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Standard Guide for Assessment of Absorbable Polymeric Implants[1]

This standard is issued under the fixed designation F2902; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

ε[1] NOTE—Editorial corrections were made throughout in May 2017.

1. Scope

1.1 This guide describes general guidelines for the chemical, physical, mechanical, biocompatibility, and preclinical assessments of implantable synthetic polymeric absorbable devices. This guide also describes evaluation methods that are potentially useful and should be considered when assessing absorbable implants or implant components.

1.2 The described evaluations may assist a manufacturer in establishing the safety and effectiveness of an absorbable implant device. This listing of assessment methods may also be utilized to assist in establishing substantial equivalence to an existing commercially marketed device. However, these polymeric material-oriented guidelines do not necessarily reflect the total needs for any particular implant application (for example, orthopedic, cardiovascular, sutures, and dermal fillers), which may require additional and potentially essential application-specific evaluations.

1.3 This guide is intended to cover all forms of absorbable polymeric components and devices, including solid (for example, injection-molded) and porous (for example, fibrous) forms. This guide is also intended to cover devices fabricated from amorphous and/or semi-crystalline absorbable polymer systems.

1.4 This guide has been generated with principal emphasis on the evaluation of devices formed from synthetic polymers that degrade *in vivo* primarily through hydrolysis (for example, α-hydroxy-polyesters). Evaluation methods suggested herein may or may not be applicable to implants formed from materials that, upon implantation, are substantially degraded through other mechanisms (for example, enzymatically induced degradation).

1.5 This guide references and generally describes various means to assess absorbable materials, components, and devices. The user needs to refer to specific test methods for additional details. Additionally, some of the recommended test methods may require modification to address the properties of a particular device, construct, or application.

1.6 Adherence to all aspects of these guidelines is not mandatory, in that assessments and tests listed within this guide are not necessarily relevant for all absorbable implant systems and applications.

1.7 Absorbable polymers used as a matrix to control the *in vivo* release of bioactive agents (drugs, antimicrobials, and so forth) may be evaluated according to many of the methods described herein. However, additional test methods not covered by this guide will likely be needed to evaluate a bioactive agent's composition, loading, release kinetics, safety, and efficacy.

1.8 Composites of absorbable polymers with ceramics and/or metals may be evaluated according to many of the methods described herein. However, additional test methods not covered by this guide will likely be needed to evaluate the composite's other component(s).

1.9 The values stated in SI units are to be regarded as standard. No other units of measurement are included in this standard.

1.10 *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.*

1.11 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

D570 Test Method for Water Absorption of Plastics

[1] This guide is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.11 on Polymeric Materials.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

D638 Test Method for Tensile Properties of Plastics
D695 Test Method for Compressive Properties of Rigid Plastics
D732 Test Method for Shear Strength of Plastics by Punch Tool
D792 Test Methods for Density and Specific Gravity (Relative Density) of Plastics by Displacement
D1042 Test Method for Linear Dimensional Changes of Plastics Caused by Exposure to Heat and Moisture
D1922 Test Method for Propagation Tear Resistance of Plastic Film and Thin Sheeting by Pendulum Method
D2857 Practice for Dilute Solution Viscosity of Polymers
D2990 Test Methods for Tensile, Compressive, and Flexural Creep and Creep-Rupture of Plastics
D3079 Test Method for Water Vapor Transmission of Flexible Heat-Sealed Packages for Dry Products
D3164 Test Method for Strength Properties of Adhesively Bonded Plastic Lap-Shear Sandwich Joints in Shear by Tension Loading
D3418 Test Method for Transition Temperatures and Enthalpies of Fusion and Crystallization of Polymers by Differential Scanning Calorimetry
D3420 Test Method for Pendulum Impact Resistance of Plastic Film
D3846 Test Method for In-Plane Shear Strength of Reinforced Plastics
D4404 Test Method for Determination of Pore Volume and Pore Volume Distribution of Soil and Rock by Mercury Intrusion Porosimetry
D4603 Test Method for Determining Inherent Viscosity of Poly(Ethylene Terephthalate) (PET) by Glass Capillary Viscometer
D5225 Test Method for Measuring Solution Viscosity of Polymers with a Differential Viscometer
D5296 Test Method for Molecular Weight Averages and Molecular Weight Distribution of Polystyrene by High Performance Size-Exclusion Chromatography
D5748 Test Method for Protrusion Puncture Resistance of Stretch Wrap Film
E96/E96M Test Methods for Water Vapor Transmission of Materials
E128 Test Method for Maximum Pore Diameter and Permeability of Rigid Porous Filters for Laboratory Use
E328 Test Methods for Stress Relaxation for Materials and Structures
E398 Test Method for Water Vapor Transmission Rate of Sheet Materials Using Dynamic Relative Humidity Measurement
E467 Practice for Verification of Constant Amplitude Dynamic Forces in an Axial Fatigue Testing System
E793 Test Method for Enthalpies of Fusion and Crystallization by Differential Scanning Calorimetry
E794 Test Method for Melting And Crystallization Temperatures By Thermal Analysis
E1356 Test Method for Assignment of the Glass Transition Temperatures by Differential Scanning Calorimetry
E1441 Guide for Computed Tomography (CT) Imaging
E1570 Practice for Computed Tomographic (CT) Examination
E2207 Practice for Strain-Controlled Axial-Torsional Fatigue Testing with Thin-Walled Tubular Specimens
F99 Guide for Writing a Specification for Flexible Barrier Rollstock Materials
F316 Test Methods for Pore Size Characteristics of Membrane Filters by Bubble Point and Mean Flow Pore Test
F748 Practice for Selecting Generic Biological Test Methods for Materials and Devices
F1249 Test Method for Water Vapor Transmission Rate Through Plastic Film and Sheeting Using a Modulated Infrared Sensor
F1635 Test Method for *in vitro* Degradation Testing of Hydrolytically Degradable Polymer Resins and Fabricated Forms for Surgical Implants
F1925 Specification for Semi-Crystalline Poly(lactide) Polymer and Copolymer Resins for Surgical Implants
F1980 Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
F1983 Practice for Assessment of Selected Tissue Effects of Absorbable Biomaterials for Implant Applications
F2097 Guide for Design and Evaluation of Primary Flexible Packaging for Medical Products
F2210 Guide for Processing Cells, Tissues, and Organs for Use in Tissue Engineered Medical Products (Withdrawn 2015)[3]
F2313 Specification for Poly(glycolide) and Poly(glycolide-co-lactide) Resins for Surgical Implants with Mole Fractions Greater Than or Equal to 70 % Glycolide
F2450 Guide for Assessing Microstructure of Polymeric Scaffolds for Use in Tissue-Engineered Medical Products
F2477 Test Methods for *in vitro* Pulsatile Durability Testing of Vascular Stents
F2502 Specification and Test Methods for Absorbable Plates and Screws for Internal Fixation Implants
F2559 Guide for Writing a Specification for Sterilizable Peel Pouches
F2579 Specification for Amorphous Poly(lactide) and Poly(lactide-co-glycolide) Resins for Surgical Implants
F2791 Guide for Assessment of Surface Texture of Non-Porous Biomaterials in Two Dimensions

2.2 *ISO Standards:*[4]
ISO 178 Plastics — Determination of flexural properties
ISO 180 Plastics — Determination of Izod impact strength
ISO 527-1 Plastics — Determination of tensile properties — Part 1: General principles
ISO 527-2 Plastics — Determination of tensile properties — Part 2: Test conditions for moulding and extrusion plastics
ISO 527-3 Plastics — Determination of tensile properties — Part 3: Test conditions for films and sheets
ISO 604 Plastics — Determination of compressive properties

[3] The last approved version of this historical standard is referenced on www.astm.org.
[4] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

