Technical Information Report

AAMI TIR17: 2017/(R)2020

Compatibility of materials subject to sterilization

AAMI
Advancing Safety in Health Technology

AAMI Technical Information Report

AAMI TIR17:2017/(R)2020
(Revision of AAMI TIR17:2008)

Compatibility of materials subject to sterilization

Approved 11 June 2017 and reaffirmed 23 December 2020 by
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

AAMI Technical Information Report

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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.

Published by

AAMI
901 N. Glebe Road, Suite 300
Arlington, VA 22203

Printed in the United States of America

ISBN 978-1-57020-700-6

Contents

Page

Committee representation

Association for the Advancement of Medical Instrumentation

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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.

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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.

AAMI Technical Information Report **AAMI TIR17:2017/(R)2020**

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: Ssubstance 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 ºC, 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 ≥ 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.

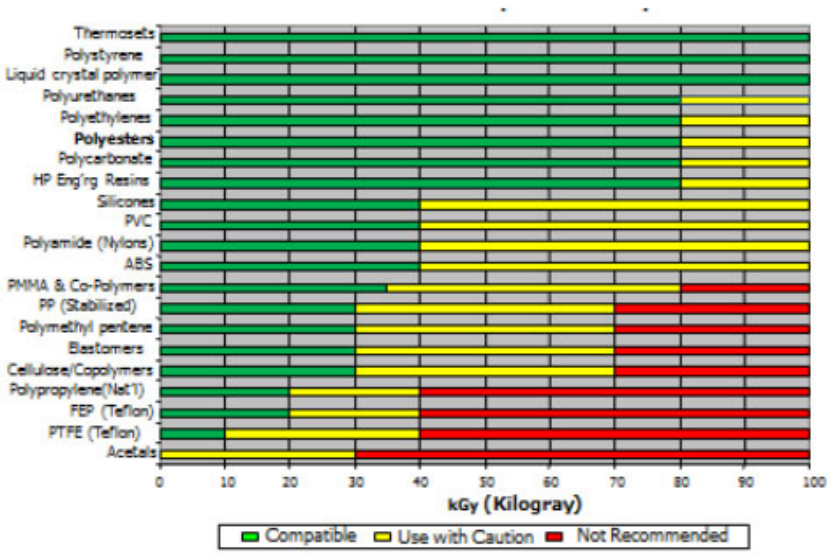


Figure 1—Relative radiation stability of medical polymer "families"

(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_2O-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 O_2 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 homogenously 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 [N_2] and carbon dioxide [CO_2]) 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 N_2 and CO_2. 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 (butEO 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 *entirely* 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 Association2007, 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 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:

a) 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.

b) 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 dissembled. 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:

a) Wrapped items and large load require longer times for adequate heating (because of the need for air or chemical penetration and heat diffusion).

b) Non-aqueous liquid products must be dry heat sterilized in non-permeable packages, such as aluminum foil, glass, and porcelain jars.

c) Non-liquid (solid) products typically need permeable packaging, unless processed by aseptic fill.

d) 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 (NO_2) is an effective gaseous sterilant for health care products. The NO_2 process is conducted at ambient or below-ambient chamber pressures and at room temperature. The key process variables include NO_2 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 NO_2 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 NO_2 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 NO_2 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 NO_2 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 NO_2 minimize damage and contamination of the filled vials, syringes, and cartridges. NO_2 has been successfully used to sterilize some biologics such as collagen and bone products. The use of NO_2 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 NO_2 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 sulfhydral 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.

Table 21—Peracetic acid vapor packaging

Most commonly used	Not commonly used
Tyvek®	Pouch films containing nylon
Low-density polyethylene (LDPE)	Cellulosic materials (e.g. paper, cotton)
High-density polyethylene (HDPE)	
polyethylene terephthalate (PET)	

3.2.8 Liquid peracetic acid sterilization

3.2.8.1 Background

Liquid peracetic acid (LPA), or a combination of hydrogen peroxide and peracetic acid, is used for chemical disinfection and sterilization. The microbiocidal effects and broad-spectrum activity of peracetic acid (also referred to as peroxyacetic acid) at relatively low concentrations have been known since the early 1900s (Freer and Novy, 1902; Block, 2001).

One peracetic acid formulation-based process for liquid chemical sterilization uses chemistry designed for single use in an automated system where sterilization is achieved via contact for 6 minutes at 46ºC to 60ºC (115°F to 140°F). Devices processed in this system are liquid chemically sterilized and rinsed with extensively treated potable water. The typical cycle time is about 23 minutes. The processed load should be used immediately; processor packaging does not allow for terminal sterilization.

For information on the development, validation, and routine control of liquid chemical sterilization processes, see ANSI/AAMI/ISO 14937 and ANSI/AAMI/ISO 14160.

Typical steps in the LPA process include the following:

1) Device placed into dedicated tray
2) Device connected to flow ports (if required)
3) Device exposed to liquid chemical sterilant
4) Device rinsed

3.2.8.2 Typical uses

The liquid chemical sterilization process is used for the chemical “sterilization” of manually cleaned, immersible, reusable critical and semicritical heat-sensitive medical devices, including endoscopes and their accessories. Devices sterilized in processes that incorporate the use of liquid chemical sterilants cannot be labelled as “sterile.” (FDA, 2016)

Liquid peracetic acid at varied concentrations (either alone or with other chemicals) is used for the sterilization of tissue implants, bone implants, and tissue engineering scaffolds (see ANSI/AAMI/ISO 14160). Peracetic acid sterilant is a final step in what are typically multi-step processes. This use is not within the scope of this document.

Liquid peracetic acid is used in sterilant solutions at concentrations of ~500 to 5,000 parts per million (ppm). Some of these solutions have sterilization claims for reusable medical devices, requiring an exposure time of between 2 and 8 hours at specified conditions. The variation in concentration of peracetic acid is the key reason for the differences in exposure time required for sterilization. Differences in formulation also translate to significant differences in material compatibility. Furthermore, the potential for material changes due to prolonged soaking or repeated prolonged soaking must be considered. See 3.2.8.4.

3.2.8.3 Process parameters and variability

In sterilization with peracetic acid, the process variations and parameters described in Table 22 must be considered:

Table 22—Liquid peracetic acid sterilization parameters

Parameter	Typical ranges
Sterilant	Liquid peracetic acid (35%) is diluted within a buffered, specially formulated system to an approximately 0.2% (approximately 2,000 ppm) "use dilution."
Temperature	Product temperatures do not exceed 60°C, with typical temperatures ranging from 46°C to 55°C.
RH	Not applicable for liquid chemical sterilization, as this is a liquid system.
Pressure	The liquid chemical sterilization process occurs at atmospheric pressure.
Time	Sterilant contact time is 6 minutes, within an overall cycle time of 23 minutes.
Mechanism of action	Peracetic acid is an extremely active antimicrobial agent with the hydroxyl radical identified as the lethal species. Peracetic acid has broad-spectrum activity against viruses, bacteria, yeasts, and bacterial spores, even at low temperatures.

3.2.8.4 General material compatibility

Table H.1 in Annex H lists various specific materials and describes their general compatibility with liquid peracetic acid via contact for 6 minutes at 46ºC to 60ºC (115°F to 140°F) in a solution that contains liquid peracetic acid (35%) and hydrogen peroxide (6.5 %), sulfuric acid (1%), acetic acid (40%), tetrasodium EDTA (5%to 10%) and 1H-benzotriazole, sodium salt (5% to 10%), diluted to the approximately 0.2% (approximately 2,000 ppm) peracetic acid "use dilution.". 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.
Devices must be able to be submersed or be designed to withstand submersion (e.g., have a waterproof cap to protect electrical connections).

Table 23 provides general information on the compatibility of various types of materials with liquid peracetic acid.

Table 23—General compatibility of various types of materials with liquid peracetic acid

Material Type	General Compatibility
Thermoplastics	Most thermoplastics are LPA sterilized with limited effects, depending on the grade.
Thermosets	Most thermosets are LPA sterilized with limited effects, depending on the grade.
Elastomers	Most elastomers are LPA sterilized with limited effects, depending on the grade.
Adhesives	Most adhesives are LPA sterilized with limited effects, if compatible with liquid submersion.
Metals	Most metals are LPA sterilized with limited effects. Copper and brass are not compatible.
Glass and ceramics	Most types of glass and ceramics are LPA sterilized with limited effects.
Silicone	Most silicones are LPA sterilized with limited effects.
Liquids	Liquids should not be processed in LPA.
Contact Surfaces	Sterilization of limited contact surfaces is possible.
Cellulosics	Items made of materials that contain cellulose (e.g., cotton, paper, cardboard, wood pulp), such as linens, huck towels, and gauze sponges, are not compatible with LPA.
Bioabsorbables	Oxidizable components could be affected.

NOTE 1—See Annex H for a more detailed material impacts assessment.
NOTE 2—Refer to Section 5.4 for information regarding biocompatibility.

3.2.8.5 Pharmaceuticals and biologics

There are no current commercial applications of LPA for pharmaceuticals and biologics.

3.2.8.6 Packaging

Devices are placed in processor trays or containers within the dedicated system, which controls the process parameters needed to ensure standardized and effective liquid chemical sterilization. Upon successful completion of the liquid chemical sterilization cycle, devices are ready for immediate use.

Table 24—Liquid peracetic acid packaging

Most commonly used	Not commonly used
Dedicated processor trays and containers (for processing only, not for storage)	Sterilization wrap, pouches

3.2.9 Hydrogen peroxide–ozone sterilization

3.2.9.1 Background

Hydrogen peroxide (H_2O_2) and ozone (O_3) are both known as oxidizing agents with strong antimicrobial properties. The hydrogen peroxide–ozone process uses both sterilants, sequentially, under vacuum for terminal sterilization. For information on the development, validation, and routine control of hydrogen peroxide–ozone sterilization processes, see ANSI/AAMI/ISO 14937.

A typical hydrogen peroxide–ozone process cycle includes the following steps:

1) Preconditioning (vacuum)
2) Hydrogen peroxide vaporization and injection
3) Ozone injection and dwell
4) Repetition of the previous three steps
5) Evacuation and ventilation

3.2.9.2 Typical uses

Hydrogen peroxide–ozone sterilization has been used since 2010 for sterilization of medical devices. It has proven to be effective in the sterilization of general instruments, single-channel flexible endoscopes, and rigid and semi-rigid channeled devices, including single-channel and double-channel rigid endoscopes and multi-channeled flexible endoscopes. Hydrogen peroxide–ozone sterilization offers a process compatible with a wide range of materials.

3.2.9.3 Process parameters and variability

In the hydrogen peroxide–ozone process, the vaporized hydrogen peroxide is gradually injected until a predetermined chamber pressure is reached. Ozone is then injected as a mixture of ozone and oxygen gas. In this process, no post-sterilization aeration is required.

The product design should ensure that functionality and safety are not compromised by exposure to the anticipated range of sterilization conditions. The parameters shown in Table 25 are explained in terms of typical ranges, but are not prescriptive or limiting to those ranges.

Table 25—Hydrogen peroxide–ozone sterilization parameters

Parameter	Typical ranges
Sterilant	Composition of the hydrogen peroxide solution used: 50 wt% Hydrogen peroxide concentration in the chamber: 45 to 65 mg/L. The hydrogen peroxide concentration in the chamber could vary significantly. Injected ozone dose: 2 mg/L.
Temperature	Chamber temperature: 41°C ± 3°C Load temperature: 20°C to 26°C
RH	RH could vary significantly.
Pressure	Chamber pressure variation: 1 Torr (0.13 kPa) to atmospheric
Time	Cycle length (inclusive of preconditioning and aeration): ≥46 min. Hydrogen peroxide injection phase: 3.5 to 10 minutes Period of ozone injection and dwell: 6 minutes (hydrogen peroxide remains in the chamber during this phase) Number of exposure phases: 2
Mechanism of Action	The primary sterilant used is H_2O_2, which is a strong oxidizer. The microbiocidal properties of hydrogen peroxide can be attributed to the formation of highly reactive hydroxyl radicals (•OH) as a result of decomposition of hydrogen peroxide molecules. Ozone as the second sterilant, when injected into the chamber, contributes by various mechanisms to the microbiocidal efficacy of the process.

3.2.9.4 General material compatibility

Table I.1 in Annex I lists various specific materials and describes their general compatibility with hydrogen peroxide–ozone 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.

Because of the presence of two oxidizing agents (hydrogen peroxide and ozone), the desirable materials for this process must offer acceptable resistance against oxidative chemistry. Although some polymers (e.g., polyurethane) are not compatible with ozone, they can be safely and repeatedly sterilized using the hydrogen peroxide–ozone process.

Table 26 provides general information on the compatibility of various types of materials with hydrogen peroxide and ozone.

Table 26—General compatibility of various types of materials with hydrogen peroxide and ozone

Material type	General compatibility
Thermoplastics	Most thermoplastics are hydrogen peroxide–ozone sterilized with limited effects.
Thermosets	Most thermosets are hydrogen peroxide–ozone sterilized with limited effects.
Elastomers	Most elastomers are hydrogen peroxide–ozone sterilized with limited effects.
Adhesives	Adhesives are generally compatible with hydrogen peroxide–ozone sterilization, except for those containing large quantities of amines as curing or cross-linking agents.

Material type	General compatibility
Metals	Most metals are hydrogen peroxide–ozone sterilized with limited effects, but the hydrogen peroxide decomposers (e.g., copper and silver) should not be present in large quantities. Colored anodized aluminium might exhibit fading or degradation after repeated exposures.
Glass and ceramics	Most types of glass and ceramics are hydrogen peroxide–ozone sterilized with limited effects, but oxides should not be present in large quantities.
Silicone	Most silicones are hydrogen peroxide–ozone sterilized with limited effects.
Liquids	Liquids cannot be sterilized (because hydrogen peroxide–ozone sterilization is a deep-vacuum process).
Contact surfaces	Sterilization of limited contact surfaces is possible.
Cellulosics	Cellulosics are not compatible and must be avoided.
Bioabsorbables	Oxidizable components might be affected.

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

NOTE 2—See Section 5.4.2 for information regarding biocompatibility.

3.2.9.5 Pharmaceuticals and biologics

There are no current commercial applications of hydrogen peroxide–ozone sterilization for pharmaceuticals and biologics.

3.2.9.6 Packaging

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 conditions; 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 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 27—Hydrogen peroxide–ozone 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	

4 Manufacturing process and design considerations

4.1 General considerations

The functional performance of many polymeric materials can be affected more by processing variables than by the chosen method of sterilization. Reviewing processing issues related to health care product materials will help prevent problems and increase the probability of designing and implementing sterilization-compatible health care products.

Manufacturing process variables such as molding, extrusion, film calendar, subassembly, and product assembly can profoundly affect the subsequent physical performance of a polymer. Like other engineered systems, polymeric molecules tend to fail at the point of greatest cumulative stress. Polymers respond to the combined effect of stresses and environmental exposures. Hence, for success in material qualification, it is important to understand and control all of the variables affecting polymers, such as the following:

- Shrinkage stress
- Residual molding stress
- Processed-in stress
- Applied stress
- Sonic welding
- Rapid crystallization
- Designed-in-loading
- Solvent or chemical attack
- Hydrolysis or inadequate drying
- Ultraviolet radiation
- Temperature
- Regrinding
- Oxidation

These effects are even more noteworthy in conjunction with sterilization processing, because molecules that are already stressed can be more susceptible to sterilization degradation. Guidance in Annexes A through I is, in general, applicable to materials processed at optimum conditions.

4.2 Impact of manufacturing processing vs. impact of sterilization

In selecting a sterilization method, it is important to consider the tradeoff between material stresses and the economics of processing. This tradeoff is especially important for molding, extrusion, and calendar processes. For example, unless other directions are provided in order to comply with component specifications, an injection molding cycle will usually be optimized for maximum output of parts rather than optimization of physical properties. Because the overall cost of a molding cycle is predominantly dictated by the time required for heat removal and for the molten polymer to become a solid, running a cycle with mold and melt temperatures that are lower than the ideal is attractive. Doing so, however, ensures that the quality of the part will be compromised. Such a compromise can be critical in the case of health care products intended for sterilization. Poor processing of materials, with residual stresses, can potentially reduce material performance—regardless of the sterilization method employed.

“Quality” optimized processing parameters, based on quality improvements, often result in reduced overall costs, despite output reduction. Increasing mold temperature, for example, has been shown to improve physical properties, such as impact strength, by a factor of 10 or more (which is significantly greater than any effect on impact strength that results from sterilization processing). The substantial and dominating effects of other material processing variables could explain the inconsistencies in the literature on the sterilization compatibility of some materials. See Figure 2.

