American National Standard

ANSI/AAMI/ISO 14937:2009

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

Association for the Advancement of Medical Instrumentation

Objectives and uses of AAMI standards and recommended practices

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

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

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

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

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

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

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

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

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

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

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Requests for interpretations of AAMI standards and recommended practices must be made in writing, to the AAMI Vice President, Standards Policy and Programs. An official interpretation must be approved by letter ballot of the originating committee and subsequently reviewed and approved by the AAMI Standards Board. The interpretation will become official and representation of the Association only upon exhaustion of any appeals and upon publication of notice of interpretation in the "Standards Monitor" section of the *AAMI News*. The Association for the Advancement of Medical Instrumentation disclaims responsibility for any characterization or explanation of a standard or recommended practice which has not been developed and communicated in accordance with this procedure and which is not published, by appropriate notice, as an *official interpretation* in the *AAMI News*.

American National Standard

ANSI/AAMI/ISO 14937:2009
(Revision of ANSI/AAMI/ISO 14937:2000)

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

Approved 2 October 2009 by
Association for the Advancement of Medical Instrumentation

Approved 27 October 2009 by
American National Standards Institute, Inc.

Abstract: Specifies general requirements for the characterization of a sterilizing agent and for the development, validation and routine monitoring and control of a sterilization process for medical devices. Applies to sterilization processes in which microorganisms are inactivated by physical and/or chemical means. Intended to be applied by process developers, manufacturers of sterilization equipment, manufacturers of products to be sterilized and organizations responsible for sterilizing medical devices.

Keywords: sterilization, general requirements, characterization

AAMI Standard

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All AAMI standards, recommended practices, technical information reports, and other types of technical documents developed by AAMI are *voluntary*, and their application is solely within the discretion and professional judgment of the user of the document. Occasionally, voluntary technical documents are adopted by government regulatory agencies or procurement authorities, in which case the adopting agency is responsible for enforcement of its rules and regulations.

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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 60601-1:2005 Technical Corrigendum 1 and 2	ANSI/AAMI ES60601-1:2005 ANSI/AAMI ES60601-1:2005/C1:2009 (amdt)	Major technical variations C1 Identical to Corrigendum 1 and 2
IEC 60601-1-2:2007	ANSI/AAMI/IEC 60601-1-2:2007	Identical
IEC 60601-2-2:2009	ANSI/AAMI/IEC 60601-2-2:2009	Identical
IEC 60601-2-4:2002	ANSI/AAMI DF80:2003	Major technical variations
IEC 60601-2-19:2009	ANSI/AAMI/IEC 60601-2-19:2009	Identical
IEC 60601-2-20:2009	ANSI/AAMI/IEC 60601-2-20:2009	Identical
IEC 60601-2-21:2009	ANSI/AAMI/IEC 60601-2-21:2009	Identical
IEC 60601-2-24:1998	ANSI/AAMI ID26:2004/(R)2009	Major technical variations
IEC 60601-2-47:2001	ANSI/AAMI EC38:2007	Major technical variations
IEC 60601-2-50:2009	ANSI/AAMI/IEC 60601-2-50:2009	Identical
IEC 80601-2-30:2009	ANSI/AAMI/IEC 80601-2-30:2009	Identical (with inclusion)
IEC 80601-2-58:2008	ANSI/AAMI/IEC 80601-2-58:2008	Identical
IEC/TR 60878:2009	ANSI/AAMI/IEC TIR60878:2003	Identical
IEC/TR 62296:2009	ANSI/AAMI/IEC TIR62296:2009	Identical
IEC 62304:2006	ANSI/AAMI/IEC 62304:2006	Identical
IEC/TR 62348:2006	ANSI/AAMI/IEC TIR62348:2006	Identical
IEC/TR 80002-1:2009	ANSI/IEC/TR 80002-1:2009	Identical
ISO 5840:2005	ANSI/AAMI/ISO 5840:2005	Identical
ISO 7198:1998	ANSI/AAMI/ISO 7198:1998/2001/(R)2004	Identical
ISO 7199:2009	ANSI/AAMI/ISO 7199:2009	Identical
ISO 8637:2004	ANSI/AAMI RD16:2007	Major technical variations
ISO 8638:2004	ANSI/AAMI RD17:2007	Major technical variations
ISO 10993-1:2009	ANSI/AAMI/ISO 10993-1:2009	Identical
ISO 10993-2:2006	ANSI/AAMI/ISO 10993-2:2006	Identical
ISO 10993-3:2003	ANSI/AAMI/ISO 10993-3:2003/(R)2009	Identical
ISO 10993-4:2002 and Amendment 1:2006	ANSI/AAMI/ISO 10993-4:2002/(R)2009 and Amendment 1:2006/(R)2009	Identical
ISO 10993-5:2009	ANSI/AAMI/ISO 10993-5:2009	Identical
ISO 10993-6:2007	ANSI/AAMI/ISO 10993-6:2007	Identical
ISO 10993-7:2008	ANSI/AAMI/ISO 10993-7:2008	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999/(R)2005	Identical
ISO 10993-10:2002 and Amendment 1:2006	ANSI/AAMI BE78:2002/(R)2008 ANSI/AAMI BE78:2002/A1:2006/(R)2008	Minor technical variations Identical
ISO 10993-11:2006	ANSI/AAMI/ISO 10993-11:2006	Identical
ISO 10993-12:2007	ANSI/AAMI/ISO 10993-12:2007	Identical
ISO 10993-13:1998	ANSI/AAMI/ISO 10993-13:1999/(R)2004	Identical
ISO 10993-14:2001	ANSI/AAMI/ISO 10993-14:2001/(R)2006	Identical
ISO 10993-15:2000	ANSI/AAMI/ISO 10993-15:2000/(R)2006	Identical
ISO 10993-16:1997	ANSI/AAMI/ISO 10993-16:1997/(R)2009	Identical
ISO 10993-17:2002	ANSI/AAMI/ISO 10993-17:2002/(R)2008	Identical
ISO 10993-18:2005	ANSI/AAMI BE83:2006	Major technical variations
ISO/TS 10993-19:2006	ANSI/AAMI/ISO TIR10993-19:2006	Identical
ISO/TS 10993-20:2006	ANSI/AAMI/ISO TIR10993-20:2006	Identical
ISO 11135-1:2007	ANSI/AAMI/ISO 11135-1:2007	Identical

International designation	U.S. designation	Equivalency
ISO/TS 11135-2:2008	ANSI/AAMI/ISO TIR11135-2:2008	Identical
ISO 11137-1:2006	ANSI/AAMI/ISO 11137-1:2006	Identical
ISO 11137-2:2006 (2006-08-01 corrected version)	ANSI/AAMI/ISO 11137-2:2006	Identical
ISO 11137-3:2006	ANSI/AAMI/ISO 11137-3:2006	Identical
ISO 11138-1: 2006	ANSI/AAMI/ISO 11138-1:2006	Identical
ISO 11138-2: 2006	ANSI/AAMI/ISO 11138-2:2006	Identical
ISO 11138-3: 2006	ANSI/AAMI/ISO 11138-3:2006	Identical
ISO 11138-4: 2006	ANSI/AAMI/ISO 11138-4:2006	Identical
ISO 11138-5: 2006	ANSI/AAMI/ISO 11138-5:2006	Identical
ISO/TS 11139:2006	ANSI/AAMI/ISO 11139:2006	Identical
ISO 11140-1:2005	ANSI/AAMI/ISO 11140-1:2005	Identical
ISO 11140-3:2007	ANSI/AAMI/ISO 11140-3:2007	Identical
ISO 11140-4:2007	ANSI/AAMI/ISO 11140-4:2007	Identical
ISO 11140-5:2007	ANSI/AAMI/ISO 11140-5:2007	Identical
ISO 11607-1:2006	ANSI/AAMI/ISO 11607-1:2006	Identical
ISO 11607-2:2006	ANSI/AAMI/ISO 11607-2:2006	Identical
ISO 11737-1: 2006	ANSI/AAMI/ISO 11737-1:2006	Identical
ISO 11737-2:2009	ANSI/AAMI/ISO 11737-2:2009	Identical
ISO 13408-1:2008	ANSI/AAMI/ISO 13408-1:2008	Identical
ISO 13408-2:2003	ANSI/AAMI/ISO 13408-2:2003	Identical
ISO 13408-3:2006	ANSI/AAMI/ISO 13408-3:2006	Identical
ISO 13408-4:2005	ANSI/AAMI/ISO 13408-4:2005	Identical
ISO 13408-5:2006	ANSI/AAMI/ISO 13408-5:2006	Identical
ISO 13408-6:2006	ANSI/AAMI/ISO 13408-6:2006	Identical
ISO 13485:2003	ANSI/AAMI/ISO 13485:2003/(R)2009	Identical
ISO 14155-1:2003	ANSI/AAMI/ISO 14155-1:2003/(R)2008	Identical
ISO 14155-2:2003	ANSI/AAMI/ISO 14155-2:2003/(R)2008	Identical
ISO 14160:1998	ANSI/AAMI/ISO 14160:1998/(R)2008	Identical
ISO 14161:2009	ANSI/AAMI/ISO 14161:2009	Identical
ISO 14708-3:2008	ANSI/AAMI/ISO 14708-3:2008	Identical
ISO 14708-4:2008	ANSI/AAMI/ISO 14708-4:2008	Identical
ISO 14937:2009	ANSI/AAMI/ISO 14937:2009	Identical
ISO/TR 14969:2004	ANSI/AAMI/ISO TIR14969:2004	Identical
ISO 14971:2007	ANSI/AAMI/ISO 14971:2007	Identical
ISO 15223-1:2007 and A1:2008	ANSI/AAMI/ISO 15223-1:2007 and A1:2008	Identical
ISO 15225:2000 and A1:2004	ANSI/AAMI/ISO 15225:2000/(R)2006 and A1:2004/(R)2006	Identical
ISO 15674:2009	ANSI/AAMI/ISO 15674:2009	Identical
ISO 15675:2009	ANSI/AAMI/ISO 15675:2009	Identical
ISO 15882:2008	ANSI/AAMI/ISO 15882:2008	Identical
ISO 15883-1:2006	ANSI/AAMI ST15883-1:2009	Major technical variations
ISO/TR 16142:2006	ANSI/AAMI/ISO TIR16142:2005	Identical
ISO 17664:2004	ANSI/AAMI ST81:2004	Major technical variations
ISO 17665-1:2006	ANSI/AAMI/ISO 17665-1:2006	Identical (with inclusions)
ISO/TS 17665-2:2009	ANSI/AAMI/ISO TIR17665-2:2009	Identical
ISO 18472:2006	ANSI/AAMI/ISO 18472:2006	Identical
ISO/TS 19218:2005	ANSI/AAMI/ISO 19218:2005	Identical
ISO 22442-1:2007	ANSI/AAMI/ISO 22442-1:2007	Identical
ISO 22442-2:2007	ANSI/AAMI/ISO 22442-2:2007	Identical
ISO 22442-3:2007	ANSI/AAMI/ISO 22442-3:2007	Identical
ISO 25539-1:2003 and A1:2005	ANSI/AAMI/ISO 25539-1:2003/(R)2009 and A1:2005/(R)2009	Identical
ISO 25539-2:2008	ANSI/AAMI/ISO 25539-2:2008	Identical
ISO 81060-1:2007	ANSI/AAMI/ISO 81060-1:2007	Identical
ISO 81060-2:2009	ANSI/AAMI/ISO 81060-2:2009	Identical