ISO 1628-1 Plastics — Determination of the viscosity of polymers in dilute solution using capillary viscometers — Part 1: General principles
ISO 1628-5 Plastics — Determination of the viscosity of polymers in dilute solution using capillary viscometers — Part 5: Thermoplastic polyester (TP) homopolymers and copolymers
ISO 1805 Fishing nets — Determination of breaking load and knot breaking load of netting yarns
ISO 2062 Textiles — Yarns from packages — Determination of single-end breaking force and elongation at break using constant rate of extension (CRE) tester
ISO 6721-2 Plastics — Determination of dynamic mechanical properties — Part 2: Torsion-pendulum method
ISO 9000 Quality Management Systems—Fundamentals and Vocabulary
ISO 9001 Quality Systems Management
ISO 10993 Biological Evaluation of Medical Devices
ISO 11135 Sterilization of Health Care Products—Ethylene Oxide
ISO 11137 Sterilization of Health Care Products—Radiation
ISO 11607-1 Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems.
ISO 13485 Medical Devices—Quality Management Systems—Requirements for Regulatory Purposes
ISO 13781 Poly(L-lactide) Resins and Fabricated Forms for Surgical Implants—In Vitro Degradation Testing
ISO 13934-1 Textiles —Tensile properties of fabrics — Part 1: Determination of maximum force and elongation at maximum force using the strip method
ISO 14130 Fibre-reinforced plastic composites — Determination of apparent interlaminar shear strength by short-beam method
ISO 15814 Implants for Surgery—Copolymers and Blends Based on Polylactide—In Vitro Degradation Testing
ISO/TS 12417 Cardiovascular Implants and Extracorporeal Systems—Vascular Device-Drug Combination Products
ISO 80000–9 Quantities and units — Part 9: Physical chemistry and molecular physics

2.3 *AAMI Standards:*[5]
AAMI STBK9–1 Sterilization—Part 1: Sterilization in Health Care Facilities
AAMI STBK9–2 Sterilization—Part 2: Sterilization Equipment
AAMI STBK9–3 Sterilization—Part 3: Industrial Process
AAMI TIR17 Compatibility of Materials Subject to Sterilization

2.4 *U. S. Code of Federal Regulations:*[6]
21 CFR Part 58 Title 21 Food And Drug Administration, Part 58—Good Laboratory Practice for Nonclinical Laboratory Studies
21 CFR Part 820 Title 21 Food And Drug Administration, Part 820—Quality System Regulation

2.5 *U. S. Pharmacopeia (USP) Standards:*[7]
<232> Elemental Impurities – Limits
<233> Elemental Impurities – Procedures
<724> Drug Release
<905> Uniformity of Dosage Units
<1207> Sterile Product Packaging—Integrity Evaluation
<1208> Sterility Testing—Validation of Isolator Systems
<1209> Sterilization—Chemical and Physiochemical Indicators and Integrators
<1211> Sterilization and Sterility Assurance of Compendial Articles

2.6 *NIST Document:*[8]
NIST SP811 Special Publication SP811: Guide for the Use of the International System of Units (SI)

2.7 *Other Documents:*[9]
ICH Q3C International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Quality Guideline: Impurities: Residual Solvents

3. Terminology

3.1 *Definitions:*

3.1.1 *absorbable, adj*—in the body, an initially distinct foreign material or substance that either directly or through intended degradation can pass through or be metabolized or assimilated by cells and/or tissue.

NOTE 1—See Appendix X4 for a discussion regarding the usage of absorbable and other related terms.

3.1.2 *bioactive agent, n*—any molecular component in, on, or with the interstices of a device that is intended to elicit a desired tissue or cell response.

3.1.2.1 *Discussion*—Growth factors, antibiotics, and antimicrobials are typical examples of bioactive agents. Device structural components or degradation products that evoke limited localized bioactivity are not included.

3.1.3 *plasticizer, n*—substance incorporated into a material to increase its workability, flexibility, or distensibility.

3.1.4 *porogen, n*—one or more added materials that, upon removal, produce voids that result in generation of a porous structure.

3.1.4.1 *Discussion*—The need for inclusion of a porogen is process dependent, with many porous structures able to be generated without the utilization of porogens. A porogen can be a gas, liquid, or solid and can be either intentionally or unintentionally added.

[5] Available from Association for the Advancement of Medical Instrumentation (AAMI), 4301 N. Fairfax Dr., Suite 301, Arlington, VA 22203-1633, http://www.aami.org.

[6] Available from U.S. Government Printing Office Superintendent of Documents, 732 N. Capitol St., NW, Mail Stop: SDE, Washington, DC 20401, http://www.access.gpo.gov.

[7] Available from U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.

[8] Available from National Institute of Standards and Technology (NIST), 100 Bureau Dr., Stop 1070, Gaithersburg, MD 20899-1070, http://www.nist.gov.

[9] Available from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Secretariat, c/o IFPMA, 15 ch. Louis-Dunant, P.O. Box 195, 1211 Geneva 20, Switzerland, http://www.ich.org.

4. Significance and Use

4.1 This guide is aimed at providing guidance for assessments and evaluations to aid in preclinical research and development of various absorbable components and devices.

4.2 This guide includes brief descriptions of various intended uses, processing conditions, assessments, and both qualitative and quantitative analyses for raw materials to finished product components.

4.3 The user is encouraged to utilize appropriate ASTM and other standards to conduct the physical, chemical, mechanical, biocompatibility, and preclinical tests on absorbable materials, device components, or devices prior to assessment in an *in vivo* model.

4.4 Whenever an absorbable material is mixed or coated with other substances (bioactive, polymeric, or otherwise), the physical and degradation properties of the resulting composite may differ significantly from the base polymer. Thus, unless prior experience can justify otherwise, performance characterizations described herein should be conducted on the composite construct rather than on individual components.

4.5 Assessments of absorbable materials should be performed in accordance with the provisions of the FDA Good Laboratories Practices Regulations 21 CFR 58, where feasible.

4.6 Studies to support regulatory approval for clinical or commercial use, or both, should conform to appropriate nationally adopted directives or guidelines, or both, for the development of medical devices [for example, CE approval; US-FDA Investigational Device Exemption (IDE), Pre- Market Approval (PMA), or 510K submission].

4.7 Assessments based upon data from physical, chemical, mechanical, biocompatibility, and preclinical testing models are highly valuable but carry inherent limitations. Thus, the clinical relevance of each assessment needs to be carefully considered and the user is cautioned that pre-clinical evaluations may not be predictive of human clinical performance.

5. Fabrication and Processing Related Features and Considerations

5.1 *Thermal Processing*—Synthetic absorbable implants are routinely fabricated through thermal means, with typical examples including extrusion and both injection and compression molding. Extrusion is typically used to manufacture fibrous forms (for example, woven or knitted meshes, monofilament or braided sutures, fibrous nonwovens), as well as films and tubes. Injection molding typically includes screws, tacks, barbs, pins, and bone anchors. Compression molding is a common method for fabrication of plates and panels.

5.1.1 *Thermal Degradation Control*—The act of thermal processing can potentially degrade absorbable polymers. In addition, any presence of moisture will introduce an additional degradation mechanism, which will occur rapidly at elevated processing temperatures. Consequently, the impact of actual processing conditions—including temperature, moisture, and their variations—on the resulting product should be both understood and appropriately controlled.

5.1.2 *Mode of Manufacture*—Consideration should be made toward the method of manufacture (e.g., injection molding versus compression molding versus extrusion), which can induce differing levels of thermal stress – potentially resulting in dissimilar degradation profiles within otherwise dimensionally identical devices.

5.2 *Solvent Casting*—Synthetic absorbable implants can be fabricated through dissolution in a solvent followed by casting into a desired form. This process is typically utilized in the formation of films, but other forms are possible.

5.2.1 *Compositional Purity*—The purity of the solvent(s) utilized in the casting process must be known and of a grade suitable for the intended application. The overall system (that is, incoming raw materials and all device fabrication processes) needs to maintain a level of particle control appropriate for the intended application. It is important to note that the act of solvating a hydrolysable polymer inherently increases its chain motion, thereby increasing its potential for reactivity. If any chemically reactive moiety (such as water) is present in the solvent, degradation can increase significantly from the polymer's solid state condition. Consequently, the impact of actual processing conditions (for example, solution temperature, moisture content) on the resulting product should be both understood and controlled.

5.2.2 *Chemical Compatibility*—All components of a solvent casting system need to possess a level of compatibility suitable for the intended application. Examples of incompatibility include, but are not limited to, reactivity (unintended generation of differing chemical moieties within the solution) and phase separation (unintended formation of colloids/precipitates/particles that may be detrimental to overall biocompatibility and/or desired *in vivo* performance).

5.2.3 *Solvent Removal*—The solvent casting process inherently includes a drying step to remove the major portion of the solvent. Any remaining residual solvent will effectively temporarily plastisize the device, potentially affecting its initial physical properties. In addition, residual solvent may pose biocompatibility-related issues, details of which are addressed in Section 8.

5.2.4 *Dimensional Control*—As with any forming process, casting dimensions (including thickness) shall be controlled within limits determined to be suitable for the intended application.

5.3 *Coating*—Polymers with hydrolysable segments can be applied to a device using various methods ranging from dip-coating (aqueous or organic solvent) to vapor deposition.