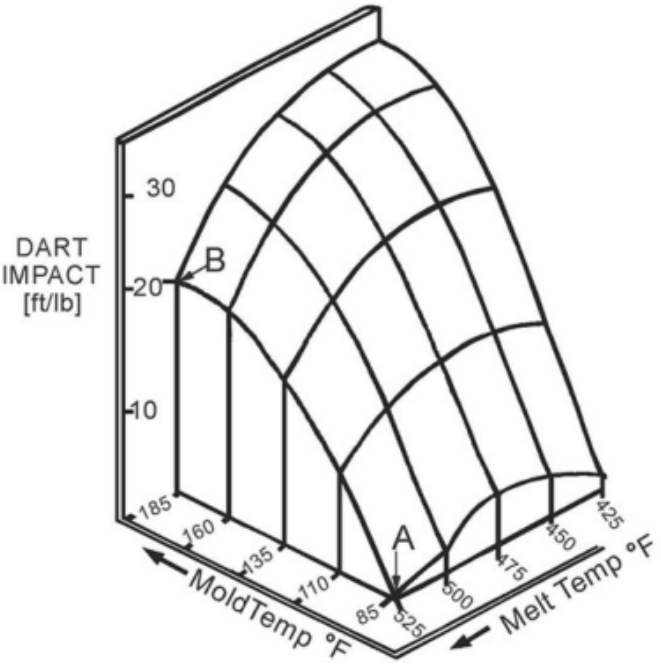


Figure demonstrates that impact strength increases by 20 times in ABS material simply by raising the mold temperature from 85 °F to 185 °F.

Condition A:
Melt 525 °F, mold 85 °F, impact 1 ft-lb
Condition B:
Melt 525 °F, mold 185 °F, impact 20 ft-lb

Figure 2—Impact of process variables on physical properties—Acrylonitrile butadiene styrene (ABS)

4.2.1 Manufacturing processing considerations for injection molding

Mold temperature, melt temperature, and mold filling rate in injection molding can affect a polymer's physical properties (e.g., elongation, impact, and tensile strength) much more than sterilization processing. Therefore, it is important to monitor the control samples carefully, even noting the mold cavity number, which often affects performance. Warm molds and easy filling rates produce ductile parts. Brittle parts are produced in cold molds with tortuous filling and poor venting. Table 28 lists 14 ways to recognize cold-molded parts that are likely to reduce product performance capabilities.

Table 28—How to recognize cold-molded parts

1	Part has no flash.
2	Part has poor gloss or dull finish.
3	Part has no shrink marks.
4	Dimensions are high-tolerance or oversized.
5	There are packing rings (blush) at gate.
6	Warping is reduced.
7	Part is cloudy or shows loss of transparency.
8	Part is crazed when contacting solvent.
9	There is a visible weld line opposite gate.
10	Part cracks when bent or flexed.
11	Part is heavier than standard.
12	Part sticks in cavity but is free on cores.
13	Part distorts when heated.
14	Durometer readings are higher than standard (harder).

4.3 Product design considerations

Product design can have a significant influence on the long-term performance and reliability of a product or component. If a product is poorly designed, the sterilization process can lead to premature part failure caused by increased sensitivity to processing conditions and environmental attack. To compensate for the effects of all the stresses that lead to losses in physical properties, appropriate design guidelines should be incorporated, as indicated in the following paragraphs. For each polymer, the material suppliers' design guidelines, which might be specific to the polymer's unique morphology and chemistry, should be followed. Such guidelines can make the polymer less susceptible to various processing and environmental stresses.

Products intended to be sterilized by gas or vapor should be designed so that the vapor or heated water can access the areas to be sterilized. In some cases, as in the case of steam sterilization of stoppered bottles or vials, the closures must be pre-wetted or treated to contain a minimum moisture content, so as to facilitate sterilization (e.g., the moisture content of bottle stoppers must be controlled to facilitate heat transfer and to avoid dry heat conditions). Likewise, the packaging must be designed to facilitate the transfer of the sterilant to the products and to withstand processing conditions.

In terms of device construction compatibility, it is important to recognize that product presentation might affect the chosen sterilization method's efficiency. For example, in steam or EO sterilization of wrapped items, products of large mass and loads that are large or dense might require longer times for adequate heating, moisture penetration, and heat diffusion. Changes in sterilization conditions might negatively affect the materials and device performance.

For injection molding, the following guidelines should be used:

a) Avoid thick-to-thin transitions.

b) Incorporate generous radii everywhere.

c) Avoid interference fits and long-term creep loading exceeding 20% of yield strength.

d) Design molds for fast and easy filling, with gates sized and located to minimize material flow pressures and paths.

e) Design the part for easy ejection to minimize ejection forces and molded-in stresses.

Figure 3 illustrates guidelines for molding design.

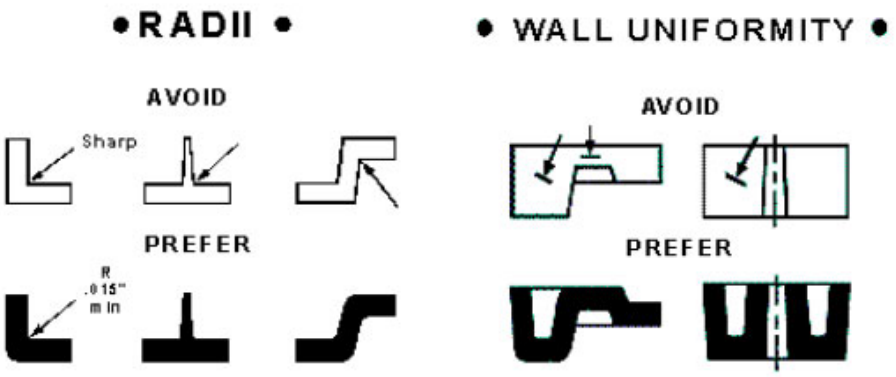


Figure 3—Molding design guidelines

An appropriate failure or reliability analysis should be performed to ensure that critical failure modes are understood and addressed appropriately. For critical components, functional safety factors should be established to apply after all manufacturing, environmental, and sterilization processing is complete and the components have been aged (Stubstad and Hemmerich, 1994).

5 Material testing

5.1 General considerations

The second stage of the qualification process is the testing of sterilization materials for product functionality and biocompatibility. Tests included should evaluate specific properties essential to the product's intended function. Material compatibility derived from reference information alone is inadequate for determining the proper function and performance of the material or product.

When performing the qualification of a material or using data from such qualification tests, one should be aware that some commonly used generic material names actually represent a wide family of chemical compounds. This is especially true of elastomers or adhesives, for which compatibility will be affected by the use of additives, fillers, curing agents, and different curing schedules. These variations in chemical composition can widely change the compatibility of two compounds represented by the same generic name (e.g., ethylene propylene diene monomer [EPDM], epoxy).

5.2 Definition of requirements for product functionality

Before testing is initiated, the functional product requirements should be determined and specified. Material qualification tests should challenge the effect of sterilization on the functional requirements of the product, the dominant or critical failure modes, or both. During testing and as part of the design process, the potential failure modes should be identified, through a documented risk analysis or reliability plan (see ANSI/AAMI/ISO 14971), failure mode and effects analysis (FMEA), or another tool. This plan should consider field experience and complaint files on related products, product design specifications, and common product use. Another valuable method of identifying potential failure modes is to challenge samples to failure. For example, in radiation sterilization, a product is exposed to radiation overdosing (e.g., 100 kGy), and then the product's failure modes are investigated. It is important to identify critical failure modes before beginning shelf-life testing. Without this knowledge, aging studies might not be meaningful or efficient.

5.3 Definition of worst-case sterilization processing conditions

5.3.1 General considerations

Worst-case sterilization processing conditions should be established and used to qualify materials and products for function and safety. Worst-case conditions are ones that are not expected to be exceeded during routine sterilization processing. Such conditions are different for each sterilization process, but are those that are determined to have an effect on the material or product. These conditions are as follows:

- Dose
- Temperature
- Humidity
- Pressure (change rate and/or level)
- Time
- Sterilant concentration

Other factors that must be considered are processing variability and the number of times the product might be sterilized.

5.3.2 Considerations for processing conditions unique to radiation sterilization

The major concern for radiation processing is the maximum acceptable dose. Figure 4 displays the concept of a qualification dose equal to or exceeding the product's maximum dose specification. Figure 5 provides an example of a target qualification dose.

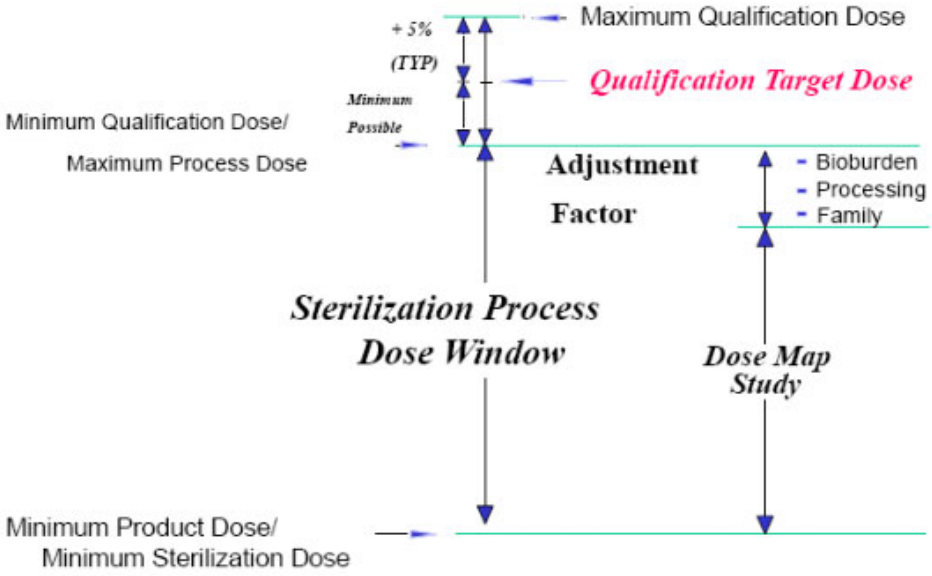


Figure 4—Concept of a qualification dose

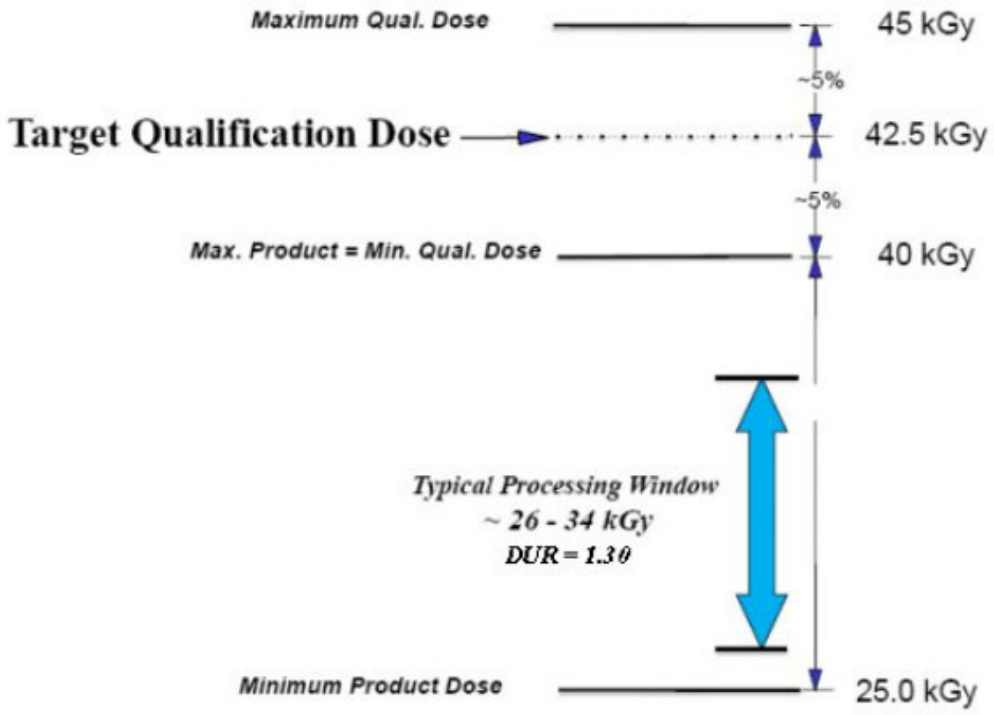


Figure 5—Example of a target qualification dose

Material qualification performed at a low dose rate can reveal greater degradation (e.g., embrittlement) than at a high dose rate, 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). Conversely, a material formerly qualified at a high dose rate can require more substantial qualification in the low-dose-rate application. 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).

5.4 Product functionality testing

The factors listed below relate to device and package integrity testing and should be considered when defining challenge tests and acceptable criteria for a given sterilization method:

a) Tests should be used that specifically challenge the dominant or critical failure modes that have been identified (see 5.2). See the ANSI/AAMI/ISO 11607 series for package integrity challenge tests and validation guidance. See Table 29 for a list of selected standard test methods that can apply to product functionality testing.

NOTE—It is necessary to design tests to challenge the specific failure mode of the product in a given application.

b) Whenever possible, tests should be designed to yield variable data rather than attribute data. Variable data are required to iterate an aging factor (AF) or to use the most advanced methods for estimating shelf life. Zero-failure test results should be avoided when possible, because they diminish understanding of ultimate product performance and failure modes.

c) Test units should consist of products constructed of the same or equivalent components or subassemblies and manufactured by the same or equivalent manufacturing processes as those used for routine production. Variability in raw materials, manufacturing processes, and storage conditions should be addressed during qualification. The test units should be finished devices in the final package. Subassemblies and even specially prepared test samples are satisfactory in certain cases; however, justification for their use should be documented.

d) Acceptance criteria should be defined for all tests. The criteria chosen should reflect customers' essential functional or safety requirements according to design specifications, rather than arbitrary levels that restrain the validation process unnecessarily. The criteria should also be a function of the variability and criticality of the parameter being tested. For devices that can be reprocessed, acceptable limits of reuse should be defined, setting the maximum number of reuses.

e) A sufficient number of product samples should be selected, so that the acceptance criteria can be met in a statistically valid manner. (See ISO/TR 8550-1.)

f) A written test protocol should be developed, specifying the accelerated aging conditions (e.g., temperature, humidity, heat cycling), transportation simulation considerations, time intervals, sample sizes, and specific tests and acceptance criteria to be undertaken at each test time interval. Thermal cycling is particularly valuable in assessing designs that involve differentials in expansion coefficients, especially with adhesive bonding. Relatively large samples might be required, and proper resource planning must be executed to ensure adequate accelerated aging oven space, ambient storage, human resources, and test equipment. Adequate controls should be designed into the protocol (e.g., using one batch for all samples or randomizing samples) so that appropriate comparisons can be made between time intervals.

g) Samples should be manufactured and processed as specified in the protocol.

h) Aging should be initiated after most sterilization byproducts and residuals have decayed or dissipated. Depending on the sterilization process, this can take hours (in the case of hydrogen peroxide, for example) to 48 hours (in the case of radiation processing). Zero-time samples and controls are then tested, with samples from the aged and control groups removed and tested at the appropriate times in accordance with the protocol.

NOTE—Degradation reaction rates during the first 48 hours after sterilization are typically much higher than rates following this initial period. Indeed, for many materials, degradation induced by sterilization processing is largely complete during this initial period. The time frame for high reaction rates depends on the characteristics of the material under investigation and the sterilization process.

i) Product test results should be evaluated with appropriate statistical methods to determine whether the product meets the acceptance criteria for each test interval.

