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Standard Guide for ~~Characterization and Testing of Substrate Materials for Tissue-Engineered Medical Products~~Characterization and Testing of Raw or Starting Biomaterials for Tissue-Engineered Medical Products[1]

This standard is issued under the fixed designation F 2027; 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—Table 1 was editorially corrected in June 2001.~~

1. Scope

~~1.1This guide addresses material characteristics of raw or virgin materials in a nonfabricated form that will ultimately undergo additional processing into growth, support, or delivery vehicles for cells or biomolecules. This guide does not apply to packaged, sterilized, and finished tissue-engineered medical products.~~

~~1.2The purpose of the guide is to assist the developer of tissue-engineered medical products to locate relevant existing standards and test methods and to provide guidance for interim use of materials for which a standard does not exist.~~

1.1 This document provides guidance on writing a materials specification for raw or starting biomaterials intended for use in tissue engineering scaffolds for growth, support, or delivery of cells and/or biomolecules. This guide does not apply to biomaterials that are already in a scaffold form or are finished tissue-engineered medical products.

1.2 The purpose of this guide is to provide a compendium of relevant existing standards and test methods for biomaterials already commonly used within medical products and to provide characterization guidance for interim use of raw biomaterials for which a standard does not exist.

1.3 This guide covers specifications and characterizations of all the major classes of materials including polymers, ceramics, metals, composites, and natural tissues of human, animal, or plant origin. This guide does not apply to pharmaceuticals.

1.4 This guide is focused on specification of chemical, physical, and mechanical properties of the raw or starting material. It does not include safety and biocompatibility requirements since safety and biocompatibility testing is typically done on materials fabricated into a final form to include all possible effects of fabrication and sterilization techniques.

1.5 Compliance with materials specifications developed in accordance with this standard may not necessarily result in a material suitable for its intended purpose. Additional testing specific to the intend use may be required.

2. Referenced Documents

2.1 *ASTM Standards:* [2]

D 1763 Specification for Epoxy Resins

D 1898~~Practice for Sampling of Plastics~~ Practice for Sampling of Plastics[3]

E 1298 Guide for Determination of Purity, Impurities, and Contaminants in Biological Drug Products

F 67~~Specification for Unalloyed Titanium for Surgical Implant Applications~~

~~F451Specification for Acrylic Bone Cement[5]~~ Specification for Unalloyed Titanium, for Surgical Implant Applications (UNS R50250, UNS R50400, UNS R50550, UNS R50700)

F 75 Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting Alloy for Surgical Implants (UNS R30075)

F 90 Specification for Wrought Cobalt-20Chromium-15Tungsten-10Nickel Alloy for Surgical Implant Applications (UNS R30605)

~~[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 F04.42 on Tissue Characterization.~~

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[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 F04.42 on Biomaterials and Biomolecules for TEMPs.

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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* ~~, Vol 08.01.~~volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Withdrawn.

