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

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1. Scope

1.1 This document provides guidance on writing a materials specification for raw or starting materials intended for use in tissue engineering scaffolds for growth, support, or delivery of cells and/or biomolecules. This guide does not apply to materials 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 materials already commonly used within medical products and to provide characterization guidance for interim use of raw materials 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 intended use may be required.

2. Referenced Documents

2.1 *ASTM Standards:*[2]

D1763 Specification for Epoxy Resins

D1898 Practice for Sampling of Plastics (Withdrawn 1998)[3]

E1298 Guide for Determination of Purity, Impurities, and Contaminants in Biological Drug Products (Withdrawn 2014)[3]

F67 Specification for Unalloyed Titanium, for Surgical Implant Applications (UNS R50250, UNS R50400, UNS R50550, UNS R50700)

F75 Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting Alloy for Surgical Implants (UNS R30075)

F90 Specification for Wrought Cobalt-20Chromium-15Tungsten-10Nickel Alloy for Surgical Implant Applications (UNS R30605)

F136 Specification for Wrought Titanium-6Aluminum-4Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications (UNS R56401)

F138 Specification for Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless Steel Bar and Wire for Surgical Implants (UNS S31673)

F139 Specification for Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless Steel Sheet and Strip for Surgical Implants (UNS S31673)

F451 Specification for Acrylic Bone Cement

F560 Specification for Unalloyed Tantalum for Surgical Implant Applications (UNS R05200, UNS R05400)

F562 Specification for Wrought 35Cobalt-35Nickel-20Chromium-10Molybdenum Alloy for Surgical Implant Applications (UNS R30035)

F602 Criteria for Implantable Thermoset Epoxy Plastics

F603 Specification for High-Purity Dense Aluminum Oxide for Medical Application

F619 Practice for Extraction of Medical Plastics

F624 Guide for Evaluation of Thermoplastic Polyurethane Solids and Solutions for Biomedical Applications

F639 Specification for Polyethylene Plastics for Medical Applications

F641 Specification for Implantable Epoxy Electronic Encapsulants

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

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

F648 Specification for Ultra-High-Molecular-Weight Polyethylene Powder and Fabricated Form for Surgical Implants
F665 Classification for Vinyl Chloride Plastics Used in Biomedical Application
F702 Specification for Polysulfone Resin for Medical Applications
F755 Specification for Selection of Porous Polyethylene for Use in Surgical Implants
F997 Specification for Polycarbonate Resin for Medical Applications
F1088 Specification for Beta-Tricalcium Phosphate for Surgical Implantation
F1185 Specification for Composition of Hydroxylapatite for Surgical Implants
F1251 Terminology Relating to Polymeric Biomaterials in Medical and Surgical Devices (Withdrawn 2012)[3]
F1377 Specification for Cobalt-28Chromium-6Molybdenum Powder for Coating of Orthopedic Implants (UNS R30075)
F1472 Specification for Wrought Titanium-6Aluminum-4Vanadium Alloy for Surgical Implant Applications (UNS R56400)
F1537 Specification for Wrought Cobalt-28Chromium-6Molybdenum Alloys for Surgical Implants (UNS R31537, UNS R31538, and UNS R31539)
F1538 Specification for Glass and Glass Ceramic Biomaterials for Implantation
F1579 Specification for Polyaryletherketone (PAEK) Polymers for Surgical Implant Applications (Withdrawn 2011)[3]
F1581 Specification for Composition of Anorganic Bone for Surgical Implants
F1634 Practice for ***In-Vitro*** Environmental Conditioning of Polymer Matrix Composite Materials and Implant Devices
F1635 Test Method for ***in vitro*** Degradation Testing of Hydrolytically Degradable Polymer Resins and Fabricated Forms for Surgical Implants
F1713 Specification for Wrought Titanium-13Niobium-13Zirconium Alloy for Surgical Implant Applications (UNS R58130)
F1855 Specification for Polyoxymethylene (Acetal) for Medical Applications
F1873 Specification for High-Purity Dense Yttria Tetragonal Zirconium Oxide Polycrystal (Y-TZP) for Surgical Implant Applications (Withdrawn 2007)[3]
F1876 Specification for Polyetherketoneetherketoneketone (PEKEKK) Resins for Surgical Implant Applications (Withdrawn 2012)[3]
F1877 Practice for Characterization of Particles
F1925 Specification for Semi-Crystalline Poly(lactide) Polymer and Copolymer Resins for Surgical Implants
F2026 Specification for Polyetheretherketone (PEEK) Polymers for Surgical Implant Applications
F2064 Guide for Characterization and Testing of Alginates as Starting Materials Intended for Use in Biomedical and Tissue Engineered Medical Product Applications
F2103 Guide for Characterization and Testing of Chitosan Salts as Starting Materials Intended for Use in Biomedical and Tissue-Engineered Medical Product Applications
F2150 Guide for Characterization and Testing of Biomaterial Scaffolds Used in Tissue-Engineered Medical Products
F2212 Guide for Characterization of Type I Collagen as Starting Material for Surgical Implants and Substrates for Tissue Engineered Medical Products (TEMPs)
F2259 Test Method for Determining the Chemical Composition and Sequence in Alginate by Proton Nuclear Magnetic Resonance (^{1}H NMR) Spectroscopy
F2260 Test Method for Determining Degree of Deacetylation in Chitosan Salts by Proton Nuclear Magnetic Resonance (^{1}H NMR) Spectroscopy
F2313 Specification for Poly(glycolide) and Poly(glycolide-co-lactide) Resins for Surgical Implants with Mole Fractions Greater Than or Equal to 70 % Glycolide
F2347 Guide for Characterization and Testing of Hyaluronan as Starting Materials Intended for Use in Biomedical and Tissue Engineered Medical Product Applications
F2579 Specification for Amorphous Poly(lactide) and Poly(lactide-co-glycolide) Resins for Surgical Implants
F2848 Specification for Medical-Grade Ultra-High Molecular Weight Polyethylene Yarns
F3160 Guide for Metallurgical Characterization of Absorbable Metallic Materials for Medical Implants

