the equipment is suitable for the sterilization process.

The evaluation of equivalency is a three-phase process consisting of design and engineering evaluation (Phase 1), process analysis and evaluation (Phase 2), and microbiological evaluation (Phase 3).

A.9.6.2.1 Phase 1—Design and engineering evaluation

The design and engineering evaluation consists of a comparison of the equipment used in the candidate sterilization process system to the existing validated sterilization process system. Some of the factors to be considered include

— volume of the chambers,

— volume used in the chambers,

— available BTU/ft^3 of the heat source for the chambers,

— capacity of the circulation system of the chambers,

— equilibration time in the chambers,

— temperature uniformity in the chambers,

— overall cycle time in the chambers, and

— conveyor speed, if applicable.

The outcome of this evaluation is a basis for determining the extent of further qualification testing required in the second and third phases. If the evaluation shows that the equipment is not similar, it is still possible to establish process equivalency on the basis of the results of the second and third phases. Typically, the greater the similarity between the candidate equipment and existing equipment, the less testing will be required in those phases.

A.9.6.2.2 Phase 2—Process analysis and evaluation

The second phase in establishing equivalency is an analysis of all process data associated with a validated process in the candidate equipment. This data should be compared to the specification limits for that specific sterilization process. The specification limits are those established in the initial validation of the sterilization process in the existing equipment. The specifications, acceptance criteria, and load configuration should be the same as defined for the initial process validation studies. Statistical methods that evaluate both the central tendencies of the test data and its degree of variability may be used to assist in this evaluation.

An evaluation that compares the load profiles within each candidate chamber should be performed. This evaluation should be performed using the existing process parameters. The critical parameters for the process should be defined before the evaluation is performed. These parameters should include distribution and control of product temperature in the load throughout the cycle, as well as heat-up and cool-down times of the product.

A comparison of the processes from the chamber runs should indicate that the processes are equivalent in their ability to meet the existing process specification limits and any additional acceptance criteria. If the analysis of the data meets the acceptance criteria, then a reduced microbiological PQ with product may be performed (see Table A.2) to validate the candidate chambers. The data generated should be analyzed and compiled in a format that will allow for its use in future process equivalency determinations.

If the acceptance criteria are not met in the process analysis and evaluation, then it is not possible to demonstrate process equivalency even though the results of the other phases may be equivalent.

A.9.6.2.3 Phase 3—Microbiological evaluation

The third phase of the analysis of process equivalency is the performance of a microbiological evaluation. This evaluation consists of the consideration of any factors that would affect the lethality of the sterilization process.

The factors that should be evaluated include any changes to the sterilization location or manufacturing location that could affect the bioburden level of the product as presented for sterilization. An increased distance between the manufacturing facility and sterilization site could result in higher bioburden levels, particularly if the product will support microbiological growth. Differences in manufacturing environments could lead to the production of product with higher bioburden levels than previously validated, even if the product does not support microbiological growth.

A.9.6.3 Results evaluation

The results of the microbiological evaluation, in conjunction with the results of Phase 1 and Phase 2, are used to determine if a microbiological PQ should be performed (Table A.2). If the conclusions of the design and engineering evaluation (Phase 1), process analysis and evaluation (Phase 2), and microbiological evaluation (Phase 3) are equivalent, then the performance of a microbiological PQ is not necessary.

Table A.2—Evaluation results

Phase 1—Design and engineering evaluation	Phase 2—Process analysis and evaluation	Phase 3—Microbiological evaluation	Minimum # of microbiological PQ runs
Equivalent	Equivalent	Equivalent	None
Not equivalent	Equivalent	Equivalent	1
Equivalent	Equivalent	Not equivalent	1
Not equivalent	Equivalent	Not equivalent	1
Equivalent or not equivalent	Not equivalent	Equivalent or not equivalent	3

If Phase 2 and either Phase 1 or Phase 3 concluded that the processes are equivalent, or if only Phase 2 concluded that the processes are equivalent, then at least one microbiological PQ run should be performed (Table A.2). This microbiological performance qualification should be sufficient to demonstrate that the desired SAL of the process is achieved even if the equipment or microbiological evaluation is not equivalent.

If the conclusion of Phase 2 was that the processes are not equivalent, then the process should be declared “not equivalent” and should be fully validated according to the requirements of this standard before the candidate equipment is used. The results of Phase 1 or Phase 3 do not change this declaration of “not equivalent.”

If the performance of one or more microbiological PQ runs is required, then the type of cycle, specification limits, and lethality requirements established in the validation of the existing process should be used to evaluate the performance of the candidate equipment. The specification limits, lethality requirements, and acceptance criteria should be defined before the performance of the microbiological PQ.