Table 29—Physical and functional test methods for evaluation of plastic material

Test method	Test reference
Tests for embrittlement	
1. Tensile properties	
a) Tensile strength	ASTM D638, ISO 527 series, ASTM D412, ASTM D5034, ASTM D5035
b) Ultimate elongation	
c) Modulus of elasticity	
d) Work	ISO 527 series
e) Package seal strength	ASTM F88
2. Flexural properties	
a) Flange bending test	Williams et al. (1978)
b) Flexbar test	ISO 178
3. Impact resistance	ASTM D1822
4. Hardness	
a) Shore	ISO 868:2003
b) Rockwell	ASTM D785
5. Compressive strength	ISO 604:2002
6. Burst strength	ASTM F2054
a) For package seal strength	ASTM F2054
7. Tear strength	ASTM D1004, ASTM D5587, ISO 6383-1
8. Seal integrity	
a) Blue dye	ASTM F1929
Tests for discoloration	
1. Yellowness index	ASTM E313-05
2. Optical spectrometry	ASTM D1746

5.5 Material biocompatibility

5.5.1 General considerations

The evaluation of materials and products for biocompatibility is accomplished by material toxicity testing in conjunction with material characterization (see the ANSI/AAMI/ISO 10993 series for detailed information on evaluation of biocompatibility). Material characterization and screening tests for candidate materials can be accomplished early in the design process and might identify potential biosafety issues that could lead to unnecessary redesign expense later in the process. Physiochemical reactions, cytotoxicity, and hemolysis are examples of screening tests that are sensitive, inexpensive, and rapid. Biocompatibility and environmental data from material suppliers are good sources of information for use in evaluating candidate component materials. In addition, many useful databases are available for evaluating candidate materials (MEDLINE, RTECS, and TOXLINE. See the informative references in the bibliography.

In addition, chemical characterization of the materials involved plays an important role in attempts to screen materials by identifying and quantifying the bioavailability and physiochemical constituents of the device. This process includes characterization of the following:

a) The base material (e.g., molecular weight, polydispersity, linear or branched, cross-linked, composition)

b) Additives such as colors, antioxidants, and plasticizers

c) Processing aids that remain as part of the device and are potentially leachable (e.g., internal lubricants)

d) Trace components of toxicological concern (e.g., monomers of known toxicity, heavy metals, transition metal catalysts)

e) Any other questionable biological or toxicological components (e.g., particulates, pyrogens)

5.5.2 Biocompatibility concerns regarding sterilant residuals

For some of the sterilization modalities covered in this TIR, there might be sterilant residuals or byproducts of the sterilization process that can result in biocompatibility issues. See the ANSI/AAMI/ISO 10993 series of documents for detailed information on biocompatibility evaluation, including EO sterilization residuals and leachable substances.

5.6 Packaging considerations

Compatibility with sterilization methods must be considered carefully when selecting device packaging. Packaging components must enable effective sterilization while remaining functional during and after the sterilization process. Although packaging must protect the device during sterilization, shipping, and storage, it must also enable a sterile, functional product that is free of harmful residues. To meet these requirements, packaging must do the following:

a) ***Allow for sterilization**:* Allow passage of sterilant into the packaging so that the sterilant contacts all portions of the device.

b) ***Allow for sterilant residual removal:*** Allow passage of sterilant out of the packaging so that harmful sterilant residuals are not retained by the device.

c) ***Maintain sterility throughout shelf life:*** After sterilization, packaging must maintain the integrity of its sterile barrier system. It is essential to include sterilized product in aging and environmental studies so that any long-term sterilization impact is understood.

In order to ensure that these three critical conditions are met, the following essential packaging properties should be considered:

a) ***Breathability:*** With gas sterilization methods, packaging must allow sterilant gas into the packaging so that it contacts all elements of the device and the device is sterilized. Packaging must also allow sterilant gas out of the packaging so that any sterilant residuals remaining on the product are at safe levels. Although packaging must allow sterilant gas to sufficiently enter and exit, it must also remain impermeable to organisms, maintaining the integrity of the sterile barrier. Because gas sterilization techniques might involve rapid changes in pressure, packaging must be sufficiently breathable to allow for pressure equilibration without undue stress being placed on packaging seals. Overstressed packaging seals can result in compromised sterile barrier integrity.

   Package arrangement should also be considered with respect to breathability. For example, if several devices are placed within a carton, the breathable surface of the individual device package should not be unnecessarily obstructed.

   Packaging does not necessarily need to be breathable for products sterilized via radiation.

b) ***Density:*** The density with which products are packaged (e.g., number of products in a pouch, number of pouches in a shelf carton, number of shelf cartons in a shipper box, number of shipper boxes on a pallet) can affect sterilization and should be taken into account when considering packaging configuration and sterilization methods.

   The density with which products are packaged can affect sterilant penetration into a load. For gas sterilization methods, sterilant gas might require a longer time to penetrate high-density loads than low-density loads, potentially increasing sterilization time. Similarly, density might affect the passage of sterilant gas out of packaging, potentially increasing the aeration time required to eliminate harmful sterilant residuals.

   Density can also affect the temperature, humidity, and sterilant concentration profiles that products experience during sterilization. Temperature profiles throughout the length of a shipper box can vary by several degrees because of heat conduction within the shipper box. This conduction is directly affected by the density of product within the shipper box.

In radiation sterilization, variations in density throughout a load could likely lead to less uniform radiation delivered throughout the device and packaging, potentially resulting in a higher maximum dose and reduced device functionality (see Annex A).

c) ***Material considerations:*** It is important to recognize how packaging material functionality might be affected by sterilization. The compatibility of packaging components with particular sterilization methods (as indicated throughout Annexes A–I) should be considered when selecting a sterilization method.

Examples of sterilization effects on packaging include the following:

- Materials that experience significant degradation (increased brittleness, loss of strength) after radiation sterilization
- Deformation of packaging materials with a glass transition temperature lower than the maximum temperature experienced in sterilization, or materials that might be susceptible to having their glass transition temperature lowered as a result of exposure to high humidity present in some sterilization processes.

NOTE—Users should be aware that liquid chemical sterilant processing systems do not produce a terminally sterilized product in that the final devices emerge wet and unwrapped from the processor. The processed devices should be used immediately or stored in a manner similar to that of high-level-disinfected devices.

6 Accelerated aging programs

6.1 Background

Medical devices are required to meet their specified functional and performance requirements throughout their defined lifetime. One method used to assess shelf life is to age the product under real-time storage conditions for the product's intended shelf life. Real-time aging is the most reliable means of validating the safe and effective performance of a medical device throughout its shelf life, and it remains the benchmark by which an accelerated aging (AA) program is evaluated. However, because product testing should be completed before product release, real-time aging delays the introduction of potentially valuable technology to the market, with a concurrent loss of benefit to the patient. Accelerated aging programs avoid these delays.

Accelerated aging programs systematically addressed in the 1997 version of AAMI TIR17 have been published in conference proceedings (Hemmerich, 1997; Lambert and Tang, 1997, 1998), including background information, application boundaries, and methodical AA protocols (Fixed aging factor [AF] method and Iterative AF method). The methods ranged from conservative, relatively inexpensive protocols to more complex, more aggressive, and more expensive protocols. Accelerated aging program concepts have also been applied to medical device packaging (sterile barrier) materials and published (ANSI/AAMI/ISO TIR16775, ASTM F1980).

In addition, a rigorous delineation of the rationale for responsibly applying the AA methods in the medical device industry has been published (Lambert and Tang, 2000). Empirical data from several industries with aging conditions more severe than those of the medical device industry were explored, and the theoretical foundations for the Q_{10} methodology were fully developed.

6.2 New guidance

The AA programs referred to in 6.1 were initially developed for radiation sterilization or packaging, but apply to all sterilization modalities. The principles are completely transferable across sterilization modalities, although there are, naturally, individual points of guidance specific to either radiation sterilization or packaging materials. Detailed guidance on these programs is readily available to users of all sterilization modalities in the documents referenced in Annex J.

Annex J provides a brief summary of the framework, theoretical foundations, and methods for AA programs that apply to all sterilization modalities. Annex J also provides an example of a creative application of an AA program method (the iterative AF method) to enable a device material technology to get to market and benefit patients by avoiding inappropriate AA program constraints that use a more conservative AA method (the $Q_{10} = 2$, Fixed AF method). It is important to note that the foundational reason for why it is appropriate to iterate AFs with real-time data is that real-time data are the most clinically relevant data; it is appropriate that they be used to inform the choice of AFs. Annex J also provides a comparison of AA programs for medical devices with accelerated stability programs for pharmaceuticals. This comparison is provided in light of the rapid growth of the combination-device market (medical devices incorporating pharmaceutical or biologic materials) and the resulting need for clarity at regulatory points of intersection as these markets grow together.

Annex A
(informative)

Radiation sterilization—Material compatibility fundamentals

Table A.1 lists various 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 the selection of materials. Before a material is selected, the vendor or manufacturer should always be consulted for more information.

NOTE—Table A.1 shows typical radiation resistances of medical polymers in stress-free parts measured at the point where 25 % of the polymer's elongation is lost because of radiation. This circumstance might well be the "best case." If the part being considered has a significant degree of residual stress as a result of manufacture, the dose at which the 25% loss of elongation occurs can be considerably lower.

Table A.1— Material compatibility guidance for radiation sterilization—Specific materials

Radiation sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (< 50 kGy)**	**Comments**	**Resterilization (< 100 kGy)**	**Comments**
Thermoplastics				
Acrylonitril butadiene styrene (ABS)	•••	High-impact grades are not as radiation-resistant as standard impact grades because of the higher butadiene content.	L	
Fluoropolymers				
Polytetrafluoroethyle (PTFE) Perfluoro alkoxy (PFA)	•	When irradiated, PTFE and PFA are significantly damaged. The other fluoropolymers show significantly greater stability. Some (for example, PVDF) are excellent.	NL	
Perchlorotrifluoroethylene (PCTFE)	••• to ••••		L	
Polyvinyl fluoride (PVF)	•••		L	
Polyvinylidene fluoride (PVDF)	••• to ••••		L	
Ethylenetetrafluoro-ethylene (ETFE)	••• to ••••		L	
Fluorinated ethylene propylene (FEP)	••		NL	

Radiation sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (< 50 kGy)**	**Comments**	**Resterilization (< 100 kGy)**	**Comments**
Polyacrylates (e.g., polymethylmethacrylate)	●● to ●●●		NL	
Polyamides (e.g., nylon)	●● to ●●●	Nylon 10, 11, 12, and 6-6 are more stable than 6. Nylon film and fiber are less resistant.	L	Very dependent on design and use requirements.
Polycarbonate (PC)	●●● to ●●●●	Yellows—mechanical properties are not greatly affected; color-corrected radiation formulations are available.	L	
Polyesters, saturated	●● to ●●●	Polybutylene terephthalate is not as radiation-stable as polyethylene terephthalate resins.	L	
Polyethylene (PE), various densities	●●● to ●●●●	High-density polyethylene is not as stable as medium-density polyethylene and low-density.	L	
Polyimides (e.g., polyetherimide)	●●●●		L	
Polyketones (e.g., polyetheretherketone)	●●●●		L	
Polypropylene (PP)				
Natural	● to ●●	Physical properties are greatly reduced when irradiated (e.g., chain scissioning can occur). Radiation-stabilized grades, which are of high molecular weight, copolymerized and alloyed with polyethylene, with additional stabilizers should be used in most radiation applications. Use of electron beam at a high dose rate might reduce oxidative degradation.	NL	
Stabilized	●● to ●●●		NL	

Radiation sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (< 50 kGy)**	**Comments**	**Resterilization (< 100 kGy)**	**Comments**
Polystyrene (PS)	●●●●	Will begin to yellow at >50 kGy.	L	
Polysulfones	●●●●	Natural material is yellowish.	L	
Polyurethane (PU)	●● to ●●●●	Aromatic discolors; polyesters are more stable than esters.	L	
Polyvinylacetates (PVA)	●●●		NL	
Polyvinylchloride (PVC)	●●●	Cross-linking dominates and significant yellow color development occurs at doses >30 kGy). Addition of antioxidants and heat stabilizers to formulations will retard color development. High-molecular-weight organotin stabilizers improve radiation stability: color-corrected radiation formulations are available.	NL	Significant discoloration likely
PVC, plasticized	●●●	Cross-linking (stiffening) dominates.	L	Discoloration likely
Styrene acrylonitrile (SAN)	●●● to ●●●●		L	
Polyglycolic acid (PGA)	U			
Ethylene vinyl acetate (EVA)	U			
Thermosets				
Epoxy	●●●●		L	
Phenolics	●●●●	Includes the addition of mineral fillers.	L	
Polyester, unsaturated	●●●●	Includes the addition of mineral or glass fibers.	L	
Polyimides	●●●●		L	
Polyurethanes	●●●●			
Aliphatic	●●●●		L	
Aromatic	●●● to ●●●●	Darkening can occur. Possible breakdown products could be derived.	L	

Radiation sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (< 50 kGy)**	**Comments**	**Resterilization (< 100 kGy)**	**Comments**
Adhesives				
Acrylic	●● to ●●●●		L	Embrittlement possible.
Epoxy	●●●●		L	
Fluoroepoxy	●●●●		L	
Silicone	●● to ●●●●		L	
Elastomers				
Butyl	●	Friable, sheds particulate, chain scission.	NL	
Ethylene propylene diene monomer (EPDM)	●●● to ●●●●		L	
Natural rubber	●●● to ●●●●		L	
Nitrile	●●● to ●●●●	Discolors.	L	
Polyacrylic	●● to ●●●●		NL	
Polychloroprene (neoprene)	●●●	Discolors; the addition of aromatic plasticizers renders the material more stable to irradiation.	L	
Santoprene thermoplastic vulcanizates (TPV)	U			
Silicone	●● to ●●●	Cross-linking dominates. Platinum-cured silicones are superior to peroxide-cured silicones because their pre-radiation cross-link density is greater. Full cure during manufacture can reduce post-irradiation cross-link effects. Phenyl-methyl silicones are more stable than are methyl silicones.	L	Stiffening due to cross-linking likely.
Styrenic block copolymers (e.g., styrene-butadiene-styrene, styrene-ethylene-butylene-styrene)	●● to ●●●	Butadiene scissions.	L	
Urethane	●●● to ●●●●		L	
Metals				
Aluminum	●●●●		L	

Radiation sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (< 50 kGy)**	**Comments**	**Resterilization (< 100 kGy)**	**Comments**
Brass	●●●●		L	
Copper	●●●●		L	
Gold	●●●●		L	
Magnesium	●●●●		L	
Nickel	●●●●		L	
Nitinol	●●●●		L	
Silver	●●●●		L	
Stainless steel	●●●●		L	
Titanium	●●●●		L	
Ceramics/glasses				
Aluminum oxides	●●●●		L	
Silica	●●●●		L	
Zirconium oxides	●●●●		L	
Other materials				
Bioabsorbables				
Polyglycolides	● to ●●●●		NL	
Polylactides	● to ●●●●		NL	
Poly(lactic-co-glycolic acid) (PLGA) [Class 6 implantable]	U			
Cellulosics				
Cellulose ester	●●	Esters degrade less than other cellulosics.	NL	
Cellulose acetate propionate	●● to ●●●		L	
Cellulose acetate butyrate	●● to ●●●		L	
Cellulose, paper, cardboard	●● to ●●●		L	
Liquid crystal polymer (LCP)	● to ●●●●	Commercial LCPs; natural LCPs are not stable.	L	
Cyclic olefin copolymer (COC)	●● to ●●●			
Zinc ionomer (Surlyn)	●● to ●●●			
Poly(p-xylylene) (Paralene)	●●● to ●●●●			

Radiation sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (< 50 kGy)**	**Comments**	**Resterilization (< 100 kGy)**	**Comments**
Lubricants				
Silicone oils and greases (polydimethylsiloxane [PDMS] fluid)	●● to ●●●●	Tends to cross-link and puddle at higher doses; low-viscosity more stable than high-viscosity (i.e., 12,500 cSt)	NL	
Poly (p-xylylene) polymers (dry)	●● to ●●●●			
Liquid or solid lubricants containing PTFE	●● to ●●●●	PTFE scissions; however, maintains lubricating qualities; stability dependent upon carrier.		

NOTE—Primary sources: International Atomic Energy Agency, NASA/Jet Propulsion Laboratory, and polymer manufacturers' literature.

Annex B
(informative)

Ethylene oxide sterilization—Material compatibility fundamentals

Table B.1 lists various materials and their general compatibility with ethylene oxide 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 vendor or manufacturer should always be consulted for more information.

