

Standard Guide for Tissue Engineered Medical Products (TEMPs) for Reinforcement of Tendon and Ligament Surgical Repair¹

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1. Scope

1.1 This guide is intended as a resource for individuals and organizations involved in the development, production, and delivery of tissue engineered medical products (TEMPs) intended to provide a mechanical (functional) reinforcement of the surgical repair of tendons and ligaments.

1.2 Surgical repair can include procedures that repair tendon to tendon, tendon to bone, tendon to muscle, ligament to ligament, and ligament to bone. In the context of this guide, a tendon is a fibrous cord or band that connects a muscle to a bone or other structure and consists of both dense collagenous fibers and rows of elongated tendon cells. In contrast, a ligament is a band or sheet of fibrous tissue connecting two or more bones, or cartilagenous structures.

1.3 Examples of TEMPs for use in reinforcement of tendon or ligament repairs include extracellular matrices (including allograft tissue, xenograft tissue, and tissue engineered extracellular matrix), polymeric matrices, membranes, or combinations of two or more of these, with or without cells and/or molecular mediators, where the function is to reinforce the surgical repair of tendon to tendon, tendon to bone, tendon to muscle, ligament to ligament, or ligament to bone.

1.4 The products may be rapidly degrading, slowly degrading, or non-degrading.

1.5 The guide is not intended to apply to TEMPs that have a primary function to induce a biological repair through cell or molecular action, although biologic activity may be a feature of the TEMPs. Examples of products or product concepts that are not included are (a) growth factors or cytokines applied to a biologic or synthetic scaffold, and (b) platelet-enriched plasma applied to or within a biologic or polymeric scaffold, where the primary function of the product is biologic.

1.6 The guide is not intended to apply to TEMPs that have a primary function to induce a chemical repair. An example of a product or product concept that would not be included would

be a polymeric matrix containing reagents that glue collagenous tissues together.

1.7 The guide is not intended to apply to TEMPs that are designed to be used to achieve primary surgical repair of injured tendons and ligaments.

1.8 The guide is not intended to apply to TEMPs that are designed to replace tendons or ligaments.

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

- D1004 Test Method for Tear Resistance (Graves Tear) of Plastic Film and Sheet
- D2990 Test Methods for Tensile, Compressive, and Flexural Creep and Creep-Rupture of Plastics
- D3786 Test Method for Bursting Strength of Textile Fabrics—Diaphragm Bursting Strength Tester Method
- D3787 Test Method for Bursting Strength of Textiles—Constant-Rate-of-Traverse (CRT) Ball Burst Test
- D5035 Test Method for Breaking Force and Elongation of Textile Fabrics (Strip Method)
- E139 Test Methods for Conducting Creep, Creep-Rupture, and Stress-Rupture Tests of Metallic Materials
- F1635 Test Method for *in vitro* Degradation Testing of Hydrolytically Degradable Polymer Resins and Fabricated Forms for Surgical Implants
- F1978 Test Method for Measuring Abrasion Resistance of Metallic Thermal Spray Coatings by Using the Taber Abraser

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 F04.44 on Assessment 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.

F2150 Guide for Characterization and Testing of Biomaterial Scaffolds Used in Tissue-Engineered Medical Products

F2210 Guide for Processing Cells, Tissues, and Organs for Use in Tissue Engineered Medical Products

F2211 Classification for Tissue Engineered Medical Products (TEMPs)

F2212 Guide for Characterization of Type I Collagen as Starting Material for Surgical Implants and Substrates for Tissue Engineered Medical Products (TEMPs)

F2312 Terminology Relating to Tissue Engineered Medical Products

F2383 Guide for Assessment of Adventitious Agents in Tissue Engineered Medical Products (TEMPs)

F2739 Guide for Quantitating Cell Viability Within Biomaterial Scaffolds

2.2 ISO Documents:³

ISO 10993 Biological Evaluation of Medical Devices

ISO 11135–1 Sterilization of Health Care Products—Ethylene Oxide—Part 1: Requirements for Development, Validation and Routine Control of a Sterilization Process for Medical Devices

ISO 11137–1 Sterilization of Health Care Products—Radiation—Part 1: Requirements for Development, Validation and Routine Control of a Sterilization Process for Medical Devices

ISO 22442–1 Medical Devices Utilizing Animal Tissues and their Derivatives—Part 1: Application of Risk Management

2.3 U.S. Regulations:⁴

21 CFR 610.12 Sterility

21 CFR 1271 Human Cells, Tissues, and Cellular and Tissue-Based Products

2.4 ICH Document:⁵

Q1A(R2) Stability Testing of New Drug Substances and Products

3. Terminology

3.1 Unless provided otherwise in 3.2, terminology shall be in conformance with Terminology **F2312**.

3.2 Definitions:

3.2.1 *function*, *v*—the mechanism of producing the therapeutic effect of a medical product.

