

Technical Information Report

AAMI TIR17: 2017/(R)2023

Compatibility of materials
subject to sterilization

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AAMI

Abstract: This technical information report provides guidance for health care product manufacturers in the qualification of polymeric materials, ceramics, and metals for use in health care products that are sterilized by the following modalities: a) radiation (gamma, electron beam, or x-ray); b) ethylene oxide; c) moist heat (steam); d) dry heat; e) hydrogen peroxide; f) nitrogen dioxide, g) peracetic acid vapor, h) liquid peracetic acid, and i) hydrogen peroxide–ozone. Annexes address the specific sterilization modality concerns.

Keywords: material qualification, sterilization

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Comments on this technical information report are invited and should be sent to AAMI, Attn: Standards Department, 901 N. Glebe Road, Suite 300, Arlington, VA 22203.

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Committee representation

Association for the Advancement of Medical Instrumentation Compatibility of Materials Subject to Sterilization Working Group

This technical information report (TIR) was developed by the AAMI Compatibility of Materials Subject to Sterilization Working Group under the auspices of the AAMI Sterilization Standards Committee. Approval of the TIR does not necessarily mean that all working group members voted for its approval. At the time this standard was published, the **AAMI Compatibility of Materials Subject to Sterilization Working Group** had the following members:

Chair: Karl Hemmerich

Members: Agnieszka Baczek, Medline Industries Inc
Jenny Berg, Sterilucient Inc
Carolyn Braithwaite-Nelson, Spectranetics Corporation
Eunhee Cho, PhD, St Jude Medical Inc
Nancy Chobin, RN, CSPM, CFER, Sterile Processing University LLC
Sean Colwell, WuXi AppTec Inc
Emily Craven, Mevex Corporation
Chris Deneux, Becton Dickinson & Company
John DiCaro, Medtronic Inc
Mary Ann Drosnock, MS, Healthmark Industries Company Inc
Gordon Ely, MiMedx Group
Randy Eveland, PhD, STERIS Corporation
Gloria Frost, PhD, Cardinal Health
Joel Gorski, PhD, NAMSA
Doug Harbrecht, Sterility Assurance LLC
Arthur Harris, Cook Inc
Fatima Hasanain, Sterigenics International
Karl Hemmerich, Sterilization Validation Services
Mollie Holter, Smiths Medical
Nichole Jackson, Ecolab
Nupur Jain, Intuitive Surgical Inc
Carolyn Kinsley, LexaMed Ltd
Ryan Klebba, Integrated Medical Systems
Stacy Kromenhoek, Boston Scientific Corporation
Byron Lambert, Abbott Laboratories
Jean-Luc Lemyre, TSO₃ Inc
Anne Lucas, PhD, FDA/CDRH
Tania Lupu, Case Medical Inc
Jeff Martin, Sterilization and Quality System Consulting LLC
Gerry McDonnell, PhD, Johnson & Johnson
Jami McLaren, PhD, Boston Scientific Corporation
John Nedick, Olympus America Inc
Gerry O'Dell, Gerry O'Dell Consulting
Wayne Rogers, Wayne J Rogers Enterprises
Mason Schwartz, Cantel Inc
Paul Somodi, Hospira, a Pfizer company
Larry Talapa, 3M Healthcare
Don Tumminelli, HIGHPOWER Validation Testing & Lab Services Inc
Wendy Wangsgard, Nelson Laboratories LLC
Roberto Zumbado, Philips Electronics North America

Alternates: Jerome Bell, LexaMed Ltd
Tim Carlson, Becton Dickinson & Company
Peter Cheung, FDA/CDRH
Alexandra Cooper, Arthrex Inc
Mike DiCicco, PhD, Johnson & Johnson
Dave Dion, Cardinal Health
Chris Evans, Integrated Medical Systems
Veronica Falkevitz, HIGHPOWER Validation Testing & Lab Services Inc

Niki Fidopiastis, Sterigenics International
 Elyse Gaudreau, TSO₃ Inc
 Betty Howard, STERIS Corporation
 Sandra Iverson, Cantel Inc
 Britt Jones, WuXi AppTec Inc
 Peter Kalkbrenner, Sterilucent Inc
 Kaumudi Kulkarni, Healthmark Industries Corporation
 Vu Le, Abbott Laboratories
 Nicole McLees, 3M Healthcare
 Michael O'Hara, FDA/CDRH
 Dave Parente, Ecolab
 Nicole Pasquino, Case Medical Inc
 Deanna Porter, St Jude Medical Inc
 Gary Socola, HIGHPOWER Validation Testing & Lab Services Inc
 Laxmishita Sreedasyam, Boston Scientific Corporation
 Mara Tafoya, WuXi AppTec Inc
 Brian Wallace, Intuitive Surgical Inc
 Martell Winters, Nelson Laboratories LLC

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

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

Cochairs: Michael H. Scholla, MS, PhD
 Patrick Weixel

Members: Anas Aljabo, PhD, SteriPro Canada Inc
 Brett Anderson, Cochlear Ltd
 Hank Balch, University Health System
 Richard Bancroft, STERIS Corporation
 Trabue D. Bryans, BryKor LLC
 Tim Carlson, Becton Dickinson & Company
 Phil Cogdill, Medtronic Inc
 Sean Colwell, WuXi AppTec Inc
 Ramona Conner, RN, MSN, CNOR, FAAN, Association of periOperative Registered Nurses
 Lena Cordie, Qualitas Professional Services LLC
 Jacqueline Daley, Sharp Metropolitan Medical Campus
 Gordon Ely, MiMedx Group
 Lisa Foster, Adiuvo QS & SA Consulting
 Joel R. Gorski, PhD, NAMSA
 Joyce Hansen, Johnson & Johnson
 Stephanie Homuth (Independent Expert)
 Clark Houghtling, Cosmed Group Inc
 Susan G. Klacik, CCSMC, FCS, ACE, International Association of Healthcare Central Service
 Materiel Management
 Byron J. Lambert, PhD, Abbott Laboratories
 Michelle Luebke, Baxter Healthcare Corporation
 Patrick J. McCormick, PhD, Bausch & Lomb Inc.
 Gerry McDonnell, PhD, Johnson & Johnson
 Gerry O'Dell, Gerry O'Dell Consulting
 Adrian Ponce, Verrix LLC
 Janet M. Prust, 3M Health Care
 Nancy J. Rakiewicz, IUVO BioScience
 Michael H. Scholla, MS, PhD, DuPont Protection Solutions
 Joan Spear, B Braun of America Inc
 Patrick Weixel, FDA/CDRH
 Sid Wiggs (Independent Expert)
 Martell Kress Winters, SM, Nelson Laboratories LLC
 Stephen Yeadon, Boston Scientific Corporation
 William E. Young, Sterigenics International
 Roberto Zumbado, Philips

Alternates: Stacy Bohl, Boston Scientific Corporation
Jonathan Bull, Johnson & Johnson
Greg Crego, IUVO BioScience
Niki Fidopiastis, Sterigenics International
Jeffrey Marx, STERIS Corporation
Kimberly Patton, Becton Dickinson & Company
Christine Render, Cosmed Group Inc
Michael Sadowski, Baxter Healthcare Corporation
Sharon Van Wicklin, Association of periOperative Registered Nurses
Craig A. Wallace, 3M Health Care

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Foreword

This AAMI technical information report (TIR) was developed to provide additional guidance in order to improve quality and reduce the costs and time required for performing material qualifications.

One of the activities encompassed within sterilization standards is to evaluate how the mode of sterilization affects product and packaging. This element is mentioned in each of the respective industrial sterilization standards (ANSI/AAMI/ISO 11135 series, ANSI/AAMI/ISO 11137 series, ANSI/AAMI/ISO 17665-1, and ANSI/AAMI/ISO 14937). The basic requirements of these standards include the implementation of a program to demonstrate the quality, safety, and performance of the product throughout its shelf life or until its expiration date. Components of such a program are 1) expeditious material selection, 2) prudent processing of those materials, 3) testing of any specific properties essential to the product's intended function, and 4) accelerated aging programs. AAMI TIR17:1997 addressed these four components of a material qualification program for radiation sterilization, and AAMI TIR17:2008 addressed these four components for additional sterilization modalities. There have been many requests from the health care manufacturing industry to expand material compatibility information to cover more sterilization modalities. Therefore, this TIR supersedes AAMI TIR17:2008, with an expanded scope that includes the following sterilization modalities:

- Radiation
- Ethylene oxide
- Moist heat (i.e., steam)
- Dry heat
- Hydrogen peroxide
- Nitrogen dioxide
- Peracetic acid vapor
- Liquid peracetic acid
- Hydrogen peroxide–ozone

These modalities are individually addressed in Section 3 and Annexes A through I of this TIR. Guidance on the processing of materials is carried over from AAMI TIR17:2008 and is provided in Section 4. General guidance on the testing of materials is provided in Section 5. Accelerated aging program information is provided in Section 6. If it has been carried over from AAMI TIR17:2008, or if it has been subsequently published elsewhere, references have been provided. To facilitate aging programs with the advent of combination devices, the accelerated aging information is supplemented with a comparison of accelerated aging programs for devices and accelerated stability programs for pharmaceuticals.

The bulk of the guidance on the compatibility of materials subject to sterilization is provided in Section 3 and the tables found in Annexes A through I. Each sterilization modality is described in enough detail (Section 3) for the reader to understand the parameters of the sterilization process that must be considered in evaluating material compatibility. Brief reference to the application of each sterilization modality to pharmaceutical and biological agents is also provided. One of the most beneficial aspects of the guidance in each Annex is a list of compatible materials to aid in the material selection process.

This TIR contains guidelines that are not intended to be absolute or applicable in all circumstances. Judgment should be used in applying the information in this TIR.

NOTE—This document is not an AAMI standard or an American National Standard, and the material contained herein is not normative in nature.

Suggestions for improving this TIR are invited. Comments and suggested revisions should be sent to Technical Programs, AAMI, 901 N. Glebe Road, Suite 300, Arlington, VA 22203.

NOTE—This foreword does not contain provisions of the AAMI technical information report, *Compatibility of materials subject to sterilization* (AAMI TIR17:2017), but it does provide important information about the development and intended use of the document.