Committee Representation

Association for the Advancement of Medical Instrumentation

General Criteria for Sterilization Processes Working Group

The adoption of ISO 14937 as a revision of ANSI/AAMI/ISO 14937:2000 was initiated by the AAMI General Criteria for Sterilization Processes Working Group of the AAMI Sterilization Standards Committee. U.S. representatives played an active part in developing the ISO standard. Committee approval of the standard does not necessarily imply that all working group members voted for its approval.

At the time this document was published, the **AAMI General Criteria for Sterilization Processes Working Group** had the following members:

Chair: John B. Kowalski, PhD, MicroGAMMA LLC

Members:
Stanko Bodnar, Johnson & Johnson
Anne F. Booth, MS, Conmed Corp
David J. Brodersen, Covidien
Marc Chaunet, TSO3 Inc.
Michele Dawn Demeo, Memorial Hospital (Independent Expert)
Dave Dion, Cardinal Health (MP&S)
April J. Doering, St Jude Medical Inc.
Joseph R. Durbin, Hospira Worldwide Inc.
Kevin Frey, Association of Surgical Technologists (Independent Expert)
Marcia Ann Frieze, Case Medical Inc.
Joel R. Gorski, PhD, NAMSA
Charles Oren Hancock, RAC, H&W Technology LLC
Joyce M. Hansen, JM Hansen & Associates
Donna Horner, Abbott Laboratories
Geetha C. Jayan, PhD, FDA/CDRH
John B. Kowalski, PhD, MicroGAMMA LLC
Colleen Patricia Landers, RN, Canadian Standards Association
Ralph Makinen, Boston Scientific Corporation
Mary S. Mayo, CR Bard
Patrick J. McCormick, PhD, Bausch & Lomb Inc.
Gerald E. McDonnell, PhD, Steris Corporation
Russell D. Mills, Zimmer Inc.
Gerry A. O'Dell, MS, Gerry O'Dell Consulting
Bob L. Osburn, Department of Veterans Affairs National Center for Patient Safety
Rodney D. Parker, Stryker Medical Division
Vana Poovala, Philips Healthcare
Mike Sadowski, Baxter Healthcare Corporation
Donald Tumminelli, SPS Medical Supply Corp
Craig A. Wallace, 3M Healthcare
Martell Kress Winters, BS SM, Nelson Laboratories Inc.

Alternates:
Charlie Christianson, St Jude Medical Inc.
Kimbrell Darnell, CR Bard
Sylvie Dufresne, PhD, TSO3 Inc.
Jim Kaiser, Bausch & Lomb Inc.
Tania Lupu, Case Medical Inc.
Rainer Newman, Johnson & Johnson
Shaundrea L. Rechsteiner, NAMSA
Allison A Rodriguez, FDA/CDRH
John R. Scoville, Jr., Steris Corporation
Mark Seybold, Baxter Healthcare Corporation
Ian Shorr, Cardinal Health (MP&S)
David Silor, Zimmer Inc.
Wendy Wangsgard, PhD, Nelson Laboratories Inc.
Richard E. White, Hospira Worldwide Inc.
Jonathan A. Wilder, PhD, H&W Technology LLC

Kelvin J. Witcher, 3M Healthcare
William E. Young, Boston Scientific Corporation
Christine H. Yunker, Abbott Laboratories

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

Cochairs:
Victoria M. Hitchins, PhD, FDA/CDRH
William E. Young, Boston Scientific Corporation

Members:
Trabue D. Bryans, WuXi AppTec
Peter A. Burke, PhD, Steris Corporation
Nancy Chobin, RN CSPDM, St Barnabas Healthcare System (Independent Expert)
Charles Cogdill, Boston Scientific Corporation
Ramona Conner, RN MSN CNOR, Association of Perioperative Registered Nurses
Jacqueline Daley, Association for Professionals in Infection Control and Epidemiology
Kimbrell Darnell, CR Bard
Lisa Foster, Sterigenics International
Joel R. Gorski, PhD, NAMSA
Deborah A. Havlik, Hospira Worldwide Inc.
Victoria M. Hitchins, PhD, FDA/CDRH
Danny Hutson, Cardinal Health (MP&S)
Lois Atkinson Jones, MS, (Independent Expert)
Susan G. Klacik, CCSMC FCS ACE, IAHCSMM
Byron J. Lambert, PhD, Abbott Laboratories
Colleen Patricia Landers, RN, Canadian Standards Association
Lisa N. Macdonald, Becton Dickinson & Company
Jeff Martin, Alcon Laboratories Inc.
Patrick J. McCormick, PhD, Bausch & Lomb Inc.
Rainer Newman, Johnson & Johnson
Janet M. Prust, 3M Healthcare
Nancy Rakiewicz, Ethox International Inc.
Michael H. Scholla, Dupont Nonwovens
Mark Seybold, Baxter Healthcare Corporation
Andrew Sharavara, PhD, Propper Manufacturing Co Inc.
Mark N. Smith, Getinge USA
William N. Thompson, Covidien
James L. Whitby, MA MB FRCP, Independent Expert
Martell Kress Winters, BS SM, Nelson Laboratories Inc.

Alternates:
Lloyd Brown, Covidien
Glenn W. Calvert, Becton Dickinson & Company
Dave Dion, Cardinal Health (MP&S)
Steven J. Elliott, WuXi AppTec
Thomas J. Frazar, Johnson & Johnson
Kathy Hoffman, Sterigenics International
Jim Kaiser, Bausch & Lomb Inc.
Joseph J. Lasich, BS, Alcon Laboratories Inc.
Chiu S. Lin, PhD, FDA/CDRH
Natalie Lind, IAHCSMM
Ralph Makinen, Boston Scientific Corporation
Mary S. Mayo, CR Bard
David Ford McGoldrick, BS, Abbott Laboratories
Jerry R. Nelson, PhD, Nelson Laboratories Inc.
Karen Polkinghorne, Dupont Nonwovens
Mike Sadowski, Baxter Healthcare Corporation
John R. Scoville, Jr., Steris Corporation
Jason Voisinet, Ethox International Inc.
Craig A. Wallace, 3M Healthcare
Valerie Welter, Hospira Worldwide Inc.
William E. Young, Boston Scientific Corporation

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

Background of AAMI adoption of ANSI/AAMI/ISO 14937

As indicated in the foreword to the main body of this document (page x), the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard.

