



Standard Guide for Assessment of Absorbable Polymeric Implants¹

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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), 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, enzymatic action).

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.*

2. Referenced Documents

2.1 ASTM Standards:²

- D570 Test Method for Water Absorption of Plastics
- D638 Test Method for Tensile Properties of Plastics
- D695 Test Method for Compressive Properties of Rigid Plastics
- 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
- D2990 Test Methods for Tensile, Compressive, and Flexural Creep and Creep-Rupture of Plastics

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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.

D2991 Test Method for Stress-Relaxation of Plastics (Withdrawn 1990)³

D3079 Test Method for Water Vapor Transmission of Flexible Heat-Sealed Packages for Dry Products

D3418 Test Method for Transition Temperatures and Enthalpies of Fusion and Crystallization of Polymers by Differential Scanning Calorimetry

D4404 Test Method for Determination of Pore Volume and Pore Volume Distribution of Soil and Rock by Mercury Intrusion Porosimetry

D5296 Test Method for Molecular Weight Averages and Molecular Weight Distribution of Polystyrene by High Performance Size-Exclusion Chromatography

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

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 Compatibility of Absorbable/Resorbable 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

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 10993 Biological Evaluation of Medical Devices

ISO 11135 Sterilization of Health Care Products—Ethylene Oxide

ISO 11137 Sterilization of Health Care Products—Radiation

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 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 9000 Quality Management Systems—Fundamentals and Vocabulary

ISO 9001 Quality Systems Management

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

<231> Heavy Metals—Method II

<724> Drug Release

⁴ Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, <http://www.ansi.org>.

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>.

³ The last approved version of this historical standard is referenced on www.astm.org.

- <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 Other Documents:⁸

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 byproducts 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.

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 injection 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.

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.

5.2 *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,

⁸ 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>.

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

(T_g). Almost any low molecular weight 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. As a result, any plasticizer should be fully understood as to its systemic toxicity (for example, excretion, concentration in organs, and so forth). If adequate toxicological information is unavailable for the utilized plasticizer(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, depending 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 profile.

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.

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 Sterilization Processing—A summary of sterilization methods and standards is presented later 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, specimens shall be packaged and sterilized in a manner substantially consistent with that of the final device.

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.

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.

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

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 GPC IR Solubility Swelling Viscosity ASTM D5296
C—Morphology (Supramolecular 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
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

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*

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)
C—Static Strength and Stiffness	Fracture/Loosening under Anticipated Loading (for example, shear)	ASTM D638 , D695 —Tensile/compressive properties ASTM F2502 —Torque (for example, screws); Shear (for example, pins) <i>in-vitro</i> mechanical testing under analogous loading conditions
D—Stress Concentrations, Residual Stresses	Determine the potential presence and location of high stresses and their effect on performance of the device	Geometric Characterization and Measurement (for example, fillet and corner radii)—SEM, etc. <i>Note</i> —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
E—Viscoelasticity (time-dependent deformation or relaxation)	Loosening	Creep, ASTM D2990 Stress Relaxation, ASTM D2991
F—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 Characterization of aged/degraded samples, including: mechanical properties; microstructure, weight loss, molecular weight, Tg, crystallinity, dimensional stability (for example, swelling, stretching) <i>Note</i> —use sterilized samples for all evaluations or demonstrate no significant effect on all properties
G—Biocompatibility	Compatibility of Bulk Material; Compatibility of Particles and Degradation Byproducts (Synovitis—see Appendix X2) Metabolic pathways	ISO 10993 ASTM F748 Heavy metals (USP <231>)
H—Preclinical (<i>in vivo</i>) Evaluations	Localized inflammatory response; histological resolution of absorbable component(s)	<i>in vivo</i> ASTM F1983 X-ray, microCT (ASTM E1441 , E1570), ultrasound, OCT, MRI, and others Post-retrieval Optical microscopy SEM histology

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 and Fatigue*—When assessing polymer degradation under load, it may be necessary to consider and monitor creep or fatigue, or both, either 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.

(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 byproducts 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.

NOTE 4—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 maintenance of pH is essential for proper hydrolytic evaluation of a hydrolysable 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 5—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**

7.2 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 pro-

vides 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 6—When utilizing any radiation-based sterilization method, molecular weight changes needs 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.⁹

7.2.1.1 Gamma Sterilization—Gamma radiation is often utilized in the sterilization of hydrolysable polyesters. While this method has the benefit of leaving no gaseous residuals requiring removal, drops 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 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

⁹ 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.

assess the device's ability to fulfill the intended use upon its removal from a properly stored package.

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 are 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 environment.

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 Package 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; and
- (4) 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) **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.

8.2 *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 byproducts. (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 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), assessment duration, and bone/tissue turnover rate (typically higher in animals than in humans). Appendix X1.2 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 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 *Acidic Byproducts*—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 byproducts may have on the implant's functional performance.

8.2.4 *Metabolic Byproducts*—An essential aspect of implant design is to understand an absorbable device's hydrolytic/enzymatic degradation byproducts 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.

9.2 This stage of device evaluation typically involves animal experimentation. Absorbable specific guidance for *in vivo* testing can be found in 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.

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), and others (see **Table 2**—Section H).

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.

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>

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., Pihlajamäki, 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 Molecular weight 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 molecular weight; 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 byproducts 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. “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 to either an implantable device or a raw material since common utilization is routinely applied broadly to include composting and other natural processes (including ultra-violet radiation) that cause materials to either intentionally or unintentionally break down into chemical or particulate matter, or both. However, use of the term “degrade” and its derivatives is considered acceptable when referring to chain scission within the implantable device or polymer (for example, “The absorbable implant degrades through hydrolysis” or “During extrusion, absorbable polyglycolide is prone to thermal degradation”).

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