Compatibility of materials subject to sterilization

1 Scope

This document provides guidance for health care product manufacturers in the selection and qualification of polymeric materials, ceramics, and metals for use in health care products sterilized by the following methods:

- Radiation (gamma, electron beam, or x-ray)
- Ethylene oxide (EO)
- Moist heat (steam)
- Dry heat
- Hydrogen peroxide
- Nitrogen dioxide
- Vaporized peracetic acid
- Liquid peracetic acid
- Hydrogen peroxide–ozone

NOTE—All references to hydrogen peroxide sterilization in this TIR refer to sterilization in the gas phase. (Hydrogen peroxide is also used for liquid chemical sterilization, but that application is outside the scope of this TIR.)

Guidance in this TIR relates to the following:

- a) *Material selection*: Choosing sterilization-compatible materials (see Section 3 and Annexes A–I)
- b) *Material processing*: Optimizing the functional performance of materials selected to avoid processing errors that can contribute to negative effects from sterilization (see Section 4)
- c) *Material testing*: Challenging critical aspects of the product for functionality and safety after sterilization and aging (see Section 5)
- d) *Accelerated aging*: Applying programs that ensure correlation with real-time aging while reducing the cost and time required for material qualifications (see Section 6)

NOTE—The information in this TIR is not intended to provide a rationale for the use of materials without proper material qualification. The information is general and is intended only as a guide for successfully initiating material qualification programs.

2 Definitions, symbols, and abbreviations

For the purposes of this TIR, the following definitions and abbreviations apply.

NOTE—For the abbreviations of materials discussed in this TIR, see Annex L.

2.1 absorbed dose: Quantity of ionizing radiation energy imparted per unit mass of a specified material.

NOTE 1—The unit of absorbed dose is the gray (Gee), where 1 gray is equivalent to absorption of 1 joule per kilogram.

NOTE 2—For purposes of this TIR, the term dose is used to mean “absorbed dose.”

2.2 accelerated aging (AA): Storage of health care products at elevated temperatures and/or at other intensified environmental conditions in order to simulate real-time aging in a shorter amount of time.

2.3 adhesive: Substance used for sticking objects or materials together; glue.

2.4 aging factor (AF): Ratio of time between T_{RT} (recommended storage temperature) and T_{AA} (accelerated aging temperature) that is estimated or calculated to achieve the same level of functional degradation of the health care product in real time as that observed under accelerated aging.

2.5 aeration: Part of the sterilization process during which the sterilizing agent and/or its reaction products desorb from the medical device until predetermined levels are reached.

2.6 API: Active pharmaceutical ingredient.

2.7 biocompatibility: Ability of a material to elicit an acceptable biological response (based on the application of the material/device).

2.8 cellulosic: Of or containing cellulose.

2.9 ceramic: Any of various hard, brittle, heat- and corrosion-resistant materials made typically of metallic elements combined with oxygen or carbon, silicon, nitrogen, or sulfur.

2.10 compatibility: Following sterilization(s), ability of the device to remain within its specifications and functional requirements over the course of the defined shelf life and/or useful life (for devices intended to be reprocessed).

NOTE— For purposes of this document, the term compatibility does not include sterilization efficacy. Sterilization efficacy guidance can be found in such standards as ANSI/AAMI/ISO 14937 and ANSI/AAMI/ISO 11135.

2.11 DUR: Dose uniformity ratio, the ratio of maximum to minimum dose delivered to the product.

2.12 elastomer: Natural or synthetic polymer having elastic properties (e.g., rubber).

2.13 glass transition: Reversible transition in amorphous materials (or in amorphous regions within semi-crystalline materials) from a hard and relatively brittle state into a molten or rubber-like state.

2.14 health care products: Medical devices, including in vitro diagnostic medical devices and medicinal products, including biopharmaceuticals.

NOTE— For purposes of this document, the term health care product, or product, refers to the finished medical device and/or additional components within the final package.

2.15 kGy: Kilogray, a derived metric (SI) measurement unit of absorbed radiation dose of ionizing radiation. The gray is defined as the absorption of one joule of ionizing radiation by one kilogram (1 J/kg) of matter (e.g. material being exposed). One kilogray equals 1 kJ/kg.

2.16 liquid chemical sterilizing agent: Liquid chemical entity, or combination of entities, having sufficient microbicidal activity to achieve sterility under defined conditions.

2.17 LVP: Large-volume parenteral, a form of drug dosage intended for administration as an injection or infusion.

2.18 maximum acceptable dose: Dose given in the process specification as the highest dose that can be applied to a defined product without compromising safety, quality, or performance.

2.19 Q_{10} : Expected or observed change in the rate of a reaction occasioned by a 10°C change in the reaction thermal environment.

NOTE— $Q_{10} = 2$ is a common and conservative estimate for most polymer systems.

2.20 real-time aging (RT): Storage of health care products at ambient conditions in order to evaluate functional properties over time.

2.21 real-time equivalent (RTE): Amount of real time to which given accelerated aging conditions are estimated to be equivalent.

NOTE—For example, if AA samples are held at an elevated temperature for 6 months and the AF_0 for the system has been estimated to be 2, then the RTE is 1 year:

$$RTE = T_{AA} \times AF_0 = 6 \text{ months} \times 2 = 1 \text{ year}$$

2.22 RH: Relative humidity, the amount of water vapor present in air, expressed as a percentage of the amount required for saturation at the same temperature.

2.23 shelf life: Length of time that a product can remain at the typical storage conditions before use without having an unacceptable effect on functionality and biocompatibility, or the length of time chosen for its expiration.

2.24 silicone: Any of a class of synthetic materials that are polymers with a chemical structure based on chains of alternate silicon and oxygen atoms, with organic groups attached to the silicon atoms.

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

2.26 SVP: Small-volume parenteral.

2.27 t: Time over which aging studies are conducted.

NOTE— T_{RT} and T_{AA} symbolize the storage time over which real-time and accelerated aging studies have been conducted.

2.28 T: Temperature, measured in $^{\circ}\text{C}$, used in aging studies.

2.29 terminal sterilization: Process whereby product is sterilized within its sterile barrier system.

2.30 Tg: Approximate midpoint of the temperature range over which the glass transition takes place.

2.31 thermoplastic: Denoting substances (especially synthetic resins) that become plastic on heating, harden on cooling, and are able to repeat these processes.

2.32 thermoset: Prepolymer material that cures irreversibly. The cure can be induced by heat, generally above 200°C (392°F), a chemical reaction, or suitable irradiation.

2.33 Tm: Melt temperature, or the temperature of molten plastic. [ASTM D883-08]

3 Selection of materials

3.1 General considerations

In the design and development of medical products requiring sterilization, consideration should be given to customer needs, finished device performance requirements, construction materials, and sterilization methods. The product must meet safety and efficacy requirements while providing a benefit to the patient and user. The product requirements can limit the choices of materials available for construction and can ultimately determine the acceptable mode of sterilization on the basis of compatibility with various sterilization methods. Product design characteristics can affect the mode of sterilization selected; for example, gaseous modalities require that surfaces to be sterilized be accessible to the sterilant.

Materials must be selected so that the final products are compatible with the sterilizing agent. Information about compatibility of specific materials can be obtained from such sources as materials manufacturers, the published literature, and Internet searches. In the event that supporting information is not available, the effects of exposure to the sterilizing agent on the physical and chemical properties of materials and on their biological safety should be assessed (see 5.4). The effects of repeated exposure to the sterilizing agent on the material properties should be studied, using process parameters likely to maximize material effects. The materials evaluated and the outcomes of all tests should be documented, together with the criteria against which the properties of materials were assessed, before and after exposure to the sterilizing agent.

Ultimately, it is the device manufacturer's responsibility to demonstrate that the sterile device meets its intended performance requirements and is safe and effective.

3.2 Guidance specific to different sterilization modalities

Guidance is provided on the compatibility of medical device materials with each sterilization modality in Annexes A through I. Several material families are addressed within the following classes of materials: thermoplastics, thermosets, adhesives, elastomers, metals, ceramics/glasses, and other materials. Sections 3.2.1 through 3.2.9 describe each sterilization modality in enough detail for the reader to understand the sterilization process parameters that must be considered in evaluating the compatibility of materials.

The information provided in the Annexes is a general guide to the compatibility of materials that are intended to be used to initiate a successful material qualification program. It is unacceptable to use this information as the sole rationale for using a material with a given sterilization modality. For instance, the material compatibility tables in the Annexes do not provide a comprehensive list of all materials used in medical products, and they are not indicative of all applications of the materials listed. Individual materials might be found compatible with a particular sterilization modality; however, when multiple materials are combined into a finished device, the outcome might be different than that found for the individual materials.

Summaries of the sterilization modalities relative to the material compatibility fundamentals of medical devices are provided in the sections that follow. Brief reference to the application of each sterilization modality to pharmaceutical and biological agents, where applicable, is also provided.

3.2.1 Radiation sterilization (gamma, electron beam, x-ray)

3.2.1.1 Background

This sterilization method results in high levels of microbial reduction without requiring direct accessibility of all surfaces. Sterilization of any location within a product depends on the dose received at that location. As the dose distribution will vary based on product thickness and density, refer to ANSI/AAMI/ISO 11137-3 for specific methods for determining dose distribution within a product. Radiation sterilization results in products that have no sterilant residuals, are not radioactive, and are available for immediate use by the final user.

The level of ionizing energy, or dose, received by the product to achieve sterilization is measured in kilograys (kGy) and can be delivered by gamma rays, x-ray photons, or directly by high-energy electrons (electron beam sterilization, i.e., e-beam). The maximum acceptable dose received by a product will dictate product functionality and can be two times or more the minimum sterilization dose because of the irradiator's design and the product's geometry and density.

3.2.1.2 Typical use

Ionizing radiation has been used for more than half a century to commercially sterilize medical devices. Radiation methods are primarily used for single-use medical devices, including adhesive bandages, and for orthopedic devices, implantable devices, combination devices, and biologics. Electronic components and/or systems can undergo significant changes. Individual component sensitivities should be investigated. Many types of sensors (e.g.,

thermocouples, thermistors, strain gauges, piezo), resistors, inductors, and capacitors (except electrolytic ones) show no effect from exposure to radiation doses. Connectors show no effect from exposure to sterilization doses, but surface corrosion that can be caused by exposure to ozone and outgassing should be considered. Glass fiber and synthetic resin bonded paper (SRBP) and synthetic resin bonded fiber (SRBF) printed circuit boards (PCBs) can be radiation-sterilized. Radiation sterilization methods are available commercially with contract manufacturers and can be brought in-house, but they are not commonly available in health care facilities.