5.3.1 *Physical Deposition Control*—Coating characteristics—including, but not limited to, density, thickness, and/or bioactive agent loading—shall be controlled within limits determined to be suitable for the intended application.

5.3.2 *Compositional Purity*—The purity of the coating itself and any solvent(s) utilized in the coating process shall be known and of a grade suitable for the intended application. Any aqueous-based solvent systems shall utilize water that meets USP Sterile Water for Injection requirements. Non-aqueous solvent systems need to maintain a level of particle control

appropriate for the intended application. Additionally, International Conference on Harmonisation (ICH) based residual solvent limits—as described in Section 8 and in synthetic absorbable resin Specifications F1925, F2579, and F2313—need to be met. Devices are to be characterized by analytic detection limits sufficient to assure that total solvent residuals are maintained below ICH guidelines.

5.4 *Additives*—In the context of this guide, an additive is any substance that is intentionally added to the implant, regardless as to whether or not it is removed during subsequent processing. As a result, additives needing consideration can range broadly from processing aids (for example, mold release agents) to fillers to pharmaceuticals. Since *in vivo* release is categorically inherent to absorbability, a thorough understanding of any additive's biological/toxicological properties is essential to implant design. Also worthy of consideration is the impact expected additive concentration(s) may impart on manufacturing processes and/or the physical properties of the polymeric device itself.

5.4.1 *Plasticizers*—In the context of this guide, plasticization can be imparted by anything added to a macromolecular device or component that swells and/or solvates its polymeric structure to effectively lower its glass transition temperature (Tg). Almost any low molar mass molecule able to penetrate the polymeric structure—including solvents, water, and bioactive agents—carries potential to impart a plasticization effect. Thus, plasticizer should be perceived as a descriptive term that is not limited solely to the class of chemicals commonly added to modify/affect the mechanical properties of the polymer and/or device.

5.4.1.1 Any material used to plasticize absorbable polymers will, upon polymer absorption, inherently be released into the body. While local toxicity would be addressed through the implant's histological response, systemic toxicity of any plasticizer should be fully understood (for example, excretion, concentration in organs, and so forth). If adequate toxicological information is unavailable for the utilized placticizer(s), such data must be generated. Additionally, the purity of the raw material plasticizer must be known and of a grade suitable for the intended application.

5.4.1.2 The chemical composition of the plasticizer raw material shall be determined by means of an assay of the basic composition and a quantification of any expected other components (due to raw material sources and/or processing methods; for example, reactive chemical byproducts, trace metals/catalysts). Quantification of each expected other component is to be undertaken at an analytic level that brings assurance that tissue response in the final product will be suitable for the intended application. Low or non-toxic materials may need no-to-minimal monitoring, dependent on extraction efficiency and expected residual levels within the formed device. Higher toxicity materials will require elevated awareness and monitoring, dependent on extraction efficiency expected residual levels within the formed device.

5.4.1.3 The plasticizer content in the finished as-formed device must also be known, along with quantification of any expected other components possessing toxicity and/or quantities that may impact tissue response and/or display either local or systemic toxicity.

5.4.2 *Porogens*—Porogens are one or more added materials that, upon their removal, produce voids that result in a porous structure. A porogen can be a gas, liquid, or solid and can be either intentionally or unintentionally added. The need for inclusion of a porogen is process-dependent, with many porous structures able to be generated without the utilization of porogens. Any porogen needs to deliver the desired pore characteristics, which typically includes porosity, presence of open/closed cells, pore size, and so forth. Characterization of a porogen raw material should, at minimum, include:

5.4.2.1 *Dimensions*—Provide some relevant measure of the porogen's size distribution.

5.4.2.2 *Chemical Composition*—Assay the basic composition of the porogen and quantify any expected other components (due to raw material sources and/or processing methods; for example, reactive chemical byproducts, trace metals/catalysts). Quantification of each expected other component is to be undertaken at an analytic level that assures that the tissue response in the final porous product will be suitable for the intended application. Low or non-toxic materials may need no-to-minimal monitoring, depending on extraction efficiency and expected residual levels within the formed porous device. Higher toxicity materials will require elevated awareness and monitoring, the extent of which will depend on extraction efficiency and expected residual levels within the formed porous device.

5.4.2.3 *Characterization of Formed Porous Device*—The pore characteristics of the formed device should be assessed by appropriate means as summarized in Guide F2450. Additionally, any remaining residual porogen(s) or other components that display either local or systemic toxicity or have the potential to adversely impact tissue response or device performance should be quantified. Also, it should be noted that addition/elimination of porosity to/from a material can influence the local tissue response - so additional studies to understand the impact of porosity changes may be needed.

5.4.3 *Bioactive Agents*—Bioactive agents are typically considered to be pharmaceuticals, growth factors, antibiotics, or antimicrobials. Additionally, cells or specific cell surface/growth factor antigens may be components of the device. If a bioactive substance is to be released from a device or a device component, the release profile should be characterized.

5.4.3.1 *Controlled Release*—Any controlled release of a bioactive agent or substance from an absorbable device (be it from the bulk or a coating, or both) needs to be sufficiently understood and characterized to assure that the effective dosage into the surrounding tissue is both safe (that is, below toxic levels) and accomplishes the design goal.

NOTE 2—See X1.1 for more information on appropriately characterizing the controlled release of bioactive agents, drugs/pharmaceuticals,

antimicrobials, or cells, or combination thereof.

5.5 *Post-formation Thermal Processing*—Fabricated forms typically undergo at least one or more thermal processes, which may include thermally induced annealing, crosslinking, solvent extraction, and so forth. Any thermal processing of the fabricated form (including cooling/quenching processes) should be documented and the mechanical, physical, and chemical effects assessed.

5.6 *Work in Progress*—Since hydrolysable polymers can be affected by atmospheric moisture, the effects of such exposure during manufacture and prior to final packaging need to be both understood and controlled to a level that assures device performance. Device susceptibility to such exposure can be a function of multiple variables, which may include processing/storage humidity(ies) and temperature(s), polymer/device moisture uptake, device degradation rate, etc. Particular precaution should be directed toward devices that are fragile and/or temperature-sensitive.

5.7 *Sterilization Processing*—A summary of sterilization methods and standards is presented in 7.2. However, it is important to emphasize that sterilization is a manufacturing process that can have significant impact on an absorbable implant system's material or (if present) bioactive agent properties. Thus, evaluations considered to be representative of actual performance *in vivo* and/or finished product shall be conducted on devices or test specimens that have been sterilized by means that approximate the intended commercial method.

6. Device Characterizations/Assessments

NOTE 3—Sterilization of absorbable polymeric materials should be expected to cause changes in molar mass or structure, or both. This can affect the initial mechanical and physical properties of a material or device, as well as its subsequent rate of degradation. Therefore, if a test is intended to be representative of actual performance *in vivo* and/or finished product, assess the test absorbable polymeric material in a form that is representative of a product produced under standard manufacturing conditions and ready for sale.

6.1 *Compositional Properties:*

6.1.1 *Raw Material Characterization*—It is recommended that the required characteristics of all incoming raw material be specified, including absorbable resin. Factors that should be considered for inclusion within specifications for hydrolysable polyesters can be found in Specifications F1925, F2313, and F2579, which typically include a means for monitoring molar mass (M) — such as via inherent viscosity or size exclusion chromatography (SEC) [also known as gel permeation chromatography (GPC)].

NOTE 4—The term molecular weight (abbreviated MW) is obsolete and should be replaced by the SI (Système Internationale) equivalent of either relative molecular mass (Mr), which reflects the dimensionless ratio of the mass of a single molecule to an atomic mass unit (see ISO 80000-9), or molar mass (M), which refers to the mass of a mole of a substance and is typically expressed as grams/mole. For polymers and other macromolecules, use of the symbols Mw, Mn, and Mz continue, referring to mass-average molar mass, number-average molar mass, and z-average molar mass, respectively. For more information regarding proper utilization of SI units, see NIST SP811.

6.1.2 *Chemical Properties Characterization (Fabricated Device)*—It is recommended that the chemical properties of a fabricated absorbable device be specified. Factors that should be considered for inclusion within the specification can be found in Specifications F1925, F2313, and F2579. Additional items for consideration can be found in Table 1—Sections A and B of this guide.

6.1.3 *Physical Description Properties Characterization*—It is recommended that the physical properties of a fabricated absorbable device be specified. Factors that should be considered for inclusion within the specification can be found in Table 1—Sections C, D, and E.

