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Standard Guide for Characterization and Testing of Biomaterial Scaffolds Used in Tissue-Engineered Medical Products¹

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^{e1} NOTE—The designation, year date, and footnote 1 were editorially corrected in June 2002.

1. Scope

1.1 This guide is a resource of currently available test methods for the characterization of biomaterial scaffolds used to develop and manufacture tissue-engineered medical products (TEMPs).

1.2 The test methods contained herein guide characterization of the bulk physical, chemical, mechanical, and surface properties of a scaffold construct. Such properties may be important for the success of a TEMP, especially if they affect cell retention, activity and organization, the delivery of bioactive agents, or the biocompatibility and bioactivity within the final product.

1.3 This guide may be used as guidance in the selection of appropriate test methods for the generation of a raw material or original equipment manufacture (OEM) specification. This guide also may be used to characterize the scaffold component of a finished medical product.

1.4 This guide addresses natural, synthetic, or combination scaffold materials with or without bioactive agents or biological activity. This guide does not address the characterization or release profiles of any biomolecules, cells, drugs, or bioactive agents that are used in combination with the scaffold.

1.5 *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 requirements prior to use.*

2. Referenced Documents

2.1 ASTM Standards:

- D 412 Test Methods for Vulcanized Rubber and Thermoplastic Rubbers and Thermoplastic Elastomers—Tension²
- D 570 Test Method for Water Absorption of Plastics³
- D 638 Test Method for Tensile Properties of Plastics³

D 648 Test Method for Deflection Temperature of Plastics Under Flexural Load in the Edgewise Position³

D 671 Test Method for Flexural Fatigue of Plastics by Constant-Amplitude-of-Force³

D 695 Test Method for Compressive Properties of Rigid Plastics³

D 747 Test Method for Apparent Bending Modulus of Plastics by Means of a Cantilever Beam³

D 790 Test Methods for Flexural Properties of Unreinforced and Reinforced Plastics and Electrical Insulating Materials³

D 792 Test Methods for Density and Specific Gravity (Relative Density) of Plastics by Displacement³

D 882 Test Method for Tensile Properties of Thin Plastic Sheet³

D 1042 Test Method for Linear Dimensional Changes of Plastics Under Accelerated Service Conditions³

D 1238 Test Method for Flow Rates of Thermoplastics by Extrusion Plastometer³

D 1388 Test Method for Stiffness of Fabrics⁴

D 1621 Test Method for Compressive Properties of Rigid Cellular Plastics³

D 1623 Test Method for Tensile and Tensile Adhesion Properties of Rigid Cellular Plastics³

D 1708 Test Method for Tensile Properties of Plastics by Use of Microtensile Specimens³

D 1898 Practice for Sampling of Plastics⁵

D 2857 Practice for Dilute Solution Viscosity of Polymers⁶

D 2873 Test Method for Interior Porosity of Poly(Vinyl Chloride) (PVC) Resins by Mercury Intrusion Porosimetry⁶

D 2990 Test Methods for Tensile, Compressive, and Flexural Creep and Creep-Rupture of Plastics⁶

D 3016 Practice for Use of Liquid Exclusion Chromatography Terms and Relationships⁶

D 3039/D 3039M Test Method for Tensile Properties of

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 F04.43 on Tissue Engineered Biomaterials.

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² Annual Book of ASTM Standards, Vol 09.01.

³ Annual Book of ASTM Standards, Vol 08.01.

⁴ Annual Book of ASTM Standards, Vol 07.01.

⁵ Discontinued 1998; see 1997 Annual Book of ASTM Standards, Vol 08.01.

⁶ Annual Book of ASTM Standards, Vol 08.02.