3.2.1.3 Process parameters and variability

The rate of energy deposition and penetrability varies depending on the type of radiation processing. Gamma (cobalt-60) processing takes hours but has greater penetrability, whereas electron beam processes are significantly shorter (measured in seconds) but have substantially less penetrability. These fundamental process differences in energy deposition can lead to differences in processing temperature, oxidative effects, and dose uniformity ratio (DUR). A typical DUR in a gamma process is approximately 1.6 or less, whereas the DUR in an electron beam process can often exceed twice the minimum dose ($DUR \geq 2.0$). Dose and processing time are directly affected by material density, dose rate, product and packaging configuration, and load presentation.

Table 1—Radiation sterilization parameters

Parameter	Typical ranges
Sterilant	Ionizing radiation (gamma, e-beam, x-ray); typical dose range of 15 to 50 kGy. This method is usually bioburden-based, and the sterilization dose is set per ANSI/AAMI/ISO 11137-2 and the maximum allowable dose per ANSI/AAMI/ISO 11137-1.
Temperature	Ambient to 10°C to 20°C above ambient. Frozen processing can be conducted at -20°C to -80°C.
Relative humidity (RH)	Ambient, unless decreased or increased RH is controlled intentionally by package design.
Pressure	Ambient.
Time	Typical process time is Minutes to hours, depending on dose and method.
Mechanism of action	High-energy ionizing radiation produces excitations of orbital electrons that cause cleavage of bonds, resulting in ionization of molecules. The resultant energy-rich radicals initiate a series of dissociation and additional reactions that ultimately lead to chemical stability or instability. Direct ionization of DNA, key enzymes, and other essential cell components results in microorganisms' direct death and inability to reproduce. The reaction of free radicals produced in cellular fluid and the environment in which the organism resides creates a hostile environment and, indirectly, causes microorganism death.

3.2.1.4 General material compatibility

Table A.1 in Annex A lists various specific materials and their general compatibility with radiation sterilization. The information in this table is not exhaustive, and device manufacturers should use it only as a general guideline for material selection. Before a material is selected, the distributor, vendor, and/or manufacturer should always be consulted for more information.

Databases, literature sources, and manufacturers' information can be used to identify radiation-stable materials that tolerate the doses required for the particular product design and function. Most polymers are radiation-stable at the doses typically used in the radiation sterilization of health care products. Effects within a polymer can include recombination (no change), chain scission (decrease in molecular weight and strength), and cross-linking (stiffening or increase in strength). Materials subjected to radiation sterilization might potentially encounter the following effects:

- a) Changes in physical properties, such as embrittlement, discoloration, odor generation, stiffening, softening, enhancement or reduction of chemical resistance, and an increase or decrease in melt temperature that might continue to occur for several weeks after exposure

- b) Changes in chemical properties, such as decomposition, generation of gases, polymerization, and possible formation of toxic compounds
- c) Differences in expansion rates, which could affect bond strengths of mated parts
- d) Changes in material or product functionality and performance over the product's shelf life

NOTE—Radiation sterilization has been used as a manufacturing step for material modification to impart beneficial physical properties in the final device. However, radiation stability of any polymer formulation can vary significantly, depending on the following:

- Radiation dose absorbed
- Residual or functional stress (processing, part design, and function)
- Molecular weight
- Product cross-section thickness (films, coatings, and fibers)
- Morphology (e.g., percent crystalline)
- Environment during irradiation, storage, and use (e.g., oxygen, temperature, and moisture)
- Dose rate (gamma, e-beam, or x-ray)

Therefore, all polymer selections should be thoroughly challenge-tested in the specific application and processing conditions under consideration.

Figure 1 summarizes a substantial amount of the information available from government, industrial, and scientific studies and publications concerning the effects of radiation on polymer properties after exposure to various doses. Figure 1 graphically displays the dose ranges at which a number of common thermoplastics and thermosets show significant change in properties (e.g., a 25% loss in elongation). Loss of elongation is a commonly used measure of the effect of irradiation because it equates to a brittleness failure; however, a similar figure could be developed on the basis of an alternate physical property (e.g., tensile strength). Figure 1 provides a visual means of making an initial estimate of a polymer's ability to withstand a particular radiation sterilization process.

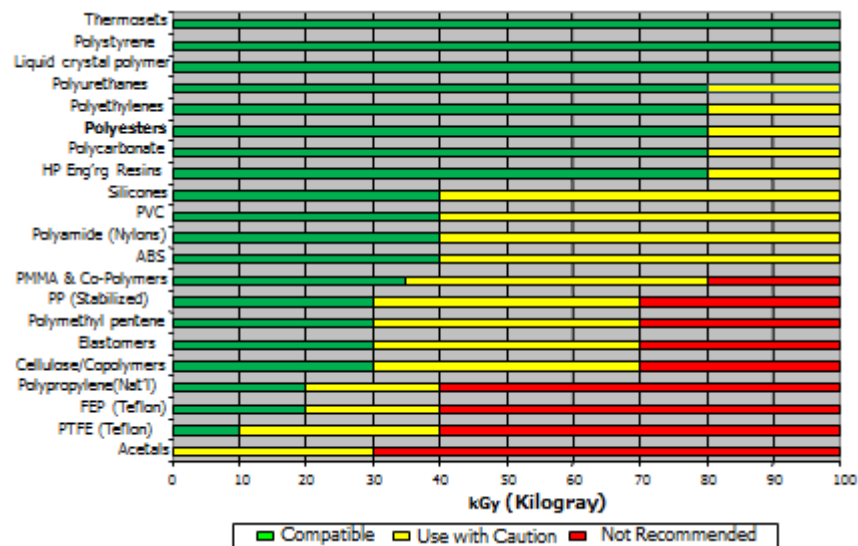


Figure 1—Relative radiation stability of medical polymer "families"

(NOTE—HP = high performance; PVC = polyvinylchloride; ABS = acrylonitrile butadiene styrene; PMMA = polymethylmethacrylate; PP = polypropylene; FEP = fluorinated ethylene propylene; PTFE = polytetrafluoroethylene.)

Table 2 provides general information on the compatibility of various types of materials with radiation.

Table 2—General compatibility of various types of materials with radiation

Material type	General compatibility
Thermoplastics	Polymers (e.g., polyacetal, unstabilized polypropylene, and polytetrafluoroethylene) are significantly degraded (see Table A.1). Aromatic materials (e.g., styrene, polyester, polycarbonate, and polysulfone) are more radiation-resistant than aliphatic materials.
Thermosets	The chemical reactions to form thermosets are terminal; thus, minimal ionizations occur upon irradiation. High heat stability is typical. Because of the lack of ionization potential, all thermosets are stable at radiation doses that are typical of medical product sterilization. Post-irradiation stability for a limited number of thermosets is described in Table A.1.
Elastomers	Elastomers containing butyl or butadiene sectional groups typically are not highly stable to radiation. Silicone elastomers are very stable. However, silicone-based elastomers are created by cross-linking reactions that are promoted by either peroxide or platinum catalysts. Because of their higher final cross-link density, platinum-cured systems tend to display less post-irradiation cross-link enhancement than do peroxide-based systems. Post-irradiation stability for a number of elastomers is described in Table A.1.
Adhesives	Because of their greater surface-to-mass ratios, adhesives will be stable to irradiation on the basis of their base compositional polymer, as shown in Figure 1 and Table A.1. However, adhesives based on cross-linking (e.g., initiated by ultraviolet) for their final properties should be anticipated to have enhanced bond characteristics after irradiation because of enhanced post-irradiation cross-link densities. This enhanced post-irradiation bond strength or cross-link should also be anticipated for bonds formed from any similar or compatible materials (e.g., polyethylene or polyethylene heat seal).
Metals	Metals are very stable under the influence of irradiation. For systems that use high-energy e-beam accelerators, neutron displacements and creation of measurable radioactive subspecies have been reported in some metals (see ANSI/AAMI/ISO 11137-1).
Glass and ceramics	Silicon-based materials, such as glass and ceramics, are very stable to irradiation. Glass severely discolors (yellows) because of the processing aids it contains for enhanced formability. Heat, time, or both will reduce or eliminate the radiation-induced color. Other physical properties are not affected.
Silicone	Most silicones are sterilized with radiation with limited effects.
Liquids	Because of ionization formed during irradiation of liquid (H ₂ O-based) systems, stabilization is difficult to predict or maintain. A buffering agent (radical scavenger) can negate the formation of hydrogen-based radicals to help maintain the liquid systems' pre-irradiation properties. Some thickening agents tend to undergo a significant loss in viscosity at relatively low doses of radiation.
Contact surfaces	For product designs using polymers that tend to cross-link (e.g., polyvinylchloride [PVC], silicone), placing surfaces in intimate contact with each other should be avoided, because cross-link bonds can develop and act to tack the surfaces together. Anti-blocking agents can be used if surface contact cannot be avoided. Flexible materials such as PVCs can leach out plasticizers; this leakage can transfer to other surfaces.
Cellulosics	Most cellulosics are sterilized with radiation with limited effects.