Table B.1— Material compatibility guidance for ethylene oxide sterilization—Specific materials

Ethylene oxide sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Thermoplastics				
Acrylonitrile butadiene styrene (ABS)	••••		L	Might be some materials property loss after multiple cycles.
Fluoropolymers				
Polytetrafluoroethylene (PTFE)	••••		L	Excellent.
Perfluoro alkoxy (PFA)	••••		L	
Perchlorotrifluoroethylene (PCTFE)	••••		L	
Polyvinyl fluoride (PVF)	••••		L	
Polyvinylidene fluoride (PVDF)	••••		L	
Ethylenetetrafluoro-ethylene (ETFE)	••••		L	
Fluorinated ethylene propylene (FEP)	••••		L	
Polyacetals (e.g., polyoxymethylene)	••••		L	
Polyacrylates (e.g., polymethylmethacrylate)	••		NL	Some loss in tensile properties after multiple cycles.
Polyamides (e.g., nylon)	••••		L	

Ethylene oxide sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Polycarbonate (PC)	●●●●	Some formulations might be subject to stress cracking and some loss of tensile properties after multiple cycles and an extended time after processing.	L	Some formulations might be subject to embrittlement, stress cracking, and some loss of tensile properties after multiple cycles.
Polyesters, saturated	●●●●	Compatible.	L	
Polyethylene (PE), various densities	●●●●	Generally compatible. High-density polyethylene might lose some tensile properties.	L	Generally compatible. High-density polyethylene might lose some tensile properties.
Polyimides (e.g., polyetherimide)	●●●●	Depends on formulation and application. Very thin tubing might present compatibility issues. Bulk structural materials are generally compatible.	L	
Polyketones (e.g., polyetheretherketone)	●●●●	Compatible.	L	
Polypropylene (PP)				
Natural	●●●●	Might be some long-term effect on tensile modulus.	L	Vendor information varies on multiple- cycle compatibility. Tensile losses up to 20% reported.
Stabilized	●●●●		L	

Ethylene oxide sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Polystyrene (PS)	● to ●●●	Some embrittlement and loss of tensile strength for some formulations has been reported.	NL	Generally not recommended for large number of cycles.
Polysulfones	●●●●		L	
Polyurethane (PU)	● to ●●●	Performance depends on formulation, cure conditions, material thickness, and end-use stresses.	L	Performance depends on formulation, cure conditions, material thickness, and end-use stresses.
Polyvinylacetates (PVA)	●		NL	
Polyvinylchloride (PVC)	●●●●	Rigid PVC might have reduced impact resistance after exposure.	L	
PVC, plasticized	●●●●	Medical-grade plasticized tubing might contain significant residual levels until aerated.	L	
Styrene acrylonitrile (SAN)	● to ●●●	Generally acceptable for one cycle, but might embrittle and lose tensile properties after multiple cycles. Might exhibit surface cracking and stress cracking after multiple cycles.	NL	Might embrittle and lose tensile properties after multiple cycles. Might exhibit surface cracking and stress cracking after multiple cycles.
Polyglycolic Acid (PGA)	U			
Polyethylene terephthalate (PET)	U			
Ethylene vinyl acetate (EVA)	U			

Ethylene oxide sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Thermosets				
Epoxy	●●● to ●●●●		L	
Phenolics	●●●		L	
Polyester, unsaturated	●●●●		L	
Polyimides	●●●●		L	
Polyurethanes				
Aliphatic	● to ●●●		L	
Aromatic	● to ●●●		L	
Adhesives				
Acrylic	●●	Some loss in tensile properties reported on multiple cycles with HCFC-124/EO blends. Some crazing could occur.	L	Some loss in tensile properties reported on multiple cycles with HCFC-124/EO blends. Some crazing could occur.
Epoxy	●●● to ●●●●		L	
Fluoroepoxy	U		U	
Silicone	●●●●		L	
Elastomers				
Butyl	●●●●	Butyl is even stable in liquid EO.	L	
Ethylene propylene diene monomer (EPDM)	●●●●	Generally compatible, but changing curing method from peroxide cure to sulfur cure might result in formation of small amounts of polyethylene oxide inside the matrix of the material.	L	

Ethylene oxide sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Natural rubber	●●●		L	Can be limited number of cycles.
Nitrile	●●●●		L	
Polyacrylic	●●		NL	
Polychloroprene (Neoprene)	●●●		L	
Santoprene thermoplastic vulcanizates (TPV)	U			
Silicone	●●●●		L	
Styrenic block copolymers (e.g., styrene-butadiene-styrene, styrene-ethylene-butylene-styrene)	●●● to ●●●●		L	
Urethane	● to ●●●		L	
Metals				
Aluminum	●●●●		L	
Brass	●●●●		L	
Copper	●●●		L	
Gold	●●●●		L	
Magnesium	U		U	
Nickel	●●●●		L	
Nitinol	U			
Silver	●●●●		L	
Stainless steel	●●●●		L	
Titanium	●●●●		L	
Ceramics/glasses				
Aluminum oxides	●●●●		L	
Silica	●●●●		L	
Zirconium oxides	●●●●		L	
Other materials				
Bioabsorbables				
Polyglycolides	●		NL	
Polylactides	●		NL	

Ethylene oxide sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Poly(lactic-co-glycolic acid) (PLGA) [Class 6 implantable]	U			
Cellulosics				
Cellulose ester	••••		L	
Cellulose acetate propionate	••••		L	
Cellulose acetate butyrate	••••		L	
Cellulose, paper, cardboard	••••		L	
Liquid crystal polymer (LCP)	U		U	
Lubricants				
Silicone oils and greases (polydimethylsiloxane [PDMS] fluid)	U			
Poly (p-xylylene) polymers (dry)	U			
Liquid or solid lubricants containing PTFE	U			

Annex C
(informative)

Moist heat sterilization—Material compatibility fundamentals

Table C.1 lists various materials and their general compatibility with moist heat 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 vendor or manufacturer should always be consulted for more information.

Table C.1—Material compatibility guidance for moist heat sterilization—Specific materials

Moist heat sterilization				
	(•) = poor (65°C–104°C) (••) = fair (105°C–120°C) (•••) = good (121°C–127°C) (••••) = excellent (132°C–138°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Thermoplastics				
Acrylonitrile butadiene styrene (ABS)	• to ••	Typically not recommended, depending on grade and filler. Run heat-resistant grade in a low temperature process.	NL	Possibly compatible with very-low-temperature cycles.
Fluoropolymers				
Polytetrafluoroethylene (PTFE)	•••	Compatible at temperatures up to 170°C or higher.	L	Degrades with long-term service.
Perfluoro alkoxy (PFA)	••••	Compatible at working temperatures up to 204°C or higher.	L	Compatible at continuous use temperatures up to 170°C.
Perchlorotrifluoroethylene (PCTFE)	••••	Compatible up to 150°C; in packaging, a moisture barrier.	L	Continuous use temperature <150°C.
Polyvinyl fluoride (PVF)	••• to ••••	Compatible at heat deflection temperatures up to 125°C or 134°C.	NL	Limited use; requires low temperatures.
Polyvinylidene fluoride (PVDF)	••••	Compatible at temperatures up to 150°C depending on grade; some grades might only tolerate temperatures up to 125°C.	L	Multiple sterilization cycles at a maximum operating temperature of 130°C.
Ethylene tetrafluoro-ethylene (ETFE)	••••	Compatible at temperatures up to 150°C.	L	

Moist heat sterilization				
	(•) = poor (65°C–104°C) (••) = fair (105°C–120°C) (•••) = good (121°C–127°C) (••••) = excellent (132°C–138°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Fluorinated ethylene propylene (FEP)	••••	Compatible at temperatures up to 170°C or 200°C.	L	Repeatable.
Polyacetals (e.g., polyoxymethylene)	•• to ••••	Compatible at temperatures up to 121°C or higher; might degas.	L	Can be used in up to 100 cycles at 121°C.
Polyacrylates (e.g., polymethylmethacrylate)	• to ••	Poor to fair compatibility; some high-resistant grades.	NL	
Polyamides (e.g., nylon)	•• to ••••	Poor to excellent, depending on grade, form, formula, and function or fit. Biaxially oriented and cast nylon are autoclavable/ retortable.	NL	Possible under some conditions to resterilize.
Polycarbonate (PC)	•• to ••••	Typically compatible at temperatures up to 121°C, but some grades can be sterilized at 134°C. Some have heat deflection up to 145°C.	NL to L	Some only compatible with a few cycles; others compatible with up to 200 cycles.
Polyesters, saturated	• to •••	Possible to good, depending on type, grade, form, and function. Some polyethylene terephthalate (PET) is acceptable (if metalized). Oriented PET (OPET) is more autoclavable.	L	Polyethylene naphthalate (PEN) is compatible with moist heat. PEN is compatible with temperatures up to 120°C.
Polyethylene (PE), various densities	• to ••••	Low-density polyethylene (LDPE) is poorly compatible. High-density polyethylene (HDPE) is fair to good up to 127°C and good up to 135°C. HDPE softens.	NL	Reinforcement of HDPE is required to improve its temperature compatibility.
Polyimides (e.g., polyetherimide)	•• to ••••	Possible to excellent, depending on grade, form, and function.	L	Polyetherimide withstands up to 4,000 cycles (e.g., 1,000 to 2,500 at 5 min and 134°C).

Moist heat sterilization				
	(•) = poor (65°C–104°C) (••) = fair (105°C–120°C) (•••) = good (121°C–127°C) (••••) = excellent (132°C–138°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Polyketones (e.g., polyetheretherketone)	••••	High temperature resistance.	L	Polyetheretherketone has great heat resistance. Good up to 2,000 hours of steam exposure. Typically, long service.
Polypropylene (PP)		Compatibility depends on grade, form, formula, and function or fit. Typically compatible at temperatures up to 125°C.	L	Heat-resistant grades are required.
Natural	••	Unstabilized PP degrades. Some types can be affected by stress during sterilization.		Unstabilized PP becomes stiffer after sterilization.
Stabilized	•• to •••	Stabilized PP is more heat-resistant.	L	Resterilization is possible.
Polystyrene (PS)	• to ••••	Syndiotatic polystyrene (SPS) and styrene/ polyphenyoxides (PPO) are good to excellent.	L	SPS is compatible with high temperature and up to 750 moist heat sterilization cycles.
Polysulfones	••••	Excellent	L	Compatible with up to 1,500 moist heat sterilization cycles.
Polyurethane (PU)	• to ••	Poor in general, but some grades might be fair. Caution: aromatic PU resin might form toxic 4,4 - methylenedianiline (MDA).	NL	
Polyvinylacetates (PVA)	• to ••	Compatibility depends on form, function, formulation, and copolymerization. For heat-stable PVA, hot-melt adhesives can be used.	U	
Polyvinylchloride (PVC)	• to ••	Rigid PVC possible with some modifiers; heat stabilizers.	NL	

Moist heat sterilization				
	(•) = poor (65°C–104°C) (••) = fair (105°C–120°C) (•••) = good (121°C–127°C) (••••) = excellent (132°C–138°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
PVC, plasticized	• to •••	Plasticized PVC has fair compatibility, depending on form, formulation and function.	NL	
Styrene acrylonitrile (SAN)	• to ••	Not recommended for moist heat sterilization. Poor to fair compatibility, depending on formulation and grade.	NL	
Polyglycolic acid (PGA)	U			
Polyethylene terephthalate (PET)	U			
Ethylene Vinyl Acetate (EVA)	U			
Thermosets				
Epoxy	•• to •••	There are numerous types of unreinforced and reinforced epoxies, and physical properties vary significantly. Heat distortion temperatures up to 243°C in some formulations.	L	
Phenolics	•• to •••	Moist heat sterilization can lead to phenolic degradation and extractables into fluids.	NL	
Polyester, unsaturated	• to •••	There are a variety of unsaturated polyesters (e.g., vinyl esters). Stability is better when cross-linked.	L	Isophthalic acid–based polyester and PE napthalate are highly temperature-resistant, and compatibility is possibly excellent.
Polyimides	••••	Bis maleimides (BMI) and acetylene-terminated polyimide (ACTP) have use-service temperatures of 127°C–232 °C and 316°C.	L	

Moist heat sterilization				
	(•) = poor (65°C–104°C) (••) = fair (105°C–120°C) (•••) = good (121°C–127°C) (••••) = excellent (132°C–138°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Polyurethanes	•• to •••	Typically possible, depending on grade, formulation, and function. There are heat-resistant cross-linked polyurethanes.	NL	
Aliphatic	• to ••	Radiation cross-linking increases its heat resistance.	NL	
Aromatic	• to ••	Thermoset PU resins do not form MDA in polyurethane (aromatic).	NL	
Adhesives				
Acrylic	• to ••	Some can tolerate moist heat sterilization, depending on grade formulation; compatibility is fair. There is an acrylic adhesive film in a tape that is heat-resistant up to 137°C.	NL	
Epoxy	• to ••••	Depending on grade and formulation, deflection temperature from 93°C–260°C.	L	Some can lose retention of initial strength after only 5 cycles.
Fluoroepoxy	••• to ••••	The compatibility of epoxy adhesives depends on cure and formulation.	L	Epoxy adhesives cured with high heat are more heat-resistant than those cured at room temperatures.
Silicone	•• to ••••	Typically good to excellent compatibility, depending on form, formulation, and function.	L	Some have good compatibility for only 6 to 8 cycles.
Elastomers				
Butyl	•• to ••••	Good compatibility, depending on type grade. Resistant to water and heat-resistant up to 120°C.	L	Halobutyl (halogenated polyisobutylene) can withstand multiple sterilization cycles.

Moist heat sterilization				
	(•) = poor (65°C–104°C) (••) = fair (105°C–120°C) (•••) = good (121°C–127°C) (••••) = excellent (132°C–138°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Ethylene propylene diene monomer (EPDM)	••• to ••••	Good compatibility up to 125°C in water and up to 134°C–150 °C in air.	NL	Requires temperatures near 105°C.
Natural rubber	• to •••	Possible to fair compatibility; there are moist heat sterilizable grades. Plastomers enhance thermal stability.	L	Hardens with use. Withstands repeated moist heat sterilization at 121°C for 20 min.
Nitrile	•• to •••	Good resistance to moisture and water; tolerates temperatures up to 120 °C.	L	Requires lower processing conditions, below 132°C.
Polyacrylic	• to ••	Polyacrylate is a heat-resistant rubber. Water resistance can be improved with reduction in heat.	NL	Resistance to water is poor.
Polychloroprene (neoprene)	•• to •••	Fair resistance to moisture at temperatures up to 110°C; intermittent moisture resistance at temperatures up to 121°C.	L	Requires lower processing conditions, below 110°C.
Santoprene thermoplastic vulcanizates (TPV)	U			
Silicone	•• to ••••	Resistant to water, barrier to moisture vapor. Also good low temperature performance.	L	Silicone rubber might become soft and sticky (tacky) after multiple exposures.
Styrenic block copolymers (e.g., styrene-butadiene-styrene, styrene-ethylene-butylene-styrene)	• to ••	Possible to fair compatibility depending on grade, type, form, and formulation.	NL	Possible at temperatures up to 99°C.
Urethane	• to ••	Some grades are heat-resistant, depending on type, form, and formulation. Aliphatic versions are typically compatible, some up to 135°C. Aromatic versions can form MDA.	NL	

Moist heat sterilization				
	(•) = poor (65°C–104°C) (••) = fair (105°C–120°C) (•••) = good (121°C–127°C) (••••) = excellent (132°C–138°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Metals				
Aluminum	••••	Aluminum foil; typically single use with inhibitors.	L	Corrosion might occur unless anodized.
Brass	••••	Used in steam traps.	L	
Copper	•••	No reaction when heated in steam, but surface blackens when heated strongly in air.	L	Copper and brass corrosion inhibitor includes triazole.
Gold	••••	No reaction when heated in air and no reaction when heated in steam.	L	
Magnesium	•••	Magnesium metal is moist heat sterilizable as titanium, but not as magnesium powder.	L	
Nickel	••••	Used in moist heat sterilizers.	L	
Nitinol	U			
Silver	••••	Virtually no reaction when heated in air and no reaction when heated in steam. Moist heat sterilization does not remove activity.	L	
Stainless steel	••••	Varies with grade and content of inhibitors.	L	Chrome: stainless steel pitting and dulling of cutting edges after sterilization cycles.
Titanium	••••	Resists corrosion.	L	Nickel-titanium alloy has improved compatibility. Titanium molybdenum is nickel-free and has good corrosion resistance.
Ceramics/glasses				
Aluminum oxide	••• to ••••	Withstands corrosion better than (anodized) aluminum.	L	

Moist heat sterilization				
	(•) = poor (65°C–104°C) (••) = fair (105°C–120°C) (•••) = good (121°C–127°C) (••••) = excellent (132°C–138°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Silica (SiO_2), glass	••••	Withstands extreme temperatures. Non-toxic.	L	Reusable. Dry heat is better than moist heat for glass.
Zirconium oxide	•• to •••	Compatibility depends on the quality of zirconium, which is regularly tested in a moist heat sterilizer for 5 hours at 134°C, which gives an indication of heat stability.	NL	Steam degrades zirconium ceramic. Resterilization is not recommended.
Other materials				
Bioabsorbables	•	Heat and hydrolysis attack bioabsorbables.		
Polyglycolides (PGA)	• to •••	Limited use of PGA might be acceptable. PGA is likely better than PLA.	NL	
Polylactides (PLA)	• to ••	Limited usage due to moisture sensitivity. Some compatible PLAs have been developed.	NL	
Cellulosics		Poor to excellent, depending on grade, form, function, formulation.		
Cellulose ester	• to ••		NL	
Cellulose acetate propionate	• to ••		NL	
Cellulose acetate butyrate	• to ••	Typically melts below 100°C, but heat-stable grade exists for low temperature steam processing.	NL	
Cellulose, paper, cardboard	• to ••••	Some papers have been used up to 134°C. A variety of materials have been successfully moist heat sterilized (e.g., Kraft, glassine, paper crepe, cellophane, parchment).	NL	Wetness can cause contamination, weakness.