International Standard ISO 14937:2009 was developed as a revision to the 2000 edition by Working Group (WG) 11, *General criteria for sterilization processes Working Group*, of Technical Committee ISO/TC 198, *Sterilization of health care products.* The revision was prepared to address advancements in the field since the 2000 edition was published.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 198, administered by the Association for the Advancement of Medical Instrumentation on behalf of the American National Standards Institute. The U.S. made a considerable contribution to this International Standard.

AAMI encourages its committees to harmonize their work with international standards as much as possible. Upon review of ISO 14937, the AAMI General criteria for sterilization processes Working Group decided to adopt 14937, verbatim, as a revision of ANSI/AAMI/ISO 14937:2000.

AAMI and ANSI procedures require that standards be reviewed every five years and, if necessary, revised to reflect technological advances that may have occurred since publication.

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

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

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

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

NOTE—Beginning with the foreword on page ”x”, this American National Standard is identical to ISO 14937:2009.

Foreword

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

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

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

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

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

This second edition cancels and replaces the first edition (ISO 14937:2000) and ISO 14937:2000/Cor.1:2003 which have been technically revised.

Introduction

A sterile medical device is one that is free of viable microorganisms. International Standards that specify requirements for validation and routine control of sterilization processes require, when it is necessary to supply a sterile medical device, that adventitious microbiological contamination of a medical device prior to sterilization be minimized. Even so, medical devices produced under standard manufacturing conditions in accordance with the requirements for quality management systems (see, for example, ISO 13485) could, prior to sterilization, have microorganisms on them, albeit in low numbers. Such medical devices are non-sterile. The purpose of sterilization is to inactivate the microbiological contaminants and thereby transform the non-sterile medical devices into sterile ones.

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

This International Standard describes requirements that, if met, will provide a sterilization process with appropriate microbicidal activity intended to sterilize medical devices. Furthermore, compliance with the requirements ensures that the sterilization process is both reliable and reproducible so that predictions can be made, with reasonable confidence, that there is a low level of probability of there being a viable microorganism present on a medical device after sterilization. Specification of this probability is a matter for regulatory authorities and can vary from country to country (see, for example, EN 556-1 and ANSI/AAMI ST67).

Generic requirements of the quality management system for design and development, production, installation and servicing are given in ISO 9001 and particular requirements for quality management systems for medical device production are given in ISO 13485. The standards for quality management systems recognize that, for certain processes used in manufacturing, the effectiveness of the process cannot be fully verified by subsequent inspection and testing of the product. Sterilization is an example of such a process. For this reason, sterilization processes are validated for use, the performance of the sterilization process is monitored routinely and the equipment is maintained.

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

a) the microbiological status of incoming raw materials and/or components;

b) the validation and routine control of any cleaning and disinfection procedures used on the medical device;

c) the control of the environment in which the medical device is manufactured, assembled and packaged;

d) the control of equipment and processes;

e) the control of personnel and their hygiene;

f) the manner and materials in which the medical device is packaged;

g) the conditions under which the medical device is stored.

The type of contamination on a medical device to be sterilized varies, and this influences the effectiveness of a sterilization process. Medical devices that have been used in a health care setting and that are being presented for resterilization in accordance with the manufacturer's instructions (see ISO 17664) should be regarded as special cases. There is the potential for such medical devices to possess a wide range of contaminating microorganisms and residual inorganic and/or organic contamination in spite of the application of a cleaning process. Hence, particular attention has to be given to the validation and control of the cleaning and disinfection processes used during reprocessing.

The requirements are the normative parts of this International Standard with which compliance is claimed. The guidance given in Annex E is not normative and is not provided as a checklist for auditors. The guidance provides explanations and methods that are regarded as being a suitable means for complying with the requirements. Methods other than those given in the guidance can be used if they are effective in achieving compliance with the requirements of this International Standard.

The development, validation and routine control of a sterilization process comprise a number of discrete but interrelated activities, for example, calibration, maintenance, product definition, process definition, installation qualification, operational qualification and performance qualification. While the activities required by this International Standard have been grouped together and are presented in a particular order, this International Standard does not require that the activities be performed in the order that they are presented. The activities required are not necessarily sequential, as the program of development and validation can be iterative. The responsibility for carrying out the activities required by this International Standard will vary from case to case. This International Standard requires that the responsibilities of the various parties be defined (see 4.2) but does not specify to whom the responsibilities are allocated. Annex E provides guidance on allocation of responsibility.

This International Standard has three distinct applications:

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

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

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

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

1 Scope

1.1 Inclusions

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

NOTE Although the scope of this International Standard is limited to medical devices, the requirements specified herein can also be applied to sterilization processes for other health care products.

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

1.1.3 This International Standard is intended to be applied by process developers, manufacturers of sterilization equipment, manufacturers of medical devices to be sterilized, and organizations responsible for sterilizing medical devices.

1.1.4 This International Standard specifies the elements of a Quality Management System which are necessary to assure the appropriate characterization of the sterilizing agent, development, validation and routine monitoring and control of a sterilization process.

NOTE It is not a requirement of this International Standard to have a full quality management system. The necessary elements are normatively referenced at appropriate places in the text (see, in particular, Clause 4). Attention is drawn to the standards for quality management systems (see ISO 13485) that control all stages of production or reprocessing of medical devices. National and/or regional regulations for the provision of medical devices might require the implementation of a full quality management system and the assessment of that system by a third party.

1.2 Exclusions

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

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

1.2.3 This International Standard does not specify requirements for characterization of an agent or for development, validation and routine control of a process for inactivating the causative agents of spongiform encephalopathies such as scrapie, bovine spongiform encephalopathy and Creutzfeldt-Jakob

disease. Specific recommendations have been produced in particular countries for the processing of materials potentially contaminated with these agents.

NOTE See also ISO 22442-1, ISO 22442-2 and ISO 22442-3.

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

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10012, *Measurement management systems — Requirements for measurement processes and measuring equipment*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

ISO 11138-1:2006, *Sterilization of health care products — Biological indicators — Part 1: General requirements*

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

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

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

ISO 13485:2003, *Medical devices — Quality management systems — Requirements for regulatory purposes*

IEC 61010-2-040, *Safety requirements for electrical equipment for measurement, control and laboratory use — Part 2-040: Particular requirements for sterilizers and washer-disinfectors used to treat medical materials*

3 Terms and definitions

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

3.1
bioburden
population of viable microorganisms on or in product and/or sterile barrier system

[ISO/TS 11139:2006, definition 2.2]

3.2
biological indicator
test system containing viable microorganisms providing a defined resistance to a specified sterilization process

[ISO/TS 11139:2006, definition 2.3]

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

[ISO/TS 11139:2006, definition 2.5]

3.4
chemical indicator
non-biological indicator
test system that reveals change in one or more pre-defined process variables based on a chemical or physical change resulting from exposure to a process

[ISO/TS 11139:2006, definition 2.6]

3.5
corrective action
action to eliminate the cause of a detected non-conformity or other undesirable situation

NOTE 1 There can be more than one cause for a non-conformity.

NOTE 2 Corrective action is taken to prevent recurrence whereas **preventive action** (3.17) is taken to prevent occurrence.

NOTE 3 There is a distinction between **correction** (3.6) and corrective action.

[ISO 9000:2005, definition 3.6.5]

3.6
correction
action to eliminate a detected non-conformity

NOTE A correction can be made in conjunction with a **corrective action** (3.5).

[ISO 9000:2005, definition 3.6.6]

3.7
development
act of elaborating a specification

[ISO/TS 11139:2006, definition 2.13]

3.8
establish
determine by theoretical evaluation and confirm by experimentation

[ISO/TS 11139:2006, definition 2.17]

3.9
fault
one or more of the process parameters lying outside of its/their specified tolerance(s)

[ISO/TS 11139:2006, definition 2.19]

3.10
health care product(s)
medical device(s), including *in vitro* diagnostic medical device(s), or medicinal product(s), including biopharmaceutical(s)

[ISO/TS 11139:2006, definition 2.20]

3.11
installation qualification
IQ
process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification

[ISO/TS 11139:2006, definition 2.22]

3.12
material safety data sheet
MSDS
document specifying the properties of a substance, its potential hazardous effects for humans and the environment, and the precautions necessary to handle and dispose of the substance safely

[ISO/TS 11139:2006, definition 2.23]

3.13
medical device
instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of

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

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

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

— supporting or sustaining life,

— control of conception,

— disinfection of medical devices,

— providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body

and which does not achieve its primary 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

[ISO 13485:2003, definition 3.7]

NOTE This definition from ISO 13485:2003 has been developed by the Global Harmonization Task Force (GHTF 2002).

3.14
operational qualification
OQ
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[ISO/TS 11139:2006, definition 2.27]

3.15
parametric release
declaration that a product is sterile, based on records demonstrating that the process parameters were delivered within specified tolerances

[ISO/TS 11139:2006, definition 2.29]

3.16
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 specifications

[ISO/TS 11139:2006, definition 2.30]

3.17
preventive action
action to eliminate the cause of a potential non-conformity or other undesirable potential situation

NOTE 1 There can be more than one cause for a potential non-conformity.

