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Standard Guide for Accelerated Aging of Sterile Medical Device Packages[1]

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ε[1] NOTE—Editorial changes were made throughout in February 2000.

1. Scope

1.1 This guide provides information for developing accelerated aging protocols to rapidly determine the effects, if any, due to the passage of time and environmental effects on the sterile integrity of packages and the physical properties of their component packaging materials.

1.2 Information obtained using this guide may be used to support expiration date claims for medical device packages.

1.3 The accelerated aging guideline addresses the primary medical package in whole and does not address the package and product interaction or compatibility that may be required for new product development. Package and product compatibility and interactions should be addressed as a material analysis process before package design.

1.4 Real-time aging protocols are not addressed in this guide; however, it is essential that real-time aging studies be performed to confirm the accelerated aging test results using the same methods of evaluation.

1.5 Methods used for package process validation, which include the machine process, the effects of the sterilization process, distribution, handling, and shipping events, are beyond the scope of this guide.

1.6 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*

D 3078 Test Method for Determination of Leaks in Flexible Packaging by Bubble Emission[2]

D 4169 Practice for Performance Testing of Shipping Containers and Systems[2]

D 4332 Practice for Conditioning Containers, Packages, or Packaging Components for Testing[2]

F 88 Test Method for Seal Strength of Flexible Barrier Materials[2]

F 1140 Test Methods for Failure Resistance of Unrestrained and Nonrigid Packages for Medical Applications[2]

F 1327 Terminology Relating to Barrier Materials for Medical Packaging[2]

F 1585 Guide for Integrity Testing of Porous Barrier Medical Packages[2]

F 1608 Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)[2]

F 1929 Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration[2]

2.2 *ISO Standard:*

ANSI/AAMI/ISO 11607, Packaging for Terminally Sterilized Medical Devices[3]

3. Terminology

3.1 *Definitions*—For general definitions of packaging for medical devices see ANSI/AAMI/ISO 11607. For terminology related to barrier materials for medical packaging see Terminology F 1327.

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *accelerated aging (AA), n*—storage of samples at an elevated temperature (T_{AA}) in order to simulate real time aging in a reduced amount of time.

3.2.2 *accelerated aging factor (AAF), n*—an estimated or calculated ratio of the time to achieve the same level of physical property change as a package stored at real time (*RT*) conditions.

3.2.3 *accelerated aging temperature (T_{AA}), n*—the elevated temperature used to conduct the aging studies, and it is based on the ambient temperature or the estimated temperature of usage, or storage of this package, or both.

3.2.4 *accelerated aging time (AAT), n*—the length of time at which the accelerated aging is conducted.

3.2.5 *ambient temperature (T_{RT}), n*—storage temperature for real-time aging (*RT*) samples that represents storage conditions.

3.2.6 *package shelf life, n*—the amount of real time that a package can be expected to remain in storage at ambient conditions, or under specified conditions of storage, and maintain its critical performance properties.

[1] This guide is under the jurisdiction of ASTM Committee F-2 on Flexible Barrier Materials and is the direct responsibility of Subcommittee F02.60 on Medical Packaging.

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[2] *Annual Book of ASTM Standards*, Vol 15.09.

[3] Available from the American National Standards Institute, 11 W. 42nd St., 13th Floor, New York, NY 10036.

3.2.7 *real-time aging (RT), n*—storage time of samples at ambient conditions.

3.2.8 *real-time equivalent (RTE), n*—amount of real-time aging to which given accelerated aging conditions are estimated to be equivalent.

3.2.9 *zero time (t_0), n*—the beginning of an aging study.

3.3 *Symbols:*

Q_{10} = an aging factor for 10°C increase or decrease in temperature.
T_m = temperature at which a material melts.
T_g = glass transition temperature.
T_α = alpha temperature; heat distortion temperature.

4. Significance and Use

4.1 As package components and adhesives age, they may break down, become brittle, or lose their bonding capabilities. This aging characteristic may result in the potential loss of package integrity.

4.2 The ANSI/AAMI/ISO 11607 states that, "the manufacturer shall demonstrate that, under the rigors of distribution, storage, handling, and aging, the integrity of the final package is maintained at least for the claimed shelf-life of the medical device under storage conditions specified by the manufacturer, as long as the package is undamaged or unopened."

4.3 The most valid aging program is to age the package under real-life (ambient) storage conditions for the intended shelf-life. Since such testing would be completed prior to market release, this approach would delay, unnecessarily in many cases, the introduction of potentially valuable technology to the market with a loss of benefit to the patient. Avoiding unnecessary delays in bringing technology to the market is the reason for developing and utilizing accelerated aging programs.