Moist heat sterilization				
	(•) = poor (65°C–104°C) (••) = fair (105°C–120°C) (•••) = good (121°C–127°C) (••••) = excellent (132°C–138°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Liquid crystal polymer (LCP)	••••	Autoclavable/retortable; parts can withstand moist heat temperatures of 135 °C. Might be limited to 1 or 2 runs at 134°C. More tolerant at 121°C.	NL, L	Resterilizable at lower temperatures. Can withstand up to 1,000 hours at 121°C.
Lubricants				
Silicone oils and greases (polydimethylsiloxane [PDMS] fluid)	U			
Poly (p-xylylene) polymers (dry)	U			
Liquid or solid lubricants containing PTFE	U			

Annex D
(informative)

Dry heat sterilization—Material compatibility fundamentals

Table D.1 lists various materials and their general compatibility with dry heat 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 vendor or manufacturer should always be consulted for more information.

NOTE—The addition of heat additive stabilizers and fillers to heat-sensitive polymers can improve their tolerance to dry heat sterilization.

Table D.1— Material compatibility guidance for dry heat sterilization—Specific materials

Dry heat sterilization				
	(•) = poor (66°C–104°C) (••) = fair (105°C–159°C) (•••) = good (160°C–189°C) (••••) = excellent (190°C–199°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Thermoplastics				
Acrylonitrile butadiene styrene (ABS)	• to ••	Possible/poor, depending on grade, filler, function, and formulation; heat-resistant grade for low-temperature process.	NL	Possible at low temperatures.
Fluoropolymers	•• to ••••			
Polytetrafluoroethylene (PTFE)	•• to ••••	Compatible up to 170°C or higher.	L	Grades with long-term service.
Perfluoro alkoxy (PFA)	••••	Working temperatures up to 204°C.	L	Up to 170°C.
Perchlorotrifluoroethylene (PCTFE)	••••	Up to 150°C.	L	Up to 150°C.
Polyvinyl fluoride (PVF)	••• to ••••	Heat deflection temperature up to 125°C–134 °C.	NL	Limited use.
Polyvinylidene fluoride (PVDF)	••••		L	Maximum operating temperature is 130°C.
Ethylene tetrafluoro-ethylene (ETFE)	••••	Up to150°C.	L	
Fluorinated ethylene propylene (FEP)	••••	Up to 170°C or 200°C.	L	
Polyacetals (e.g., polyoxymethylene)	•• to ••••	Up to 121°C or higher; might degas.	L	Up to 100 cycles at 121°C.

Dry heat sterilization				
	(•) = poor (66°C–104°C) (••) = fair (105°C–159°C) (•••) = good (160°C–189°C) (••••) = excellent (190°C–199°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Polyacrylates (e.g., polymethylmethacrylate)	• to ••	Possible to poor; some high-resistant grades up to 108°C, but transition might take place over a range.	NL	
Polyamides (e.g., nylon)	• to ••••	Compatibility depends on type, form, function, and formulation.	NL to L	Possible to resterilize some heat-resistant forms. Aromatic PAs more resistant.
Polycarbonate (PC)	•• to •••	Some grades can be sterilized at 134°C; no stacking.	L	Some only compatible for a few cycles; others to 200 cycles.
Polyesters, saturated	• to ••	Depends on type grade, form, and function. Some good polyethylene terephthalate (PET) films; low temperatures required.	NL	Polyethylene naphthalate (PEN) is better than PET.
Polyethylene (PE), various densities	• to ••	Poor to possible/poor; high-density polyethylene (HDPE) fair. Polyolefin, possibly fair.	NL	Reinforcement of HDPE is required to improve its temperature compatibility.
Polyimides (e.g., polyetherimide)	••• to ••••	Depends on grade, form, and function.	L	Polyetherimide withstands up to 4,000 cycles (e.g., 1000–2500 cycles at 5 min at 134 °C).
Polyketones (e.g., polyetheretherketone)	••••	High temperature resistance.	L	Polyetheretherketone has great heat resistance (up to 20,000 hours of dry heat.)
Polypropylene (PP)	•••	Depends on grade, form, formula, function, and fit.	NL to L	
Natural		Might degrade.	NL	
Stabilized	•• to •••	Can be stabilized through antioxidants. (Avis et al., 1991)	L	No stress.

Dry heat sterilization				
	(•) = poor (66°C–104°C) (••) = fair (105°C–159°C) (•••) = good (160°C–189°C) (••••) = excellent (190°C–199°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Polystyrene (PS)	• to ••••	Standard PS has poor compatibility. Heat-resistant styrene is compatible up to 110°C. Syndiotatic polystyrene (SPS) is excellent and styrene/ polyphenyoxides (PPO) are good.	L	Use SPS.
Polysulfones	••• to ••••	Typically, all types are excellent. However, polyether sulfone (PES) is less resistant.	L	
Polyurethane (PU)	• to ••	Poor, but some grades possible.	NL	
Polyvinylacetates (PVA)	• to ••	Heat-stable PVA with hot-melt adhesives required; compatibility depends on form, formulation, and function.	NL	
Polyvinylchloride (PVC)	• to ••	Rigid PVC is poor, but possible with modifiers and heat stabilizers (e.g., metallic stearates).	NL	
PVC, plasticized	• to ••	Depends on form, formulation, and function. Plasticizers are heat stabilizers.	NL	
Styrene acrylonitrile (SAN)	• to ••	Possible/poor; depends on grade.	NL	
Polyglycolic acid (PGA)				
Polyethylene terephthalate (PET)				
Ethylene vinyl acetate (EVA)				

Dry heat sterilization				
	(•) = poor (66°C–104°C) (••) = fair (105°C–159°C) (•••) = good (160°C–189°C) (••••) = excellent (190°C–199°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Thermosets				
Epoxy	•• to ••••	Good heat-resistant types of epoxies required, but physical properties can vary. Heat distortion temperatures up to 243°C.	L	Some with mechanical strength stable to 204°C. Properties decrease with increased exposure at about 100 hours.
Phenolics	•• to •••	Some compatible up to 150°C.	L	
Polyester, unsaturated	••• to ••••	There are a variety of unsaturated polyesters. Better cross-linked. Some have maximum working temperatures up to 170°C.	L	Isophthalic acid–based polyester has high temperature resistance.
Polyimides	••• to ••••	Bis maleimides (BMI) and acetylene-terminated polyimide (ACTP) have use-service temperatures of 127°C–232°C and 316°C.	L	
Polyurethanes		Typically poor, depending on grade, form, and function. There are heat-resistant cross-linked polyurethanes.	NL	
Aliphatic	• to ••	Cross-linking by radiation increases its resistance.	NL	
Aromatic	• to ••	No MDA, aromatic.	NL	
Adhesives				
Acrylic	• to ••	Depends on grade and formulation. Acrylic adhesive film in a tape is compatible up to 137°C.	NL	
Epoxy	•• to ••••	Depending on grade and formulation, deflection temperature from 93°C to 260°C.	L	Some can lose retention of initial strength after only five cycles.

Dry heat sterilization				
	(•) = poor (66°C–104°C) (••) = fair (105°C–159°C) (•••) = good (160°C–189°C) (••••) = excellent (190°C–199°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Fluoroepoxy	•• to •••	Compatibility of epoxy adhesives depends on cure and formulation.	L	Epoxy adhesives cured with heat are more heat-resistant than those cured at room temperatures.
Silicone	•• to ••••	Typically excellent. Depending on form, formulation, and function—good to excellent.	L	
Elastomers		(Avis et al., 1991; Rogers, 2113)		
Butyl	• to ••••	Resistance to water and heat.	L	
Ethylene propylene diene monomer (EPDM)	•• to •••	Up to 134°C–150 °C in air; others only up to 120°C.	L	Continuous use operation temperature of 105°C.
Natural rubber	• to •••	Poor; some moist heat sterilizable grades; plastomer enhances thermal resistance. To 110°C.	NL	Hardens with use; some discoloration over time.
Nitrile	•• to •••	Tolerates temperatures up to 120 °C.	NL	Lower conditions required: below 110°C.
Polyacrylic	••••	Polyacrylate is a heat-resistant rubber, up to 125°C.	Possible	
Polychloroprene (Neoprene)	•• to •••	Fair resistance to moisture, up to 110°C; intermittent to 121°C possible.	NL	Resterilization is possible at processing temperatures below 110°C.
Santoprene thermoplastic vulcanizates (TPV)	U			
Silicone	•• to ••••	Excellent resistance. Some parts and finished devices might do better at lower temperatures.	L	Silicone rubber might become soft and sticky (tacky).

Dry heat sterilization				
	(•) = poor (66°C–104°C) (••) = fair (105°C–159°C) (•••) = good (160°C–189°C) (••••) = excellent (190°C–199°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Styrenic block copolymers (e.g., styrene-butadiene-styrene, styrene-ethylene-butylene-styrene)	• to •••	Possible, poor, fair, or good, depending on grade, type, form, and formulation.	NL	Possibly compatible at temperatures up to 100°C.
Urethane	• to ••	Some heat-resistant grades, depending on type, form, and formulation. Some compatible up to 135°C.	NL	Compatibility improved with silicone.
Metals				
Aluminum	••••		L	Colorants used in some anodized aluminum might fade (be oxidized) and can become colorless.
Brass	••••	Used in steam traps.	L	
Copper	••••	Surface may blacken when heated strongly in air.	L	Copper and brass corrosion inhibitor includes triazole.
Gold	••••	No reaction when heated in air or steam	L	
Magnesium	••	Magnesium metal.	U	
Nickel	••••	Used in moist heat sterilizers.	L	
Nitinol	U			
Silver	••••	Virtually no reaction when heated in air.	U	
Stainless steel	••••	Varies with grade and content of inhibitors.	L	Chrome/stainless steel pitting and dulling of cutting edges after sterilization cycles.
Titanium	••••	Resists corrosion.	L	Nickel-titanium alloy improved; titanium molybdenum is nickel-free and has good corrosion resistance.

Dry heat sterilization				
	(•) = poor (66°C–104°C) (••) = fair (105°C–159°C) (•••) = good (160°C–189°C) (••••) = excellent (190°C–199°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Ceramics/glasses				
Aluminum oxides	•••	Withstands corrosion more than aluminum.	U	
Silica	••••	Withstands extreme temperatures and is relatively inert.	L	
Zirconium oxides	•• to •••	Depends on the quality of zirconium. Quality is regularly tested in a moist heat sterilizer for 5 hours at 134°C.	L	
Other materials				
Bioabsorbables		Sensitive to heat and hydrolysis attack. A case where normal dry heat cannot sterilize biologic material; however, unusually low vacuum-processing dry heat temperature process might be possible.		
Polyglycolides (PGA)	•• to •••	Cross-linked PGA is resistant.	NL	
Polylactides (PLA)	• to ••	There are improved grades of PLA.	NL	
Poly(lactic-co-glycolic acid) (PLGA) [Class 6 implantable]	U			
Cellulosics				
Cellulose ester	• to ••			
Cellulose acetate propionate	• to ••	Possible.	NL	
Cellulose acetate butyrate	• to ••	Typically distorts below 100°C, but heat-stable. Grades exist for low-temperature processing.	NL	

Dry heat sterilization				
	(•) = poor (66°C–104°C) (••) = fair (105°C–159°C) (•••) = good (160°C–189°C) (••••) = excellent (190°C–199°C)		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Cellulose, paper, cardboard	• to •••	Some papers are stable up to 134°C. A variety of items have been moist heat sterilized (e.g., Kraft, glassine, paper, crepe cellophane parchment, filters).	NL	Wetness could cause contamination, weakness.
Liquid crystal polymer (LCP)	••• to ••••	Parts withstand 135°C, but depending on form up to 340°C. Good to excellent.	L	Some grades stable at continuous service temperatures to 240°C.
Lubricants				
Silicone oils and greases (polydimethylsiloxane [PDMS] fluid)	U			
Poly (p-xylylene) polymers (dry)	U			
Liquid or solid lubricants containing PTFE	U			

Annex E
(informative)

Hydrogen peroxide sterilization—Material qualification fundamentals

Table E.1 lists materials and 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 vendor or manufacturer should always be consulted for more information.

Table E.1— Material compatibility guidance for hydrogen peroxide sterilization—Specific materials

Hydrogen peroxide sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Thermoplastics				
Acrylonitrile butadiene styrene (ABS)	••••		L	No change after >100 cycles.
Fluoropolymers				
Polytetrafluoroethylene (PTFE)	••••		L	No change after >100 cycles.
Perfluoro alkoxy (PFA)	••••		L	No change after >100 cycles.
Perchlorotrifluoro-ethylene (PCTFE)	••••		L	No change after >100 cycles.
Polyvinyl fluoride (PVF)	••••		L	No change after >100 cycles.
Polyvinylidene fluoride (PVDF)	••••		L	No change after >100 cycles.
Ethylenetetrafluoro-ethylene (ETFE)	••••		L	No change after >100 cycles.
Fluorinated ethylene propylene (FEP)	••••		L	No change after >100 cycles.
Polyacetals (e.g., polyoxymethylene)	••••		L	Significant color changes or slight material changes after 10–100 cycles. Grade-dependent.
Polyacrylates (e.g., polymethyl-methacrylate)	••	Grade-dependent.	NL L	Plasma H_2O_2: Significant material changes or crazing after 10–50 cycles. Gaseous H_2O_2: No change after 50 cycles.

Hydrogen peroxide sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Polyamides (e.g., nylon)	●●		L	Dependent on grade: might have no effect or could have severe material degradation after 10–100 cycles.
Polycarbonate (PC)	●●●●		L	No change after >100 cycles.
Polyesters, saturated	●●●●		L	
Polyethylene (PE), various densities	●●●●		L	No change after >100 cycles.
Polyimides (e.g. polyetherimide)	●●●●		L	No change after >100 cycles.
Polyketones (e.g. polyetheretherketone)	●●●●		L	No change after >100 cycles.
Polypropylene (PP)	●●●●		L	No change after >100 cycles.
Natural	U			
Stabilized	U			
Polystyrene (PS)	●●●●		L	No change after >100 cycles.
Polysulfones	●●●●		L	No change after >100 cycles. Grade-dependent
Polyurethane (PU)	●●●		L	Plasma H_2O_2: Some color loss or loss of gloss after 100 cycles. Gaseous H_2O_2: No change after 200 cycles.
Polyvinylacetates (PVA)	●●●●		L	No change after >100 cycles.
Polyvinylchloride (PVC)	●●●●		L	No change after >100 cycles.
PVC, plasticized	●●●●		L	No change after >50 cycles.
Styrene acrylonitrile (SAN)	●●●●		L	No change after >100 cycles.
Polyglycolic acid (PGA)	U			
Polyethylene terephthalate (PET)	U			
Ethylene vinyl acetate (EVA)			L	Slight color change after >50 cycles.
Thermosets				
Epoxy	●●●●	Grade-dependent	U	Grade-dependent

Hydrogen peroxide sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Phenolics	•••	Grade-dependent	U	Grade-dependent
Silicone	••••	Grade-dependent	L	Grade-dependent
Polyester, unsaturated	U		NL	
Polyimides	••••	Grade-dependent	U	Grade-dependent
Polyurethanes		Grade-dependent	U	Grade-dependent
Aliphatic	•••			
Aromatic	•••			
Adhesives				
Epoxy	••••		U	Grade-dependent
Fluoroepoxy	••		U	
Silicone	••		U	
Elastomers				
Butyl	•••		NL	
Ethylene propylene diene monomer (EPDM)	•• to •••		L	
Natural rubber	•••		NL	Might degrade after three cycles.
Nitrile	•••		L	Grade-dependent.
Polyacrylic	••		L	Grade-dependent.
Polychloroprene (neoprene)	••••		L	Severe material degradation after 100 cycles.
Santoprene thermoplastic vulcanizates (TPV)			L	No change after >100 cycles. Grade-dependent.
Silicone	••••		L	No change after >100 cycles.
Styrenic block copolymers (e.g., styrene-butadiene-styrene, styrene-ethylene- butylene-styrene)	••••		L	Some color change or surface changes after 50 cycles.
Urethane	•••		L	Grade-dependent.
Metals				
Aluminum	••••		L	No change after >100 cycles.

