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Standard Classification for Tissue Engineered Medical Products (TEMPs)[1]

This standard is issued under the fixed designation F 2211; 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.

1. Scope

1.1 This classification outlines the aspects of tissue engineered medical products that will be developed as standards. This classification excludes traditional transplantation of organs and tissues as well as transplantation of living cells alone as cellular therapies.

1.2 This classification does not apply to any medical products of human origin regulated by the U.S. Food and Drug Administration under 21 CDR Parts 16 and 1270 and 21 CFR Parts 207, 807, and 1271.

1.3 This standard does not purport to address specific components coverd in other standards. Any safety areas associated with the medical product's use will not be addressed in this standard.*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:*

F 2027 Guide for Characterization and Testing of Substrate Materials for Tissue-Engineered Medical Products[2]

F 2064 Guide for Characterization and Testing of Alginates as Starting Materials Intended for Use in Biomedical and Tissue-Engineered Medical Products Application[2]

F 2103 Guide for Characterization and Testing of Chitosan Salts as Starting Materials Intended for Use in Biomedical and Tissue-Engineered Medical Product Applications[2]

F 2131 Test Method for *In Vitro* Biological Activity of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2) Using the W-20 Mouse Stromal Cell Line[2]

F 2150 Guide for Characterization and Testing of Biomaterial Scaffolds Used in Tissue-Engineered Medical Products[2]

2.2 *Federal Documents:*[3]

US FDA CFR 21, Part 3 [3.2(e)] Product Jurisdiction

21 CFR Parts 16 and 1270 Human Tissues, Intended for Transplantation

21 CFR Parts 207, 807, and 1271 Human Cells, Tissues, and Cellular and Tissue-Based Products: Establishment Registration and Listing

2.3 *ISO Standard:*

ISO 10993 Biological Evaluation of Medical Devices[4]

NOTE 1—*International Standards:*There are no known standards developed by the international community specifically for TEMPS; however, ASTM International has an effort initiated in 1997 and several colleagues of the international community (IEC, CEN, ISO) have been coordinating and contributing to the ASTM TEMPs standards. Also, the international community is in the process of formulating a direction for their standards and regulations for this area. Recently, several draft documents have been circulated for input regarding code of practice for Products using Material of Human Origin, from the U.K., EUCOMED position paper concerning the need for future regulation of human tissue products for Europe and "Pre-clinical Safety Assessment of Tissue Engineered Medical Products (TEMPs): An Investigation on Assays and Guidelines for Biocompatibility Testing."[5]

3. Terminology

3.1 *tissue engineering*, *n*—the application, *in vivo* and *in vitro*, of scientific principles and technologies to form tissue engineered medical products (TEMPs) used for medical treatments and as diagnostics. The various technologies and principles are common practices and methods in engineering and biomedical sciences such as cell, gene, or drug therapy, embryology or other forms of developmental biology, surgical methods and technologies used to create traditional devices and biologics. Tissue engineering could be applied to create products for non-human use as well.

3.2 *tissue engineered medical products (TEMPs)*, *n*—medical products that repair, modify, or regenerate the recipients' cells, tissues, and organs, or their structure and function, or combination thereof. TEMPs may achieve a therapeutic potential from cells, biomolecules, scaffolds, and other materials, and processed tissues and derivatives used in various combinations or alone. TEMPs are unique from conventional organ transplants. TEMPs may be used *in vivo* or *in vitro* for disease, injury, elective surgery, and as a diagnostic.

[1] This classification is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.41 on Classification and Terminology for TEMPs.

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[2] *Annual ASTM Book of Standards*, Vol 13.01.

[3] Available from U.S. Government Printing Office Superintendent of Documents, 732 N. Capitol St., NW, Mail Stop: SDE, Washington, DC 20401.

[4] Available from International Organization for Standardization (ISO), 1 rue de Varembé, Case postale 56, CH-1211, Geneva 20, Switzerland.

[5] Available from Rijksinstituut voor Volksgezondheid en Milieu, (National Institute of Public Health and the Environment) The Netherlands.

3.3 For other definitions used in this classification, refer to the terms developed by the subcommittee on tissue engineered medical products terminology.

3.3.1 *Discussion*—ASTM Committee F04 is continuing to refine definitions for tissue engineered medical products (TEMPs) and related areas. A terminology standard for TEMPS will be published.