3.2.2 *reinforcement*, *n*—the process of strengthening the surgical repair of tendon or ligament.

4. Summary of Guide

4.1 It is the intent of this guide to provide a compendium of information that may be related to the functional characteristics

of the TEMPs used to reinforce surgical repair of injured tendons and ligaments. TEMPs may be composed of the following individual components: biological products (for example, cells, organs, tissues, derivatives, and processed biologics), biomaterials (for example, substrates and scaffolds composed of natural and/or synthetic polymers), and active biomolecules (for example, recombinant proteins) (see Terminology **F2312** for the complete definition). Examples of TEMPs are listed in Classification **F2211**.

4.2 Throughout this guide, the reader is referred to other documents that may provide specific information that can be applied in the manufacture and testing of TEMPs. Although many of these documents were not written with TEMPs in mind, parts are often applicable. Most of the potentially applicable position papers and guidance documents from many regions of the world can be accessed via the internet. New documents are produced continually.

4.3 The application of this guide does not guarantee clinical success of a finished product but will help to ensure consistency in the properties and characterization of a given TEMP developed for the purpose of mechanically reinforcing surgical repair of tendons and ligaments.

4.4 This guide does not suggest that all the listed tests be conducted. The decision regarding applicability or suitability of any particular test method remains the responsibility of the supplier or user of the material based on applicable regulations, characterizations, and preclinical/clinical testing.

5. Significance and Use

5.1 Injuries to tendons or ligaments are frequently treated by surgery to repair the damaged tissues and facilitate the healing process. The potential of TEMPs to enhance the outcomes (including function, pain, anatomy) of the surgical repair has been recognized.

5.2 Examples of tissues that when injured may be appropriate for repair using TEMPs: rotator cuff with a partial or full tear; Achilles tendon; Achilles tendon after harvesting for anterior cruciate ligament repair; patella tendon; patella tendon after harvesting for anterior cruciate ligament repair; quadriceps tendon; posterior cruciate ligament; medial collateral ligaments; lateral collateral ligaments; flexor tendons.

5.3 TEMPs may be used with the intent to improve the surgical outcome of tendon or ligament repair by (a) assuming some of the mechanical load experienced at the repair site to stabilize the surgical repair, (b) improving the natural biological healing process, or (c) a combination of these mechanisms.

5.4 TEMPs should improve clinical outcome. This may be accomplished by reducing or eliminating pain, returning function, shortening the recovery time following surgery, facilitating early mobility, improving return of strength, improving mobility, or other clinically relevant parameters.

5.5 The mechanism used by TEMPs to improve surgical repair should be understood and this conclusion should be supported by experimental results and should be supportive of the primary function of the TEMP.

³ Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, <http://www.ansi.org>.

⁴ 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>.

⁵ 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>.

5.6 TEMP with the primary function of mechanical reinforcement may also have a secondary, biological function.

5.7 When the product is used to improve the body's natural biological repair process of tendons or ligaments, the product should allow cell attachment, migration, infiltration, extracellular matrix deposition and organization, formation of tendon or ligament repair tissue, integration with adjacent tendon, ligament or bone, tendon-bone attachment, or more than one of these actions.

5.8 When the TEMP is used to provide a mechanical support of the surgical repair of a tendon or ligament, the product may provide enhanced mechanical properties of the repaired construct immediately after the surgery. Ideally, TEMPs would have mechanical properties similar to the uninjured native tissue being repaired. After surgery, the TEMP should limit the amount of tendon/ligament separation from the bone, or separation of the fractured ends of the tendon or ligament, or reduce the number of patients that have these as outcomes of the surgery. The TEMP may allow functionality to return to the repaired tendon or ligament in a shorter time than without the use of the product.