Hydrogen peroxide sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Brass	••••		L	No change after >100 cycles.
Copper	•••		L	Limited to small amounts.
Gold	••••		L	Limited to small amounts.
Magnesium	•••		L	Limited to small amounts.
Nickel	•••		L	Limited to small amounts.
Nitinol	U			
Silver	• to •••		L	Limited to small amounts.
Stainless steel	••••		L	No change after >100 cycles.
Titanium	••••		L	No change after >100 cycles.
Ceramics/glasses				
Aluminum oxides	••••		**L**	Limited to small amounts.
Silica	••••		**L**	No change after >100 cycles.
Zirconium oxides	••••		**L**	Limited to small amounts.
Other materials				
Bioabsorbables				
Polyglycolides	• to •••		NL	
Polylactides	• to •••		NL	
Poly(lactic-co-glycolic acid) [PLGA] [Class 6 implantable]	U			
Cellulosics				
Cellulose ester	•		NL	Do not process.
Cellulose acetate propionate	•		NL	Do not process.
Cellulose acetate butyrate	•		NL	Do not process.
Cellulose, paper, cardboard	•		NL	Do not process.
Liquid crystal polymer (LCP)	••••		L	No change after >100 cycles.

Hydrogen peroxide sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Lubricants				
Silicone oils and greases (polydimethylsiloxane [PDMS] fluid)	U			
Poly(p-xylylene) polymers (dry)	U			
Liquid or solid lubricants containing PTFE	U			

NOTE 1—Advanced Sterilization Products provided information for this table based on published (Feldman and Hui, 1997; Hui et al, 1999) and unpublished studies conducted in STERRAD® Sterilization Systems.

NOTE2—STERIS Corporation provided information for this table based on published (McDonnell et al., 2009) and unpublished studies conducted in V-PRO Low Temperature Sterilization Systems and VHP Sterilization and Decontamination Systems.

Annex F
(informative)

Nitrogen dioxide sterilization—Material qualification fundamentals

Table F.1 lists materials and their general compatibility with nitrogen dioxide 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 vendor or manufacturer should always be consulted for more information.

Table F.1—Material compatibility guidance for nitrogen dioxide stability of materials—Specific materials

Nitrogen dioxide sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (>10 cycles)**	**Comments**
Thermoplastics				
Acrylonitrile butadiene styrene (ABS)	●●●●		L	No change after >100 cycles.
Fluoropolymers				
Polytetrafluoroethylene (PTFE)	●●●●		L	No change after >100 cycles.
Perfluoro alkoxy (PFA)	●●●●		L	
Perchlorotrifluoroethylene (PCTFE)	●●●●		L	
Polyvinyl fluoride (PVF)	●●●●		L	
Polyvinylidene fluoride (PVDF)	●●●●		L	
Ethylenetetrafluoro-ethylene (ETFE)	●●●●		L	
Fluorinated ethylene propylene (FEP)	●●●●		L	No change after >100 cycles.
Polyacetals (e.g., polyoxymethylene)	●		NL	Significant material changes after 10–100 cycles.
Polyacrylates (e.g., polymethylmethacrylate)	●●●●		L	
Polyamides (e.g., nylon)	●		NL	Severe material degradation after 10–100 cycles. Grade-dependent.
Polycarbonate (PC)	●●●●		L	No change after >100 cycles.

Nitrogen dioxide sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (>10 cycles)**	**Comments**
Polyesters, saturated	••••		L	
Polyethylene (PE), various densities	••••		L	No change after >100 cycles.
Polyimides (e.g., polyetherimide)	••••		L	No change after >100 cycles.
Polyketones (e.g., polyetheretherketone)	••••		L	No change after >100 cycles.
Polypropylene (PP)	••••		L	No change after >100 cycles.
Natural	••••		L	
Stabilized	••••		L	
Polystyrene (PS)	•• to ••••	Grade-dependent; some discoloration of polymer additives	L	No change after >100 cycles.
Polysulfones	••••		L	Grade-dependent.
Polyurethane (PU)	••		NL	Material degradation after 10–100 cycles. Grade-dependent.
Polyvinylacetates (PVA)	••••		L	No change after >100 cycles.
Polyvinylchloride (PVC)	••••		L	Some color change or surface changes after 50 cycles.
PVC, plasticized	••• to ••••	Grade-dependent; some discoloration of polymer additives	L	Color change, but no other change after >100 cycles.
Styrene acrylonitrile (SAN)	••••		L	
Polyglycolic acid (PGA)	••		NL	
Polyethylene terephthalate (PET)	••••		L	
Ethylene vinyl acetate (EVA)	•		NL	
Thermosets				
Epoxy	••••	Grade-dependent.	L	
Phenolics	•• to •••	Discoloration; grade-dependent.	U	Grade-dependent.
Polyester, unsaturated	•• to •••	Discoloration; grade-dependent.	U	Grade-dependent.

Nitrogen dioxide sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	Single use (1 or 2 cycles)	Comments	Resterilization (>10 cycles)	Comments
Polyimides	••••	Grade-dependent.	L	
Polyurethanes	••		NL	
Aliphatic	•		NL	Material degradation after 10–100 cycles. Grade-dependent.
Aromatic	•		NL	Material degradation after 10–100 cycles. Grade-dependent.
Acrylic	••••		L	
Epoxy	••••		L	
Fluoroepoxy	••••		L	
Silicone	•••		L	
Elastomers				
Butyl	••••		L	Some color change or surface changes might occur.
Ethylene propylene diene monomer (EPDM)	••• to ••••		L	Some color change or surface changes might occur.
Natural rubber	••• to ••••		L	Some color change or surface changes might occur.
Nitrile	••••		L	Grade-dependent.
Polyacrylic	••••		L	Grade-dependent.
Polychloroprene (neoprene)	••••		L	Severe material degradation after 100 cycles.
Santoprene thermoplastic vulcanizates (TPV)	••		NL	
Silicone	••••		L	Some color change or surface changes might occur.
Styrenic block copolymers (e.g., styrene-butadiene-styrene, styrene-ethylene-butylene-styrene)	••••		L	Some color change or surface changes might occur.
Urethane	••		NL	Grade-dependent.

Nitrogen dioxide sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (>10 cycles)**	**Comments**
Metals				
Aluminum	• to ••	Depends on RH; low RH has better compatibility	L	
Brass	•• to •••	Depends on RH; low RH has better compatibility	L	
Copper	•• to •••	Depends on RH; low RH has better compatibility	L	
Gold	••••			
Magnesium	•• to •••	Depends on RH; low RH has better compatibility	L	
Nickel	•• to •••	Depends on RH; low RH has better compatibility	L	
Nitinol	•		NL	
Silver	•• to •••	Depends on RH; low RH has better compatibility	L	
Stainless steel	••••		L	No change after >100 cycles.
Titanium	••••		L	No change after >100 cycles.
Ceramics/glasses				
Aluminum oxides	••••		L	Limited to small amounts.
Silica	••••		L	No change after >100 cycles.
Zirconium oxides	••••		L	Limited to small amounts.
Other materials				
Bioabsorbables				
Polyglycolides	•• to ••••	Discoloration; grade-dependent.	U	
Polylactides	•• to ••••	Discoloration; grade-dependent.	U	
Poly(lactic-co-glycolic acid) (PLGA) [Class 6 implantable]	••	Discoloration; grade-dependent.	NL	

Nitrogen dioxide sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (>10 cycles)**	**Comments**
Cellulosics				
Cellulose ester	••	Discoloration; increased resistance.	NL	Do not process.
Cellulose acetate propionate	••	Discoloration; increased resistance.	NL	Do not process.
Cellulose acetate butyrate	••	Discoloration; increased resistance.	NL	Do not process.
Cellulose, paper, cardboard	••	Depends on RH, low RH has better compatibility, increased resistance.	NL	Do not process.
Liquid crystal polymer (LCP)	••••		L	No change after >100 cycles.
Lubricants				
Silicone oils and greases (polydimethylsiloxane [PDMS] fluid)	••••		L	
Poly (p-xylylene) polymers (dry)	••••		L	
Liquid or solid lubricants containing PTFE	••••		L	

Annex G
(informative)

Peracetic acid (PA) vapor sterilization—Material compatibility fundamentals

Table G.1 lists materials and their general compatibility with a peracetic acid vapor sterilization process. 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 vendor or manufacturer should always be consulted for more information.

Table G.1—Material compatibility guidance for peracetic acid vapor sterilization—Specific materials

Peracetic acid vapor sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Thermoplastics				
Acrylonitrile butadiene styrene (ABS)	••••	No change	L	No change after >10 cycles.
Fluoropolymers	••••	No change	L	No change after > 30 cycles.
Polytetrafluoroethylene (PTFE)	••••	No change	L	No change after >30 cycles.
Perfluoro alkoxy (PFA)	••••	No change	L	No change after >30 cycles.
Perchlorotrifluoroethylene (PCTFE)	••••	No change	L	No change after >10 cycles.
Polyvinyl fluoride (PVF)	••••	No change	L	No change after >30 cycles.
Polyvinylidene fluoride (PVDF)	••••	No change	L	No change after >30 cycles.
Ethylenetetrafluoro-ethylene (ETFE)	••••	No change	L	No change after >10 cycles.
Fluorinated ethylene propylene (FEP)	••••	No change	L	No change after >30 cycles.
Polyacetals (e.g., polyoxymethylene)	••••	No change	L	No change after >30 cycles.
Polyacrylates (e.g., polymethylmethacrylate)	••••	No change	L	No changes in extractables/leachables after 4 cycles.
Polyamides (e.g., nylon)	••••	No change	L	No change after >10 cycles.

Peracetic acid vapor sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Polycarbonate (PC)	●●●●	No change	L	No change after > 30 cycles.
Polyesters, saturated	●●●●	No change	L	No change after > 30 cycles.
Polyethylene (PE), various densities	●●●●	No change	L	No change after > 30 cycles.
Polyimides (e.g., polyetherimide)	●●●●	No change	L	No change after >30 cycles.
Polyketones (e.g., polyetheretherketone)	●●●●	No change	L	No change after >30 cycles.
Polypropylene (PP)	●●●●	No change	L	No change after >30 cycles.
Natural	●●●●	No change	L	No change after >30 cycles.
Stabilized	●●●●	No change	L	No change after >30 cycles.
Polystyrene (PS)	●●●●	No change	L	No change after >10 cycles.
Polysulfones	●●●●	No change	L	No change after >30 cycles.
Polyurethane (PU)	●●●●	No change	L	No change after >10 cycles. Grade-dependent for depyrogenation cycles only.
Polyvinylacetates (PVA)	●●●●	No change	L	No change after >10 cycles.
Polyvinylchloride (PVC)	●●●●	No change	L	No change after >30 cycles.
PVC, plasticized	●●●●	No change	L	No change after >30 cycles.
Styrene acrylonitrile (SAN)	U			
Polyglycolic acid (PGA)	●●●●	No change	L	No change after >10 cycles.
Polyethylene terephthalate (PET)	●●●●	No change	L	No change after >10 cycles.
Ethylene vinyl acetate (EVA)	●●●●	No change	L	No change after >10 cycles.

Peracetic acid vapor sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Thermosets				
Epoxy	U			
Phenolics	••••	No change	L	No change after >10 cycles.
Polyester, unsaturated	••••	No change	L	No change after >10 cycles.
Polyimides (Kapton)	••••	No change	L	No change after >10 cycles.
Polyurethanes	••••	No change	L	No change after >10 cycles.
Aliphatic	U			
Aromatic	U			
Adhesives				
Acrylic	••••	No change	L	No change after > 10 cycles.
Epoxy (non-peroxide cured)	••		U	Recommend the use of peroxide-cured
Fluoroepoxy	•••		L	No change after >30 cycles.
Silicone	••••	No change	L	No change after >30 cycles.
Elastomers				
Butyl	•		NL	
Ethylene propylene diene monomer (EPDM)	••••	No change	L	No change after >30 cycles.
Natural rubber	••••		NL	Might degrade after 10 cycles.
Nitrile	••••	No change	L	No change after >30 cycles.
Polyacrylic	••••	No change	L	No change after >30 cycles.
Polychloroprene (Neoprene)	••		NL	
Santoprene thermoplastic vulcanizates (TPV)	U			
Silicone	••••	No change	L	No change after >30 cycles.

Peracetic acid vapor sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Styrenic block copolymers (e.g., styrene-butadiene-styrene, styrene-ethylene-butylene-styrene)	●●●●	No change	L	No change after > 10 cycles.
Urethane	●●●●	No change	L	No change after > 10 cycles. Grade-dependent for depyrogenation cycles only.
Metals				
Aluminum	●●●●	No change	L	No change after >30 cycles.
Aluminum alloy black anodize	●●●	Slight change	L	After >10 cycles, black anodize color turned silver. No corrosion.
Brass	●●●●	No change	L	No change after >10 cycles.
Copper	●●●●	No change	L	Slightly dull after >10 cycles.
Gold	●●●●	No change	L	No change after >30 cycles.
Magnesium	●●●	Slight color change	NL	Corrosion observed after 5 cycles.
Nickel	●●●●	No change	L	No change after >30 cycles.
Nitinol	●●●●	No change	L	No change after >10 cycles.
Silver	●●●●	No change	L	Slight color change after >10 cycles.
Stainless steel	●●●●	No change	L	No change after >30 cycles.
Titanium	●●●●	No change	L	No change after >30 cycles.
Chromium	●●●●	No change	L	No change after >10 cycles.
Ceramics/glasses				
Aluminum oxides	●●●●	No change	L	No change after >10 cycles.
Silica	●●●●	No change	L	No change after >30 cycles.
Zirconium oxides	●●●●	No change	L	No change after >10 cycles.

Peracetic acid vapor sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) = not likely (L) = likely (U) = unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (> 10 cycles)**	**Comments**
Other materials				
Bioabsorbables	●●●●	No change after >2 cycles.	U	
Polyglycolides	U			
Polylactides	U			
Poly(lactic-co-glycolic acid) (PLGA) [Class 6 implantable]	●●●●	No change	L	No change after >10 cycles.
Acrylic (Acrylate polymer)	●●●●	No change	L	No change after >10 cycles.
Cellulosics	●●●●	No change	L	No change after >10 cycles.
Cellulose ester	U			
Cellulose acetate propionate	U			
Cellulose acetate butyrate	U			
Cellulose, paper, cardboard	U			
Lubricants				
Silicone oils and greases (polydimethylsiloxane [PDMS] fluid)	U			
Poly (p-xylylene) polymers (dry)	U			
Liquid or solid lubricants containing PTFE	U			

NOTE—REVOX Sterilization Solution provided the information in this table based on unpublished studies conducted in a REVOX Sterilization System. All polymer tests used the following measurements: mass, dimensions, and Fourier transform infrared spectroscopy (FTIR) scans. All metals tested used the following measurements: mass, dimensions, and ASTM G31-72 (corrosion test).

Annex H
(informative)

Liquid peracetic acid sterilization—Material compatibility fundamentals

Table H.1 lists materials and their general compatibility with liquid chemical sterilization in an automated system via contact for 6 minutes at 46ºC to 60ºC (115°F to 140°F). The solution containing liquid peracetic acid (35%) with hydrogen peroxide (6.5%), sulfuric acid (1%), acetic acid (40%), tetrasodium EDTA (5% to 10%) and 1H-benzotriazole, sodium salt (5% to 10%) is diluted to an approximately 0.2% (approximately 2,000 ppm) peracetic acid "use dilution." 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 vendor or manufacturer should always be consulted for more information.

NOTE—Table H.1 shows only "Resterilization" information as currently liquid peracetic acid is not used for single use sterilization.

Table H.1—Material compatibility guidance—Specific materials

Liquid peracetic acid sterilization		
	(NL) = not likely (L) = likely (U) = unknown	
Material	**Resterilization (> 10 cycles)**	**Comments**
Thermoplastics		
Acrylonitrile butadiene styrene (ABS)	L	No change after >900 cycles.
ABS – Glass filled	L	No change after 300 cycles
Fluoropolymers		
Polytetrafluoroethylene (PTFE)	L	No change after 300 cycles.
Perfluoro alkoxy (PFA)	L	
Perchlorotrifluoroethylene (PCTFE)	L	
Polyvinyl fluoride (PVF)	L	
Polyvinylidene fluoride (PVDF)	L	
Ethylenetetrafluoro-ethylene (ETFE)	L	
Fluorinated ethylene propylene (FEP)	L	
Polyacetals (e.g., polyoxymethylene)	L	No change after 900 cycles.
Polyacrylates (e.g., polymethylmethacrylate)	L	No change after 100 cycles.
Polyamides (e.g., nylon)	L	Grade-dependent. Slight fading in color after 200 cycles or material degradation after <100 cycles.