Material type	General compatibility
Bioabsorbables	Effects of radiation have been noted in bioabsorbables but can be minimized or negated by altering the design or formulation of the product, controlling the environmental conditions (e.g., temperature, oxygen), and/or adding a radical scavenger.
Additional notes	Those polymers that cross-link more than they scission generally perform better in the radiation environment. Antioxidants and radical scavengers improve radiation resistance; the impact of these additives on biocompatibility should be considered. The material with the highest molecular weight possible for the application (with the narrowest molecular weight distribution) should be used. Materials with low O₂ permeability are more radiation- resistant. Materials used in thin films and fibers should be selected with caution because of the enhanced effect of oxidation resulting from the large surface-to-mass relationship. The effects of radiation on polymers generally are cumulative with each subsequent exposure of a product. Therefore, the effects from a total dose from one continuous irradiation would be equivalent to the same total dose from multiple irradiations. This cumulative effect relates to total absorbed dose and not to the number of exposures. Incremental dosing to achieve a cumulative exposure might be needed in the following cases: • Materials that are prone to radiation-induced oxidative scissioning • Devices with large surface-to-mass designs • Devices that require incremental exposures to achieve minimum dose to avoid thermal effects Color development, which occurs at widely differing doses in different polymers, usually diminishes to some extent with storage time after irradiation. Discoloration usually appears before any measurable loss in physical properties. This is the case with polyvinylchloride and polycarbonate, in which radiation-induced yellowing from conjugated double bonds develops at a dose much lower than is necessary to cause any reduction in its physical properties; however, the color that is developed can be undesirable. Odors can develop from irradiated polymers as a result of specific radio-stabilizing chemistries and the formation of free radicals. The polymers that most often exhibit post-irradiation odors are polyethylene, polyvinylchloride, and polyurethane. If the reaction chemistries of the odors are understood, they can often be mitigated through the use of antioxidants, reduced processing temperatures, or a polymer with a higher molecular weight. Odor reduction can also be accomplished through the use of gas-permeable packaging or elevated temperature conditioning. Amorphous materials provide better radiation enhancement than semi-crystalline materials.

NOTE 1—Material qualification performed at a low dose rate (gamma) can reveal greater degradation (e.g., embrittlement) than a high dose rate (e-beam) radiation, as a result of enhanced oxidative effects (Cleland et al., 1993; Ishigaki and Yoshii, 1992; Williams, 1995; Farrell and Hemmerich, 1995). Consequently, a material that formerly qualified at a low dose rate (gamma) will typically require minimal qualification to demonstrate material compatibility at a higher dose rate (e-beam). This consideration is important to keep in mind for materials that degrade oxidatively (e.g., polypropylene and aliphatic nylon) or for materials used in applications that have large surface-to-mass ratios (e.g., films, fibers, adhesives).

NOTE 2—See Annex A for a more detailed material impacts assessment.

NOTE 3—Refer to Section 5.4 for information regarding biocompatibility.

3.2.1.5 Pharmaceuticals and biologics

Radiation methods have been used to sterilize pharmaceuticals, active pharmaceutical ingredients (APIs), biologics, and combination devices. Irradiation of biological materials (tissue, bone, serum, proteins) enhances the formation of free radicals, which propagate chain scission or cross-linking that might degrade performance. There are several strategies for mitigating degradation effects:

- a) The use of low temperature (e.g., dry ice) might reduce the rate of free-radical interaction due to reduced mobility, which will eventually enhance the product stability post-irradiation.
- b) Oxygen-deprived atmospheres, such as argon or nitrogen, might also reduce or modify the free-radical formation, which will eventually enhance the product stability post-irradiation.
- c) The state of the material (liquid or solid) might affect the stability of the product, based on the water content in the product. Minimizing water content in the sample can reduce the activity of the free radicals and limit product degradation. Therefore, more degradation is observed in the aqueous state than in the solid (dry) state in different type of materials. Additives (radical scavengers and energy absorbers) can promote recombination as the most likely post-irradiation reaction for many biological products.

3.2.1.6 Packaging

Radiation sterilization does not require gas-permeable packaging. Packaging density and configuration should be considered in the dose-setting process. Attempts should be made to evenly distribute mass homogeneously throughout the package. To avoid undesirable discoloration or changes in seal strength, packaging materials should be selected in accordance with the guidelines in Table A.1.

As a pre-sterilization processing step, purging or vacuum steps are sometimes used to eliminate effects of oxidation. If gas displacement is used, an inert gas (e.g., argon, nitrogen) might reduce or modify free radical formation, which might enhance the product stability post-irradiation.

Sealed packaging containing inert gases can be used to reduce the effects of oxidation.

Table 3—Radiation packaging

Most commonly used	Not commonly used
Pouches and header bag	NA
Lidded trays	
Polyethylene-to-polyethylene sealed pouches	
Multi-barrier films	
Metallized films	
Corrugate and paperboard	

3.2.2 Ethylene oxide (EO) sterilization

3.2.2.1 Background

Ethylene oxide (EO) is a traditional and effective sterilant for health care products. The parameters of the sterilization process are gaseous EO concentration, temperature, relative humidity, and time. The development, validation, and routine control of EO sterilization processes are covered in ANSI/AAMI/ISO 11135.

Typically, EO sterilization can occur in various forms of processing: deep evacuation, dynamic conditioning, air displacement, balanced pressure, and diffusion. Steps in an EO sterilization cycle can include the following:

- 1) Preconditioning
- 2) Air removal
- 3) Leak-rate check
- 4) Conditioning
- 5) EO injection
- 6) EO exposure

- 7) EO removal
- 8) Flushing
- 9) Air/inert gas admission
- 10) Aeration (inside or outside the chamber)

3.2.2.2 Typical uses

Ethylene oxide has been used since the mid-20th century for sterilization of medical devices. It has proved to be very useful in sterilizing a wide range of products, including single-use devices, reusable devices (e.g., rigid and flexible endoscopes), surgical kits, hospital equipment, combination products, enzymes, and electronic devices that are moisture- or heat-sensitive. The method is widespread within industry and health care facilities.

3.2.2.3 Process parameters and variability

EO sterilization typically uses 100% EO as the sterilant. The use of diluents with EO (such as nitrogen [N₂] and carbon dioxide [CO₂]) is much less common. All U.S. health care facilities currently use 100% EO as the sterilant.

In EO sterilization, the following process variations or parameters might need to be considered:

Table 4—EO sterilization parameters

Parameter	Typical ranges
Sterilant	Typical range of concentration: 450 mg/L to 800 mg/L The composition of the sterilant can vary from 100% EO to mixtures of EO and a diluent. EO sterilant mixtures can be manufactured in custom percentages to provide flexibility to meet custom sterilization parameters. Common diluents include N₂ and CO₂. Micro-dose or gas-diffusion sterilization (flexible-chamber EO) uses an alternative EO sterilizing mixture that is typically 84% to 97% by weight mix with hydrocarbons. EO is measured by weight (grams) rather than mg/L (concentration).
Temperature	Typical range of chamber temperature: 37°C to 63°C. Lower- and ambient-temperature EO cycles are possible but not typical. Preconditioning, aeration, and product load temperature might be lower or higher than chamber temperature.
RH	Typical range of relative humidity: 40% to 80% RH. Lower- and ambient-RH cycles are possible but not typical. Observed relative humidity values might be different than the process control points.
Pressure	Typical pressures: 6 kiloPascals (kPa) to atmospheric. Gas mixtures might experience pressures of 6 to 310 kPa. Ambient pressure cycles (with no pressure changes) are possible but not typical. An EO cycle might have multiple pressure changes and rates of change exceeding 6 kPa/minute.
Time	Typical cycle length (inclusive of preconditioning and aeration): hours to days. Typical EO exposure time: 60 to 360 minutes. Shorter and longer exposure times can occur. Typical mechanical aeration time: 8 to 12 hours at 50°C to 60°C.
Mechanism of action	EO is an alkylation agent. EO alkylation typically affects the N-7 position of guanine in DNA, which is especially susceptible. The alkylation interferes with separation of the strands and prevents mitosis or reproduction.

NOTE 1—The sterilization process can be modified to accommodate materials that can be moisture-, temperature-, or gas-concentration-sensitive, although these modifications might affect the degree and speed of lethality.

NOTE 2—EO preconditioning and conditioning phases have been used as a manufacturing step for material modification to impart beneficial physical properties in final devices.

3.2.2.4 General material compatibility

Table B.1 in Annex B lists various specific materials and describes their general compatibility with EO sterilization. The information in this table is not exhaustive, and device manufacturers should use it only as a general guideline for material selection. Before material is selected, the distributor, vendor, and/or manufacturer should always be consulted for more information.

Table 5 provides general information on the compatibility of various types of materials with EO.

Table 5—General compatibility of various types of materials with EO

Material type	General compatibility
Thermoplastics	Most thermoplastics are EO sterilized with limited effects.
Thermosets	Most thermosets are EO sterilized with limited effects.
Elastomers	Most elastomers are EO sterilized with limited effect(s).
Adhesives	Most adhesives are EO sterilized with limited effects.
Metals	Most metals are EO sterilized without any corrosion or dulling of sharp metal instruments.
Glass and Ceramics	Most glass and ceramics are sterilized without any erosion.
Silicone	Most silicones are sterilized with limited effects (but EO residuals in implantable prostheses might be unacceptable).
Liquids	Liquids are not typically sterilized with EO.
Contact surfaces	The effects on contact surfaces of anti-blocking EO sterilization will depend on the type of contact surface (e.g., smooth vs. rough), type of material, and the nature of the anti-blocking agent.
Cellulosics	Most cellulosics are EO sterilized with minimal effects.
Bioabsorbables	Most biosorbables (e.g., polyL-lactide [PLLA], polylactic acid [PLA], polyhydroxybutyrate [PHB], polyglycolic acid [PGA], polylactic-co-glycolic acid [PLGA], and polycarbonate [PCL]) can be sterilized with EO, depending on its concentration, humidity, and temperature.

NOTE 1—See Annex B for a more detailed material impacts assessment.

NOTE 2—Refer to Section 5.4 for information regarding biocompatibility.

3.2.2.5 Pharmaceuticals and biologics

Ethylene oxide can be used to surface-sterilize the containers and/or packaging systems of pharmaceutically active components. It has been successfully used to sterilize combination devices, dry powders, and procedural trays with small vials of antibiotics, antiseptics, and anesthetic. The use of EO as a terminal sterilization process for pharmaceuticals or biologics can be limited, because the EO process might affect compounds in the following ways:

- Creation and accumulation of limiting byproducts
- Alkylation
- Hydrolytic impact
- Moisture loss
- Nonvolatile residuals (e.g., particulates)
- Thermal degradation
- Volatilization

Ethylene oxide has been successfully used to sterilize biologics such as collagen and bone products. When using EO, a “cold” cycle (in which gas dwell temperature does not exceed 47°C) can be developed and applied, as long as the “cold” cycle will provide adequate sterilization of the product. Ethylene oxide can be used to surface-sterilize the containers and/or packaging systems of biologic active components (e.g., for tissue cell attachment and spreading).