6.1.4 *Thermal Properties Characterization*—It is recommended that the thermal properties of a fabricated absorbable device be specified. Factors that should be considered for inclusion within the specification can be found in Table 1—Section F.

6.2 *Mechanical/Performance Properties*—The objective of any mechanical characterization is to adopt relevant evaluation methods that approximate the expected clinical loading of the device (for example, don't rely solely on tensile testing when clinical loading is in shear). Besides understanding and modeling normal service conditions, mechanical characterizations should assess the worst-case clinical failure mode and then evaluate device performance under similar conditions. Worst case failure may be the result of numerous combined factors, which can include materials composition, physiological fluids and temperatures, effects of clinical placement, and *in vivo* loading conditions. However, the user is cautioned that such pre-clinical testing does not, in itself, assure suitability to a particular application and may not be predictive of human clinical performance. Mechanical properties that should be considered for inclusion within a specification can be found in Table 2—Sections A to F.

6.2.1 *Initial Characteristics/Properties*—Characterize the relevant initial (that is, as-manufactured) mechanical properties of the device. The initial dimensional and net mechanical characteristics of the device will need to reflect the intended application and the resulting design. An example of mechanical characterizations appropriate for absorbable implants designed toward a specific function can be found in Specification F2502. However, each different absorbable application or design approach will likely require appropriate variations in the applied assessment method(s).

6.2.2 *Hydrolytic Degradation Properties (Degradation Profiling/Modeling)*—Characterize the loss of relevant mechanical properties of the device over time under conditions that are representative of expected *in vivo* service conditions. Once conditioned for a clinically relevant time interval, evaluations may include destructive mechanical testing or testing until failure (in the case of static or cyclic loading evaluations). Depending on the indicated use of a device, clinical relevance may indicate the need for one or more of the following conditioning methods.

NOTE 5—Hydrolytic environments that are intended to mimic *in vivo* conditions typically include buffered saline-based water baths. In such baths, attention toward buffer capacity and careful monitoring and maintenance of pH throughout the evaluation is essential for proper hydrolytic evaluation of a hydrolysable device.

NOTE 6—Since loss of mechanical properties within an absorbable polymeric device is typically the result of chain scission, concurrent

TABLE 1 Chemical and Physical Properties

Property, Behavior, or Characteristics	Applicable Issues/Design Considerations	Potentially Relevant Analyses, Characterizations, and Test Methods
A—Chemical Composition	**Main Ingredients**: Polymers (incl copolymer ratio), Chain extenders, Cross-linking agents, Coating composition, Plasticizer(s)/processing aids **Purity/Trace Elements:** Catalysts Low Mw components (water solvent, monomers, oligomers) **Stereoregularity and Optical Purity**	NMR GC HPLC Residual Ignition AA ICP IR GPC Karl-Fischer Titration Polarimeter (optical rotation
B—Molecular Structure	**Polymer Blending** **Crosslinking** **Copolymer block/branch length** **Copolymer conversion efficiency** **Mn, Mw, Polydispersity, MWD**	NMR IR Solubility Swelling GPC/SEC – ASTM D5296 Inherent Viscosity: • ASTM D4603 • ISO 1628-5 • ASTM D2857 • ASTM D5225 • ISO 1628–1 • NOTE— Choice of solvent and temperature should be reported (see F1925, F2313, and/or F2579 for more detail on IV testing of absorbable polymers and related reporting requirements).
C—Morphology (Supermolecular Structure)	**% Crystallinity** **Phases** (Types, amount, and orientation)	X-ray diffraction DSC DTA Optical Microscopy Birefringence X-ray diffraction Draw ratio
D—Composite Structure	**Laminate Structure:** Ply thickness and orientation Ply orientation and stacking sequence (incl symmetry) **Reinforcement**: Location within part 3D orientation Volume or weight fraction Contacts/cross-overs, homogeneity Cross-section shape Fiber—twist and denier Weave—types, ends/mm **Coatings**—number and thickness of each layer **Voids:** Mean Vol % Interconnections Depth and Profile	Scanning Electron Microscopy (SEM) Optical Microscopy Micro-CT Porosimetry Transmission Electron Microscopy (TEM)
E—Physical Properties	**Water Absorption** **Dimensional Changes** **Density** (mass and volume) (smallest and largest device sizes) **Porosity Distribution** **Surface Area:** (smallest and largest device sizes)—determined by overall external dimensions, not intended to include internal surfaces with microporous structures **Surface Characteristics**—(Texture, patterns, roughness, and so forth)	ASTM D570 ASTM D1042 ASTM D792 ASTM F2450 Porosimetry (ASTM D4404) Porometry (ASTM E128, F316 ASTM F2791
F—Thermal Properties	**Glass Transition Temperature** **Crystallization Temperature** **Melting Temperature**	ASTM D3418 ASTM E793 ASTM E794 ASTM E1356

monitoring of molar mass should be considered since measurable loss can be expected prior to any detectable degradation of mechanical properties.

TABLE 2 Mechanical, Degradation, and Performance Properties

Property/Behavior	Applicable Issues/Design Considerations	Potentially Relevant Analyses, Characterizations, and Test Methods
A—Cyclic Fatigue	Fracture, Deformation, Wear, and Loosening	ASTM E467 (Axial Fatigue) ASTM F2477 (Pulsatile Durability) ASTM E2207 (Strain-Controlled Axial-Torsional Fatigue)
B—Static Strength and Stiffness	Fracture/Loosening under Anticipated Loading (for example, shear)	ASTM D638, D695—Tensile/compressive properties ISO 527-1, ISO 527-2, ISO 527-3, ISO 604, ISO 2062, ISO 13934-1 —Tensile/Compressive Properties ASTM F2502—Torque (for example, screws); Shear (for example, pins) *in-vitro* mechanical testing under analogous loading conditions ISO 178 - Flexural properties ISO 180 - Izod impact strength ISO 14130 – Shear Strength • ASTM D732 • ASTM D3846 • ISO 1805 • ISO 6721-2 • ASTM D1922 • ASTM D5748 • ASTM D3420 • ASTM D3164
C—Stress Concentrations, Residual Stresses	Determine the potential presence and location of high stresses and their effect(s) on the performance of the device	Geometric Characterization and Measurement (for example, fillet and corner radii)—SEM, etc. *Note*—SEM does not provide information on stress, but can be used to help understand/bound the radii of sharp corners, etc., and do bounding analyses on stress concentrations, etc. Stress Analysis Finite Element Analysis (FEA) Mechanical Testing
D—Viscoelasticity (time-dependent deformation or relaxation)	Loosening	Creep, ASTM D2990 Stress Relaxation, ASTM E328
E—Wear and Degradation	Effect of Sterilization Significant effects from implant contact with other materials reasonably expected within a clinical use setting Shelf-life Strength retention after cyclic loading in 37°C buffered saline Fracture/loosening	ASTM F1635, F2502, ISO 13781 Characterization of aged/degraded samples, including: mechanical properties; microstructure, weight loss, molar mass (molecular weight), Tg, crystallinity, dimensional stability (for example, swelling, stretching) *Note*—use sterilized samples for all evaluations or demonstrate no significant effect on all properties
F—Biocompatibility	Compatibility of Bulk Material; Compatibility of Particles and Degradation Products (Synovitis—see Appendix X2) Metabolic pathways	ISO 10993 ASTM F748 Elemental Impurities – Limits <232> Elemental Impurities – Procedures <233>
G—Preclinical (*in vivo*) Evaluations	Localized inflammatory response; histological resolution of absorbable component(s)	*in vivo* ASTM F1983 ISO 10993–6 X-ray, microCT (ASTM E1441, E1570), ultrasound, OCT, MRI, and others Post-retrieval Optical microscopy SEM histology

6.2.2.1 *Mechanically Unloaded Hydrolytic Evaluation*—Conditioning of a hydrolysable device under mechanically unchallenged hydrolytic conditions at 37°C in water or buffered saline is described in Test Method F1635. Additional more specific polymer-related guidance may be found in ISO 13781 and ISO 15814. While testing of unloaded specimens is a common means to obtain a first approximation of the degradation profile of an absorbable material or device, it does not necessarily represent actual *in vivo* service conditions, which can include mechanical loading in a variety of forms (for example, static tensile, cyclic tensile, shear, bending, torsion, and so forth). If the performance of a device under its indicated use includes loading, hydrolytic aging alone can NOT be considered as sufficient to fully characterize the device.