NOTE 2 Preventive action is taken to prevent occurrence, whereas **corrective action** (3.5) is taken to prevent recurrence.

[ISO 9000:2005, definition 3.6.4]

3.18
process challenge device
PCD
item designed to constitute a defined resistance to a sterilization process and used to assess performance of the process

[ISO/TS 11139:2006, definition 2.33]

3.19
process parameter
specified value for a process variable

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

[ISO/TS 11139:2006, definition 2.34]

3.20
process variable
condition within a sterilization process, changes in which alter microbicidal effectiveness

EXAMPLES Time, temperature, pressure, concentration, humidity, wavelength.

[ISO/TS 11139:2006, definition 2.35]

3.21
recognized culture collection
depository authority under the Budapest Treaty on *The International Recognition of the Deposit of Microorganisms for the Purpose of Patent and Regulation*

[ISO/TS 11139:2006, definition 2.38]

3.22
reference microorganism
microbial strain obtained from a recognized culture collection

[ISO/TS 11139:2006, definition 2.39]

3.23
requalification
repetition of part of validation for the purpose of confirming the continued acceptability of a specified process

[ISO/TS 11139:2006, definition 2.40]

3.24
services
supplies from an external source, needed for the function of equipment

EXAMPLES Electricity, water, compressed air, drainage.

[ISO/TS 11139:2006, definition 2.41]

3.25
specify
stipulate in detail within an approved document

[ISO/TS 11139:2006, definition 2.42]

3.26
sterile
free from viable microorganisms

[ISO/TS 11139:2006, definition 2.43]

3.27
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** (3.28)].

[ISO/TS 11139:2006, definition 2.45]

3.28
sterilization
validated process used to render a product free from viable microorganisms

[ISO/TS 11139:2006, definition 2.47]

NOTE In a sterilization process, the nature of microbial inactivation is exponential, and the survival of a microorganism on an individual item can thus be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero. (See sterility assurance level in ISO/TS 11139.)

3.29
sterilization load
product to be, or that has been, sterilized using a given sterilization process

[ISO/TS 11139:2006, definition 2.48]

3.30
sterilization process
series of actions or operations needed to achieve the specified requirements for sterility

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

[ISO/TS 11139:2006, definition 2.49]

3.31
sterilizing agent
physical or chemical entity, or combination of entities, that have sufficient microbicidal activity to achieve sterility under defined conditions

[ISO/TS 11139:2006, definition 2.50]

3.32
survivor curve
graphical representation of the inactivation of a population of microorganisms with increasing exposure to a microbicidal agent under stated conditions

[ISO/TS 11139:2006, definition 2.51]

3.33
test for sterility
technical operation, defined in a Pharmacopoeia, performed on product following exposure to a sterilization process or following an aseptic manufacturing process

3.34
test of sterility
technical operation performed as part of development, validation or requalification to determine the presence or absence of viable microorganisms on product or portions thereof

[ISO/TS 11139:2006, definition 2.54]

3.35
validation
documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications

[ISO/TS 11139:2006, definition 2.55]

4 Quality management system elements

4.1 Documentation

4.1.1 Procedures for characterization of a sterilizing agent, development, validation, and routine control of a sterilization process and product release from sterilization shall be specified.

4.1.2 Documents and records required by this International Standard shall be reviewed and approved by designated personnel (see 4.2.1). Documents and records shall be controlled in accordance with the applicable clauses of ISO 13485.

4.2 Management responsibility

4.2.1 The responsibility and authority for implementing and meeting the requirements described in this International Standard shall be specified. Responsibility shall be assigned to competent personnel in accordance with the applicable clauses of ISO 13485.

4.2.2 If the requirements of this International Standard are undertaken by organizations with separate quality management systems, the responsibilities and authority of each party shall be specified.

4.3 Product realization

4.3.1 Procedures for purchasing shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.

4.3.2 Procedures for identification and traceability of product shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.

4.3.3 A system complying with the applicable clause(s) of ISO 13485 or ISO 10012 shall be specified for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this International Standard.

4.4 Measurement, analysis and improvement — Control of non-conforming product

Procedures for control of product designated as non-conforming and for correction, corrective action and preventive action shall be specified. These procedures shall comply with the applicable clauses of ISO 13485.

5 Sterilizing agent characterization

5.1 General

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

5.2 Sterilizing agent

The sterilizing agent shall be specified. The specification shall include, if appropriate, conditions of storage of the sterilizing agent to maintain the sterilizing agent within its specification for the duration of the stated shelf life.

5.3 Microbicidal effectiveness

5.3.1 Microbicidal effectiveness studies shall

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

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

c) identify reference microorganism(s) that has (have) known high resistance to the sterilizing agent;

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

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

EXAMPLES Interactions with materials and residues from manufacturing, cleaning and/or disinfection.

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

EXAMPLES The environment, materials and residues from manufacturing, cleaning and/or disinfection.

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

5.3.2 The test method(s), acceptance criteria and justification for the choice of test microorganisms shall be documented. Test results shall be recorded (see 4.1.2).

5.4 Effects on materials

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

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

5.4.3 The materials tested and the outcomes of tests shall be recorded (see 4.1.2), together with the criteria against which the properties of materials were assessed before and after exposure to the sterilizing agent.

5.5 Safety and the environment

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

5.5.2 The potential effect on the environment of any substance which could be released, either deliberately or accidentally, during or following use of the sterilizing agent, shall be assessed and measured for the control of the substance(s) established. This assessment, including the potential effect (if any) and the measures for control (if identified), shall be recorded (see 4.1.2).

6 Process and equipment characterization

6.1 General

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

6.2 Process characterization

6.2.1 The process parameters, together with their tolerances, shall be specified. These tolerances shall be based upon knowledge of the combination of process parameters yielding minimal acceptable microbicidal effectiveness. Processing at such process parameters shall routinely yield safe and functional product.

NOTE The establishment of the process parameters follows the definition of process variables [see 5.3.1 d)], including those process variables that are excluded or minimized in ensuring the effectiveness of the sterilization process.

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

6.2.3 Any treatment of product that is required prior to exposure to the sterilizing agent to ensure effectiveness of the sterilization process shall be specified.

6.2.4 Any treatment of product that is required following exposure to the sterilizing agent to ensure safety of product shall be specified as part of the sterilization processes.

6.3 Equipment characterization

6.3.1 The equipment to deliver the process in a safe manner within the tolerances stipulated for the process parameters shall be specified.

6.3.2 The specification shall include, but is not limited to:

a) physical description of the equipment and necessary ancillary items, including materials of construction;

b) specification of the sterilizing agent (see 5.2) and the means by which it is provided, including any additives or precursors necessary for its delivery;

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

d) faults recognized by the sterilizing equipment;

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

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

6.3.3 Software used to control and/or monitor the process shall be prepared in accordance with a quality management system that provides documented evidence (see 4.1.2) that the software meets its design intention.

NOTE Attention is drawn to ISO 90003.

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

7 Product definition

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

7.2 Product to be sterilized, including the packaging materials to be used and the manner in which product is to be presented to the sterilization process, shall be specified.

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

NOTE See, for example, ISO 17664.

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

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

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

NOTE International Standards for equipment to be used in cleaning and disinfecting medical devices (ISO 15883 series) include methods to demonstrate the effectiveness of a cleaning and disinfecting process.

8 Process definition

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

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

a) selecting the process parameters and, if practicable, demonstrating their attainment by measurements;

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

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

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

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

c) be placed either at positions in product where it has been determined that sterilizing conditions are most difficult to achieve or within a process challenge device (PCD).

8.4 If chemical indicators are used as part of the establishment of the sterilization process, they shall comply with ISO 11140-1 and any subsequent parts of ISO 11140 that are applicable to the process. Chemical indicators shall be placed either at positions in product where it has been determined that sterilizing conditions are most difficult to achieve or within a PCD (see 8.6).

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

8.6 If PCDs are used as part of the establishment of the sterilization process, their appropriateness shall be determined. PCDs shall present a challenge equivalent to or greater than that at the position in product where it has been determined that sterilizing conditions are most difficult to achieve.

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

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

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

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

8.11 The sterilization process shall be specified.

9 Validation

9.1 General

The purpose of validation is to demonstrate that the sterilization process established in the process definition (see Clause 8) can be delivered effectively and reproducibly to the sterilization load. Validation

consists of a number of identified stages: installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

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

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

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

9.2 Installation qualification

9.2.1 Equipment

9.2.1.1 Equipment to be used in the sterilization process, including any ancillary items, shall be specified.

9.2.1.2 Sterilization equipment shall comply with IEC 61010-2-040.

9.2.1.3 The operating procedures for the equipment shall be specified. These operating procedures shall include, but are not limited to:

a) step-by-step operating instructions;

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

c) instructions for maintenance and calibration;

d) details of contacts for technical support.