Liquid peracetic acid sterilization		
	(NL) = not likely (L) = likely (U) = unknown	
Material	**Resterilization (> 10 cycles)**	**Comments**
Polycarbonate (PC)	L	No change after 300 cycles.
Polyesters, saturated		
Polyethylene (PE), various densities	L	No change after 600 cycles.
Polyimides (e.g., polyetherimide)	L	No changes after 600 cycles.
Polyketones (e.g. PEEK, polyetheretherketone)	L	No change after 600 cycles.
Polypropylene (PP)	L	No change after 900 cycles.
Natural	U	
Stabilized	U	
Polystyrene (PS)		
Polysulfones	L	No change after 600 cycles.
Polyurethane (PU)	L	No change after 300 cycles.
Polyvinylacetates (PVA)	U	
Polyvinylchloride (PVC)	L	No change after 900 cycles.
Chlorinated polyvinyl chloride (CPVC)	L	No change after 600 cycles. Might embrittle after extended use.
PVC, plasticized	L	
Styrene acrylonitrile (SAN)	U	
Polyglycolic acid (PGA)	U	
Polyethylene terephthalate (PET)	U	
Ethylene vinyl acetate (EVA)	L	
Thermosets		
Epoxy	U	Grade-dependent.
Phenolics	U	Grade-dependent.
Polyester, unsaturated	NL	
Polyimides	U	Grade-dependent.
Polyurethanes	U	Grade-dependent.
Aliphatic		
Aromatic		
Adhesives		
Acrylic	NL	

Liquid peracetic acid sterilization		
	(NL) = not likely (L) = likely (U) = unknown	
Material	**Resterilization (> 10 cycles)**	**Comments**
Epoxy	U	Grade-dependent.
Fluoroepoxy	U	
Silicone	U	
Elastomers		
Butyl	U	
Ethylene propylene diene monomer (EPDM)	L	No change after 600 cycles.
Fluoroelastomer (Viton)	L	No change after 900 cycles.
Natural rubber	L	No change after 300 cycles.
Nitrile	U	
Polyacrylic	U	
Polychloroprene (neoprene)	U	
Santoprene thermoplastic vulcanizates (TPV)	U	
Silicone	L	No change after 900 cycles.
Styrenic block copolymers (e.g., styrene-butadiene-styrene, styrene-ethylene-butylene-styrene)	U	
Urethane	U	
Metals		
Aluminum	L	No change after 300 cycles. Colorants used in some anodized aluminum might fade (be oxidized) and can become colorless. This can vary significantly, depending on the anodization process used.
Brass	NL	Degradation can occur in <100 cycles.
Brass, nickel-plated	L	No change after 300 cycles. Nickel plating must be present or degradation of brass can occur in <100 cycles.
Copper	L	
Gold	L	
Magnesium	U	
Nickel	L	No change after 300 cycles.
Nitinol	U	
Silver	U	

Liquid peracetic acid sterilization		
	(NL) = not likely (L) = likely (U) = unknown	
Material	**Resterilization (> 10 cycles)**	**Comments**
Stainless steel	L	No change after 900 cycles.
Titanium	L	No change after 400 cycles.
Ceramics/glasses		
Aluminum oxides	U	
Silica (glass)	L	No change after 300 cycles.
Zirconium oxides	U	
Other materials		
Bioabsorbables		
Polyglycolides	NL	
Polyactides	NL	
Poly(lactic-co-glycolic acid) (PLGA) [Class 6 implantable]	U	
Cellulosics		
Cellulose ester	NL	Do not process.
Cellulose acetate propionate	NL	Do not process.
Cellulose acetate butyrate	NL	Do not process.
Cellulose, paper, cardboard	NL	Do not process.
Liquid crystal polymer (LCP)	U	
Cyclic olefin copolymer (COC)	U	
Zinc ionomer (Surlyn)	U	
Poly(p-xylylene) (Paralene)	U	
Lubricants		
Silicone oils and greases (polydimethylsiloxane [PDMS] fluid)	U	
Poly (p-xylylene) polymers (dry)	U	
Liquid or solid lubricants containing PTFE	U	

NOTE: STERIS Corporation provided information for this table based on published information and unpublished studies conducted in liquid peracetic acid sterilization systems.

Annex I
(informative)

Hydrogen peroxide–ozone sterilization—Material compatibility fundamentals

Table I.1 lists materials and their general compatibility with hydrogen peroxide-ozone 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 vendor or manufacturer should always be consulted for more information.

Table I.1—Material compatibility guidance for hydrogen peroxide–ozone sterilization—Specific materials

Hydrogen peroxide–ozone sterilization				
	(●) = poor (●●) = fair (●●●) = good (●●●●) = excellent		(NL) not likely (L) likely (U) unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (>10 cycles)**	**Comments**
Thermoplastics				
Acrylonitrile butadiene styrene (ABS)	●●●●		L	Some physical changes.
Fluoropolymers				
Polytetrafluoroethylene (PTFE)	●●●●		L	No change after >100 cycles.
Perfluoro alkoxy (PFA)	●●●●		L	
Perchlorotrifluoroethylene (PCTFE)	●●●●		U	
Polyvinyl fluoride (PVF)	●●●●		U	
Polyvinylidene fluoride (PVDF)	●●●●		L	
Ethylenetetrafluoroethylene (ETFE)	●●●●		U	
Fluorinated ethylene propylene (FEP)	●●●●		U	
Polyacetals (e.g., polyoxymethylene)	●●●●		L	Some color or physical changes.
Polyacrylates (e.g., polymethylmethacrylate)	●●●		L	No change after >50 cycles.
Polyamides (e.g., nylon)	●●●		L	Grade dependent.
Polycarbonate (PC)	●●●●		L	No change after >50 cycles.
Polyesters, saturated	●●●●		L	
Polyethylene (PE), various densities	●●●●		L	No change after >100 cycles.

Hydrogen peroxide–ozone sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) not likely (L) likely (U) unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (>10 cycles)**	**Comments**
Polyimides (e.g., polyetherimide)	••••		L	No change after >50 cycles.
Polyketones (e.g., polyetheretherketone)	••••		L	No change after >50 cycles.
Polypropylene (PP)			L	No change after >100 cycles.
Natural	••••			
Stabilized	••••			
Polystyrene (PS)	••••		L	No change after >50 cycles.
Polysulfones	••••		L	Grade-dependent.
Polyurethane (PU)	•••		L	Some loss of gloss might occur after 50–100 cycles. Grade-dependent.
Polyvinylacetates (PVA)	U		U	
Polyvinylchloride (PVC)	••••		L	No change after >100 cycles.
PVC, plasticized	••••		L	
Styrene acrylonitrile (SAN)	U		U	
Polyglycolic acid (PGA)	U			
Polyethylene terephthalate (PET)	U			
Ethylene vinyl acetate (EVA)	U			
Thermosets				
Epoxy	••••	Grade-dependent.	U	Grade-dependent.
Phenolics	•••	Grade-dependent.	U	
Polyester, unsaturated	U		U	
Polyimides	U		U	
Polyurethanes		Grade-dependent.	U	Grade-dependent.
Aliphatic	•••		L	
Aromatic	•••		L	
Adhesives				
Acrylic	U		U	
Epoxy	••••		U	Grade-

Hydrogen peroxide–ozone sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) not likely (L) likely (U) unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (>10 cycles)**	**Comments**
				dependent.
Fluoroepoxy	U		U	
Silicone	•••		U	
Elastomers				
Butyl	•••		NL	
Ethylene propylene diene monomer (EPDM)	U		U	
Natural rubber	••		NL	
Nitrile	•••		L	
Polyacrylic	•••		L	Grade-dependent.
Polychloroprene (Neoprene)	•••		U	
Santoprene thermoplastic vulcanizates (TPV)	U			
Silicone	••••		L	No change after >100 cycles.
Styrenic block copolymers (e.g., styrene-butadienestyrene, styrene-ethylenebutylene-styrene)	U		U	
Urethane	•••		L	
Metals				
Aluminum	••••		L	No change after >100 cycles.
Brass	••••		L	No change after >50 cycles.
Copper	•••		L	Limited quantities.
Gold	•••		L	Limited quantities.
Magnesium	•••		L	Limited quantities.
Nickel	•••		L	Limited quantities.
Nitinol	U			
Silver	••		L	Limited quantities.
Stainless Steel	••••		L	No change after >100 cycles.
Titanium	••••		L	No change after >100 cycles.
Ceramic/glasses				
Aluminum oxides	••••		L	Limited quantities.

Hydrogen peroxide–ozone sterilization				
	(•) = poor (••) = fair (•••) = good (••••) = excellent		(NL) not likely (L) likely (U) unknown	
Material	**Single use (1 or 2 cycles)**	**Comments**	**Resterilization (>10 cycles)**	**Comments**
Silica	••••		L	No change after >100 cycles
Zirconium oxides	••••		L	Limited quantities.
Other materials				
Bioabsorbables	U		U	
Polyglycolides			U	
Polylactides			U	
Poly(lactic-co-glycolic acid) (PLGA) [Class 6 implantable]	U			
Cellulosics			NL	
Cellulose ester	•		NL	
Cellulose acetate propionate	•		NL	
Cellulose acetate butyrate	•		NL	
Cellulose, paper, cardboard	•		NL	
Liquid crystal polymer (LCP)	••••		L	
Lubricants				
Silicone oils and greases (polydimethylsiloxane (PDMS) fluid)	U			
Poly (p-xylylene) polymers (dry)	U			
Liquid or solid lubricants containing PTFE	U			

NOTE—TSO_3 Inc. provided information for this table based on unpublished studies conducted in a STERIZONE® VP4 Sterilizer.

Annex J
(informative)

Accelerated aging programs

J.1 Summary of accelerated aging principles and programs applicable to all sterilization modalities

From the perspective of first principles, the most reliable means of validating the safe and effective performance of a medical device throughout its shelf life is to let the device age on a real-time basis for the duration of its shelf life and then to test its functionality. The downside to this plan is the time required. Life-saving technology might not be brought to market as rapidly as possible because of this constraint. This type of conservative diligence might be necessary if there is no safe alternative. However, for most materials, there are safe and conservative alternatives.

A robust foundation for aging in the medical device industry has been laid through the aging work done to apply polymers in severe environments such as the space, nuclear, and geosynthetic industries. In comparison, typical shelf-life storage conditions in hospitals or device manufacturer warehouses are quite controlled and mild. By far, the most common aging tool used in accelerated aging (AA) programs for medical devices is temperature. An aging factor (AF) is defined to correlate the rate of aging at shelf-life conditions to the rate of aging at an elevated temperature. The most critical aspect of applying a temperature-based AA method is the definition of the AF. A common and conservative AF is based on $Q_{10} = 2$. This AF defines the rate of aging at a temperature elevated 10ºC above shelf-life conditions as two times as fast as aging at shelf-life conditions. The $Q_{10} = 2$ AF is derived from Arrhenius's description of the rates of chemical reactions (Arrhenius, 1889). The derivation and the surrounding assumptions have been described to demonstrate the theoretical foundation of the $Q_{10} = 2$ AF. An overview of the empirical evidence from other more severe industries adds to the confidence of using the $Q_{10} = 2$ relation in a safe and conservative manner in the medical device industry (Lambert and Tang, 2000).

Along with defining an appropriate AF, responsible application of simple temperature-based AA models requires sufficient characterization of the medical device polymers to ensure that the model is being applied appropriately. For example, it would be inappropriate to age a device at a temperature so close to its melting point that it significantly distorts. Also, aging at elevated temperatures that necessitate extreme extrapolation to elevated temperatures is not appropriate unless clear necessity is demonstrated. Hence, maintaining an aging temperature below 60ºC is recommended if information is not available to support moving to higher temperatures. Finally, the need to characterize materials is evident if AF approximations from the literature more aggressive than $Q_{10} = 2$ are being used. To see if the information from the literature applies, it is important to understand how the materials of the device in question compare with the material being reported in the literature in terms of chemical composition, molecular weight, additive loading, and processing history.

NOTE—Current ICH guidance for long-term stability studies specifies 25 ± 2°C at 60 ± 5% RH or 30 ± 2°C at 65 ±5% RH.

A foundational AA model is called the Fixed AF method. This model applies the $Q_{10} = 2$ AF and is both simple and conservative. For example, suppose that a medical device manufacturer uses the $Q_{10} = 2$ model for aging polymeric devices, and the devices are aged at 10ºC higher than typical storage conditions. The devices will simulate aging to their shelf life in half the time required to age at real-time conditions. Numerically, this can be stated as follows:

$$t_{AA} = \frac{RTE}{AF_0} = \frac{RTE}{2}$$

Equation J.1

where t_{AA} = time to age the samples at the elevated temperature

RTE = real-time equivalent, the shelf life being simulated

AF_0 = original AF (in this example, $AF_0 = Q_{10} = 2$)

For other aging temperatures, AF can be calculated from the following:

$$AF_0 = Q_{10}^{\frac{T_{AA} - R_{TT}}{10}}$$

Equation J.2

where T_{AA} = elevated temperature at which devices are aged

T_{RT} = room temperature of device storage conditions

By way of simple illustration, refer back to the previous example. Suppose that the device is aged at 30ºC above shelf-life conditions (e.g., T_{RT} = 20ºC and T_{AA} = 50ºC). In this example, with Q_{10} = 2 still being used, from Equation J.2:

$$AF_0 = 2^{\frac{50-20}{10}} = 2^3 = 8$$

From Equation J.1:

$$t_{AA} = \frac{RTE}{8}$$

Hence, aging at the elevated temperature will take one-eighth the time required for real-time aging.

As in all AA programs, the model must be validated with real-time data. Using the guidelines above, the manufacturer must demonstrate that the device functions acceptably after real-time aging as well as after real-time equivalent (RTE) aging.

The Fixed AF method, with a Q_{10} = 2, is most often quite conservative. Often, a device can be aged more aggressively; that is, the time to age the device to verify a given shelf life might be reduced or the shelf life might be extended for a given elevated-temperature aging time. However, it is the burden of the device manufacturer to validate a more aggressive AF. A method for doing so is the Iterative AF method. In this method, real-time and AA data are collected simultaneously. The data are correlated to gain feedback on the relative rates of aging. If indeed the Q_{10} = 2 is overly conservative, the required data can be collected with this method to iterate the AF to a more realistic value. Subsection J.2 contains an example of creative application of the Iterative AF method to allow a beneficial device material technology to get to market and benefit patients by avoiding inappropriate AA program constraints that use the more conservative Q_{10} = 2 accelerated aging method (i.e., the Fixed AF method).

With even greater expenditure of resources, a manufacturer can use more advanced methods to define an even better estimate of the real AF for a medical device system. One approach is to age the device at multiple elevated temperatures. The benefit of such an investment is the most reliable and aggressive AF possible, which translates to speed to market, extended shelf life, or both. References to several such methods are provided in the bibliography.

Humidity, ultraviolet light, ozone, or other gases can also be used to validate the shelf life of a medical device if the aging process of the materials can be shown to correlate with these environmental factors. It should be noted that

aging can be accelerated when multiple aging processes are involved. One should carefully define the combined effect of the accelerating aging in establishing the protocol for these aging process validations. For example, if the aging process is first-order relative to the concentration of ozone, the combined AF can be as high as 4 when doubling the ozone concentration and elevating the temperature by 10ºC. Manufacturers of combination devices should take special note of humidity as an AF because pharmaceuticals can be quite sensitive to humidity. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has developed guidelines that are recommended for adoption by the regulatory bodies of the European Union, Japan, and the United States. (The guidelines most relevant to this discussion at listed in the bibliography). Accelerated aging of medical devices and accelerated stability of pharmaceuticals are compared in J.3. Also, ASTM F1980 provides guidance on understanding water content vs. relative humidity in addressing humidity as an AF.

J.2 Example: Getting a product to market by applying the Iterative AF method

A device manufacturer has traditionally used the relatively low-resource Fixed AF method to qualify products using the conservative and responsible Q_{10} = 2 assumption to calculate the AF. A 3-year shelf life has been qualified using an aging temperature (T_{AA}) of 55°C, a room temperature (T_{RT}) of 20°C, and a resulting AF of 11.3 (i.e., the manufacturer aged the device for 13.8 weeks to qualify a 3-year shelf-life). Real-time aging was run in parallel.