6.2.2.2 *Mechanically Loaded Hydrolytic Evaluation*—The objective of loading is to approximate (at 37°C in buffered saline) the actual expected device service conditions so as to better understand potential physicochemical changes that may occur. Such testing can be considered as necessary if clinically relevant device loading can reasonably be expected under *in vivo* service conditions. Whenever possible, mechanical evaluation of an implant should include loading that is comparable to expected *in vivo* service conditions, with test specimens loaded in a meaningful manner that—as closely as practical—

represents *in vivo* conditions, both in magnitude and in type of loading. Clinically relevant cyclic load tests may include testing to failure or for a specified number of cycles followed by testing to evaluate physicochemical properties.

(1) Physiochemical Changes—When assessing hydrolytic degradation under a mechanical load, consideration should be given to the potential significance of any alterations to the chemical or physical properties, or both, of the polymeric device, the scope of which includes cracking or crazing, accelerated local degradation (for example, in regions of stress concentration), extension, swelling, fracture, and so forth.

(2) Creep, Relaxation, and Fatigue—When assessing polymer degradation under load, it may be necessary to consider and monitor creep, relaxation, and/or fatigue, any combination of which may be significant. Fatigue is crack initiation and growth due to imposition of repeated or cyclic stresses. Creep is time-dependent deformation under imposed stresses (constant or cyclic) and is frequently observed in viscoelastic materials (for example, plastics), especially as temperatures are elevated. Creep is also known as cold flow when it occurs at room temperature. Creep rate is dependent on factors such as temperature, thermal history, degree of crystallinity, and both the presence and extent of filler material(s). Creep testing is typically conducted under constant load. Relaxation is similar to creep, dependent on many of the same factors, but is measured as the time-dependent reduction in stress under imposed deformation. Additional information regarding the measurement and analysis of creep in plastics can be found in the reference cited in Section X1.4.

(3) Static and Cyclic Loading—Whenever possible, mechanical evaluation of an implant should include loading that is comparable to expected *in vivo* service conditions. It is necessary to recognize that static loading and cyclic loading are not inherently comparable and that, unless experimentally proven otherwise, using one to replace the other could lead to significant misinterpretation of results.

(4) Fixturing Considerations—Fixturing may introduce artifactual performance and/or degradation issues. An example is the use of rigid closed cell foam block, which restricts swelling expansion to elevate pull-out strength test results from sample compression within the block. In this same example, restricted perfusion due to the closed cell nature of the block can also result in concentration of acidic degradation products that can lead to accelerated degradation when compared to a normal perfused and buffered *in vivo* condition. When unavoidable, the implications of these artifacts should be considered when evaluating the performance of the device.

6.2.2.3 *Macroscopic Observations*—Besides monitoring the loss of mechanical properties, observe for any preferential (that is, non-homogeneous) degradation modes. If non-homogenous degradation is present, divide the sample as needed to approximate the range of degraded properties, and analyze accordingly. Observe for any changes in morphology or failure mode as degradation progresses.

NOTE 7—Generation of opacity may be a result of polymer crystallization. If over 1 mm in length, document macroscopic observation of the entire implant with a photograph. Where possible, provide photos of regional and microscopic observations.

7. Packaging, Sterility, Shelf-Life, and Labeling

7.1 *Packaging*—Suitability of a device for intended use typically includes its provision within a sterile package sufficiently durable to adequately protect that sterility during normal handling and storage. With an absorbable product where a device's physical, mechanical, and chemical characteristics are additionally susceptible to hydrolytic degradation, maintenance of the device's critical performance must also include reliable ongoing control and/or removal of moisture from both the product and package interior. Therefore, packaging for devices fabricated from hydrolysable polymers must be designed so that any moisture ingress is controlled. Control can be facilitated through utilization of moisture-resistant materials (for example, foil-lined packaging) and desiccants. However, regardless of design, no package can inherently be assumed to be moisture-proof. Consequently, some level of package desiccation should be considered.

7.1.1 *Package Components*—Moisture vapor transmission rates for the various available packaging materials, sealing layers, and desiccant capacity all need to be considered in the package design.

7.1.2 *Package Sealing*—Particular attention should be directed toward both thoroughness and consistency in executing the package sealing process, along with comprehensive assessment of the moisture-vapor transmission occurring through the plane of that sealing layer.

7.1.3 *Moisture Vapor Specific Test Methods for Consideration:*

7.1.3.1 Test Method D3079.
7.1.3.2 Test Method F1249.
7.1.3.3 Test Methods E96/E96M
7.1.3.4 Test Method E398
7.1.4 *General Packaging Guidance for Consideration:*
7.1.4.1 Guide F2097
7.1.4.2 Guide F2559
7.1.4.3 Guide F99
7.1.4.4 ISO 11607-1

7.2 *Sterilization*—A summary of common sterilization methods, testing, and quality assurance can be found in USP <1207>, <1208>, <1209>, and <1211>. AAMI maintains a 3-volume set of sterilization standards and recommended practices containing 46 different standards: AAMI STBK9–1, AAMI STBK9–2, and AAMI STBK9–3. The following provides a listing of typical sterilization methods and a brief description of their applicability to devices constructed of absorbable materials:

7.2.1 *Radiation Sterilization:*

NOTE 8—When utilizing any radiation-based sterilization method, molar mass changes need to be both monitored and assessed for their potential impact on the clinical performance aspect(s) of the device. A comprehensive discussion regarding radiation sterilization methods can be found in Burg, et al.[10]

7.2.1.1 *Gamma Sterilization*—Gamma radiation is often utilized in the sterilization of hydrolysable polyesters. While

[10] Burg, K. J. L. and Shalaby, S. W., "Radiation Sterilization of Medical and Pharmaceutical Devices," *Radiation Effects of Polymers: Chemical and Technological Aspects*, ACS, Washington, DC, 1996, pp. 240–245.

this method has the benefit of leaving no gaseous residuals requiring removal, changes in the molar mass of the component materials should be both expected and monitored.

7.2.1.2 *e-Beam Sterilization*—Electron beam irradiation involves using high energy electrons to sterilize medical and pharmaceutical goods by damaging the DNA strands of any microorganisms that may be present.

7.2.1.3 Guidance for gamma, e-Beam, and x-ray sterilization can be found in Parts 1, 2, and 3 of ISO 11137.

7.2.2 *Ethylene Oxide (ETO/EO) Sterilization*—Refer to previously cited AAMI reference.

7.2.2.1 All ETO processes involve absorbable product exposure to combinations of temperature and humidity that may impact the product directly (chemically and/or physically) or could result in residual moisture that, if not removed before final package sealing, may adversely affect shelf-life.

7.2.2.2 Guidance for ethylene oxide sterilization can be found in Parts 1 and 2 of ISO 11135.

7.2.3 *Steam Sterilization*—Steam is generally considered to not be a viable sterilization option since hydrolysable polymers are highly susceptible to uncontrollable damage under autoclave conditions.

7.2.4 *Alternative Sterilization Methods*—Other methods may potentially be used to achieve sterility, such as Dry Heat Sterilization, Hydrogen Peroxide Sterilization, and Ozone Sterilization.

7.2.4.1 It should be noted that the application of 'dry heat' above a polymer's glass transition temperature can render an amorphous material crystalline, which can affect material properties.

7.2.5 *Device-Packaging Susceptibility*—Each of the above cited sterilization methods have the potential to cause changes to the physical-chemical nature of the device, which may affect product performance. Thus, the user of this standard needs to assure that the entirety of the device and packaging are compatible with the chosen sterilization method. For guidance evaluating device susceptibility, see AAMI TIR17.

7.3 *Packaged Product Shelf-Life:*

7.3.1 Shelf-life is the amount of real-time that a packaged product can be expected to remain under specified storage conditions while assuring maintenance of its critical performance properties. Since each device has an intended use and design, any shelf-life determination must directly or indirectly assess the device's ability to fulfill the intended use upon its removal from a properly stored package.

7.3.1.1 The shelf-life of the packaged product will be governed either by product stability or by the validated shelf-life of the packaging system, whichever is shorter.

7.3.1.2 The shelf-life of the packaging system is determined through sterility assurance testing, which is not within the scope of this guide.

7.3.2 *Packaged Final Product*—Any final packaged product will include many different components. Those components, each of which possesses its own unique susceptibility to aging, are not limited to the device itself and include:

7.3.2.1 *Packaging*—commonly composed of multiple structural and adhesive layers and compositions, each of which is unique and will be altered and/or damaged at some elevated temperature.

7.3.2.2 *Implant Device*—composed of one or more structural components and compositions, all of which will be altered and/or damaged at some elevated temperature.