3.4 For specific definitions related to specific standards, refer to the general index and the individual standards.

4. Significance and Use

4.1 This classification outlines aspects of TEMPs which includes their individual components.

4.2 The categories outlined in this classification are intended to list, identify, and group the areas pertinent to Tissue Engineered Medical Products. This classification will be used by the Tissue Engineered Medical Products subcommittees for the organization of the development of standards for the field of tissue engineering, TEMPs, and protocols for their use. The development of products from the new tissue engineering technologies necessitates creation and implementation of new standards (**1**).[6]

4.3 Since interactions may occur among the components used in TEMPs, new standard descriptions, test methods, and practices are needed to aid the evaluation of these interactions. The degree of overall risk for any given TEMP is reflected by the number and types of tests required to demonstrate product safety and efficacy.

5. Classification of Tissue Engineered Medical Products

5.1 Aspects of TEMPs are classified according to the product components, site of action, therapeutic target, therapeutic effect, mode of action, duration of therapy, and lifetime (see Fig. X2.1). TEMPs are composed of cells, biomolecules, tissues, and biomaterials, alone or in combination, which are designed, fabricated, and specified through the principles of tissue engineering. The human body is composed of several organ systems that are coordinated to achieve the functions necessary for life. For the purposes of the ASTM Committee F04 TEMPs standard effort, 10 organ and tissue systems have been classified. They are: Integument, Hematopoietic, Cardiovascular, Musculoskeletal, Respiratory, Digestive, Nervous, Urinary, Endocrine, and Reproductive. (See X2.3 for examples of each of the human systems). Examples of product applications under development are given in X2.5.

6. Components

6.1 TEMPs are often combination products, as defined by the U.S. FDA 21 CFR Part 3 [3.2(e)], Product Jurisdiction, that incorporate attributes of at least two of the medical product classifications, that is, a traditional biologic, device, or drug. However, in other countries, the definition may be different. For example, the European Union (EU) defines a combination product as having two active components. Also, what is referred to in the U.S. as a carrier often is an excipient in the EU. In many cases, interactions occur among these combined materials to stimulate repair and regeneration of tissues and organ function. The biological materials, cells, and cellular products (therapeutic biomolecules) are often used to provide the biological message to initiate the repair function. Additionally, the three-dimensional material (natural or synthetic biomaterials) may provide the architecture for the structural support of the cells and repository for bioactive substances. The interaction results in the integration of the product with the patient, maintenance of the biological integrity of the product, and controlled signaling between the product and the patient's cells. Synthetic biomaterials used in the product can also have interactions and effects on the product performance.

6.2 Cells (under jurisdiction of Subcommittee F04.45), that is, of autologous, allogeneic, xenogeneic origin or genetically modified cells of any species, may be components of the TEMP. The cells may be viable, inactivated, or nonviable. They may be embryonic, neonatal, adult, stem, or progenitor cells. As such, it is important to verify aspects of TEMP production, that is, cell or tissue sourcing, procurement, good tissue practices, facilities, storage, transportation, and distribution. Other features of cells used for TEMPs may include genotype and phenotype characterization and safety, that is, absence of adventitious agents. When feasible, standardized methods should be provided.

6.2.1 Other aspects of TEMPs with cells may be product specific. Here, the TEMP developers may need to rely upon standards and methodologies appropriate for the cell type and species. For instance, if the TEMP is comprised of non-human cells, the xenogeneic cell identity and safety and immunological responses must be considered. The use of cells from other animal species presents additional issues and increased regulatory surveillance including those of ethics and public perception.

6.2.2 Other aspects of TEMPs may require unique measures used by the TEMP developers and accepted by the regulatory agencies for cell type specific characterizations, process and test methods, and end-product use and performance. Since live cells may be used, the maintenance of their viability, and genetic/phenotypic functional integrity should be addressed. Microbiological safety is critical, thus the verified absence of adventitious agents must be addressed and methodologies provided.

6.2.3 Standards will be developed to identify general methods of processing the cells, matrices, and tissue used for the TEMPs; to preserve cells and tissues used for TEMPs; to enumerate cells of various kinds; to characterize cell and tissue viability; to identify general methods for *vitro* production and testing of TEMPs; and, to characterize general features of cells.