Polymer Matrix Composite Materials⁷

- D 3417** Test Method for Enthalpies of Fusion and Crystallization of Polymers by Differential Scanning Calorimetry (DSC)⁶
- D 3418** Test Method for Transition Temperatures of Polymers by Differential Scanning Calorimetry⁶
- D 4001** Test Method for Determination of Weight-Average Molecular Weight of Polymers by Light Scattering⁶
- D 4404** Test Method for Determination of Pore Volume and Pore Volume Distribution of Soil and Rock by Mercury Intrusion Porosimetry⁸
- D 4603** Test Method for Determining Inherent Viscosity of Poly(Ethylene Terephthalate) (PET) by Glass Capillary Viscometer⁹
- D 5226** Practice for Dissolving Polymer Materials⁹
- D 5296** Test Method for Molecular Weight Averages and Molecular Weight Distribution of Polystyrene by High Performance Size-Exclusion Chromatography⁹
- D 5732** Test Method for Stiffness of Nonwoven Fabrics Using the Cantilever Test¹⁰
- D 6125** Test Method for Bending Resistance of Paper and Paperboard (Gurley Type Tester)¹¹
- D 6420** Test Method for Determination of Gaseous Organic Compounds by Direct Interface Gas Chromatography-Mass Spectrometry¹²
- D 6474** Test Method for Determining Molecular Weight Distribution and Molecular Weight Averages of Polyolefins by High Temperature Gel Permeation Chromatography⁹
- D 6539** Test Method for Measurement of Pneumatic Permeability of Partially Saturated Porous Materials by Flowing Air¹³
- D 6579** Practice for Molecular Weight Averages and Molecular Weight Distribution of Hydrocarbon and Terpene Resins by Size-Exclusion Chromatography¹⁴
- E 128** Test Method for Maximum Pore Diameter and Permeability of Rigid Porous Filters for Laboratory Use¹⁵
- E 177** Practice for Use of the Terms Precision and Bias in ASTM Test Methods¹⁶
- E 456** Terminology for Relating to Quality and Statistics¹⁶
- E 473** Terminology Relating to Thermal Analysis¹⁶
- E 691** Practice for Conducting an Interlaboratory Study to Determine the Precision of a Test Method¹⁶
- E 793** Test Method for Enthalpies of Fusion and Crystallization by Differential Scanning Calorimetry¹⁶
- E 794** Test Method for Melting and Crystallization Temperatures By Thermal Analysis¹⁶

- E 967** Practice for Temperature Calibration of Differential Scanning Calorimeters and Differential Thermal Analyzers¹⁶
- E 968** Practice for Heat Flow Calibration of Differential Scanning Calorimeters¹⁶
- E 996** Practice for Reporting Data in Auger Electron Spectroscopy and X-Ray Photoelectron Spectroscopy¹⁷
- E 1078** Guide for Procedures for Specimen Preparation and Mounting in Surface Analysis¹⁷
- E 1142** Terminology Relating to Thermophysical Properties¹⁶
- E 1294** Test Method for Pore Size Characteristics of Membrane Filters Using Automated Liquid Porosimeter¹⁸
- E 1298** Guide for Determination of Purity, Impurities, and Contaminants in Biological Drug Products¹⁸
- E 1356** Test Method for Assignment of the Glass Transition Temperatures by Differential Scanning Calorimetry or Differential Thermal Analysis¹⁶
- E 1642** Practice for General Techniques of Gas Chromatography Infrared (GC/IR) Analysis¹⁷
- E 1829** Guide for Handling Specimens Prior to Surface Analysis¹⁷
- F 151** Test Method for Residual Solvents in Flexible Barrier Materials¹¹
- F 316** Test Method for Pore Size Characteristics of Membrane Filters by Bubble Point and Mean Flow Pore Test¹⁹
- F 748** Practice for Selecting Generic Biological Test Methods for Materials and Devices²⁰
- F 1249** Test Method for Water Vapor Transmission Rate Through Plastic Film and Sheet Using a Modulated Infrared Sensor¹¹
- F 1251** Terminology Relating to Polymeric Biomaterials in Medical and Surgical Devices²⁰
- F 1634** Practice for In-Vitro Environmental Conditioning of Polymer Matrix Composite Materials and Implant Devices²⁰
- F 1635** Test Method for In Vitro Degradation Testing of Poly (L-lactic Acid) Resin and Fabricated Form for Surgical Implants²⁰
- F 1884** Test Method for Determining Residual Solvents in Packaging Materials¹¹
- F 1980** Guide for Accelerated Aging of Sterile Medical Device Packages¹¹
- F 1983** Practice for Assessment of Compatibility of Absorbable/Resorbable Biomaterials for Implant Applications¹¹
- F 2025** Practice for Gravimetric Measurement of Polymeric Components for Wear Assessment²⁰
- F 2027** Guide for Characterization and Testing of Substrate Materials for Tissue-Engineered Medical Products²⁰
- G 120** Practice for Determination of Soluble Residual Contamination in Materials and Components by Soxhlet Extraction¹⁵

⁷ Annual Book of ASTM Standards, Vol 15.03.

⁸ Annual Book of ASTM Standards, Vol 04.08.

⁹ Annual Book of ASTM Standards, Vol 08.03.

¹⁰ Annual Book of ASTM Standards, Vol 07.02.

¹¹ Annual Book of ASTM Standards, Vol 15.09.

¹² Annual Book of ASTM Standards, Vol 11.03.

¹³ Annual Book of ASTM Standards, Vol 04.09.

¹⁴ Annual Book of ASTM Standards, Vol 06.03.

¹⁵ Annual Book of ASTM Standards, Vol 14.04.

¹⁶ Annual Book of ASTM Standards, Vol 14.02.

¹⁷ Annual Book of ASTM Standards, Vol 03.06.

¹⁸ Annual Book of ASTM Standards, Vol 11.05.

¹⁹ Discontinued 1995; see 1994 Annual Book of ASTM Standards, Vol 11.02.

²⁰ Annual Book of ASTM Standards, Vol 13.01.