6. Components of TEMPs for Tendon or Ligament Surgical Repair

6.1 The following describes the components (polymers, matrices, cells, bioactive molecules) that may be used to manufacture TEMPs, and if human cells or tissues are to be included, then 21 CFR 1271 may be used.

6.2 Synthetically-Derived Matrices:

6.2.1 *Polymer Types*—The polymers used should allow manufacture of a product that is biocompatible. The polymer may already be used in clinically marketed products, or may represent an untested material.

6.2.2 *Structure*—The material can be manufactured in sizes that can be cut to size, or in a size appropriate for surgical implantation without alteration. The shape, size (including thickness), and flexibility of the device should allow for easy positioning within the surgical site without requiring permanent surgical anatomic modification, and preferentially allow delivery to the surgical site using minimally invasive or arthroscopic surgery. The structure should allow for fixation of the product at the site such that the product will function as intended.

6.2.3 *Degradation*—The material may be rapidly degrading (for example, polyglycolic acid), slowly degrading (for example, poly L-lactic acid), or non-degrading (for example, polytetrafluoroethylene). The degradation features of the material should be selected for the particular tissue site and function of the implant, and the patient.

6.2.4 *Analyses*—Polymeric matrices in the manufactured product may be tested for chemical composition, purity and contaminants, porosity and void volume, mechanical properties, degradation rate, stability, leachable compounds, as well as residual solvents and crosslinking agents.

6.3 Biologically-Derived Matrices:

6.3.1 *Native Matrices*—Tissues derived from animal or human tissues may be used. These tissues are usually processed

to remove cells, cell debris, and viral components. Additionally, the tissue may be crosslinked. They may contain a variety of extracellular matrix proteins, glycoproteins, carbohydrates, lipids, as well as growth factors. It is likely that most products will be predominantly composed of collagen.

6.3.2 *Other Naturally-Derived Matrices*—Other naturally-derived matrices used as a scaffold material in these TEMPs may be derived from human, animal, or other biologic sources. They are usually used in purified form, but may be used in combinations with other naturally-derived matrix components, or synthetic polymers. They may also be treated by crosslinking to provide additional mechanical properties and decreased porosity, and may be combined with other extracellular proteins.

6.3.3 *Cell Culture-Derived TEMPs*—The extracellular matrix may be generated by culture of cells (most likely with a scaffold) *in vitro*. The culture conditions will often be optimized to allow rapid deposition of extracellular matrix. If the scaffold is degrading rapidly, then it acts as a support for matrix deposition; if it is degrading slowly or not at all, it can also add mechanical properties to the construct.

6.3.4 *Analyses*—Tests may include cell content, cell membrane content, biochemical composition, growth factors and other mediators, and other biological activities. Biologically occurring matrices may also be tested as is done for synthetic polymers, for chemical composition, purity and contaminants, porosity and void volume, mechanical properties, degradation rate, and stability. Guide F2150 may be used for testing scaffolds for TEMPs, and Guide F2212 may be used when type I collagen is used as a component of the TEMP.

6.4 *Cells*—Cells may be included in the TEMP as a component of the product, secondary to the primary mechanism of mechanical reinforcement. The considerations raised in this section are general in nature, and more detailed characterization and control over manufacture and testing of a cellular component, if used, will be needed. General requirements may be found in applicable regulatory guidance documents, including Guide F2210.

6.4.1 *Cell Performance Requirements*—The cells should deposit an extracellular matrix that contributes to the TEMP's mechanical strength, or enhances biologic performance, or both. The cells should be able to proliferate to generate the appropriate number of cells required to form a TEMP, achieve appropriate characteristics during proliferation and matrix deposition, and be qualified as safe through appropriate testing. They may be autologous, allogeneic, or xenogeneic.

6.4.2 *Cell Types*—The cell types are likely to be tendon and ligament fibroblasts, but may also be other cell types or be derived from other cell sources, for example dermal fibroblasts or cells derived from a stem cell population. A careful characterization of the cell population is recommended to support development of appropriate quality assessment methods. If more than one cell population is to be used, then both the *in vitro* and *in vivo* cell-cell interactions at different cell ratios and concentrations should be understood.

6.4.3 *Analyses*—Analytical assessment of cells can include cell number, metabolism, extracellular matrix synthesis, proteomic profiling, gene expression, or other methods appropriate