7.3.2.3 *Device Additives or Modifiers*—non-structural components that effect a particular physical and/or mass transfer characteristic to the device. Examples include: plasticizers, drug release coatings, excipients—the function of which will be altered and/or damaged at some elevated temperature.

7.3.2.4 *Bioactive Agents*—components of the device that directly influence the amount or composition of the cells surrounding the device. Examples are: pharmacological agents, drugs, antimicrobials, and so forth—the function of which will be altered and/or damaged at some elevated temperature.

7.3.2.5 *Delivery Aids*—adjunctive components that facilitate delivery of the device. Examples include sutures (attached to the device), catheters, drill bits, and so forth—the function of which will be altered and/or damaged at some elevated temperature.

7.3.3 *Critical Performance Properties*—It is the manufacturer's responsibility to understand all facets of the finished packaged and sterilized product to allow accurate identification of the aspect(s) of the device that is (are) most appropriate for determining shelf-life. Determination of critical performance parameters should include consideration of the utilized materials, the device indications, and the market being serviced. Direct assessment of the device's critical aspect(s) is preferable, with an indirect assessment allowable only after correlation to the device's critical performance parameter(s) has been established.

7.3.3.1 *Materials Understanding*—It is the manufacturer's responsibility to have a detailed understanding of how the respective device components perform under expected *in vivo* and shelf-life aging conditions. For example, inherent to its composition, polyglycolide-based sutures materials can hydrolyze at room temperature, potentially affecting their ability to approximate tissue under load. The manufacturer needs to understand how such hydrolytic susceptibility (be it in-process or under storage) can impact the *in vivo* performance of the device.

7.3.3.2 *Device Indications*—It is the manufacturer's responsibility to fully understand reasonable performance expectations for the device, which may be its critical aspects and thereby indicate the most relevant test(s) to apply. For example, sutures are typically knotted, which indicates knot strength is more clinically relevant than straight sample tensile strength.

7.3.3.3 *Market Observation/Understanding*—It is the manufacturer's responsibility to understand/project its device's failure mode(s) and monitor its actual performance in the market. Such understanding can be acquired through direct clinical experience and/or the monitoring of complaints (for example, by means of US-FDA Medical Device Reporting requirements).

7.3.4 *Packaged Product Evaluation:*

7.3.4.1 Shelf-life assessment of packaged absorbable product should include real-time exposure to thermal and moisture challenge conditions that, at a minimum, reflect the expected storage and transportation environments.

7.3.4.2 Real-time testing of the product's critical aspects under conditions analogous to actual storage conditions is the only definitive means for both assessing and predicting the shelf-life/life-span of a packaged absorbable device.

7.3.4.3 *Packaged Product Stability Testing (Real-Time/Accelerated Aging)*—A written testing program should be designed to assess the stability characteristics of the packaged and sterilized absorbable device. The results of such stability testing should be used in determining appropriate storage conditions and expiration dates. The written program should include:

(1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;

(2) Storage conditions for samples retained for testing;

(3) Reliable, meaningful, and specific test methods, which shall include a method indicative of molar mass;

(4) Established acceptance criteria for each test result; and

(5) Testing of the device product in the same container-closure system as that in which it is marketed.

7.3.4.4 For a new absorbable product contained in an established moisture-proof packaged system, an expiration date needs to be supported with either correlating real-time evaluation data or accelerated aging data utilizing a real-time validated method.

(1) Accelerated aging of polymers usually involves storage at elevated temperature. The maximum temperature used for accelerated aging shall be reliably below the onset of any thermal transition (e.g., glass transition temperature).

(2) Appendix X3 provides a non-exhaustive compilation of references that describe features common to an appropriate characterization of thermally accelerated degradation, some of which are specific to lactide/glycolide-based polymeric devices/specimens.

7.3.4.5 For a new absorbable product contained in any new packaging system, any expiration date needs to be supported by correlating real-time evaluation data.

7.3.4.6 *Accelerated Studies*—In combination with basic stability information on the device, any related components, and the packaging system, may be used to support tentative expiration dates. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf-life studies (per 7.3.4.4 above), real-time stability studies must be conducted with testing at appropriate and relevant sampling intervals until the tentative expiration date is verified or the appropriate expiration date determined.

7.4 *Labeling:*

7.4.1 The following provides labeling aspects that may be considered as unique to absorbable devices:

7.4.1.1 *Acceptable Storage Temperature*—The actual/modeled storage temperature range determined to be acceptable for the packaged device shall be displayed on the label. An effort should be made to avoid use of imprecise terms such as "room temperature," which can vary depending on climatic zones.

7.4.1.2 *Thermal Sensitivity*—Shelf-life inherently assumes storage under specific condition. If excursions from the modeled conditions present a significant risk of failure to the device, its components, or the package, the manufacturer should take measures to mitigate the risk. For example, thermal exposure history display stickers can be utilized to alert the user.

7.4.1.3 *Degradation Characteristics*—A general description of the principle of degradation along with both the expected rate for loss of mechanical properties and *in vivo* absorption of the device should be included within the provided documentation (for example, Instructions for Use). Any known adverse events associated with device degradation and/or the *in vivo* absorption process should also be described.

7.4.1.4 *Biocompatibility*—In some polymer systems, unique complications may arise as a result of the degradation process (for example, synovitis—see 8.2.2.2) In such situations, an explanation of how to clinically deal with the material-specific situation needs to be included in the Precautions for Use section.

8. Biocompatibility

8.1 *Composition/Design Suitability:*

8.1.1 The sterilized packaged absorbable device should conform to biocompatibility testing norms, such as those described in the ISO 10993 series or Practice F748.

8.1.2 *Residual Solvents:*

8.1.2.1 If any solvent is utilized in any device manufacturing or purification step, determine the residual levels of any utilized solvent(s) by gas chromatography or other suitable method. Acceptable residual levels of a particular solvent should be reflective of toxicity, with a maximum acceptable limit consistent with ICH Q3C. The detection limit for the chosen analytic method shall be adequate to assure compliance with the applicable ICH guideline and the determined residual(s) and applied concentration limit(s) shall be reported. If no ICH concentration guideline has been established for a utilized solvent, an investigation of the solvent's toxicity and determination of a limit suitable for the intended device application will be necessary.

8.1.3 *Dimensional Concerns:—*

8.1.3.1 As with any implant, its physical presentation (i.e., dimensions, mechanical characteristics, geometry, appropriate placement) will carry significant influence on the overall clinical performance of the device. While the initial properties of a structural device are highly important to its function, during degradation that same device can be expected to fracture over time into increasingly smaller fragments/particles (see 8.2), all of which carry potential to migrate. Thus, the device's initial dimensions combined with the timing for its subsequent fragmentation and particulate resolution should be considered for its potential impact on tissue response.

8.2 *Degradation Mechanism(s)*—Besides understanding the appropriate composition design for the intended use, absorbable polymer-based devices should address any potential impacts that could arise during degradation *in vivo*. Consequently, it is essential to fully understand the mechanism of implant degradation, ranging from the mode through which a device loses its physical integrity to its compositional breakdown products. (See Table 2—Section G).

8.2.1 *Degradation Modes*—Two commonly recognized modes of degradation are described below. However, this listing should not be considered as all-inclusive, with it incumbent upon the user of this standard to fully understand the degradation characteristics of any utilized absorbable polymer either through experimentation or through specific reference.

8.2.1.1 *Bulk Degradation*—where chain scission occurs simultaneously throughout the profile of the construct, resulting in a substantially consistent loss of properties.

8.2.1.2 *Bioerosion*—where degradation occurs primarily through interactions occurring at the implant surface, resulting in gradual erosion of the construct.

8.2.2 *Debris*—Of particular note is the manufacturer's need to address the potential for implant degradation processes to generate loose debris and/or fragments, which carry the potential to initiate adverse tissue response, including in soft tissue and intra-articular applications. Such debris can present itself in a variety of sizes, ranging from implant fracture to the generation of micron size particles. Relevant implant fracture processes and/or mechanisms with the potential to adversely affect critical areas (for example, by generation of loose debris/fragments) should be evaluated and, if applicable, mitigated through redesign and/or reformulation. Factors that may affect the significance or detectability of debris include implant location, tissue mobility, synovial fluid (in joint spaces), local tissue metabolism, assessment duration, and bone/tissue turnover rate (typically higher in animals than in humans). The risks associated with implant fragmentation and the generation of particles should be assessed in light of the intended application. For example, particles released within a bony defect may have a response that is different from the same particles released into soft tissue. Appendix X2 provides a non-exhaustive compilation of articles describing the potential impact of debris generated during the degradation process.