3.2.2.6 Packaging

Characteristics of optimal packaging for EO include those listed below. Optimal packaging

- a) is highly permeable to EO, gases, air, and moisture;
- b) is resistant to pressure changes;
- c) is stable under deep vacuum and high pressures;
- d) is highly compatible at low temperatures (ambient to 60°C);
- e) has low absorption to EO; and
- f) desorbs any EO gas retained.

For reusable device sterilization, best packaging practices include the use of metal baskets and disposable sterilization wraps, because of their small volume-to-vent (V-to-V) ratio. The V-to-V ratio is a measure of the ability of the sterilant to flow into and out of the sterilization container or packaging. This ratio is defined as the interior volume of the sterilization container divided by the total cross-sectional area of the perforated vent holes. Metal baskets, disposable sterilization wraps, and some brands of plastic trays wrapped in disposable sterilization wraps have a relatively small V-to-V ratio.

One should understand the pressure changes of the process (rate and/or magnitude) in relation to the packaging materials’ ability to equilibrate with the process. Pressure changes and elevated temperatures and humidity might affect the strength of package seals and internal package equilibrium.

Secondary and tertiary packaging (corrugate) might affect %RH, temperature, and gas distribution and/or penetration, as well as EO residual and air removal.

Woven, nonwoven, peel-pouch packages, and some rigid container materials are permeable to EO and do not impede the rapid aeration of contents. Woven materials, however, might absorb a large amount of the RH needed for EO sterilization.

Table 6—EO packaging

Most commonly used	Not commonly used
Paper: lid to tray or pouch	
Spun polyethylene (Tyvek®): lid to tray or pouch	
Tray or pouch materials (e.g., acrylonitrile, polycarbonate, polyethylene, polyethylene terephthalate (PET) laminate, PET/polypropylene laminate, PET glycol-modified, polyester/polyethylene/ethylene vinyl acetate (EVA), polyester/polypropylene, nylon, polystyrene or unplasticized PVC with porous lids)	PET (e.g., Mylar®), PETG, nylon (without porous lids) Full metallized film package
Polyethylene plastic bags (designed for use as a sterile package and not more than 5 mil thick)	Packages made <i>entirely</i> from: Foil, cellophane, PVC, impervious polypropylene film, polyester film made from stretched PET, polyamide (nylon), polyvinylidene chloride
Peel-pouches: spun-bonded olefin polyethylene–polyester laminate, paper/polyethylene–polyester laminate, paper/polypropylene–polyester laminate	Cellophane

Most commonly used	Not commonly used
Wraps: woven textile, nonwoven textile, nonwoven polypropylene, coated and uncoated paper	
Rigid sterilization container systems	
Plastic trays with paper or spun-bonded olefin lids	

3.2.3 Moist heat (steam) sterilization

3.2.3.1 Background

Moist heat is a traditional and broadly used method for heat sterilization of reusable and single-use devices. Typically, temperature, pressure, RH (moisture), and time are the key parameters used in the development, validation, and routine control of moist heat processes (ANSI/AAMI/ISO 17665-1; ANSI/AAMI ST79 Parenteral Drug Association 2007, 2010, 2012, 2013a)

Moist heat sterilization is used in various forms. Typical steps include the following:

- 1) Preconditioning
- 2) Heating (i.e., come-up)
- 3) Exposure
- 4) Post-conditioning (i.e., cool-down)
- 5) Drying

3.2.3.2 Typical uses

Moist heat sterilization has been used since the late 19th century. Moist heat is widely used in pharmaceutical health care facilities for the sterilization of such products as large-volume parenterals (LVPs), small-volume parenterals (SVPs), combination products, and aseptically filled products; in medical health care facilities (clinics, doctors' offices, dental offices, hospitals, veterans' facilities, laboratories, veterinary offices) for the sterilization of reusable medical devices and biologics; and in medical device manufacturers' facilities. Moist heat systems use saturated steam, steam-air mixtures with air-over-pressure (AOP), or superheated water with AOP (immersion or water spray/cascade).

3.2.3.3 Process parameters and variability

Table 7—Moist heat sterilization parameters

Parameter	Typical ranges
Sterilant	Steam (water vapor)
Temperature	Typically 105°C to 135°C
Relative Humidity	Typically up to 100% RH
Pressure	Typical Pressures: 4.5 to 313 kPa Rates of pressure change: Refer to EN 285 for details on pressure changes.
Time	Typical exposure times: 3 to 270 minutes Typical processing times: 10 to 300 minutes

Parameter	Typical ranges
Mechanism of action	Moist heat inactivates microorganisms by enzyme inactivation, misfolding of proteins to cause protein denaturation, and possible deamination and hydrolysis of some amino acid residues (e.g., asparagine). Only at hydration levels (increased levels of spore core water) high enough to permit intermolecular disulfide exchange or entanglement does protein unfolding lead to irreversible protein aggregation, which would compromise the viability of the spore.

3.2.3.4 General material compatibility

Table C.1 in Annex C lists various specific materials and describes their general compatibility with steam sterilization. The information in this table is not exhaustive, and device manufacturers should use it only as a general guideline for material selection. Before a material is selected, the distributor, vendor, and/or manufacturer should always be consulted for more information.

Table 8 provides general information on the compatibility of various types of materials with moist heat.

Table 8—General compatibility of various types of materials with moist heat

Material type	General compatibility
Thermoplastics	Thermoplastics might be compatible with steam sterilization, depending on their relevant thermal properties and the processing temperatures. Cross-linking polymers with irradiation (PEEK, polyamide-imide, and high-molecular-weight polyethylene) typically makes them more heat-resistant. Styrenics (ABS, polystyrene) and polyesters (polybutylene terephthalate [PBT] or PETG) have poor resistance to high-heat/high-moisture environments. Polymers such as PVC, polyacetals, and polyamides might become hydrated (which results in a cloudy appearance). Post-cycle drying can remove hydration effects. High-density polyethylene (HDPE) and PVC can be moist heat sterilized, but only at lower temperatures (e.g., <121°C) and for limited lengths of time.
Thermosets	Thermosets can be compatible with steam sterilization but might break down at high temperatures. Moist heat sterilization performed at lower temperatures will result in improved thermoset compatibility.
Elastomers	Elastomers are moist heat sterilized with limited effects, with the exceptions of urethane and polyurethane.
Adhesives	Adhesives are moist heat sterilized with limited effects. Polyurethane and silicone adhesive might be sensitive to moist heat sterilization.
Metals	Metals are moist heat sterilized with limited effects. Some metals (e.g., iron, copper, brass, carbon steel, aluminum, certain grades of stainless steel) might require anti-corrosion treatment (e.g., anodization, passivation). Dissimilar metals (e.g., stainless steel, carbon steel) must be separated.
Glass and ceramics	Glass and ceramics are moist heat sterilized with limited effects.
Silicone	Silicones are moist heat sterilized with limited effects.
Liquids	Aqueous liquids are moist heat sterilized with limited effects, although consideration should be given to heat-sensitive components. Non-aqueous liquids (e.g., oils, grease) are not typically moist heat sterilized.
Contact surfaces	Moist heat will cause materials to expand, and differences in expansion rates of mated materials could be damaging. Variation in impact might also depend on the type of contact surfaces (e.g., smooth vs. rough). Melting of thermoplastic contact surfaces might cause unwanted adherence.

Material type	General compatibility
Cellulosics	Most cellulosic materials are moist heat sterilized with limited effects.
Bioabsorbables	Most bioabsorbables are not typically sterilized with moist heat. Polyethersulfone (PES), non-gelling starch with calcium phosphates, absorbable hemostats (e.g., oxidized cellulose, absorbable gelatin foam, human fibrin foam, calcium alginate), and surgical ligatures and sutures (e.g., surgical absorbable catgut) are heat-stable and may be sterilized with moist heat.

NOTE 1—See Annex C for a more detailed material impacts assessment.

NOTE 2—Refer to Section 5.4 for information regarding biocompatibility.

3.2.3.5 Pharmaceuticals and biologics

A wide variety of heat-tolerant parenteral solutions (LVPs, SVPs) are terminally sterilized using moist heat processes (e.g., saline, amino acids, dextrose). A large variety of laboratory media and solutions are also moist heat sterilized. Moist heat sterilization has been successfully used to sterilize combination products (e.g., prefilled syringes).

The major limitations of moist heat sterilization of pharmaceuticals are as follows:

- Creation and accumulation of byproducts
- Potential denaturation and coagulation of proteins
- Hydrolysis
- Nonvolatile residuals (e.g., particulates)
- Thermal degradation

In many situations, moist heat temperatures are too high for biological materials to function properly. Absorbable hemostats of biological origin (e.g., human fibrin foam) and surgical ligatures and sutures (e.g., sterilized surgical absorbable catgut) can be moist heat sterilized.

3.2.3.6 Packaging

The suitability of packaging for moist heat sterilization depends on the thermostability of the polymer and the size and wall thickness of the package and its contents, including any sharp corners that might pierce the package. There are two classes of packaging used in moist heat sterilization: breathable and non-breathable:

- Non-breathable systems are used for liquids (e.g., LVPs, SVPs). The package should be designed to allow heating of the contents without content loss or expansion or an impact on product stability. Consideration should be given to pressure changes in the process (rate and/or magnitude) in relation to the packaging materials' ability to equilibrate with the process.
- In breathable systems, the product and packaging should be designed to allow for the removal of air, pressure changes, and the penetration of moist heat without potential contamination.

NOTE—Handling moist heat sterilized packages that are still warm and/or wet might compromise the barrier properties of the sterile barrier system, increasing the potential for contamination.