9.2.2 Installation

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

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

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

9.2.2.4 Prior to IQ, the calibration status of all instrumentation (including any test instruments) used for monitoring, controlling, indicating or recording shall be confirmed (see 4.3.3).

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

9.3 Operational qualification

9.3.1 Prior to OQ, the calibration status of all instrumentation (including any test instruments) used for monitoring, controlling, indicating, or recording shall be confirmed (see 4.3.3).

9.3.2 OQ shall demonstrate that the installed equipment is capable of delivering the specified process (see 8.11) within defined tolerances.

9.4 Performance qualification

9.4.1 Calibration activities (see 4.3.3) shall be completed for instruments used in PQ.

9.4.2 The manner of presenting the product for sterilization, including the orientation of product, shall be specified.

9.4.3 Product used in PQ shall be packaged identically to that to be sterilized routinely.

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

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

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

9.4.7 If tests of sterility are performed on product subjected to conditions as specified in 9.4.5, such tests shall be performed in accordance with ISO 11737-2.

9.4.8 If chemical indicators are used in PQ, they shall comply with 8.4.

9.4.9 If PCDs are used in PQ, they shall comply with 8.6.

9.4.10 PQ shall include a series of at least three successful exposures of product to the sterilization process, within defined tolerances, in order to demonstrate the reproducibility of the process. Results from PQ outside of defined tolerances shall be reviewed and corrective actions determined and instituted before initiating a new series of exposures.

The series of three successful exposures shall be performed consecutively, unless finding outside defined tolerances can be attributed to factors not relevant to the effectiveness of the process being validated. Such findings shall be documented as unrelated to performance of the sterilization process.

EXAMPLES The finding might be attributed, but not limited to, power failures, loss of services or failure of external monitoring equipment.

9.4.11 The levels of any process residues following exposure to the upper tolerances of the process parameters shall be demonstrated as being below the specified limits identified in the health-based risk assessment (see 8.8).

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

NOTE Information gathered in accordance with 8.9 can be used to meet this requirement.

9.5 Review and approval of validation

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

9.5.2 Information gathered or produced during IQ, OQ and PQ shall be recorded and reviewed for acceptability (see 4.1.2). The results of this review shall be recorded (see 4.1.2).

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

10 Routine monitoring and control

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

10.2 There shall be evidence through measurements, supplemented as necessary by biological indicators (see 10.5) or chemical indicators (see 10.6), that the sterilization process was delivered within the defined tolerances (see also 9.5.3).

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

10.4 All records shall be retained in accordance with 4.1.2.

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

10.6 If chemical indicators are used in routine monitoring, they shall comply with 8.4.

10.7 If PCDs are used in routine monitoring and control, they shall comply with 8.6.

11 Product release from sterilization

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

11.2 Parametric release shall only be used if all process parameters are specified, controlled and directly monitored. Records of process parameters shall be retained (see 4.1.2).

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

11.4 If the criteria specified in 11.1 are not met, product shall be considered as non-conforming and handled in accordance with documented procedures (see 4.4).

12 Maintaining process effectiveness

12.1 General

The continued effectiveness of the system for ensuring the condition of product presented for sterilization (see 7.3) shall be demonstrated (see 7.4).

12.2 Recalibration

The accuracy and reliability of the instrumentation used to control and monitor the sterilization process shall be verified periodically (see 4.3.3).

12.3 Maintenance of equipment

12.3.1 Preventative maintenance shall be planned and performed in accordance with documented procedures. The procedure for each planned maintenance task and the frequency at which it is to be carried out shall be specified. Records of maintenance shall be retained (see 4.1.2).

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

12.3.3 The maintenance scheme, maintenance procedures and maintenance records shall be reviewed periodically by a designated person. The results of the review shall be recorded (see 4.1.2).

12.4 Requalification

12.4.1 Requalification of a sterilization process, carried out for defined product and specified equipment, shall be performed at defined intervals. The extent to which requalification is carried out shall be justified.

12.4.2 Requalification procedures shall be specified and records of requalification shall be retained (see 4.1.2).

12.4.3 Requalification data shall be reviewed against specified acceptance criteria in accordance with documented procedures. Records shall be retained (see 4.1.2) of reviews of requalification data together with corrections made and corrective actions taken if specified acceptance criteria are not met (see 4.4).

12.5 Assessment of change

12.5.1 Any change in the sterilization equipment that could affect delivery of the sterilization process shall be assessed. If the effectiveness of the sterilization process is judged to be affected, a repeat of part or all of IQ, OQ or PQ shall be carried out (see Clause 9). The outcome of this assessment, including the rationale for decisions reached, shall be recorded (see 4.1.2).

12.5.2 Any change in product, its package, or the presentation of product for sterilization shall be assessed for the effect on the appropriateness of the sterilization process. Based on the nature of the change, parts of process definition (see Clause 8) and/or PQ (see 9.4) shall be undertaken. The outcome of the assessment, including the rationale for the decisions reached, shall be recorded (see 4.1.2).

Annex A
(normative)

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

A.1 General

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

A.2 Identification of reference microorganism

The data obtained in the demonstration of microbicidal effectiveness shall identify a suitable reference microorganism to be employed as a representative model of high resistance during sterilizing agent characterization and, if applicable, process definition studies.

NOTE Generally a bacterial spore is selected.

A.3 Selection of microorganisms

In selecting microorganisms to be used in demonstrating the microbicidal effectiveness of a sterilizing agent, the following shall be considered:

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

b) microorganisms with known resistance to well-characterized sterilization processes;

c) types of microorganisms (aerobic and anaerobic Gram positive and Gram negative bacteria, bacterial spores, mycobacteria, fungi including sporing forms, yeasts, parasites and viruses);

d) microorganisms present on the materials of construction of the product and in the environment in which the product is manufactured;

e) microorganisms that have been isolated during determinations of bioburden undertaken on typical product to be processed and, if applicable, microorganisms likely to be present on a re-usable medical device as a result of its prior use on a patient.

The microorganisms selected and the rationale for their choice shall be recorded (see 4.1.2). These microorganisms may be designated by a recognized culture collection reference or other identifier that allows the source to be traced.

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

NOTE 2 Inactivation of viruses and/or parasites [see A.3 c)] is a particular consideration in processes used to sterilize products containing material of animal origin (see also ISO 22442-3), as well as when reprocessing medical devices in health care facilities.

NOTE 3 In considering the information obtained with respect to microorganisms given in A.3 e), it should be noted that the resistance of microorganisms isolated from product can be modified by recultivation.

Table A.1 — Examples of potential test microorganisms

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

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

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

Annex B
(normative)

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

B.1 General

The methods described in ISO 11137-2 are examples of how process definition can be achieved based on inactivation of the microbial population in its natural state.

B.2 Product selection

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

B.3 Procedure

B.3.1 Expose product to the sterilizing agent in predetermined increment(s) of the anticipated sterilization process. Establish the required accuracy and precision of increments, and control and monitor the delivery of the sterilizing agent to meet defined limits.

B.3.2 Following exposure to the sterilizing agent, subject products individually to a test of sterility in accordance with ISO 11737-2.

B.3.3 To define the sterilization process, use knowledge of the relationship between the proportion of products exhibiting no growth in tests of sterility and the extent of exposure to the sterilizing agent.

B.4 Maintaining process effectiveness

Confirm the continued appropriateness of the sterilization process at defined intervals using product representative of routine production (see 12.4).

Annex C
(normative)

Approach 2 — Process definition based on inactivation of reference microorganisms and knowledge of bioburden

C.1 General

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

C.2 Procedure

C.2.1 Establish the location(s) within product at which sterility is most difficult to achieve.

C.2.2 Create a challenge to the sterilization process, comprising a known number of microorganisms with known resistance to the sterilizing agent, by one of the following approaches:

a) placing biological indicators within product at position(s) where sterility is most difficult to achieve;

b) inoculating with reference microorganisms the position(s) within product where sterility is most difficult to achieve.

C.2.3 Package the challenge in the same manner as product produced routinely and include it within the sterilization load.

C.2.4 Treat the sterilization load with the sterilizing agent under conditions selected to deliver less lethality than those conditions to be used routinely, such that not all the reference microorganisms have been inactivated.

C.2.5 If the sterilization process involves treatment with a chemical agent, establish that its microbicidal and/or microbiostatic action(s) have been appropriately neutralized prior to the estimation of survivors.

NOTE See ISO 11138-1:2006, Annex B, for information on a method to determine growth inhibition.

C.2.6 Determine the number of microorganisms surviving, either by direct enumeration or estimated by a most probable number technique.

C.2.7 Calculate the rate of inactivation of the reference microorganisms.

C.2.8 From a knowledge of the bioburden (established in accordance with 7.4) and the rate of inactivation of the reference microorganisms, determine the extent of treatment required to achieve the specified requirements for sterility.