A new coating is to be applied to the device to address a new patient need. The specification is that over the shelf life of the device, the coating integrity must stay less than 90% of the time at zero value. The new coating failed functional testing after 13.8 weeks at 55°C. The research and development (R&D) team was confident that the bench test used to evaluate the coating was clinically relevant and set at the right level. Several options were available to the manufacturer: for example, reduce the shelf life; see if a reduced T_{AA}, resulting in an extension of the time required for the AA study, would help; redesign the coating; or delay introduction of the coating until real-time data on the coating was available. However, the R&D team had initial real-time data available for the new coating in addition to the aging data at 55°C. The R&D team's observation was that the real-time degradation of coating integrity was slower than that predicted by the AA model. The team decided to determine the actual AF for the coating (i.e., to challenge the Q_{10} = 2 assumption by using the Iterative AF method).

The R&D team began by comparing the rate of coating degradation at room temperature with the degradation rate at the AA temperature (55°C). The team plotted coating degradation vs. real time, both at room temperature and at AA conditions (55°C). See Figure J.1.

Next, team members evaluated the Fixed AF method (using the Q_{10} = 2 assumption). Figure J.2 shows coating degradation vs. real-time aging and real-time equivalent aging (using an AF of 11.3) for room temperature and AA data, respectively. Figure J.3 is the same graph, with the scales changed to clarify the slopes of the lines (i.e., so that the degradation rates are easier to see). It is clear that the fixed AF model with the Q_{10} = 2 assumption is more conservative than real-time aging. This finding indicates that the Iterative AF method might be appropriate. As already noted, it is appropriate to use real-time data to adjust aging models because real-time data are the most clinically relevant data.

The next step of the analysis is to select an AF that fits the real-time data. Results are shown in Figure J.4. A Q_{10} value of 2.5 appears to be a better fit with the real-time data. A statistical review of the uncertainty of the regression was then completed to ensure that the Q_{10} estimate could be claimed with appropriate confidence, and a report was completed and approved to document the process used and conclusions.

NOTE—If the uncertainty were too large, the team would either reduce the AF estimate or collect more real-time data and continue to iterate the AF estimates with the additional data.

Finally, age estimates (RTE) for coating integrity degradation were recalculated using the updated AF. Again using an aging temperature (T_{AA}) of 55°C and a room temperature (T_{RT}) of 20°C, the team found that the resulting AF is 24.7 (i.e., 6.3 weeks of aging data equates to a 3-year shelf life). Degradation data at 6.3 weeks at 55°C was still above the coating specification (>90% of the time at zero value). The conclusion, therefore, is that the new coating is initially qualified for a 3-year shelf life. Real-time testing of the new coating will continue and the estimates of the actual AF will continue to be updated and confirmed.

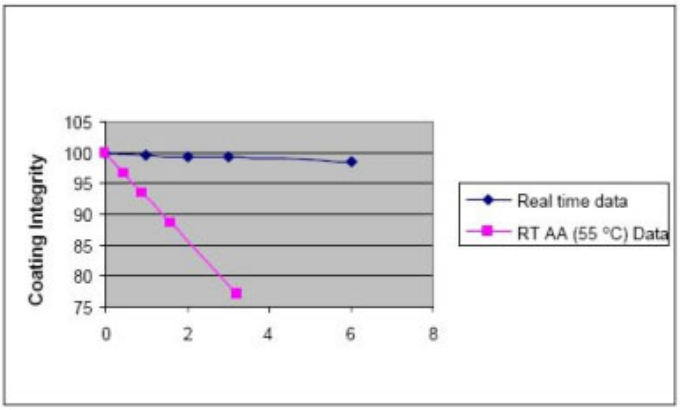


Figure J.1—Comparison of real-time (RT) data at room temperature and at AA conditions (55°C)

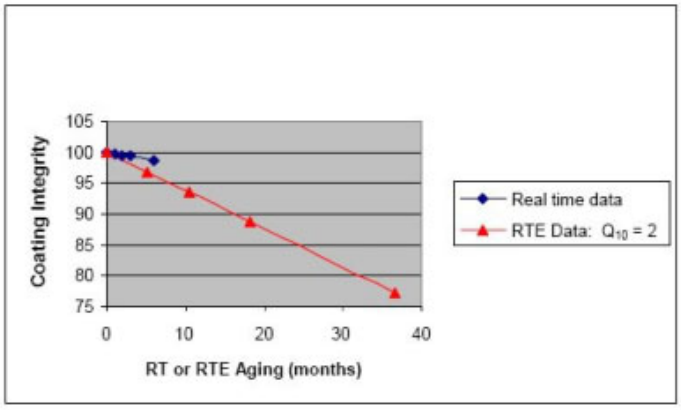
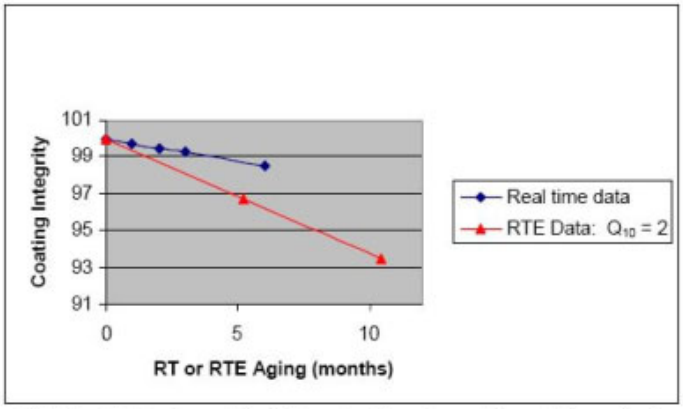


Figure J.2—Comparison of real-time (RT) data at room temperature with real-time equivalent (RTE) data at 55°C using the Q_{10} = 2 assumption



NOTE—Scale changed to better visualize slopes (degradation rates).

Figure J.3—Comparison of real-time (RT) data at room temperature with real-time-equivalent (RTE) data at 55°C using the Q_{10} = 2 assumption

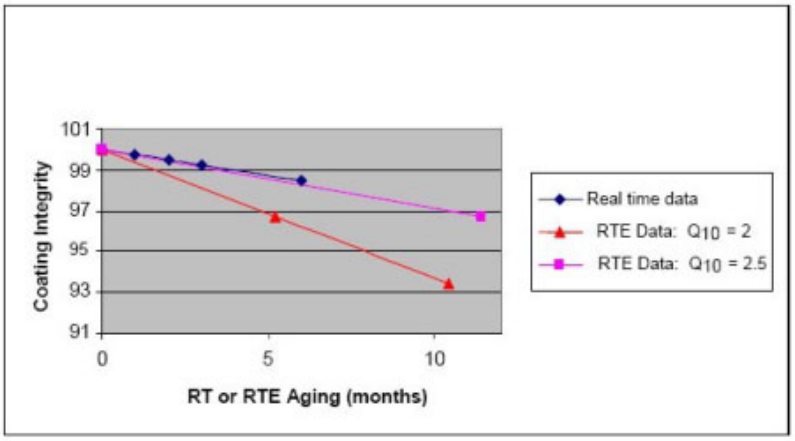


Figure J.4—Comparison of real-time (RT) data at room temperature with real-time-equivalent (RTE) data at 55°C using both the Q_{10} = 2 assumption and a Q_{10} value of 2.5

J.3 Combination device and drug products

For products that might incorporate a combination of medical device materials (such as polymer, metal, glass, and ceramic materials) with bioactive or pharmaceutical drug products, the stability of the substance and the device will need to be considered. One must not only consider the functional and safe performance of a device but also demonstrate the stability of active materials. Common practice within the pharmaceutical industry is to apply ICH guidelines for evaluating drug product stability. These guidelines have a conditioning referred to as "accelerated stability." The concept of accelerated stability differs from accelerated aging. To prevent confusion for manufacturers developing combination devices, this subsection addresses the differences between accelerated stability for pharmaceuticals and AA for devices.

The stability of a combination device and drug substance or drug product can be evaluated according to the ICH guidelines. The ICH provides tripartite guidelines for stability testing of new drug substances and products. The purpose of stability testing is to provide evidence of how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity and light, and to establish a shelf life for the drug product and recommended storage conditions.

The common international guideline for long-term stability studies, ICH Q1A(R2), specifies 25°C ± 2°C at 60% ± 5% relative humidity. Accelerated stability studies are specified at 40°C ± 2°C and at 75% ± 5% relative humidity. Accelerated stability studies also allow the interpretation of data and information on short-term spikes in storage conditions, in addition to the excursions allowed by controlled room temperature (see USP).

For medical devices, AA techniques are typically used to predict the future performance of critical product materials. Most of these theories are based on the work of Arrhenius (1889), which predicts that the aging rate will double for every 10°C that the temperature is raised. Although this model is sufficient as an initial approximation for polymer material performance, it is not adequate for predicting the life of a drug product. Drug degradation does not typically correspond to the average Arrhenius model. In addition, Arrhenius does not consider that humidity can have detrimental effects on drug products and excipients independent of temperature.

For pharmaceuticals, product stability is governed by the ICH Q1A(R2), *Stability testing of new drug substances and products*. This guideline is the basis for generating a stability data package for drug products to be registered in the European Union, Japan, and the United States. AA methods for drugs and devices can be run under the same conditions; however, the ICH guidelines must be followed for drug outputs to comply with pharmaceutical standards. Studies of device aging can use these guidelines if they meet the desired shelf-life time. This is a key point of differentiation between device aging and pharmaceutical aging. Device aging can be run at any responsible temperature, but, as noted previously, pharmaceutical accelerated stability must be run at 40°C and 75 % RH.

For drug outputs, the long-term storage condition is used to establish shelf life. Units must not demonstrate any significant change after long-term storage to establish an acceptable shelf life. A “significant change” is defined as a 5% change in assay from the original value or failure to meet any of the predetermined acceptance criteria.

Accelerated aging testing is conducted to increase the rate of chemical degradation or physical change of the drug substance. Data from these studies will help to predict long-term results on nonaccelerated product and will help to evaluate short-term excursions outside the normal label storage conditions of the product. Device aging criteria should be determined to establish the long-term performance and safety for the product. Although this typically involves AA to expedite development and time to market, consideration must be given to the established guidelines for pharmaceuticals.

The pharmaceutical guidelines represent a most conservative approach for stability and prediction for long-term performance and safety. It can be desirable for manufacturers to conduct device aging studies in parallel with studies at ICH conditions to gather critical process data without affecting time to market. Manufacturers might also wish to establish equivalence between AA and real-time stability so that future product changes can be evaluated rapidly with high confidence that results will be similar after real-time stability.

Annex K
(informative)

Example of a device evaluation process

It is important to recognize that sterilization modality selection is a cross-functional activity requiring specific knowledge of the device materials and functionality, sterilization methods, operations considerations, and regulatory pathways. One cannot choose a method based on its lowest impact on functionality if it cannot achieve product sterility; likewise, you cannot choose a method on the basis of its ability to sterilize the device if it degrades product performance beyond acceptable limits. Additionally, your business might have significant investment in one particular sterilization method for which there is an institutional preference to utilize.

In the design phase of medical device development, sterilization modalities and product impact should be considered in the early stages of material selection and prototype testing. The team should understand all the implications of method selection from its impact on device functionality and the lethality of the sterilization process to business drivers. Unless previous knowledge exists that sterilization methods will not negatively affect device performance, any study evaluating functional attributes (bench studies, animal studies) should incorporate a sterilization exposure.

Consult your own design control system. Although there are many possible approaches to selecting a sterilization process during product development, an example of a device sterilization modality selection process is shown in Figure K.1.

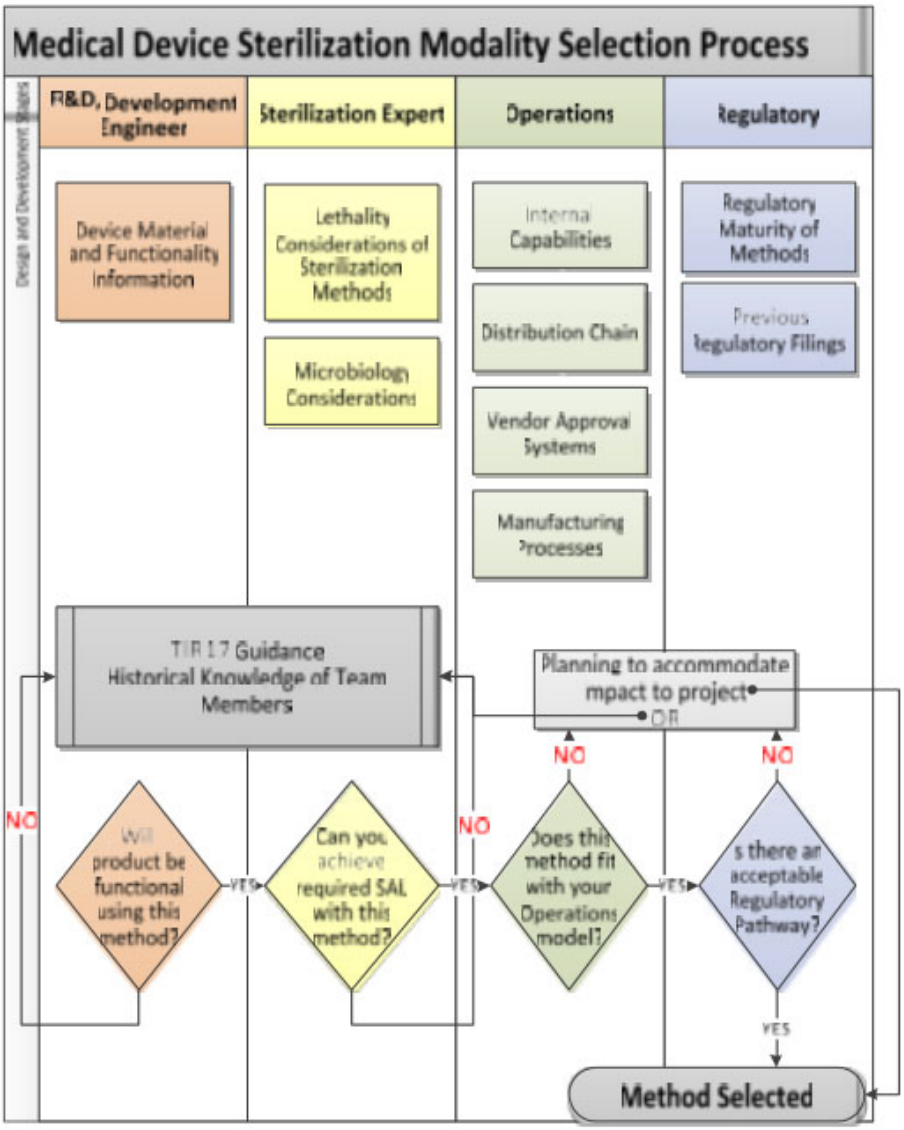


Figure K.1—Example of a device sterilization modality selection process

Annex L
(informative)

Material abbreviations

Table L.1—Material abbreviations

Abbreviation	Material
ABS	Acrylonitrile butadiene styrene
EPDM	Ethylene propylene diene monomer
EVA	Ethylene-vinyl acetate
DEHP	Bis(2-ethylhexyl) phthalate
ETFE	Ethylenetetrafluoroethylene
FEP	Fluorinated ethylene propylene
HDPE	High-density polyethylene
LCP	Liquid crystal polymer
LDPE	Low-density polyethylene
PC	Polycarbonate
PCL	Poly(ε-caprolactone)
PCTFE	Perchlorotrifluoroethylene
PE	Polyethylene
PEEK	Polyether ether ketone
PES	Polyethersulfone
PET	Polyethylene terephthalate
PETG	Polyethylene terephthalate glycol modified
PFA	Perfluoro alkoxy
PGA	Polyglycolic acid (polyglycolide)
PHB	Polyhydroxybutyrate
PLA	Polylactic acid
PLGA	Poly(lactic-*co*-glycolic acid)
PLLA	Poly(L-lactide)
PMMA	Poly(methyl methacrylate)
PP	Polypropylene
PS	Polystyrene
PTFE	Polytetrafluoroethylene
PU	Polyurethane
PVA	Polyvinylacetate
PVDF	Polyvinylidene fluoride
PVC	Polyvinyl chloride
PVF	Polyvinyl fluoride
SAN	Styrene acrylonitrile

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