4.4 Due to the complexity of aging processes, the use of accelerated aging programs do involve some risk. The manufacturer is exposed to risk of unnecessary product obsolescence from conservative aging programs that predict shelf lives shorter than reality. In addition, since accelerated aging often is on the critical path for market release, overly conservative aging programs increase the time required to collect aging data, and thereby delay the release of products to the patient.

4.5 Conservative accelerated aging factors (AAFs) must be used if little information is known about the package under investigation. With more information about the system under investigation and with information demonstrating the correlation between real time performance and accelerated aging performance, more aggressive and accurate AAFs may be defined.

NOTE 1—AAF methods are beyond the scope of this guide.

5. Accelerated Aging Theory

5.1 Accelerated aging of materials refers to the accelerated variation of their properties over time, the properties of interest being those related to safety and function of the material or package.

5.2 In an aging study, the material or package is subjected to an external stress, which is more severe, or more frequently applied than the normal environmental stress, for a relatively short period of time.

5.3 Accelerated aging techniques are based on the assumption that the chemical reactions involved in the deterioration of materials follow the Arrhenius reaction rate function. This function states that a 10°C increase or decrease in temperature of a homogeneous process results in approximately, a two times or ½-time change in the rate of a chemical reaction (Q_{10})[4].

5.4 Determining the Q_{10} involves testing products at various temperatures and defining the differences in reaction rate for a 10° change in temperature. Modeling the kinetics of material deterioration is complex and difficult and is beyond the scope of this guide.[5] For more details on modeling kinetics of materials.

6. Accelerated Aging Plan

6.1 *Characterization of Materials*—In order to apply AA theory, an understanding of the materials of the package under investigation is necessary. Items to be considered include the following:

6.1.1 Processing history;

6.1.2 Morphology (glassy, amorphous, semi-crystalline, highly crystalline, % crystallinity, etc.);

6.1.3 Thermal transitions (T_m, T_g, T_α);

6.1.4 Chemical structure (aliphatic, aromatic, repeating units, repeating unit sequence, end groups, side chains);

6.1.5 Molecular weight and molecular weight distribution; and,

6.1.6 Additives, processing agents, catalysts, lubricants, residual solvents, and fillers.

6.2 *Accelerated Aging Plan-Design Guidelines*:

6.2.1 Temperature boundaries, based on the characterization of the device and package materials, must be considered in order to assure that initial, conservative aging factors are applied appropriately.

6.2.2 *Ambient Temperature (T_{RT})*—Select an ambient storage temperature representative of actual product storage and use conditions.

NOTE 2—This temperature normally is between 20–25°C for normal hospital type storage. A temperature of 25°C is conservative and may be appropriate when detailed information about the storage environment is not available; however, any temperature that represents the normal storage conditions for the product can be selected, for example, 22°C.

6.2.3 *Accelerated Aging Temperature (T_{AA})*—Considering the characterization of the materials under investigation, select a temperature for the accelerated aging testing. As the aging temperature increases, the aging factor also increases and the aging duration decreases; however, the benefits in efficiency from raising the aging temperature must be balanced by the risks involved with extrapolating increasingly high aging temperature properties to room temperature properties (see Appendix X1). Guidelines for selecting an aging temperature are as follows:

[4] Hemmerich, Karl J., "General Aging Theory and Simplified Protocol for Accelerated Aging of Medical Devices," *Medical Plastics and Biomaterials*, July/August 1998, pp. 16–23.

[5] Nelson, Wayne, "Accelerated Testing Statistical Models, Test Plans, and Data Analyses," John Wiley and Sons, New York, 1999.

6.2.3.1 Keep T_{AA} below the temperature at which the product/package distorts. Consider the thermal transitions of the materials under investigation, for example, the choice of T_{AA} should be at least 10°C less than T_g.

6.2.3.2 Keep T_{AA} at or below 60°C unless a higher temperature has been demonstrated to be appropriate. Temperatures higher than 60°C are not recommended due to the higher probability in many polymeric systems to experience nonlinear changes, such as percent crystallinity, formation of free radicals, and peroxide degradation.

NOTE 3—If packages containing liquid or other volatile components are tested, lower temperatures may be required for safety reasons.

6.2.3.3 When elevated temperature aging is not feasible, for example, with materials with very low heat distortion temperature or materials that undergo major morphological changes at even slightly elevated temperatures, then real-time aging is the only option.