8.2.2.1 *Implant Fragmentation*—Physical degradation can be either general or localized in nature depending on an implant's design, processing, and composition. Physical form and/or tissue loading can interact to lead to concentration of stresses into particular regions of an implant (that is, stress concentration), leading to preferential (that is, accelerated) degradation in the stress-concentrated areas. Such regional degradation can result in implant fracture and potential generation of unstressed fragments with persisting mechanical integrity. These smaller fragments can potentially migrate to cause tissue damage remote from the implant site. Fragment size and tissue impact can vary based on an implant's structure and dimensions (for example, large solid devices bring increased potential for larger particles), polymer morphology (that is, crystalline or amorphous), degradation rate (that is, short-term versus long-term persistence of fragments), and a variety of processing and *in vivo* loading factors.

8.2.2.2 *Particle-Induced Synovitis*—Particulate-induced synovitis is inflammation of a synovial membrane caused by either migrated or locally generated particles. Particle sources can vary, but most reported cases are attributed to debris generated from structurally articulating plastic or metallic implant components. While most literature accounts describe particle release from permanent implants, synovitis from particles generated from absorbable implants has also been reported (see Appendix X2). In addition to direct fragmentation, absorbable particulates can also be the result of selective hydrolytic degradation of a semi-crystalline polymer's amorphous tie chains, which can result in polymeric crystallites that can endure significantly beyond loss of the implant's mechanical integrity. Such persistence can potentially lead to synovitis and/or formation of a sterile sinus—an abscess initiated by an aseptic inflammatory response to the presence of persistent particles. Such crystallites can form from polymeric crystallinity that may or may not be present at implantation, since physiological fluid at 37°C may effectively lower the glass transition temperature to allow chain mobility and subsequent potential for crystallization *in vivo*.

8.2.3 *Absorbable Particles*—The degradation of absorbable particles injected as part of a treatment to smooth wrinkles, treat facial fat atrophy, and/or provide soft tissue augmentation may have a delayed reaction and potential formation of small bumps and lumps.

8.2.4 *Acidic Degradation Products*—Alpha-hydroxy esters and other degradable polymers with hydrolysable functional groups can generate acidic degradation artifacts that can impact local tissue response. An implant manufacturer must understand the impact any degradation products may have on the implant's functional performance.

8.2.5 *Heterogenous Degradation*—During degradation of hydrolysable polymer, acidic products can accumulate within the core of the device, which can lead to an acid-catalyzed increase in the rate of hydrolysis. This increased rate can result in a more rapid degradation within the core, thereby producing a more rapid loss of mechanical properties and introducing the potential for formation of acidic pockets that can affect tissue response.[11]

8.2.6 *Metabolic Products*—An essential aspect of implant design is to understand an absorbable device's hydrolytic/enzymatic degradation products and their respective excretion route (for example, relevant metabolic pathways). If not already established, the information needs to be generated.

9. Preclinical (*in vivo*) Evaluations

9.1 The recommendations of this guide for *in vivo* evaluations are general in nature, because each application will require its own model(s) and issues. Focus should be toward defining the level of material, manufacturing, and design feature control needed to allow a meaningful finished device evaluation.

[11] I. Grizzi, H. Garreau, S. Li, M. Vert, "Hydrolytic degradation of devices based on poly(DL-lactic acid) size-dependence," *Biomaterials*, Vol 16, Issue 4, March 1995, pp. 305-311.

9.2 This stage of device evaluation typically involves animal experimentation. Absorbable specific guidance for *in vivo* testing can be found in both ISO 10993–6 and Practice F1983. However, in some unique applications other evaluation approaches may be warranted (for example, cadaveric bone is considered a better osteoporotic model).

9.3 All preclinical evaluations should provide as much relevance to the intended human use as practical. Before any preclinical study, a comprehensive review of the published literature should be conducted to assure that the selected animal model is the most appropriate for the intended device indication(s). Since no animal study can fully represent the clinical situation, all preclinical evaluations should acknowledge known limitations of the selected model. It is important to recognize that the body temperatures of animal models vary and are typically higher than humans, thereby carrying the potential to accelerate the degradation rate when compared with clinical conditions (See Pietrzak reference in Section X3.1.8).

9.4 *Retrieval Time Frames*—Selected retrieval times should reflect both their clinical relevance and the expected degradation properties of the polymer/implant system. Expected degradation is a combination of prior *in vitro* and/or preclinical evaluation experience(s). Retrievals should target time durations that will demonstrate a pattern of consistent continuing degradation leading to a final histological resolution of the device or absorbable polymeric component, if not already established through prior experimentation (direct or via reference) with a fundamentally similar polymer construct.

9.5 *Preclinical Assessment Methods*—Non-application-specific preclinical assessment methods that should be considered include Xray/CT, MicroCT, Magnetic Resonance Imaging (MRI), histology, and others (see Table 2—Section H).

9.6 For further information on preclinical evaluation of absorbable constructs, see ISO 10993 – Part 6 on Implantation.

10. Quality Systems Management

10.1 *Manufacturing Control Guidance*—Acceptable levels of manufacturing control are highly desirable and likely to be required of commercially distributed products. General guidelines for achieving acceptable levels of manufacturing/testing quality control may be found in the following standards:

10.1.1 United States Code of Federal Regulations (CFR), Title 21, Part 820 or other relevant national regulations.

10.1.2 *ANSI/ISO/ASQ Q9000*—Provides fundamentals for quality management systems as described in the ISO 9000 family (informative); and specifies quality management terms and their definitions (normative).

10.1.3 ISO 13485

10.1.4 ISO 9001

11. Keywords

11.1 absorbable; degradable; bioabsorbable; bioresorbable; biodegradable; degradation; hydrolysis; hydrolytically degradable polymers; resorbable; surgical implants

APPENDIXES

(Nonmandatory Information)

X1. GUIDELINE DOCUMENTS

X1.1 *Controlled Release*—For more information on appropriately characterizing the controlled release of bioactive agents, see: ISO/TS 12417; US-FDA DRAFT Guidance for Industry—Coronary Drug-Eluting Stents—Nonclinical and Clinical Studies, March-2008, available online at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072196.pdf

X1.2 *Drugs/Pharmaceuticals/Antimicrobials*—For more information on appropriately characterizing the purity and/or quality of a drug/pharmaceutical (Stability Testing, Impurity Testing, and so forth), see the International Conference on Harmonisation (ICH) Quality Guidelines located at: http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html. Additional pharmaceutical characterization guidance can be found in USP <905> (Uniformity of Dosage Units) and <724> (Drug Release).

X1.3 *Cells*—For more information on appropriately characterizing the purity and/or quality of a living cell, see Guide F2210. Additional standards relevant to the culturing and manipulation of cells for tissue engineering applications can be found in various documents generated by ASTM Committee F04 on Medical and Surgical Materials and Devices—Division IV on Tissue Engineered Medical Products (TEMPs). A complete listing of ASTM TEMPs standards can be surveyed at the following web locations:

(1) Subcommittee F04.41 on Classification and Terminology for TEMPs, http://www.astm.org/COMMIT/SUBCOMMIT/F0441.htm

(2) Subcommittee F04.42 on Biomaterials and Biomolecules for TEMPs, http://www.astm.org/COMMIT/SUBCOMMIT/F0442.htm

(3) Subcommittee F04.43 on Cells and Tissue Engineered Constructs for TEMPs, http://www.astm.org/COMMIT/SUBCOMMIT/F0443.htm

(4) Subcommittee F04.44 on Assessment for TEMPs , http://www.astm.org/COMMIT/SUBCOMMIT/F0444.htm

(5) Subcommittee F04.45 on Adventitious Agents Safety, http://www.astm.org/COMMIT/SUBCOMMIT/F0445.htm

(6) Subcommittee F04.46 on Cell Signaling, http://www.astm.org/COMMIT/SUBCOMMIT/F0446.htm

X1.4 Creep Measurement——Additional information regarding the measurement of creep in plastics can be found in the United Kingdom's National Physical Laboratory (NPL) Measurement Good Practice Guide Number 2, "Measurement and analysis of creep in plastics," (Tomlins, P.E.). An Adobe Acrobat pdf version of this publication is available at:

http://www.npl.co.uk/publications/measurement-and-analysis-of-creep-in-plastics

X2. PARTICLE-INDUCED SYNOVITIS REFERENCES

The following provides a partial compilation of clinical examples of synovitis sterile sinus-related issues and respective references:

X2.1 *Absorbable Bone Pins*—Gill, L. H., Martin, D. F., Coumas, J. M., Kiebzak, G. M., "Fixation with Bioabsorbable Pins in Chevron Bunionectomy," *The Journal of Bone and Joint Surgery*, Vol 79, 1997, pp. 1510–1518.