Annex D
(normative)

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

D.1 General

This approach to process definition has been widely employed, particularly for products to be re-processed in health care establishments. Qualifying a sterilization process for such products employs an approach different from that adopted with virgin product. This is because the challenge to the sterilization process is difficult to define and preprocessing treatments such as cleaning are difficult to validate and control (see 7.3 and 7.4). Therefore, sterilization processes applied in these situations are often conservative and employ a treatment that exceeds that needed to achieve the specified requirements for sterility. This approach has been referred to as the "overkill approach." Guidance on this approach can be found in ISO 14161.

D.2 Procedure

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

D.2.2 Create a challenge to the sterilization process, comprising a known number of microorganisms with known resistance to the sterilizing agent, by one of the following approaches:

a) placing biological indicators within product at position(s) where sterility is most difficult to achieve;

b) inoculating with reference microorganisms the position(s) within product where sterility is most difficult to achieve.

D.2.3 Package the challenge in the same manner as product produced routinely and include it within the sterilization load.

D.2.4 Treat the sterilization load with the sterilizing agent under conditions designed to deliver an exposure reduced in relation to that in the anticipated sterilization process.

D.2.5 Identify the extent of treatment that inactivates 10^6 microorganisms at the selected position(s).

NOTE There are several approaches to identify the extent of treatment to inactivate 10^6 microorganisms. For example:

1) with an initial challenge equal to or greater than 10^6 viable microorganisms, this extent of treatment can be identified conservatively as the treatment after which no surviving microorganisms are recovered,

2) with an initial challenge greater than 10^6 viable microorganisms, this extent of treatment can be identified as the treatment after which a 6-log reduction in viable microorganisms is observed,

or

3) with an initial challenge less than 10^6 viable microorganisms, this extent of treatment can be identified by extrapolation from the treatment after which, for example, a 4-log reduction in viable microorganisms is observed.

D.2.6 If the sterilization process involves treatment with a chemical agent, establish that its microbicidal and/or microbiostatic action(s) have been appropriately neutralized prior to the estimation of the number of survivors.

NOTE See ISO 11138-1:2006, Annex B, for information on a method to determine growth inhibition.

D.2.7 Repeat exposure of fresh challenges to the level of treatment identified in D.2.5 on at least two further occasions.

D.2.8 If the inactivation of 10^6 microorganisms has been confirmed following D.2.7, determine the extent of treatment for the sterilization process by extrapolation to a predicted probability of a surviving microorganism of 10^{-6} or better, taking into account the nature of the inactivation kinetics effected by the sterilizing agent and the number and resistance of the microorganisms on the biological indicator/inoculated product.

NOTE 1 This approach is best suited to sterilizing agents that exhibit linear inactivation kinetics. In such cases, the extent of treatment can be defined conservatively as twice that employed in D.2.6. For sterilizing agents that do not exhibit linear inactivation kinetics, the nature of the inactivation kinetics should be investigated in order to derive a relationship from which it can be predicted that the specified probability of a microorganism surviving is not exceeded on applying the sterilization process.

NOTE 2 A knowledge of the inactivation kinetics can be obtained as in 5.3.1 b); the nature of the inactivation kinetics can be influenced by the product.

Annex E
(informative)

Guidance on application of this International Standard

NOTE For ease of reference, the numbering of clauses in this Annex corresponds to that in the normative part of this standard.

E.1 Scope

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

E.2 Normative references

The requirements given in documents that are included as normative references are requirements of this International Standard only to the extent that they are cited in normative parts of this International Standard; the citation may be to a whole standard or limited to specific clauses.

E.3 Terms and definitions

No guidance offered.

E.4 Quality management system elements

E.4.1 Documentation

Requirements for the control of documents and records are specified in 4.2.3 and 4.2.4 of ISO 13485:2003.

In ISO 13485, the requirements for documentation relate to the generation and control of documentation (including specifications and procedures) and records.

E.4.2 Management responsibility

E.4.2.1 Requirements for responsibility and authority are specified in 5.5 of ISO 13485:2003 and requirements for human resources in 6.2 of ISO 13485:2003.

In ISO 13485, the requirements for management responsibility are related to management commitment, customer focus, quality policy, planning, responsibility, authority and communication, and management review.

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

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

E.4.2.2 The development, validation and routine control of a sterilization process are likely to involve a number of separate parties, each of whom is responsible for certain elements. This International Standard does not require particular elements to be carried out by specific parties but does require that the party accepting particular responsibilities is defined and that this definition of responsibilities is documented. This documented definition of responsibilities should be within the quality management system(s) of the identified parties and can form part of a contractual relationship.

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

— the elements listed might not occur sequentially, as the design and testing program can be iterative in part;

— responsibilities for the elements can vary from case to case.

The organization accepting responsibilities for defined elements is required to assign these elements to appropriately trained and qualified personnel.

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

Scenario 1 — Health care facility: in this scenario, the user of the sterilization process is a health care facility. Three parties are involved in complying with this International Standard: the health care facility, the sterilizer manufacturer and the medical device manufacturer. The assignment of responsibilities and the means used to undertake these responsibilities might be as follows.

— Quality management system elements: each party has its own quality management system. The limits of responsibility of each party are laid down in formal contracts.

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

— Process/equipment characterization: the sterilizer manufacturer has undertaken the process/equipment characterization, developed the equipment specification and has the necessary regulatory approval to place the product on the market. The health care facility reviews the equipment specification in conjunction with the sterilizer manufacturer to confirm that the services and infrastructure necessary to operate the sterilization equipment are available.

— Product definition: the health care facility has identified the medical devices that it intends to reprocess. The instructions for reprocessing these medical devices provided by the medical device manufacturer include instructions for cleaning and disinfection. Also, these instructions confirm that the proposed method for sterilization is appropriate. The medical device manufacturer has undertaken process definition studies in collaboration with the sterilizer manufacturer in order to substantiate the reprocessing instructions provided. The health care facility reviews the data on the

effectiveness of its cleaning processes and confirms they are adequate for the particular device(s) and sterilization process.

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

— Validation: the health care facility contracts with the sterilizer manufacturer to undertake IQ and OQ in accordance with documented procedures. The health care facility undertakes PQ and then reviews and approves the validation exercise.

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

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

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

Scenario 2 — Medical device manufacturer using in-house facilities: in this scenario, the user of the sterilization process is a manufacturer of single-use medical devices who is installing in-house facilities for sterilization. The parties involved are the medical device manufacturer and the sterilizer manufacturer. The allocation of responsibilities and the means used to undertake these responsibilities might be as follows.

— Quality management system elements: each party has its own quality management system. The limits of responsibility of each party are laid down in formal contracts.

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

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

— Product definition: the medical device manufacturer is responsible for the specification of the product and its manufacture.

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

— 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.

— Routine control and monitoring: this is carried out by the medical device manufacturer in accordance with documented procedures.

— Product release from sterilization: this is carried out by the medical device manufacturer in accordance with documented procedures.

— Maintaining process effectiveness: this is carried out by the medical device manufacturer in accordance with documented procedures.

Scenario 3 — Medical device manufacturer using a sterilization subcontractor: in this scenario, the user of the sterilization process is a manufacturer of single-use medical devices who is using a sterilization subcontractor to deliver the sterilization process. Additionally, the medical device manufacturer is using a contract laboratory to undertake defined testing as part of the product release procedures. The parties involved are the medical device manufacturer, the sterilization subcontractor, and the contract laboratory. The allocation of responsibilities and the means used to undertake these responsibilities might be as follows:

— Quality management system elements: each party has its own quality management system. The limits of responsibility of each party are laid down in formal contracts.

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

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

— Product definition: the medical device manufacturer is responsible for the specification of the product and its manufacture.

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

— Validation: the sterilization subcontractor undertakes IQ and OQ in accordance with documented procedures. The medical device manufacturer then undertakes PQ using the installed sterilization equipment, confirming that the equipment is capable of delivering the defined sterilization process. The medical device manufacturer reviews and approves the validation exercise. A contract laboratory might perform microbiological testing in accordance with methods agreed with the medical device manufacturer.

— Routine control and monitoring: this is carried out by the sterilization subcontractor and the contract laboratory in accordance with documented procedures agreed with the medical device manufacturer.

— Product release from sterilization: this is carried out by the medical device manufacturer in accordance with documented procedures, on the basis of records provided by the sterilization subcontractor and the contract laboratory.

— 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 the product prior to sterilization and takes responsibility for requalification; the sterilization subcontractor carries out any necessary repetition of part or all of IQ or OQ.

E.4.3 Product realization

NOTE In ISO 13485, the requirements for product realization relate to the product lifecycle from the determination of customer requirements, design and development, purchasing, control of production, and calibration of monitoring and measuring devices.

E.4.3.1 Requirements for purchasing are specified in 7.7 of ISO 13485:2003. In particular, it should be noted that the requirements in 7.4 of ISO 13485:2003 for the verification of purchased product apply to all product and services received from outside the organization.

E.4.3.2 Requirements for identification and traceability are specified in 7.5.3 of ISO 13485:2003.

E.4.3.3 Requirements for calibration of monitoring and measuring devices are specified in 7.6 of ISO 13485:2003.

