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

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ε[1] NOTE—Table 1 was editorially corrected in June 2001.

1. Scope

1.1 This 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.

1.2 The 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.

2. Referenced Documents

2.1 *ASTM Standards:*

D 1763 Specification for Epoxy Resins[2]
D 1898 Practice for Sampling of Plastics[3]
E 1298 Guide for Determination of Purity, Impurities, and Contaminants in Biological Drug Products[4]
F 67 Specification for Unalloyed Titanium for Surgical Implant Applications[5]
F 451 Specification for Acrylic Bone Cement[5]
F 560 Specification for Unalloyed Tantalum for Surgical Implant Applications[5]
F 603 Specification for High-Purity Dense Aluminum Oxide for Surgical Implant Application[5]
F 604 Specification for Silicone Elastomers Used in Medical Applications[5]
F 624 Guide for Evaluation of Thermoplastic Polyurethane Solids and Solutions for Biomedical Applications[5]
F 641 Specification for Implantable Epoxy Electronic Encapsulants[5]
F 665 Classification for Vinyl Chloride Plastics Used in Biomedical Application[5]
F 702 Specification for Polysulfone Resin for Medical Applications[5]
F 748 Practice for Selecting Generic Biological Test Methods for Materials and Devices[5]
F 749 Practice for Evaluating Material Extracts by Intracutaneous Injection in the Rabbit[5]
F 755 Specification for Selection of Porous Polyethylene for Use in Surgical Implants[5]
F 756 Practice for Assessment of Hemolytic Properties of Materials[5]
F 763 Practice for Short-Term Screening of Implant Materials[5]
F 813 Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices[5]
F 895 Test Method for Agar Diffusion Cell Culture Screening for Cytotoxicity[5]
F 981 Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Bone[5]
F 997 Specification for Polycarbonate Resin for Medical Applications[3]
F 1088 Specification for Beta-Tricalcium Phosphate for Surgical Implantation[5]
F 1185 Specification for Composition of Ceramic Hydroxylapatite for Surgical Implants[5]
F 1251 Terminology Relating to Polymeric Biomaterials in Medical and Surgical Devices[5]
F 1425 Specification for Virgin Poly (L-lactic Acid) Resin for Surgical Implants[3]
F 1439 Guide for Performance of Lifetime Bioassay for the Tumorigenic Potential of Implant Materials[5]
F 1472 Specification for Wrought Ti-6Al-4V Alloy for Surgical Implant Applications[5]
F 1579 Specification for Polyaryletherketone (PAEK) Resins for Surgical Implant Applications[5]
F 1581 Specification for Composition of Anorganic Bone for Surgical Implants[5]
F 1634 Practice for In Vitro Environmental Conditioning of Polymer Matrix Composite Materials and Implant Devices[5]

[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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[2] *Annual Book of ASTM Standards,* Vol 08.01.
[3] Discontinued; see *1997 Annual Book of ASTM Standards,* Vol 08.01.
[4] *Annual Book of ASTM Standards,* Vol 11.05.
[5] *Annual Book of ASTM Standards,* Vol 13.01.

F 1635 Test Method for In Vitro Degradation testing of Poly (L-Lactic Acid) Resin and Fabricated Forms for Surgical Implants[5]

F 1855 Specification for Polyoxymethylene Acetal for Medical Applications[5]

F 1876 Standard Specification for Polyetherketoneetherketoneketone (PEKEKK) Resins for Surgical Implant Applications[5]

F 1926 Test Method for Evaluation of the Environmental Stability of Calcium Phosphate Coatings[5]

2.2 *Other Document:*

U.S. Pharmacopeia, Edition XXIII[6]

2.3 *ISO Standards:*[7]

ISO 6474:1994 Implants 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/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

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 12442-1 Animal tissues and their derivatives utilized in the manufacture of medical devices—Part 1: Analysis and management of risk

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

ISO 111607 Product packaging

2.4 Code of Federal Regulations, Title 21, Part 820. Federal Register Vol. 43, No 141. July 21, 1978[8]

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.

4. Descriptive Chemical and Physical Information

4.1 The substrate material shall have specifications for an extensive set of chemical and physical properties such as, but not limited to, those listed in Table 1.

4.2 The 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 Table 1 and are suggested as guides for new standards development or for interim use for those materials without existing standards.

4.2.1 *Metals*—Specification F 1472, Specification F 560, Specification F 67, and ISO/DIS 10993-15 - Part 15.

4.2.2 *Ceramics*, (for example, calcium phosphate, calcium carbonate, aluminum oxide, glasses) Specification F 603, Specification F 1088, Specification F 1185, Specification F 1581, Test Method F 1926, ISO 6474:1994, and ISO/DIS 10993-14 - Part 14.

4.2.3 *Polymers*—Specification D 1763, Practice D 1898, Specification F 451, Specification F 604, Guide F 624, Specification F 641, Classification F 665, Specification F 702, Specification F 755, Specification F 997, Terminology F 1251, Specification F 1425, Specification F 1579, Practice F 1634, Test Method F 1635, Specification F 1855, Specification F 1876, and ISO/DIS 10993-13 - Part 13.

4.2.4 Other General Test Methods—ISO/CD 10993-18—Part 18, ISO/NWI 10993-19—Part 19.

4.3 The following web site is suggested as an additional resource for relevant existing standards: www.fda.gov/cdrh/modact/recstand.html.

5. Sampling

5.1 It is suggested that the requirements shall be determined for each lot of the substrate material by sampling sizes and procedures in accordance with Practice D 1898 or some other equivalent.

TABLE 1

Chemical	Physical
Composition	density
Purity	molecular weight
Stability during storage	viscosity
Additives	compresseion strength
Trace elements	tension strength
Extractables (metals or solvents)	elastic modulus
Degradation kinetics	fatigue strength
Resorption kinetics	yield strength
Resorption kinetics	hardness
Degradation products	foreign particles
	structure - long range
	- short range

[6] Available from US Pharmacopia, Vol. 23 Mack Publishing Co., Easton, PA, 1995.

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

[8] National Archives and Records Administration, 700 Pennsylvania Ave, NW, Washington, DC 20408.

6. Handling, Packaging, and Labeling

6.1 The product should be handled and packaged as specified in USP 661 or ISO 111607 and prEN 12442-2 — Part 2, and ISO 111607.

7. Quality Program Requirements

7.1 The manufacturer should conform to Quality Systems Regulations (see CFR 21, Part 820) or its equivalent.

8. Biocompatibility

8.1 Many materials have been shown to produce a well-characterized level of biological response following long-term clinical use in laboratory animals. When new applications of a material, or modifications to the material or physical forms of the material, are being considered, then the recommendations and test methods of the following standards should be considered: Practice F 748, F 619, Practice F 749, Practice F 756, Practice F 763, Practice F 813, Practice F 981, and Guide F 1439-92 as well as Test Method F 895, ISO 10993-1, ISO/DIS 10993-9, Part 9, ISO/DIS 10993-17 - Part 17, prEN 12442-1 – Part 1, and prEN 12442-3– Part 3.

9. Keywords

9.1 biomaterials; ceramics; composites; materials; metals; polymers; substrates; tissue-engineered medical products