X2.2 *Suture Anchors*:

X2.2.1 Park, H. B., et al. "Suture Anchors and Tacks for Shoulder Surgery, Part II, The Prevention and Treatment of Complications," *The American Journal of Sports Medicine*, Vol 34, No. 1, January 2006, pp. 136–144.

X2.2.2 Glenoid osteolysis after arthroscopic labrum repair with a bioabsorbable suture anchor Marco SPOLITI, From S. Camillo-Forlanini Hospital, Rome, Italy.

X2.3 *Tacks*:

X2.3.1 Major, N. M., and Banks, M. C., "MR Imaging of Complications of Loose Surgical Tacks in the Shoulder," *The American Journal of Roentgenology*, Vol 180, No. 2, 2003, pp. 377–380.

X2.3.2 Wilkerson, J. P., Zvijac, J. E., Uribe, J. W., Schürhoff, M. R., and Green, J. B., "Failure of polymerized lactic acid tacks in shoulder surgery," *J Shoulder Elbow Surg*, Vol 12, 2003, pp. 117–21.

X2.4 *General Orthopedic*:

X2.4.1 Yetkin, H., Senköylü, A., Cila, E., Öztürk, A. M., Simsek, A., "Biodegradable Implants in Orthopaedics and Traumatology," *Turk J Med Sci*, Vol 30, 2000, pp. 297–301.

X2.4.2 Weiler, A., Hoffmann, R. F. G., Stähelin, A. C., Helling, H., Südkamp, N. P., "Biodegradable Implants in Sports Medicine: The Biological Base," *J Arthroscopy & Related Surgery*, Vol 16, No. 3, April 2000, pp. 305–321.

X2.4.3 Böstman, O., Pihlajamaki, H., "Clinical biocompatibility of biodegradable orthopaedic implants for internal fixation: a review," *Biomaterials*, Vol 21, No. 24, December 2000, pp. 2615–2621.

X2.4.4 Konan, S., Haddad, F. S., "A clinical review of bioabsorbable interference screws and their adverse effects in anterior cruciate ligament reconstruction surgery," *The Knee*, Vol 16, No. 1, January 2009, pp. 6–13.

X3. ACCELERATED DEGRADATION REFERENCES

NOTE X3.1—It is essential that any accelerated study projections be validated with correlative real-time aging data.

The following provides selected references perceived to be relevant to the development of evaluations involving the accelerated degradation of hydrolysable materials:

X3.1.1 Nelson, W., *Accelerated Testing Statistical Models, Test Plans, and Data Analyses*, John Wiley and Sons, New York, 1999.

X3.1.1.1 Comprehensive overview of accelerated aging factors and techniques

X3.1.2 AAMI TIR17—Compatibility of Materials Subject to Sterilization (see Section 6, Annex G, and Annex G references).

X3.1.2.1 Accelerated aging and combination device product stability programs

X3.1.3 Guide F1980 for Accelerated Aging of Sterile Barrier Systems for Medical Devices

X3.1.3.1 General planning for accelerated aging of packaging

X3.1.4 Deng, M., Zhou, J., Chen, G., Burkley, D., Xu, Y., Jamiolkowski, D., Barbolt, T., "Effect of load and temperature on in vitro degradation of poly(glycolide-co-l-lactide) multifilament braids," *Biomaterials*, Vol 26, No. 20, July 2005, pp. 4327–4336.

X3.1.4.1 Effect of loading during degradation; effect of degradation temperatures; reaction order determination; Arrhenius relationship

X3.1.5 Deng, M., Chen, G., Burkley, D., Zhou, J., Jamiolkowski, D., Xu, Y., Vetrecin, R., "A study on in vitro degradation behavior of a poly(glycolide-co-l-lactide) monofilament," *Acta Biomaterialia*, Vol 4, No. 5, September 2008, pp. 1382–1391.

X3.1.5.1 Molar mass and mechanical property loss over time; effect of degradation temperatures; reaction order determinations; Arrhenius relationship; activation energy; morphological observations

X3.1.6 Tsuji, H., Tsuruno, T., "Accelerated hydrolytic degradation of Poly(l-lactide)/Poly(d-lactide) stereocomplex up to late stage," *Polymer Degradation and Stability*, Vol 95, No. 4, April 2010, pp. 477–484.

X3.1.6.1 Impact of hydrolytic degradation (accelerated) on crystallinity and molar mass; Arrhenius relationship

X3.1.7 Han, X., Pan, J., Buchanan, F., Weir, N., Farrar, D., "Analysis of degradation data of poly(l-lactide–co-l,d-lactide) and poly(l-lactide) obtained at elevated and physiological temperatures using mathematical models," *Acta Biomaterialia*, Vol 6, No. 10, October 2010, pp. 3882–3889.

X3.1.7.1 Detailed summary and analysis of degradation models; Arrhenius relationship

X3.1.8 Pietrzak, W. S., Kumar, M., Eppley, B. L., "The Influence of Temperature on the Degradation Rate of LactoSorb Copolymer," Journal of Craniofacial Surgery, Vol 14, No. 2, March 2003, pp. 176–183.

X3.1.8.1 Thermal sensitivity of hydrolysis; Arrhenius relationship; temperature variation in animal models

X3.1.9 Suming, L., "Hydrolytic Degradation Characteristics of Aliphatic Polyesters Derived from Lactic and Glycolic Acids," Journal of Biomedical Materials Research (Applied Biomaterials), Vol 48, 1999, pp/ 342–353.

X3.1.9.1 Heterogenous degradation; differences in degradation rate dependent on composition, crystallinity

X4. NOMENCLATURE OF ABSORBABLE AND RELATED TERMS

X4.1 Synthetic implants fabricated from hydrolysable alpha-hydroxy polyesters have been described as "absorbable" since the first polyglycolide-based sutures were commercialized in the United States in the 1970s. At that time, both poly(glycolide) (DEXON—Davis and Geck) and poly(glycolide-co-lactide) copolymer (VICRYL—Ethicon) based sutures were classified as "Absorbable Surgical Suture" by the United States Pharmacopeia (USP) and the United States Food Drug Administration (US-FDA), a designation that remains to this day. In contrast with "Nonabsorbable Surgical Suture," synthetic glycolide-lactide and collagen-based sutures undergo hydrolytic and/or enzymatic driven chain scission, generating degradation products that are then absorbed by the body. Since this designation, other terms such as "degradable" and "resorbable" have been used interchangeably to describe absorbable implants, with the prefix "bio-" often applied to all these terms.

X4.2 Based on historical usage and regulatory precedent, this guide preferentially utilizes the term absorb/absorbable/absorption to describe implantable synthetic hydrolysable polymers devices. The prefix "bio" is avoided since it is redundant in the context of implant applications. These same terms are also applied to natural polymers (e.g., collagen) and metals intended to undergo corrosion *in vivo*, since any degradation product — be it proteinaceous or ionic — will inherently be absorbed by the host organism. The prefix "bio" is avoided since it is redundant in the context of implant applications. "Resorb" and its derivatives are avoided since they are accepted medical terms routinely utilized to describe natural resorption processes present in dynamic tissue, such as osteoclastic driven bone remodeling. "Degrade" and its various derivatives are avoided when referring categorically to either an implantable device or raw material since common utilization is routinely applied broadly to include other natural processes unrelated to medical device use that cause materials to either intentionally or unintentionally break down into chemical or particulate matter. However, use of the term "degrade" and its derivatives is considered acceptable when specifically referring to breakdown processes (e.g., chain scission, corrosion) within the absorbable materials or implantable device (for example, "The absorbable implant degrades through hydrolysis" or "During extrusion, absorbable polyglycolide is prone to thermal degradation")

X4.3 Since a variety of alternative terms to absorbable have been historically utilized interchangeably both within and across surgical disciplines (but intermittently with inferred differentiation), the user of this document is cautioned that effective searches of the published literature should include all potential terms used to describe an absorbable implant or material. These include, but are not limited to:

- Absorbable and its derivatives.
- Bioabsorbable and its derivatives.
- Degradable and its derivatives.
- Biodegradable and its derivatives.
- Resorbable and its derivatives.
- Bioresorbable and its derivatives.