E.4.4 Measurement, analysis and improvement — Control of non-conforming product

In ISO 13485, the requirements for measurement, analysis and improvement relate to process monitoring, control of non-conforming product, analysis of data and improvement (including corrective and preventive actions).

Procedures for control of non-conforming product and corrective action are specified in 8.3 and 8.5.2 respectively of ISO 13485:2003.

E.5 Sterilizing agent characterization

E.5.1 General

No guidance offered.

E.5.2 Sterilizing agent

No guidance offered.

E.5.3 Microbicidal effectiveness

E.5.3.1 Many chemicals and processes can be shown to have antimicrobial activity. Not all, however, meet the criteria for a sterilizing agent. The intent and approach of the studies on microbicidal effectiveness are to:

— provide a definition of the sterilizing agent and the associated process and equipment sufficient to establish and maintain reproducible conditions for studies on microbicidal effectiveness; this activity should be documented;

— develop and validate methods for the growth of microorganisms and their inoculation on to carriers for exposure to the sterilizing agent; these procedures include recovery and enumeration of microorganisms from the carriers and estimation of the fraction of exposed carriers rendered sterile; the necessity for neutralization of residues of the sterilizing agent should be considered [see the guidance in E.5.3.1 g)];

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

— identify the highly resistant microorganism(s) [reference microorganism(s)] appropriate for detailed microbial inactivation studies;

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

— define the kinetics of microbial inactivation; confirm that the lethal action can be extrapolated to predict the probability of a microorganism surviving exposure to a defined treatment using the inactivation data obtained with the highly resistant microorganism(s).

Guidance specific to 5.3.1 a): qualitative studies can be used to test the activity of the candidate sterilizing agent against a range of microorganisms. The purpose of these studies is two-fold:

1) to demonstrate that a range of different types of microorganism is sensitive, to some degree, to the action of the sterilizing agent;

2) to choose one or more highly resistant microorganisms for more quantitative inactivation studies.

If, during these studies, bacterial spores are found to be essentially insensitive to the action of the candidate sterilizing agent, the use of the candidate sterilizing agent for sterilization applications is not permissible. The candidate sterilizing agent might, however, be suitable for other purposes, e.g. low-level disinfection.

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

Guidance specific to 5.3.1 b): quantitative microbial inactivation studies are undertaken to demonstrate that the sterilizing agent, when applied in a defined manner, can reliably yield calculable numbers of surviving microorganisms. These studies generally involve the use of graded exposure to or contact with the sterilizing agent to generate survival data defining the inactivation of the previously identified highly resistant microorganism(s). To define the upper section of the microbial survival curve, direct enumeration methods are generally used. For the section of the curve where there is a low number of survivors occurring, fraction negative data are employed. In the construction of such survival curves, the practical lower limit of estimation of average numbers of surviving microorganisms is 0,01. The extent of treatment to provide a probability of a surviving microorganism lower than this limit is inferred by extrapolation.

The empirical relationship can, for example, be defined in an equation or represented as a graph relating extent of treatment to the numbers and probability of surviving microorganisms. The relationship may also be presented in a tabulation of values.

In situations where the survival curve is log-linear, i.e. a plot on semi-log paper yields a straight line and extrapolation is readily performed. A curve that is concave in relation to the X-axis can, when fitted with a straight line, yield a somewhat conservative estimate of the extent of treatment needed to attain a defined probability of survival of a microorganism. Caution shall be used if the microbial inactivation studies indicate a result that is best approximated by a survivor curve that is convex in relation to the X-axis.

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

NOTE 1 Microbial inactivation and failure to recover viable test microorganisms from the surface of an inoculated carrier exposed to the sterilizing agent might not be distinguishable. In this context, use of tracer agents (such as radiolabelled microorganisms) could be useful.

Microbial inactivation studies require the use of test methods validated for the specific sterilizing agent. During the design and validation of the test methods, particular attention should be paid to test conditions that result in spurious data arising from, for example, inadequate recovery conditions, the occurrence of microbiostasis, and false positives. Loss of viability of surviving microorganisms should be considered arising from, for example, transport of test materials to a contract laboratory. Development of the test methods and/or their performance can be carried out in-house or in a contract laboratory.

Guidance specific to 5.3.1 c): selection of test microorganisms for microbial inactivation studies should be justified. Methods to be qualified could include:

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

2) preparation of consistent inocula of test microorganisms;

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

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

NOTE 2 See also Note 1.

Guidance specific to 5.3.1 d): studies on sterilizing agent characterization may be performed with laboratory, prototype or routine production-type equipment. For each situation, sufficient definition of the sterilizing agent and equipment is required in order to ensure reproducible conditions.

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

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

Guidance specific to 5.3.1 e): no guidance offered.

Guidance specific to 5.3.1 f): no guidance offered.

Guidance specific to 5.3.1 g): before commencing any investigation of microbial inactivation, it is necessary to ensure that the results of the investigation are not influenced adversely by microbicidal or microbiostatic effects due to carry-over of the sterilizing agent or its residual derivatives into the recovery system; such effects can be reduced by:

1) dilution of the sterilizing agent;

2) removal of the sterilizing agent;

3) neutralization of the microbicidal or microbiostatic action of the sterilizing agent by reaction with an appropriate agent.

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

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

E.5.3.2 No guidance offered.

E.5.4 Effects on materials

E.5.4.1 This subclause considers the effects of the sterilizing agent on material likely to be used to manufacture product to be sterilized. Both short-term and long-term effects on materials should be assessed. Consideration of effects of the sterilizing agent on product is given in Clause 7.

E.5.4.2 Consideration should include the short-term and long-term effects of repeated exposures.

E.5.4.3 No guidance offered.

E.5.5 Safety and the environment

E.5.5.1 No guidance offered.

E.5.5.2 ISO 14001 provides a specification for an environmental management system. ISO 14040 provides guidance on designing a life cycle assessment study.

E.6 Process and equipment characterization

No guidance offered.

E.7 Product definition

E.7.1 This clause describes product considerations that are addressed when evaluating a sterilization process. The sterilization process has to yield sterile, safe and functional product. Certain process conditions can adversely effect the integrity of medical devices and packages. Some packaging materials and devices could impede the sterilization process. Therefore, the effects of the sterilization process on materials and design characteristics and on packaging configurations and materials are evaluated. This evaluation is usually conducted during product development.

E.7.2 Product can be subjected to various environmental stresses during sterilization, such as pressure changes, elevated temperature, and changes in relative humidity. Product could also react with the sterilizing agent and/or any diluent(s). The product design has to ensure that functionality and safety are not compromised by exposure to the anticipated range of sterilization conditions. Typically, the maximum conditions would represent the most severe challenge to the product, including the package. If applicable, the effects of multiple exposures to the sterilization process are evaluated.

Design tolerances and configuration: these are important in ensuring effective delivery of the sterilizing agent and its distribution.

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

Packaging considerations: the major function of a package for a sterilized medical device is to ensure that the medical device remains sterile throughout its defined shelf life. During sterilization, the package is intended to withstand the process conditions without a negative effect on overall product quality (e.g. generation of particulates).

Packaging considerations are addressed in more detail in ISO 11607-1 and ISO 11607-2.

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

The ability of the protective packaging to protect product during customary handling and distribution should be demonstrated. If the protective packaging is to be exposed to the sterilization process, it has to be demonstrated that the protective packaging can withstand the process without losing its ability to protect product. Furthermore, it shall be demonstrated that the secondary packaging does not affect the attainment of sterilizing conditions during the sterilization process and that resterilization, if applied, has no effect on the secondary packaging.

Attention is also drawn to ISO 17664.

E.7.3 No guidance offered.

E.7.4 No guidance offered.

E.8 Process definition

E.8.1 Process definition is undertaken to define the process parameters for a sterilization process that will achieve the specified requirements for sterility for a defined product without adversely affecting product functionality. Therefore, process definition includes at least two pieces 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 sterility for the product.

As sterilization does not typically improve product performance, a careful selection of values and tolerances for each process variable should be undertaken during process definition. In general, those

variables which, when increased, significantly improve sterilization effectiveness without adversely affecting product performance should be maximized during process definition. Conversely, those variables which, when increased, adversely affect product performance without significantly improving sterilization effectiveness should be minimized during process definition. In addition, if a threshold exists above which significant adverse effects on product or packaging are observed, it should be documented.

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

E.8.2 The sterilization process will be defined based on the inactivation of microorganisms. These microorganisms could be either natural contamination on the product or reference microorganisms that present at least as great a challenge to the sterilization process as does the bioburden on the product. There are, however, a number of stages in the determination of process effectiveness that should be performed in order to have confidence in the selection of the process parameters. If biological indicators are to be used, the stages include the selection of the biological indicator, the determination of the most difficult-to-sterilize location, the assessment of lethality at this location, and the evaluation of the influence of packaging and load configuration.