Table 9—Moist heat packaging

Most commonly used	Not commonly used
Breathable systems	
Cloths: Muslin (cotton), denim, and broadcloth	Papers (multiple-sterilization, often dimensionally unstable)
Cellulosics: Paper, ethyl cellulose, cellophane, glassine	Thermoplastic films (low-density polyolefin)
Cotton and cotton–polyester fibers	

Most commonly used	Not commonly used
Thermoplastic films: High-density polyolefin, polycarbonate, PET/PP laminate, polyester/nylon/PP, PP film, spun PE (Tyvek®)	
Metal (e.g., stainless steel, aluminum) or plastic trays (e.g., PP) pans with lids that might include wire mesh or filters.	
Non-breathable systems	
Glass	Nylon
Polypropylene, HDPE (not recommended for use at temperatures above 127°C)	Polyamide
Co-polymers (e.g., PE/PP)	PVC (di(2-ethylhexyl) phthalate [DEHP] plasticized)
PVC (not DEHP plasticized)	
Polyester	

3.2.4 Dry heat sterilization

3.2.4.1 Background

Dry heat sterilization is defined as heat without moisture. Dry heat has been used to destroy microorganisms and pyrogens. It is a method suitable for heat-resistant and moisture-sensitive materials. The temperature of dry heat sterilization determines the time required for sterilization and the compatibility of materials. Product density, geometry, mass, thickness, and heat absorbance will affect overall sterilization time. The development, validation, and routine control of dry heat processes are covered in ANSI/AAMI/ISO 20857, ANSI/AAMI ST40, ANSI/AAMI ST50, and Parenteral Drug Association(2013b).

Typical dry heat sterilization cycles include the following general steps:

- 1) Preparation (as applicable)
- 2) Loading (as applicable)
- 3) Heat-up
- 4) Exposure

3.2.4.2 Typical uses

Dry heat is used for decontaminating and sterilizing metal equipment used in animal facilities (e.g., cages), aseptic processing in the pharmaceutical industry (e.g., glassware), and sterilization of silicone prostheses (e.g., implantables).

Dry heat is used for materials that are heat-resistant, items that cannot be steam sterilized because of damage from steam, items resistant to gas penetration (e.g., oil, powders, and greases), and instruments that cannot be disassembled. Dry heat sterilization can prevent rust and corrosion of instruments and equipment, allowing them to be repeatedly sterilized.

3.2.4.3 Process parameters and variability

Dry heat sterilization can be delivered through heated chemicals, convection, conduction, infrared radiation, heated forced air, or incineration. The dry heat sterilization process can be performed in a convection oven, with infrared radiation, with high-velocity forced air, or through continuous belt sterilizers in a radiant-heat tunnel. Table 10 describes typical dry heat sterilization parameters.

Table 10—Dry heat sterilization parameters

Parameter	Typical ranges
Sterilant	Typically, dry heat sterilization cycles operate at elevated temperatures without moisture.
Temperature	Typical range of chamber temperature: 150°C to 250°C. Product load temperature might be lower or higher than chamber temperature.
RH	Dry heat is typically performed without any moisture, or 0% RH.
Pressure	Typical pressure: atmospheric (for traditional ovens), unless forced air velocity is applied.
Time	Exposure time can vary from minutes to days, depending on the temperature, type of sterilizer, and product requirements (sterilization and/or depyrogenation). Increased temperatures might reduce the overall sterilization cycle time. Some dry heat sterilizers have integrated blowers to decrease cool down time.
Mechanism of action	In dry heat sterilization, thermal inactivation of organic matter is caused by oxidative free-radical damage and drying (dehydration) of cells.

3.2.4.4 General material compatibility

Table D.1 in Annex D lists various specific materials and describes their general compatibility with dry heat sterilization (not indicative of the higher temperatures associated with depyrogenation). The information in this table is not exhaustive, and device manufacturers should use it only as a general guideline for material selection. Before a material is selected, the distributor, vendor, and/or manufacturer should always be consulted for more information.

Table 11 provides general information on the compatibility of various types of materials with dry heat.

Table 11—General compatibility of various types of materials with dry heat

Material type	General compatibility
Thermoplastics	The higher the % crystallinity in a polymer, the greater the heat resistance. Inversely, the greater the % amorphous in the polymer, the lower the heat resistance of the polymer will be. Aromatic polymers are better for dry heat sterilization than aliphatic polymers. Melting and/or deflection/maximum temperature can vary with thermoplastic formulation changes and/or cross-linking.
Thermosets	Most thermosets are dry heat sterilized with limited effects.
Elastomers	Most elastomers are dry heat sterilized with limited effects. Thermoplastic-based elastomers are not suitable for dry heat sterilization.
Adhesives	Heat-resistant adhesives are dry heat sterilized with limited effects.
Metals	Most metals are dry heat sterilized with limited effects.
Glass and ceramics	Most glass and ceramics are dry heat sterilized with limited effects. A common problem with ceramics is the tendency to crack because of thermal stress.
Silicone	Most silicones are dry heat sterilized with limited effects. Dry heat sterilization might cause silicone to temporarily swell, a design consideration when selecting configuration and packaging.
Liquids	Dry heat sterilization is not compatible with aqueous liquids.

Material type	General compatibility
Contact surfaces	Contact surfaces at high dry heat sterilization temperatures might bond; reducing the temperature might reduce this effect. The high temperatures required for dry heat sterilization might damage soldered joints.
Cellulosics	Most cellulosics are dry heat sterilized with limited effects, although charring might occur at higher temperatures.
Bioabsorbables	Bioabsorbables are not typically dry heat sterilized.
Additional notes	In some industries, dry heat sterilization is used with or without chemicals and high velocity air at higher temperatures (e.g., 130°C to 190°C) for faster processing and reduced corrosion, dulling, pitting, or cracking of sharp instruments.

NOTE 1—See Annex D for a more detailed material impacts assessment.

NOTE 2—Refer to Section 5.4 for information regarding biocompatibility.

3.2.4.5 Pharmaceuticals and biologics

Some examples of dry heat sterilized pharmaceuticals include pharmaceutically treated gauze dressing, dry bulk drugs, drugs in non-aqueous liquids, glycine, glycerine, non-aqueous embolics, some steroid and hormonal implants, and sulfonamide powder zinc peroxide. Dry heat can sterilize biologics such as absorbent gelatin foam, collagen, glucosamine, human fibrin foam, and sutures such as sutures made from cat gut.

3.2.4.6 Packaging

Packaging for dry heat sterilization must be heat-resistant. Non-permeable and moisture-sensitive package materials may be used, providing for more freedom in design. Some general principles include the following:

- Wrapped items and large load require longer times for adequate heating (because of the need for air or chemical penetration and heat diffusion).
- Non-aqueous liquid products must be dry heat sterilized in non-permeable packages, such as aluminum foil, glass, and porcelain jars.
- Non-liquid (solid) products typically need permeable packaging, unless processed by aseptic fill.
- The packaging design must take into account the potential for thermal expansion of the packaging and/or device.

Table 12—Dry heat packaging

Most commonly used	Not commonly used
Aluminum foil	Acrylonitrile
Ceramic jars with aluminum lids	ABS
Glass	Low-density polyethylene (LDP)
Metals (e.g., trays)	Polystyrene
Paper (up to 160°C)	PVC
PET/PP	PETG
PET/nylon/PP	
Some polyamides	
Porcelain (apothecary jars)	
Muslin (up to 204°C)	

3.2.5 Hydrogen peroxide sterilization

3.2.5.1 Background

Hydrogen peroxide (H_2O_2) is an oxidizing agent that can be used for sterilization as either a liquid or gas. It is also known as hydrogen dioxide. The information presented here applies only to sterilization with hydrogen peroxide in the gas phase. Many materials can be sterilized without an impact on material properties or functionality.

For information on the development, validation, and routine control of H_2O_2 sterilization processes, see ANSI/AAMI/ISO 14937.

Typical hydrogen peroxide sterilization cycles include the following general steps:

- 1) Evacuation
- 2) Peroxide injection (transfer to sterilization chamber)
- 3) Exposure
- 4) Vent with filtered air
- 5) Evacuation
- 6) Plasma (if used)
- 7) Vent to atmosphere

3.2.5.2 Typical uses

Hydrogen peroxide gas is used in many different applications to sterilize medical items, including low-pressure processes to sterilize reusable medical devices (e.g., in a hospital or clinical setting) and single-use devices or drug product packaging (in manufacturing facilities). The low-pressure sterilization cycles operate at low temperature and are suitable for processing medical devices sensitive to heat and moisture. Devices appropriate for hydrogen peroxide sterilization in low-pressure cycles include metal instruments, rigid and flexible endoscopes, and surgical powered equipment and batteries. Material compatibility varies, depending on the sterilizer and sterilization cycle chosen.

Hydrogen peroxide sterilization is used for the low-temperature surface sterilization of devices. Pressures can range from atmospheric to deep vacuum levels. The hydrogen peroxide sterilant does not penetrate to the product but sterilizes the surface of the packaging or device.

3.2.5.3 Process parameters and variability

Two general types of terminal low-pressure sterilization methods using hydrogen peroxide as the sterilant are available: hydrogen peroxide gas plasma and vaporized hydrogen peroxide. In sterilization with hydrogen peroxide gas, process variations or parameters that might need to be considered are identified in Table 13.

Table 13—Hydrogen peroxide/hydrogen peroxide gas plasma sterilization parameters

Parameter	Typical ranges
Sterilant	Depending on the sterilization system and sterilization cycle chosen, chamber concentration can range from 59% to 94% (wt/wt) H_2O_2 or 8 to 26 mg/L H_2O_2 in subatmospheric pressure cycles. The concentration of sterilant for surface sterilization applications performed at subatmospheric or atmospheric pressure is typically 35% to 59% (wt/wt) or 0.3 to 2.5 mg/L H_2O_2 .