A.9.6.4 Maintenance of equivalency

The established process equivalency program must define the requirements that the equipment must meet to produce repeatable performance characteristics annually. The analysis should define the acceptable range of the operating parameters and level of variability to maintain equivalency from year to year.

A.9.6.5 Documentation

All decisions related to the outcome of the analysis to determine if candidate equipment may be declared equivalent to the existing sterilization process equipment must be documented. At a minimum, the documentation package should include

a) the complete specification for the candidate equipment, which should fully describe the equipment, operating specifications and tolerances, and reference or provide a list of applicable operating procedures, calibration procedures, and maintenance schedules;

b) evidence or assessment of the ability of the equipment to deliver the intended process, including a reference to the current OQ;

c) the results of the comparison between the candidate process equipment and the existing, validated process equipment, which comparison should clearly demonstrate that all major systems and critical parameters were assessed, and include statistical analyses, if used;

d) evidence or assessment of the product conditions during processing in the candidate equipment to demonstrate equivalence to the existing process;

e) the results of evaluation of additional factors that could affect the lethality of the sterilization process;

f) the documented conclusion that the candidate equipment is equivalent to the equipment specifically referenced in the current validation study to achieve the specified SAL, which statement should include or

reference the results of any additional testing performed to supplement the existing validation study and any further testing performed for confirmation/qualification of routine release of product from the existing, validated cycle;

g) approval by the sterilization specialist and other individuals as required by the normal change control practices within the organization; and

h) the listing of applicable sterilizer operating procedures and specifications issued or changed to authorize use of the candidate equipment for routine processing of product.

A.9.7 Validation report

The validation report should be approved by the same functions that approved the original protocol.

A.10 Routine monitoring and control

A.10.1 Process control systems

In the development and qualification phase, the process is established as capable and reproducible. During this evaluation, control variables are identified and referred to in a process validation file. A standard operating procedure (SOP) is generated from the validation file for routine process execution and control. In accordance with the SOP, the key control variables (materials, loading, operating parameters, and so forth) are read and monitored during routine sterilizer use to verify process control and acceptability.

a) The relationships between temperature controller, control program (if applicable), sterilizer temperature probe, and load temperature distribution are established to ensure that materials at all locations in the sterilizer will meet the required time at temperature during exposure.

b) The timer setting should reflect the minimum exposure time at the location in the sterilizer that is the last to reach the set point. When manual timing is required, temperature documentation intervals should be appropriately determined on the basis of the length of the exposure period.

c) The time required to reach the set point (heat-up time) is reviewed and documented for each cycle to verify process control and ensure that product integrity has been maintained.

d) The load configuration is inspected to verify that it reflects the configuration established during qualification. A new load size qualification can be established by comparing the temperature distribution during minimum and maximum load validation studies. If the minimum and maximum loads are determined to be equivalent, then loads of intermediate sizes can be considered qualified.

e) The airflow settings for sterilizers so equipped are documented and should reflect the SOP specification. A pressure reading for sterilizers so equipped should also be reviewed and documented for each sterilizer run.

f) For continuous systems, the speed of the conveyor is verified and documented for each sterilization run.

A.10.2 Process recording systems

Microprocessor-based systems produce a record of the events of the sterilization process. This record is compared to the operational parameters included in the SOP and signed by the individual verifying process acceptability. Manual system records include a predetermined recording format to document the chamber load and configuration, cycle identification, run date, and cycle events such as time, temperature, airflow, and (if applicable) pressure readings. This information is gathered during the cycle or derived from remote monitoring devices.

A.10.3 Microbiological testing

Biological indicators are placed in the product load in locations determined to be the most difficult to sterilize. Alternatively, the appropriate PCDs may be used. The locations in the sterilizer shown to have the shortest time at temperature should be challenged by the BI or PCD.

If parametric release has been established, microbiological testing is not required.

A.11 Product release

A.11.1 General

Sterilized products should not be stored in areas subject to great fluctuations in humidity, pressure, and/or temperature. The transportation and distribution system should be designed to prevent damage to the packaging. If

appropriate, the package should be labeled with an expiration date, and a system should be established to ensure first-in, first-out usage.

Failure to meet the physical specification or failure of the BI or other PCD to meet its specified requirements should lead to the sterilization load being placed in quarantine, the cause of failure investigated, and the investigation documented.

If the process parameters are outside their specified tolerances, product should not be released. Product should be evaluated in accordance with nonconforming product procedures. The decision on the disposition of the product should be documented.

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

A.11.2 Product release using biological indicators

If BIs or other PCDs are used to monitor the sterilization cycle for product release, records of the physical sterilization process parameters and results of indicator testing are reviewed to demonstrate the effective delivery of the dry heat sterilization process. Guidance on the selection, use, and interpretation of results of BIs is contained in ANSI/AAMI/ISO 14161.