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

E.8.3 A review of the data obtained from the microbial inactivation studies (see E.5.3) should be conducted to select a biological indicator. The biological indicator should have a relatively high resistance to the sterilizing agent when compared to other microorganisms. In addition, the challenge presented by the biological indicator should be compared to that of the product bioburden and, if the challenge is greater than that of the product bioburden, it can be considered as appropriate for process definition and subsequent validation studies. While it is not necessary to determine the D value for each bioburden isolate, it is important to assess the more resistant portion of the bioburden population. Relative inactivation can be assessed via graded exposures to the sterilizing agent.

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

these locations within the product and the product exposed to a fraction of the sterilization process. The location that consistently yields the greatest number of survivors should be chosen.

E.8.4 No guidance offered.

E.8.5 No guidance offered.

E.8.6 No guidance offered.

E.8.7 No guidance offered.

E.8.8 If the health-based risk assessment conducted in accordance with 8.8 identifies residues of the sterilizing agent for which acceptable limits have to be set, process definition should aim to minimize the presence of such residues on or in product while meeting the specified requirements for sterility. Additionally, a post-treatment might have to be defined to further reduce the level of residues to meet specified limits. If a post-treatment is required, it is defined and validated as part of the sterilization process.

E.8.9 If product has to be resterilized, either as part of its intended use or in the event of an inadequate sterilization process being delivered, the suitability of product and packaging for resterilization and the effect of repeated exposures to the sterilization process on product functionality should be investigated.

E.8.10 No guidance offered.

E.9 Validation

E.9.1 General

A validation study has at least the three main elements as described in E.9.2 to E.9.4.

E.9.2 Installation qualification (IQ)

For new equipment, IQ begins with specifying the design, purchase and installation requirements. IQ is based on specifications that ensure that the construction and installation requirements are met. IQ should be documented, and the documentation should include drawings and details of all the construction materials, the dimensions and tolerances of the chamber in which the load will be placed (if applicable), support services, and power supplies.

IQ should be certified prior to OQ of the equipment.

E.9.3 Operational qualification (OQ)

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

E.9.4 Performance qualification (PQ)

E.9.4.1 No guidance offered.

E.9.4.2 PQ consists of documented trials and tests to establish confidence that the finished product produced by the specified process in the specified equipment meets the requirements for safety, quality and performance. Use of product items, presented in the same manner as that to be used routinely, is an important element of PQ. Material in addition to the product items used in PQ can be used to make up the sterilization load.

E.9.4.3 Product used in PQ is packaged in the same manner as that to be used routinely, but other material that is used in PQ may not need to be packaged in this manner. Changing process variables that can affect the quality of the product package should form part of the testing.

E.9.4.4 No guidance offered.

E.9.4.5 No guidance offered.

E.9.4.6 No guidance offered.

E.9.4.7 No guidance offered.

E.9.4.8 No guidance offered.

E.9.4.9 No guidance offered.

E.9.4.10 No guidance offered.

E.9.4.11 No guidance offered.

E.9.4.12 No guidance offered.

E.9.5 Review and approval of validation

No guidance offered.

E.10 Routine monitoring and control

E.10.1 Routine monitoring and control of sterilization processes are based primarily on measurements of the process parameters during the sterilization process. Supplementation of these measurements by the use of biological indicators or chemical indicators can be required.

Procedures for routine monitoring and control are needed to ensure that the process parameters of the sterilization process are within established limits during PQ. These procedures should describe tests and checks, and the frequency with which these tests and checks should be carried out.

E.10.2 In addition, routine monitoring positions for taking direct measurements are defined, as are the locations where any biological indicators or chemical indicators are to be placed. The appropriateness of routine monitoring positions, and any process challenge devices that are used, should have been demonstrated (see 9.4.4).

E.10.3 No guidance offered.

E.10.4 If product is resterilized because the initial exposure to the sterilization process was outside of its specification (see also E.8.9), records of the initial sterilization process should be included or referenced in the sterilization records.

E.10.5 No guidance offered.

E.10.6 No guidance offered.

E.11 Product release from sterilization

E.11.1 If a sterilization process operating within specified tolerances has been demonstrated to be both effective and reproducible, confirmation that the process parameters were within specification limits is taken as evidence of the adequacy of the process.

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

E.11.2 Parametric release is the declaration of adequacy of sterilization of product based on the direct measurement and evaluation of process parameters. No sample or indicator testing is required for parametric release.

The appropriateness of parametric release should be demonstrated during the development and validation of the sterilization process. For parametric release to be applied, all process parameters must be identified and monitored; for product release, values of process parameters must fall within the specified tolerances. Parametric release should only be applied when there is extensive experience with the sterilization process. Typically, parametric release is justified for a defined sterilization process and defined product rather than for generic application.

E.11.3 If biological indicators are to be used in product release, records of the physical process parameters and results of indicator testing are reviewed to demonstrate the effective delivery of the sterilization process.

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

E.11.4 Failure to meet the process specification or failure of an indicator to meet its specified requirements should lead to the affected product being placed in quarantine and the cause of failure investigated. Actions taken during the investigation should be documented and the outcome of the investigation should be recorded.

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

E.12 Maintaining process effectiveness

E.12.1 General

No guidance offered.

E.12.2 Recalibration

No guidance offered.

E.12.3 Maintenance of equipment

No guidance offered.

E.12.4 Requalification

E.12.4.1 To guard against unreported or inadvertent changes, periodic repetition of all or part of IQ, OQ and PQ is undertaken. The interval between periodic requalifications should be determined by the nature of the sterilization process and by the amount of process data available. The interval may be varied taking into account historical data that demonstrate process reproducibility and conformance with established specifications for process parameters. Typically, requalification would be performed for a specified sterilization load or for a defined or simulated product. However, if requalification detected a process change, PQ might need to be performed.

E.12.4.2 Previous validation and requalification results should be considered in deciding the requalification procedure.

E.12.4.3 Data from requalification should be compared with records of the original validation (and any subsequent requalification) to confirm that the original performance has been retained. This comparison is facilitated by a common format for validation and requalification reports.

E.12.5 Assessment of change

NOTE A change control system is employed to determine when operational or performance qualification testing is necessary. Qualification is needed if significant changes are made in the sterilization equipment (hardware or software), or process (see E.12.5.1), or to product or packaging (see E.12.5.2) that might influence sterilization effectiveness.

E.12.5.1 The following are examples (not necessarily all-inclusive) of changes that could necessitate PQ unless data are available to demonstrate equivalency prior to and after such changes.

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

b) **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).

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

E.12.5.2 The following are examples (not necessarily all-inclusive) of changes that could necessitate PQ unless data are available to demonstrate equivalency prior to and after such changes.

a) **Product**: a change in the product material, the composition or thickness of the product material, product assembly, construction or design tolerances that could influence the effectiveness of the sterilization process.

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

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

Element	Purpose	Components	Responsible party
Quality management system	To provide a structure to control all stages of the sterilization process	— Personnel and training — Documentation — Records — Review procedures — Corrective action	All parties with respect to the elements undertaken
Sterilizing agent characterization	To define the sterilizing agent and its microbicidal effectiveness	— Sterilizing agent definition — Microbicidal effectiveness — Material effects — Safety and environment	Developer of the sterilizing agent and/or sterilization process
Process/equipment characterization	To define the overall sterilization process and the equipment necessary to carry it out	— Process description — Equipment specification — Ancillary equipment and service definition	Sterilizer manufacturer, in collaboration with the developer of the sterilization process, if appropriate
Product definition	To define the product to be sterilized	— Product specification — Packaging materials — Product quality prior to sterilization	Manufacturer of product to be sterilized (and sterilizer manufacturer, depending on claims made for sterilizing equipment)
Process definition	To define the sterilization process in order to achieve sterility for identified product while maintaining safety and performance of the product	— Development — Biological safety — Process residuals — Product compatibility — Limits on resterilization	Manufacturer of product to be sterilized, in collaboration with the sterilizer manufacturer and, if appropriate, the health care facility
Validation	To demonstrate that the defined sterilization process can be delivered effectively and reproducibly to the sterilization load	— IQ — OQ — PQ — Review and approval of validation	Organization with responsibility for sterilizing the product (either product manufacturer or health care facility), in collaboration with the sterilizer manufacturer, if appropriate Product manufacturer or health care facility, in collaboration with the organization sterilizing the products and contract laboratory, if appropriate
Routine monitoring and control	To demonstrate that the validated sterilization process has been delivered within defined tolerances to all products within a sterilization load	— Sterilization load configuration — Process monitoring — Record generation — Record retention	Product manufacturer or health care facility and contract laboratory, if appropriate
Product release from sterilization	To review records of routine control procedures and determining the disposition of a particular sterilization load	— Record review — Indicator testing (if any) — Product disposition — Corrective action (if any)	Product manufacturer or health care facility
Maintaining process effectiveness	To ensure the continued acceptability of the validated sterilization process	— Product quality prior to sterilization — Calibration — Equipment maintenance	Product manufacturer or health care facility, together with organization sterilizing the product, if appropriate

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