Parameter	Typical ranges
Temperature	The physical state of the hydrogen peroxide (i.e., whether it is a gas or liquid) depends on temperature. Hydrogen peroxide vapor sterilizers run at subatmospheric pressure have chamber wall temperatures in the range of 45°C to 50°C. Hydrogen peroxide vapor sterilizers with plasma generally have chamber wall temperatures in the range of 40°C to 60°C, depending on model and cycle type. Typical product temperatures do not exceed 55°C for gas plasma sterilizers and are less than 50°C for hydrogen peroxide vapor sterilizers. For surface sterilization at subatmospheric and atmospheric pressure, the typical range of temperature is 25°C to 40°C.
RH	Subatmospheric hydrogen peroxide sterilization systems require no additional water to be added to the system. Any humidity or water present in the chamber is removed before introduction of the sterilant. The only water present comes with the sterilant injected during the sterilization phase of the sterilization process or from ambient air introduced during the cycle. For atmospheric applications, the initial RH can range from 10% to 60%, whereas process RH can range from 50% to 90%, depending on the application. No additional humidity is required to be added to the system, as the peroxide solution will provide sufficient water to achieve the saturation required.
Pressure	Because of the deep vacuum required for low-pressure sterilization, the items to be sterilized must be able to withstand the pressure changes. Some devices have special venting caps to allow pressure equalization between external and internal spaces. Physical damage to the device might occur if it is not capable of withstanding both deep vacuums and the rate of pressure change during a given cycle. Pressure during a sterilization cycle will range downwards from atmospheric pressure (approximately 760 Torr or 101.325 kPa) to the lower pressure achieved before sterilant is introduced (approximately 0.4 Torr or 0.05 kPa).
Time	Cycle times can vary from 24 minutes to more than an hour, depending on the sterilizer, the sterilization cycle chosen, and the load. For surface sterilization applications, cycles are typically 2 to 4 hours.
Plasma	Plasma will affect some materials by surface modification. In some instances, the effect is temporary. Devices to be processed should be evaluated for surface modifications and effects on functionality. Hydrogen peroxide gas plasma is only used in a subatmospheric application.
Mechanism of action	Hydrogen peroxide demonstrates broad-spectrum efficacy against viruses, bacteria, yeasts, and bacterial spores. Antibacterial activity is increased in the gaseous phase, where hydrogen peroxide acts as an oxidant by producing hydroxyl free radicals. The hydroxyl radical, being highly reactive, can attack membrane lipids, DNA, and other essential cell components, which increases the cell wall permeability. Hydrogen peroxide's rate of microbiocidal efficacy is greatly increased in the gas vs. condensed (liquid) form.

NOTE 1—Material compatibility information and considerations for one type of sterilization system do not necessarily apply to the other system or any other oxidative-based systems.

NOTE 2—Plasma is a state of matter distinguishable from a solid, liquid, or gas. Gas plasmas are highly ionized gases composed of ions, electrons, and neutral atomic particles that produce a visible glow. For more information, see Annex H of ANSI/AAMI ST58.

3.2.5.4 General material compatibility

Because of the oxidative nature of the hydrogen peroxide sterilization environment, some materials are not recommended for use. The durability of certain plastics might depend on the specific molding conditions (e.g., a medical device component with high residual stress could be less durable than a properly stress-relieved component). Material compatibility information for sterilization by hydrogen peroxide gas might not apply to

sterilization by hydrogen peroxide gas plasma. For hydrogen peroxide gas plasma systems, the low-temperature plasmas used are known to affect only a thin layer, a few atoms in depth, on the surface of nonmetallic materials; they do not affect the bulk properties of these materials.

Table E.1 lists various specific materials and describes their general compatibility with hydrogen peroxide sterilization. The information in this table is not exhaustive, and device manufacturers should use it only as a general guideline for the selection of materials. Before a material is selected, the distributor, vendor or manufacturer should always be consulted for more information.

Table 14 provides general information on the compatibility of various types of materials with hydrogen peroxide and hydrogen peroxide gas plasma.

Table 14—General compatibility of various types of materials with hydrogen peroxide and hydrogen peroxide gas plasma

Material type	General compatibility
Thermoplastics	Most thermosets are hydrogen peroxide gas sterilized with limited effects. Nylons with oxidizable functional groups do not perform well after repeated sterilization.
Thermosets	Most thermoplastics are hydrogen peroxide gas sterilized with limited effects.
Elastomers	Most elastomers are hydrogen peroxide gas sterilized with limited effects.
Adhesives	Adhesives are hydrogen peroxide gas sterilized with varying effects, depending on the composition of the adhesive.
Metals	Most metals are hydrogen peroxide gas sterilized with limited effects. Copper and some copper alloys are not compatible. Colored anodized aluminium might exhibit fading or loss of anodization after repeated exposures.
Glass and ceramics	Most glass and ceramics are hydrogen peroxide gas sterilized with limited effect(s).
Silicone	Most silicones are hydrogen peroxide gas sterilized with limited effects.
Liquids	Liquids should not be processed in cycles designed for reusable medical devices in health care facilities. The surfaces of sealed glass containers or syringes that contain liquids can be sterilized.
Contact surfaces	Sterilization of some contact surfaces is possible. See the manufacturer's instructions for use (IFU) of the individual sterilizer and sterilization cycle for specific claims.
Cellulosics	Cellulosics (e.g., cotton, paper or cardboard, linens, huck towels, gauze sponges, or any item containing wood pulp) are not compatible with hydrogen peroxide
Bioabsorbables	Bioabsorbables are not typically be sterilized with hydrogen peroxide gas because oxidizable components might be affected.

NOTE 1—See Annex E for a more detailed material impacts assessment.

NOTE 2—See Section 5.4.2 for information regarding biocompatibility.

3.2.5.5 Pharmaceuticals and biologics

Some pharmaceuticals and biologics can be sterilized with hydrogen peroxide gas; however, the effects of the oxidizing chemistry on the product must be evaluated. Terminal surface sterilization of sealed, temperature- or radiation-sensitive drug products is more common; applications include wrapped vials, syringes with hyaluronic-acid-based products, syringes with biological drug products, pre-injection mixing devices (combining components), and packaged towel products. With surface sterilization, there is no penetration to the sensitive product, and the hydrogen peroxide does not discolor or leave toxic residues on packaging materials. The use of hydrogen peroxide

gas as a terminal sterilization process for pharmaceuticals or biologics can be limited, because the process might affect compounds in the following ways:

- Creation and accumulation of limiting byproducts
- Oxidation
- Moisture loss (in atmospheric processes only)
- Thermal degradation

3.2.5.6 Packaging

Gaseous hydrogen peroxide is most often used for reprocessing medical devices in health care settings. There are also some applications for terminal sterilization of single-use devices. Packaging materials vary depending on application.

Some characteristics of optimal packaging for hydrogen peroxide are high permeability to hydrogen peroxide gas and air; resistance to pressure changes; stability under deep vacuum and high pressure changes; stability at low temperatures (ambient to 55°C); low absorption of hydrogen peroxide; and ability to desorb any hydrogen peroxide gas retained.

It is important to understand the rate and/or magnitude of the pressure changes associated with the process in relation to the packaging materials' ability to equilibrate. Pressure changes and elevated temperatures could have an impact on the strength of package seals and on internal package equilibrium.

Caution should be taken in the selection of any secondary and tertiary packaging; such packaging should not be composed of any cellulosic material (commonly corrugate).

Table 15—Hydrogen peroxide/hydrogen peroxide gas plasma packaging

Most commonly used	Not commonly used
Polypropylene sterilization wrap	Cellulosic materials (e.g., paper, cotton)
Tyvek®/plastic film pouches	
Reusable sterilization containers and trays	

3.2.6 Nitrogen dioxide sterilization

3.2.6.1 Background

Nitrogen dioxide (NO₂) is an effective gaseous sterilant for health care products. The NO₂ process is conducted at ambient or below-ambient chamber pressures and at room temperature. The key process variables include NO₂ concentration, relative humidity, depth of vacuum, chamber pressure during the exposure dwell, and exposure time.

For information on the development, validation, and routine control of NO₂ sterilization processes, see ANSI/AAMI/ISO 14937.

Typical nitrogen sterilization cycles include the following general steps:

- 1) Evacuation
- 2) Gas injection
- 3) Humidification
- 4) Sterilant exposure
- 5) Post-exposure evacuation
- 6) Repetition of exposure phases and evacuations as required
- 7) Sterilant removal and aeration

3.2.6.2 Typical uses

Nitrogen gas is used for decontamination of manufacturing equipment and sterilization of medical devices. It has been proven to be very useful in the sterilization of a wide range of products, including single-use and reusable devices, surgical kits, hospital equipment, and electronic devices. The method has applications in industrial sterilization (in-house and contract).

3.2.6.3 Process parameters and variability

Nitrogen sterilization process parameters are determined by the specific requirements of the objects being sterilized. The object geometry, material of construction, packaging, and load density must be considered when determining process parameters. In Table 16, the parameters are explained in terms of typical ranges, but are not prescriptive or limiting to those ranges.

Table 16—Nitrogen dioxide sterilization parameters

Parameter	Typical ranges
Sterilant	Typical range of concentration: 3 to 20 mg/L
Temperature	Ambient temperature cycles Typical range of chamber temperatures: 15°C to 30°C
RH	Typical range of relative humidity: 30% to 100% RH Observed relative humidity values might be different than the process control points.
Pressure	Typical pressures: 1 kPa to atmospheric Ambient pressure cycles (with no pressure changes) are possible but not typical. Pressure changes typically occur at a rate of 75 kPa/minute.
Time	Typical cycle length (inclusive of preconditioning and aeration): minutes to hours Typical total NO ₂ exposure time: 10 to 60 minutes Number of exposure phases: 1 to 4 exposures
Mechanism of action	Nitrogen dioxide reactions with microorganisms include oxidation and nitration. NO ₂ is known to react with specific molecular targets, including the nitration of protein tyrosine residues and possibly also the nitration of membrane lipids, reactions with low-molecular-weight antioxidants, and the oxidation of thiol residues. The measurable microbiocidal action is the observation of single-strand DNA breaks in the microorganisms exposed to the NO ₂ process.

NOTE—The sterilization process can be modified to accommodate materials that can be moisture-, temperature-, or gas-concentration-sensitive, although these modifications might affect the speed of lethality of the process and they do have a limit. Typically, when products are being sterilized in a vacuum chamber, the exposure phase, during which NO₂ sterilant is added to the sterilization chamber, can be repeated as needed. During this phase, humidified air and dry air are added to achieve the target cycle parameters.

3.2.6.4 General material compatibility

Table F.1 in Annex F lists various specific materials and describes their general compatibility with NO₂ sterilization. The information in this table is not exhaustive, and device manufacturers should use it only as a general guideline for material selection. Before material is selected, the distributor, vendor, and/or manufacturer should always be consulted for more information.

Table 17 provides general information on the compatibility of various types of materials with NO₂ sterilization.