F 136 Specification for Wrought Titanium-6Aluminum-4Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications (UNS R56401)
F 138 Specification for Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless Steel Bar and Wire for Surgical Implants (UNS S31673)
F 139 Specification for Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless Steel Sheet and Strip for Surgical Implants (UNS S31673)
F 451 Specification for Acrylic Bone Cement
F 560~~Specification for Unalloyed Tantalum for Surgical Implant Applications[5]~~ Specification for Unalloyed Tantalum for Surgical Implant Applications (UNS R05200, UNS R05400)
F 562 Specification for Wrought 35Cobalt-35Nickel-20Chromium-10Molybdenum Alloy for Surgical Implant Applications (UNS R30035)
F 563 Specification for Wrought Cobalt-20Nickel-20Chromium-3.5Molybdenum-3.5Tungsten-5Iron Alloy for Surgical Implant Applications (UNS R30563)
F 602 Criteria for Implantable Thermoset Epoxy Plastics
F 603 Specification for High-Purity Dense Aluminum Oxide for ~~Surgical Implant~~ Medical Application
F 604~~Specification for Silicone Elastomers Used in Medical Applications[5]~~ Specification for Silicone Elastomers Used in Medical Applications
F 619 Practice for Extraction of Medical Plastics
F 624~~Guide for Evaluation of Thermoplastic Polyurethane Solids and Solutions for Biomedical Applications[5]~~ Guide for Evaluation of Thermoplastic Polyurethane Solids and Solutions for Biomedical Applications
F 639 Specification for Polyethylene Plastics for Medical Applications
F 641~~Specification for Implantable Epoxy Electronic Encapsulants[5]~~ Specification for Implantable Epoxy Electronic Encapsulants
F 648 Specification for Ultra-High-Molecular-Weight Polyethylene Powder and Fabricated Form for Surgical Implants
F 665 Classification for Vinyl Chloride Plastics Used in Biomedical Application
F 702~~Specification for Polysulfone Resin for Medical Applications[5]~~
Specification for Polysulfone Resin for Medical Applications
F 755 Specification for Selection of Porous Polyethylene for Use in Surgical Implants
~~F748Practice for Selecting Generic Biological Test Methods for Materials and Devices[5]~~
~~F749Practice for Evaluating Material Extracts by Intracutaneous Injection in the Rabbit[5]~~
~~F 755Specification for Selection of Porous Polyethylene for Use in Surgical Implants[5]~~
~~F756Practice for Assessment of Hemolytic Properties of Materials[5]~~
~~F763Practice for Short-Term Screening of Implant Materials[5]~~
~~F813Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices[5]~~
~~F895Test Method for Agar Diffusion Cell Culture Screening for Cytotoxicity[5]~~
~~F981Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Bone[5]~~ Specification for Selection of Porous Polyethylene for Use in Surgical Implants
F 997 Specification for Polycarbonate Resin for Medical Applications
F 1088 Specification for Beta-Tricalcium Phosphate for Surgical Implantation
F 1185 Specification for Composition of ~~Ceramic~~ Hydroxylapatite for Surgical Implants
F 1251~~Terminology Relating to Polymeric Biomaterials in Medical and Surgical Devices[5]~~
~~F1425Specification for Virgin Poly (L-lactic Acid) Resin for Surgical Implants[3]~~
~~F1439Guide for Performance of Lifetime Bioassay for the Tumorigenic Potential of Implant Materials[5]~~ Terminology Relating to Polymeric Biomaterials in Medical and Surgical Devices
F 1472~~Specification for Wrought Ti-6Al-4V Alloy for Surgical Implant Applications[5]~~ Specification for Wrought Titanium-6Aluminum-4Vanadium Alloy for Surgical Implant Applications (UNS R56400)
F 1537 Specification for Wrought Cobalt-28Chromium-6Molybdenum Alloys for Surgical Implants (UNS R31537, UNS R31538, and UNS R31539)
F 1538 Specification for Glass and Glass Ceramic Biomaterials for Implantation
F 1579 Specification for Polyaryletherketone (PAEK) ~~Resins~~Polymers for Surgical Implant Applications
F 1581 Specification for Composition of Anorganic Bone for Surgical Implants
F 1634 Practice for In-Vitro Environmental Conditioning of Polymer Matrix Composite Materials and Implant Devices
F 1635~~Test Method for In Vitro Degradation testing of Poly (L-Lactic Acid) Resin and Fabricated Forms for Surgical Implants[5]~~
Test Method for ***in vitro*** Degradation Testing of Hydrolytically Degradable Polymer Resins and Fabricated Forms for Surgical Implants
F 1713 Specification for Wrought Titanium-13Niobium-13Zirconium Alloy for Surgical Implant Applications (UNS R58130)
F 1855~~Specification for Polyoxymethylene Acetal for Medical Applications[5]~~ Specification for Polyoxymethylene (Acetal) for Medical Applications