A.11.3 Parametric release

If a dry heat sterilization cycle operating within specified tolerances has been demonstrated to be both effective and reproducible, then 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 on the basis of direct measurement and evaluation of physical parameters in the chamber. No other samples or indicator testing are required for parametric release.

Parametric release is considered a design aspect of a sterilization process that can be fully characterized, and 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 must be identified and their values known. Therefore, parametric release should be supported by extensive experience of the sterilization process.

A.12 Maintaining process effectiveness

A.12.1 Maintenance

Preventive maintenance is a critical component of the system and should be covered in an SOP. This procedure should address the schedule for review of critical equipment parts, using the equipment manufacturer's instructions and historical information. A logbook should be maintained and provide a chronological record of all preventive and corrective maintenance activities performed. Equipment components that typically require preventive maintenance include (but are not limited to)

a) door gaskets,

b) heating elements,

c) shaft seals,

d) recirculation fans,

e) control equipment,

f) air filters,

g) moving belts (for product transfer),

h) motors,

i) alarms, and

j) insulation.

A.12.2 Calibration

An SOP should be written to cover calibration and calibration frequencies. All instruments or gauges that are not part of the calibration system should be clearly marked to indicate that calibration is not required.

The frequency of calibration should be based on the manufacturer's recommendations, instrument operational experience, use of redundant or secondary instrumentation for product release, and risk assessment.

Instrumentation and gauges found to be out of calibration should be reported on a "calibration exception report" that is reviewed by appropriate engineering and quality assurance personnel to assess the effect of the error on the sterility of the product processed during the period of time since the previous calibration.

Periodic audits of the calibration program should be performed to assess the adequacy of the reported data, calibration frequency, training of the technicians, and compliance of the system with the quality assurance program.

A.12.3 Requalification

Requalification is recommended if significant changes are made in the sterilization system (hardware or software), process, product, or packaging that could affect sterilization efficacy. The following are examples (not necessarily all-inclusive) of changes that could necessitate performance requalification unless data is available to establish equivalency.

a) **Product tolerances.** A significant change in the product material or design tolerances that could affect the heating rate of the product.

b) **Product design.** A significant change in the product design, including product materials, composition, or thickness, that could affect the efficacy of the sterilization process.

c) **Packaging.** Changes that could affect microbiological barrier efficacy, substantive changes in packaging design, or changes in vendors that could significantly affect physical properties and heat transfer.

d) **Equipment.** Changes that could affect specified operating parameters or substantially change the rate of heat transfer into the product.

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 heat transfer into the load.

g) **Product bioburden.** Any change in raw materials, the environment, or processing that could influence the efficacy of the sterilization cycle.

NOTE—To determine if requalification is required, process changes should be reviewed by the function that conducted the initial validation.

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

A.12.4 Change control

A.12.4.1 General

A change request form should be used to define the extent of the change and the follow-up actions (e.g., updating of drawings, specification changes, requalification) that will be required once the change is implemented. Designated engineering, manufacturing, and quality control personnel should approve the request form before the change is initiated. After the changes and follow-up actions have been completed, the form should be routed to the original approvers for final approval.

A.12.4.2 Emergency changes

When an emergency change is necessary, the following actions should be taken:

a) The responsible department head determines whether the equipment or system to be repaired is subject to change control. The validation and quality departments, or their equivalent, should be notified as soon as

possible. A record of the repair or alteration is made in the appropriate equipment or system log. A critical-change form is submitted to the appropriate department as well.

b) The quality and validation departments determine the need for requalification.

c) The quality department determines testing requirements for products manufactured on the subject system.

d) The maintenance department updates qualification records and system drawings as necessary.

A.12.4.3 Planned changes

When a planned change is to occur, the following actions should be taken:

a) The responsible department head determines if the equipment or system to be repaired is subject to change control. Typically, the maintenance and quality departments, and possibly others, are responsible for determining whether a change affects the validated functions of the sterilizer.

b) A formal change control form is initiated in accordance with the SOP to control and record modifications to the sterilizer's equipment systems. The change control form is routed to the validation, quality, and other applicable departments. If requalification is required, the responsible department is notified before the work order is initiated.

c) The maintenance or engineering department initiates the work by generating an approved work order.

d) Upon completing the work, the responsible department contacts the validation or other applicable department to initiate requalification work.

A.12.4.4 Changes not requiring requalification

Physical changes to the sterilizer that are determined by the responsible department to have no effect on sterilizer operating characteristics are documented on a work order. The technical rationale is included and approved by appropriate management personnel.

Annex B
(informative)

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