2.2 *Other Document:*
U.S. Pharmacopeia, Edition XXX or current edition[4]
ISBT 128 The Global Information Standard for Medical Products of Human Origin[5]

2.3 *ISO and CEN Standards:*[6]
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 111607 Product Packaging
ISO/DIS 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/DIS 10993-15—Part 15: Identification and Quantification of Potential Degradation Products from Metals and Alloys

[4] Available from U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.
[5] Available from ICCBBA, P.O. Box 1309, San Bernadino, CA 92423-1309, http://iccba.org.
[6] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

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

BSI BS EN 22442-1 Animal Tissues and Their Derivatives Utilized in the Manufacture of Medical Devices—Part 1: Analysis and Management of Risk

BSI BS EN 22442-2 Animal Tissures and Their Derivative Utilized in the Manufacture of Medical Devices—Part 2: Controls on Sourcing, Collection and Handling

BSI BS EN 22442-3 Animal Tissures and Their Derivative Utilized in the Manufacture of Medical Devices—Part 3: Validation of the Elimination and/or Inactivation of Virus and Transmissible Agents

2.4 *Food and Drug Administration Documents:*

Code of Federal Regulations, Title 21, Parts 610 (General Biological Products Standards), 820 (Quality system regulation), 1270 and 1271 (Human cells or tissue intended for implantation, transplantation, infusion, or transfer into a human recipient) or other of Parts 1-1499 [7]

Additional FDA Guidance Documents[8]

Selected Guidance Documents Applicable to Combination Products[9]

3. 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 material 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 materials after they have been formulated into three-dimensional scaffolds can be found in Guide F2150.

4. Significance and Use

4.1 The physico-chemical characteristics of the raw or starting material 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 materials to ensure reproducibility prior to their fabrication into implantable tissue-engineering scaffolds and/or controlled release matrices.

5. Classification of Materials

5.1 The properties of tissue-engineering scaffolds or cell delivery vehicles are, in part, a function of the type of material from which they are made. 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 basic material types listed in 5.1. Important properties that should be specified are listed and tabulated according to material type in Table 1 and Table 2. ISO 10993-18 also provides a framework for the identification of a material and the identification and quantification of its chemical constituents.

6. Chemical Requirements

6.1 *Chemical Requirements for Ceramics*—The raw or starting material shall have specifications for relevant chemical properties such as, but not limited to, those listed within Table 1, Col. 1. This includes, for ceramics: chemical formula or composition, requirements for the major and minor elemental constituents, phase content, and processing aids.

6.2 *Chemical Requirements for Metals*—The raw or starting material shall have specifications for relevant chemical properties such as, but not limited to, those listed within Table 1, Col. 2. The composition, trace elements analysis, phase content, and any surface modification (for example, pickled, ground, polished, acid-etched) should be specified quantitatively. Corrosion susceptibility should be tested.

6.3 *Chemical Requirements for Polymers*—The raw or starting material shall have specifications for relevant chemical properties such as, but not limited to, those listed within Table 1, Col. 3. In addition to specifying the chemical formula or composition, and requirements for the major and minor elemental constituents, the following aspects should be expressed quantitatively: viscosity (molecular weight), copolymer ratio (if appropriate), synthesis method, source (if naturally harvested), additives, fillers, unreacted monomer content, curing agents, catalysts, accelerators, initiators, concentration (if supplied in solution), stability, extractables, and degradation products, mechanism and kinetics. ISO 10993-9 provides guidance on identification and quantification of potential degradation products and ISO 10993-17 provides guidance on allowable limits for leachable substances. Tests for

[7] Available through this searchable database: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm.

[8] Searchable through this website: http://www.fda.gov/opacom/morechoices/industry/guidedc.htm.

[9] Available at this wesite http://www.fda.gov/oc/combination/guidance.html.