F 1873 Specification for High-Purity Dense Yttria Tetragonal Zirconium Oxide Polycrystal (Y-TZP) for Surgical Implant Applications
F 1876~~Standard Specification~~ Specification for Polyetherketoneetherketoneketone (PEKEKK) Resins for Surgical Implant Applications
F 1877 Practice for Characterization of Particles
F 1925 Specification for Virgin Poly(L-Lactic Acid) Resin for Surgical Implants
F 1926~~Test Method for Evaluation of the Environmental Stability of Calcium Phosphate Coatings~~[5] Test Method for Evaluation of the Environmental Stability of Calcium Phosphate Coatings
F 2064 Guide for Characterization and Testing of Alginates as Starting Materials Intended for Use in Biomedical and Tissue-Engineered Medical Products Application
F 2103 Guide for Characterization and Testing of Chitosan Salts as Starting Materials Intended for Use in Biomedical and Tissue-Engineered Medical Product Applications
F 2150 Guide for Characterization and Testing of Biomaterial Scaffolds Used in Tissue-Engineered Medical Products
F 2212 Guide for Characterization of Type I Collagen as Starting Material for Surgical Implants and Substrates for Tissue Engineered Medical Products (TEMPs)
F 2259 Test Method for Determining the Chemical Composition and Sequence in Alginate by Proton Nuclear Magnetic Resonance (1H NMR) Spectroscopy
F 2260 Test Method for Determining Degree of Deacetylation in Chitosan Salts by Proton Nuclear Magnetic Resonance (1H NMR) Spectroscopy
F 2347 Guide for Characterization and Testing of Hyaluronan as Starting Materials Intended for Use in Biomedical and Tissue Engineered Medical Product Applications

2.2 *Other Document:*
~~U.S. Pharmacopeia, Edition XXIII~~
U.S. Pharmacopeia, Edition XXX or current edition[4]

2.3 ~~*ISO Standards:*~~ *ISO and CEN Standards:*[5]
~~ISO 6474:1994Implants for Surgery - Ceramic Materials Based on Alumina~~
~~ISO 10993-1,Biological Evaluation of Medical Devices—Part 1: Evaluation and testing~~
~~ISO 10993-9—Part 9:Framework for identification and quantification of potential degradation products~~
~~ISO 10993-12 - Part 12:Sample preparation and reference materials~~ ISO 6474 Implants for Surgery—Ceramic Materials Based on Alumina
ISO/IEC 17025 General Requirements for the Competence of Testing and Calibration Laboratories
ISO 10993-1 Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing
ISO 10993-9—Part 9: Framework for Identification and Quantification of Potential Degradation Products
ISO 10993-12—Part 12: Sample Preparation and Reference Materials
~~ISO/DIS 10993-13 - Part 13:Identification and quantification of potential degradation products from polymeric medical devices~~ ISO 10993-13—Part 13: Identification and Quantification of Potential Degradation Products from Polymeric Medical Devices
~~ISO/DIS 10993-14 - Part 14:Identification and quantification of potential degradation products from ceramics~~ ISO 10993-14—Part 14: Identification and Quantification of Potential Degradation Products from Ceramics
~~ISO/DIS 10993-15—Part 15:Identification and quantification of potential degradation products from metals and alloys~~
~~ISO/DIS 10993-17—Part 17:Methods for the establishment of allowable limits for leachable substances using health-based risk assessment~~
~~ISO/CD 10993-18—Part 18:Chemical characterization of materials~~
~~ISO/NWI 10993-19—Part 19:Physico-chemical, mechanical and morphological characterization of materials~~
~~prEN 12442-1Animal tissues and their derivatives utilized in the manufacture of medical devices—Part 1: Analysis and management of risk~~ ISO 10993-15—Part 15: Identification and Quantification of Potential Degradation Products from Metals and Alloys
ISO 10993-17—Part 17: Methods for the Establishment of Allowable Limits for Leachable Substances using Health-Based Risk Assessment
ISO/CD 10993-18—Part 18: Chemical Characterization of Materials
ISO/NWI 10993-19—Part 19: Physico-chemical, Mechanical and Morphological Characterization of Materials
BSI BS EN 12442-1 Animal Tissues and Their Derivatives Utilized in the Manufacture of Medical Devices—Part 1: Analysis and Management of Risk