Table 17—General compatibility of various types of materials with nitrogen dioxide

Material type	General compatibility
Thermoplastics	Most thermoplastics are NO ₂ sterilized with limited effects (e.g., some discoloration could occur, depending on additives in the polymers). Polyacetals, polyamides, and polyurethane are not compatible with the NO ₂ process.
Thermosets	Most thermosets are NO ₂ sterilized with limited effects (e.g., some discoloration could occur, depending on additives in the polymers). Polyurethane is not compatible with the NO ₂ process.
Elastomers	Most elastomers are NO ₂ sterilized with limited effects (e.g., some discoloration could occur, depending on additives in the elastomers).
Adhesives	Most adhesives are NO ₂ sterilized with limited effects (e.g., some minor yellowing).
Metals	Metals used in medical devices are generally compatible with the NO ₂ process. However, specific cycle conditions might be required for certain types of metals. Stainless steel is compatible with the NO ₂ process under all conditions. Other metals, including copper, solder, and gold-plated contacts (because of pinholes in the plating), can be exposed to a reduced-humidity NO ₂ process without corrosion or degradation.
Glass and ceramics	Most glass and ceramics can be NO ₂ sterilized without any erosion or other adverse effects
Silicone	Most silicones are sterilized with limited effects.
Liquids	Liquids are not typically sterilized with NO ₂ .
Contact surfaces	Contact surfaces will not require anti-blocking agents to be NO ₂ sterilized. Surfaces in close contact could hinder flow of the sterilant gas to all surfaces.
Cellulosics	Most cellulosics, including paper used in labels and instructions and cardboard used in shipping cartons, are not compatible NO ₂ sterilization. For this reason, it is recommended that terminal sterilization with NO ₂ take place after products are packaged in the sterile barrier system and before they are placed in cellulosic containers (cartons) for shipping.
Bioabsorbables	Some bioabsorbables (e.g., PLA, PHB, PGA, PLGA, and PCL) can be sterilized with NO ₂ . Caution should be used in the addition of components that are NO ₂ sensitive (e.g., drug-eluting structures).
Additional notes	Chemical reaction between NO ₂ and polymer additives is generally limited to changes in the color of the additives within the polymers. For example, a polymer that has a high level of phenolic antioxidants might turn yellow with long, high-concentration exposure to NO ₂ . Other types of antioxidant additives do not interact with NO ₂ . Typically, such color changes do not alter the polymer, only the additive, so the functional properties of the polymer remain unchanged.

NOTE 1—See Annex F for a more detailed material impacts assessment.

NOTE 2—Refer to Section 5.4 for information regarding biocompatibility.

3.2.6.5 Pharmaceuticals and biologics

Nitrogen dioxide can be used to surface-sterilize the containers and/or packaging systems of pharmaceutical active components. The room-temperature process and low permeability rate of NO₂ minimize damage and contamination of the filled vials, syringes, and cartridges. NO₂ has been successfully used to sterilize some biologics such as collagen and bone products. The use of NO₂ as a terminal sterilization process for pharmaceuticals or biologics can be limited, because the process might affect compounds in the following ways:

- Creation and accumulation of limiting byproducts
- Oxidation
- Hydrolysis

3.2.6.6 Packaging

Product and packaging should be designed to allow for the removal of air and the penetration of sterilant gas.

Consideration should be given to the rate and/or magnitude of the pressure changes in the process in relation to the packaging materials' ability to equilibrate with the process. The NO₂ process is typically used to process products in their primary packaging, not in their secondary and tertiary packaging (commonly corrugate).

Table 18—Nitrogen dioxide packaging

Most commonly used	Not commonly used
Tyvek® pouches	Cellulosic materials (e.g., paper, cotton)
Tyvek®/Mylar® pouches	Nylon
Thermoformed trays with Tyvek® lid	Linen

3.2.7 Peracetic acid vapor sterilization

3.2.7.1 Background

Peracetic acid (PA) vapor sterilization uses a room-temperature vapor composed of three compounds: hydrogen peroxide, acetic acid, and peracetic acid. Peracetic acid is formed by the reaction of acetic acid and hydrogen peroxide; these compounds exist in equilibrium, and their eventual decomposition results in oxygen and water. The phase change of liquid peracetic acid to PA vapor at room temperature provides compatibility with materials that is different from that of liquid peracetic acid. Peracetic acid vapor sterilization has the ability to provide surface sterilization or diffusion through materials.

The PA vapor sterilization process uses a chamber at room temperature (18°C to 30°C), has a wide range of material compatibility, maintains a low level of residual that breaks down into oxygen and water, and provides turnaround times as quickly as the same day. Peracetic acid vapor sterilization can be used to terminally sterilize medical, pharmaceutical, biological, and industrial products.

For information on the development, validation, and routine control of PA vapor sterilization processes, see ANSI/AAMI/ISO 14937.

Typical PA sterilization cycles consist of the following phases:

- 1) Evacuation
- 2) Peracetic acid exposure
- 3) Evacuation/dehumidification
- 4) Vent
- 5) Final vent

3.2.7.2 Typical uses

Peracetic acid vapor sterilization was developed for the sterilization of moisture- or heat-sensitive medical devices. It has proven to be very useful in the sterilization of a wide range of products, including single-use and reusable devices, surgical kits, biologics, combination products, and electronic devices that are moisture- or heat-sensitive and cannot be sterilized by steam sterilization. The method is used within industrial (in-house and contract) facilities.

3.2.7.3 Process parameters and variability

In sterilization with peracetic acid, the process variations and parameters described in Table 19 must be considered.

Table 19—Peracetic acid vapor sterilization parameters

Parameter	Typical ranges
Sterilant	Typical range of concentration: 4 to 20 mg/L. Vapor concentration within a PA vapor sterilization system is controlled by changing the amount of sterilant vaporized during a block. The combined adjustability of pressure, blocks, hold time, and vapor concentration at room temperature allow the PA vapor sterilization system to process a wide range of moisture- and heat-sensitive materials for sterilization or depyrogenation.
Temperature	Ambient temperature cycles. Typical range of chamber temperatures: 18°C to 30°C.
RH	Typical range of relative humidity: ≥16% to <100% RH.
Pressure	Typical range of pressure: 0.13 kPa to atmospheric Vacuum pressures used within the PA vapor system typically range from 1 to 760 torr. Products that are sensitive to deep vacuum may be processed at ambient pressure. When a deep vacuum is required for sterilization, the items to be sterilized must be able to withstand the pressure changes. Some devices have special venting caps to allow pressure equalization between external and internal spaces. Physical damage to the device might occur if it is not capable of withstanding both deep vacuums and the rate of pressure change in a given cycle.
Time	Typical cycle length: 0.5 to 4 hrs, depending on device complexity Typically, no preconditioning or aeration is needed. Typical PA exposure time: 5 to 60 minutes Number of exposure phases: Typically 1 to 6 exposures
Mechanism of action	PA is thought to function by denaturing proteins, disrupting cell wall permeability, and oxidizing sulfhydryl and sulfur bonds in proteins, enzymes, and other metabolites. The PA vapor interacts with numerous cellular constituents, breaking them down and inactivating routine functionality. With the disintegration of the bacterial cell wall, internal components will no longer be contained and are unable to organize. As with other sterilization processes, the efficacy of the process can be diminished by soil challenges and test conditions.

3.2.7.4 General material compatibility

Table G.1 in Annex G lists various specific materials and describes their general compatibility with PA vapor sterilization. The information in this table is not exhaustive, and device manufacturers should use it only as a general guideline for material selection. Before material is selected, the distributor, vendor, and/or manufacturer should always be consulted for more information.

Table 20 provides general information on the compatibility of various types of materials with PA vapor sterilization.

Table 20—General compatibility of various types of materials with peracetic acid vapor

Material type	General compatibility
Thermoplastics	Most thermoplastics are PA vapor sterilized with limited effects.
Thermosets	Most thermosets are PA vapor sterilized with limited effects.
Elastomers	Most elastomers are PA vapor sterilized with limited effects. Multiple cycles of PA vapor processing has been found to reduce material compatibility. Butyl and nitrile have been found to have poor compatibility. Polychloroprene (neoprene) and rubber nitrile have been found to have fair compatibility.
Adhesives	Most adhesives are PA vapor sterilized with limited effects. Repeated exposure to PA vapor processing reduces material compatibility. The use of peroxide-cured epoxy is recommended.
Metals	Most metals are PA vapor sterilized with limited effects. For magnesium, however, corrosion has been observed after a single cycle.
Glass and ceramics	Most glass and ceramics are PA vapor sterilized with limited effects.
Silicone	Most silicones are PA vapor sterilized with limited effects.
Liquids	Saline solution has been found to be compatible (applies to small volumes found in tissue).
Contact surfaces	Compatibility depends on the composition of the surface material.
Cellulosics	Most cellulosics are PA vapor sterilized with limited effects.
Bioabsorbables	Some bioabsorbables (e.g., PLA, PGA, and PLGA) can be sterilized with PA vapor. Caution should be used in the addition of components that are PA vapor sensitive.

NOTE 1—See Annex G for a more detailed material impacts assessment.

NOTE 2—Refer to Section 5.4 for information regarding biocompatibility.

3.2.7.5 Pharmaceuticals and biologics

Peracetic acid vapor sterilization has been successfully used to sterilize pharmaceuticals (e.g., enzyme-based powders and large-molecule pharmaceuticals), combination devices (e.g., drug coatings on medical devices), dual-chamber devices, and the exterior of filled drug containers (e.g., prefilled syringes). Peracetic acid vapor has also been successfully used to sterilize some tissue-based products, such as collagen, proteins, enzymes, and decellularized matrix. The room-temperature PA vapor process can also provide depyrogenation of a wide range of polymers and metals.

The use of PA vapor as a terminal sterilization process for pharmaceuticals and biologics can be limited because the process might affect compounds via oxidation.

3.2.7.6 Packaging

Product and packaging should be designed to allow for the removal of air and the penetration of PA vapor. In some cases, however, non-breathable packaging materials have been successfully used in PA vapor sterilization. Peracetic acid vapor can be driven through non-polar packaging (e.g., polyethylene and polypropylene).

It is important to understand the rate and/or magnitude of the pressure changes associated with the process in relation to the packaging materials' ability to equilibrate. These pressure changes could have an impact on the strength of package seals and on internal package equilibrium.