6.3 *Accelerated Aging Factor (AAF) Determination*:

6.3.1 It is possible to provide guidance with respect to initial conservative estimates of aging factors. These initial estimates may be used to begin aging programs while real-time data is being collected in order to verify the initial estimate. The initial estimates suggested below are conservative in most cases when applied within the boundaries given.

6.3.2 Using the Arrhenius equation with Q_{10} equal to 2 is a common and conservative means of calculating an aging factor for polymeric systems in the moderate aging conditions typically applied to medical devices and their packaging; however, before a particular Q_{10} can be applied, the user must show that the materials of the system do not degrade within the appropriate temperature boundaries. For many polymeric materials, the reaction rate coefficient may be higher than 2.0.

6.3.3 An accelerated aging factor (AAF) estimate for a temperature range greater than 10°C is calculated from a Q_{10} value by means of the following equation:

$$AAF \equiv Q_{10}^{[(T_{AA} - T_{RT})/10]} \quad (1)$$

where:

$T_{AA} \equiv$ accelerated aging temperature (°C), and

$T_{RT} \equiv$ ambient temperature (°C).

6.3.4 The accelerated aging factor (AAF) is applied to calculate the time required for the package to be held in an accelerated aging chamber (or incubator or area) by means of the following equation:

$$\text{Accelerated Aging Time (AAT)} \equiv \text{Desired (RT)/AAF} \quad (2)$$

See Appendix X1 for a graphical representation of the time versus temperature.

NOTE 4—A more aggressive reaction rate coefficient, for example, Q_{10} = 2.2 to 2.5, may be used if the system under investigation is sufficiently well characterized in the literature. The level and nature of damage must be similar to that reported in the literature to ensure that the reaction rate coefficient and accelerated aging temperature are maintained within appropriate boundaries. This is the responsibility of the manufacturer.

6.3.5 When little information is known about the package under investigation, the guidance above is provided for selecting and verifying an appropriately conservative aging factor for the specific scenario. Risk to the manufacturer may be large since the method may predict an unduly short shelf-life; however, consideration must be given to maximizing patient safety since the necessary information to obtain a more accurate and aggressive shelf-life prediction is not readily available.

6.4 *Accelerated Aging Protocol Steps*:

6.4.1 Select the Q_{10} value.

6.4.2 Define the desired shelf life of the package, such as, marketing needs, product needs, etc.

6.4.3 Define aging test time intervals, including time zero.

6.4.4 Define test conditions, ambient temperature (T_{RT}), and accelerated aging temperature (T_{AA}).

6.4.5 Calculate the test duration using the Q_{10}, T_{RT}, and T_{AA}.

6.4.6 Define package material properties, seal strength and integrity tests, sample sizes, and acceptance criteria.

6.4.7 Age samples at T_{AA}. In parallel, age samples at real-life aging conditions (T_{RT}).

6.4.8 Evaluate the package performance after accelerated aging relative to the initial package requirements, for example, package seal strength, package integrity.

6.4.9 Evaluate package, or package performance, or both, after real time aging relative to the initial package requirements. The estimated AAF method is a simple and conservative technique for evaluating the long-term performance of a package; however, like all accelerated aging techniques, it must be confirmed by real time aging data.

6.5 See the example package shelf-life test plan (Appendix X2).

7. Post-Aging Testing Guidance

7.1 Packages and materials that have been subjected to aging, that is, accelerated and real time, must be evaluated for physical properties and integrity.

7.2 Tests selected should challenge the material or package functionality that is most critical or most likely to fail due to the stresses resulting from aging. Guide F 1585 may be used as a testing guide for porous barrier medical packaging.

7.3 Some of the physical strength properties to be considered for selection are flexure, puncture, tensile and elongation, tear, impact resistance, abrasion resistance, yellowness index, microbial barrier (Test Method F 1608), seal strength (Test Method F 88), and burst strength (Test Method F 1140).

7.4 Packages may be subjected to whole package integrity testing by using validated physical, that is, trace gas, dye leak (Test Method F 1929), bubble leak (Test Method D 3078) or microbial methods (microbial challenge of whole packages). These methods must include documentation showing that the test method has been validated.

7.5 Acceptance criteria must be established prior to any package shelf-life testing. Zero time performance data may be used as a comparison to final package performance data at the end of the shelf life test.

8. Documentation

8.1 *Accelerated Aging*:

8.1.1 A written test protocol specifying the accelerated aging conditions (test temperature, humidity, cycle, ambient temperature), time frame, sample sizes, package description, time intervals of sampling packages, and specific tests at each time interval must be developed prior to testing.