~~[4] Annual Book of ASTM Standards, Vol 11.05.~~
[4] Available from U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.
~~[5] Annual Book of ASTM Standards, Vol 13.01.~~
[5] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

prEN 12442-2—Part 2:Controls on sourcing, collection and handling
prEN 12442-3—Part 3:Validation of the elimination and/or inactivation of virus and transmissible agents BSI BS EN 12442-2—Part 2: Controls on Sourcing, Collection and Handling
BSI BS EN 12442-3—Part 3: Validation of the Elimination and/or Inactivation of Virus and Transmissible Agents
ISO 111607Product packaging
2.4 Code of Federal Regulations, Title 21, Part 820. Federal Register Vol. 43, No 141. July 21, 1978
Product Packaging
2.4 *Food and Drug Administration Documents:*[6, 7]
21 CFR Part 610 General Biological Products Standards
21 CFR Part 820 Quality System Regulation
21 CFR Part 1270 Human Tissue Intended for Transplantation
21 CFR Part 1271 Human Cells, Tissues, and Cellular and Tissue Based Products

3. Terminology

3.1*Definitions:*
3.1.1*natural materials*, *n*—synthesized or produced by living cells.
3.1.2*substrates*, *n*—raw or virgin materials that will ultimately be used in tissue-engineered medical products for growth, support, or delivery of cells or biomolecules. Summary of Guide
3.1 Novel materials that do not yet have standards associated with them are being created for use in tissue engineering applications. The lack of standardized specifications for the physical and chemical properties of these new materials may lead to variation between lots, which could create variation in observed biological performance of the final product. It is the intent of this guide to provide a compendium of existing medical product materials specifications and test methods to serve as a guide for specifying the important chemical and physical properties of new raw or starting materials. Tables of commonly specified chemical, physical, and mechanical requirements are provided for each type of material (for example, ceramic, metal, polymer, composite, natural product) to assist with the development of a specification for a new biomaterial to be utilized for tissue engineering.
3.2 This guide is focused on providing a characterization template for raw or starting materials prior to their fabrication into a scaffold or tissue-engineered medical product. Guidance for the characterization and testing of biomaterials after they have been formulated into three-dimensional scaffolds can be found in Guide F 2150.

4. Descriptive Chemical and Physical Information

4.1The substrate material shall have specifications for an extensive set of chemical and physical properties such as, but not limited to, those listed in Significance and Use
4.1 The physico-chemical characteristics of the raw or starting biomaterial used in regenerative medicine scaffolds carries significant potential to affect product performance by influencing cell behavior and/or the release of bioactive molecules or drugs. This guide describes recommended specifications or characterizations of raw or starting biomaterials to ensure reproducibility prior to their fabrication into implantable tissue engineering scaffolds and/or controlled release matrices.

5. Classification of Biomaterials

5.1 The properties of a biomaterial are a function of which type of material they are made from. All materials can be classified according to their atomic content and bonding as either a ceramic, polymer, metal, or composite. Ceramics consist of ionically or covalently bonded metallic and non-metallic elements such as calcium phosphate or aluminum phosphate and include minerals and glasses, sintered or unsintered. Polymers consist of a repeating backbone structure. Metals are made of metallic elements bonded together by metallic bonds. Composites are blends of any of the three main types of materials. Even materials derived from natural sources such as anorganic bone or chitosan fall into one of these basic types; anorganic bone is a ceramic and chitosan is a polymer.
5.2 To use this guide, first classify the material into one of the types above. Important properties that should be specified are listed and tabulated according to material type in Table 1 and Table 2.
4.2The necessary chemical and physical tests are a function of the class of material (for example, ceramic, polymer, metal, composite, or natural material). Each type of material has specific sets of properties to be specified. Natural polymers such as collagen or demineralized bone, and natural ceramics such as anorganic bone, are considered a subset of the polymers and ceramics categories respectively. The following AAMI, ISO, ASTM, and other recognized voluntary standards committee standards, include specific techniques for determining the chemical and physical properties listed in

[6] Available from US Pharmacopia, Vol. 23 Mack Publishing Co., Easton, PA, 1995.
[6] Available from Food and Drug Administration (FDA), 5600 Fishers Ln., Rockville, MD 20857, http://www.fda.gov. Additional titles (Parts 1–1499) can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm.
[7] Available from the American National Standards Institute, 25 W. 43rd St., 4th Floor, New York, NY 10036.
[7] FDA guidance documents searchable through this website, (http://www.fda.gov/opacom/morechoices/industry/guidedc.htm). Selected Guidance Documents Applicable to Combination Products may be found at this website, (http://www.fda.gov/oc/combination/guidance.html).