2.2 AAMI Standards:

AAMI STBK9-1 Sterilization—Part 1: Sterilization in Health Care Facilities²¹

AAMI STBK9-2 Sterilization—Part 2: Sterilization Equipment²¹

AAMI STBK9-3 Sterilization—Part 3: Industrial Process Control²¹

2.3 ANSI Standards:

ANSI/ISO/ASQ Q9000-2000: Quality Management Systems—Fundamentals and Vocabulary²²

ANSI/ISO/ASQ Q9001-2000: Quality Management Systems: Requirements²²

2.4 British Standards Institute:

British Standard—Animal Tissues and Their Derivatives Utilized in the Manufacture of Medical Devices—Part 1: Analysis and Management of Risk (EN 12442-1)²²

British Standard—Animal Tissues and Their Derivatives Utilized in the Manufacture of Medical Devices—Part 2: Controls on Sourcing, Collection, and Handling (EN 12442-2)²²

British Standard—Animal Tissues and Their Derivatives Utilized in the Manufacture of Medical Devices—Part 3: Validation of the Elimination and/or Inactivation of Viruses and Transmissible Agents (EN 12442-3)²²

2.5 ISO Standards:

ISO 1133-1991 Determination of the Melt-Mass Flow Rate (MFR) and the Melt Volume-Flow Rate (MVR) of Thermoplastics²²

ISO 10993-9 Biological Evaluation of Medical Devices—Part 9: Degradation of Materials Related to Biological Testing²²

ISO 10993-13 Biological Evaluation of Medical Devices—Part 13: Identification and Quantification of Degradation Products from Polymers²²

ISO 10993-14 Biological Evaluation of Medical Devices—Part 14: Identification and Quantification of Degradation Products from Ceramics²²

ISO 10993-15 Biological Evaluation of Medical Devices—Part 15: Identification and Quantification of Degradation Products from Coated and Uncoated Metals and Alloys²²

ISO 11357-1 Plastics—Differential Scanning Calorimetry (DSC)—Part 1: General Principles²²

ISO 11357-2 Plastics—Differential Scanning Calorimetry (DSC)—Part 2: Determination of Glass Transition Temperature²²

2.6 U.S. Code of Federal Regulations:

Title 21—Food and Drugs Services, Part 820—Quality System Regulation (21 CFR Part 820)²³

2.7 U.S. Pharmacopeia (USP) Standards:

Source: General Tests and Assays—USP24/NF19, Jan. 1, 2000²⁴

3. Terminology

3.1 Unless provided otherwise in 3.2, terminology shall be in conformance with Terminology F 1251.

3.2 Definitions:

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

3.2.2 *pores, n*—an inherent or induced network of channels and open spaces within an otherwise solid structure.

3.2.3 *porometry, n*—the determination of the distribution of pore diameters relative to direction of fluid flow by the displacement of a wetting liquid as a function of pressure.

3.2.4 *porosimetry, n*—the determination of pore volume and pore size distribution through the use of a nonwetting liquid (typically mercury) intrusion into a porous material as a function of pressure.

3.2.5 *porosity, n*—property of a solid which contains an inherent or induced network of channels and open spaces. Porosity can be measured by the ratio of pore (void) volume to the apparent (total) volume of a porous material and is commonly expressed as a percentage.

3.2.6 *scaffold, n*—a support, delivery vehicle, or matrix for facilitating the migration, binding, or transport of cells or bioactive molecules used to replace, repair, or regenerate tissues.

3.2.6.1 *Discussion*—ASTM Committee F04 is continuing to refine definitions for the terms tissue engineering, tissue-engineered medical products (TEMPs), and scaffold. Final definitions will be from consideration of Committee F04 and other resources such as *The Williams Dictionary of Biomaterials* (9) and will be balloted at a later date.

4. Summary of Guide

4.1 The physicochemical and three-dimensional characteristics of the scaffold material are expected to influence the properties of TEMPs. It is the intent of this guide to provide a compendium of materials characterization techniques for properties that may be related directly to the functionality of scaffolds for TEMPs.

4.2 Numerous general areas of characterization also should be considered when developing a scaffold for TEMPs. Among these are compositional identity, physical and chemical properties or characteristics, viable sterilization techniques, degradability/resorbability, and mechanical properties.

4.3 Application of the test methods contained within this guide do not guarantee clinical success of a finished product but will help to ensure consistency in the properties and characterization of a given scaffold material.

²¹ Available from the Association for the Advancement of Medical Instrumentation, 1110 N. Glebe Rd., Suite 220, Arlington, VA 22201-4795.

²² Available from American National Standards Institute, 25 W. 43rd St., 4th Floor, New York, NY 10036.

²³ Available from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20593.

²⁴ Available from U.S. Pharmacopeia, 12601 Twinbrook Pkwy., Rockville, MD 20852. The standards will be listed by appropriate USP citation number. Succeeding USP editions alternately may be referenced.