6.3 Synthetic or natural biomaterials (under jurisdiction of Subcommittee F04.43) may be used as support structures or delivery systems for therapeutic cells or biomolecules (**3**). Raw materials, referred to as substrates, may be formed or processed into scaffolds to provide load-bearing capacity, or a framework

[6] The boldface numbers in parentheses refer to the list of references at the end of this standard.

for tissue formation, or as a cell contact surface coating. Control of substrate and scaffold surface and bulk characteristics, toxicity, degradation, and replacement rates require methods selection and protocol development. Specific naturally-occurring biomaterials and derivatives, which may be produced through various methods and technologies, should be characterized first following substrate recommendations. Once processed into a scaffold, the biocompatibility and the interactions with the other product components and the patient must be evaluated.

6.3.1 Several naturally occurring materials are used for a variety of TEMPs. Standards for characterization, sourcing and test methods for alginate, chitosan, and collagen will be important for many TEMPs and are being developed.

6.4 A biomolecule (under jurisdiction of Subcommittee F04.44) may be added to the product as an individual component, the cells that are a product component may produce them, or they may be elicited from the patient's tissue by product components. When biomolecules are added to or produced by the product to impact therapy, their identity, characterization, and function should be determined using specific standards and test methods. It is important to describe the biomolecule formulation and the formulation's compatibility with the matrix. There may also be a need to control the level of non-efficacious biomolecules, which may be antigenic or toxic.

6.4.1 A test method for the *in vitro* bioassay of bone morphogenetic protein-2 has been established (Test Method F 2131F 2150) to determine the component identity, potency, and quantity. There is a need to establish bioactivity standards for other protein biomolecules that are components of TEMPs.

6.4.2 Test methods to determine protein concentration, including chromatographic purity methods for naturally occurring materials are necessary due particularly to the variability of the sources for these materials.

6.4.3 Dye-binding test methods for specific protein matrices will aid in the identity verification.

6.4.4 There is need for guidance for development of *in vitro* assays to measure release of therapeutic proteins from matrices.

6.4.5 Standards are needed for characterization and sourcing of growth factors and methods for their assay.

6.4.6 Standards are needed to develop conditions to store these materials for future use without loss of potency.

7. Characterization of TEMP

7.1 Tissue characterization (under jurisdiction of Subcommittee F04.42) is important for the final product configuration as well as component description. This is important for all phases of product development from *in vitro* testing to post-market surveillance. Given the variety of tests, it is critical to choose the appropriate method for the application such that they give information for safety and efficacy. TEMPs can be characterized with imaging modalities, mechanical testing, or biochemical measurements and other measurements, or combination thereof.

7.1.1 As the characteristics of TEMPs alter in many cases, the changes occurring in use must be monitored at various critical time points during the process of integration with the host tissue. This is particularly true when the component is designed to degrade and be replaced by the host tissue. The balance in the biodegradation and replacement rates will be influenced by the characteristics of the materials in the product and host response to the product, which also relates to the biocompatibility of the product. Therefore, monitoring during these critical phases of the product lifetime will be necessary. This in turn will impact the structural, mechanical and functional properties and require appropriate testing methods and protocols.

7.2 *Imaging Modalities*—Imaging modalities will include all forms of light microscopy (including spectral, fluorescent, and optical coherence tomography), electron microscopy, and imaging using other forms of energy. Standards for analyses that enable the relevant characterization of TEMPs (including digital image analysis) will also be developed.

7.3 *Mechanical Characterization*—Mechanical characterization will include all forms of bench-top testing for quantifying mechanical properties (including compressive, tensile, burst pressure), and testing using novel test methods for specific applications. Standards for analyses of the data and calibration will also be referenced or developed *de novo* when not otherwise available.

7.4 *Biochemical Characterization*—Biochemical characterization will include all forms of tests that determine the activity, content, purity, or identity, of any chemical constituents.

7.5 *Gene Expression Profiling*—Genetic safety can be monitored by methods of gene expression analysis and may become particularly important when xenogeneic materials are used.

8. Interactions

8.1 Characterization of the interactions among the product components and the patient is the primary focus of the TEMPs standards. The product performance, based on these interactions, and potential utility in clinical medicine, will depend on the ability to optimize these interactions. Areas important to safety and efficacy will be addressed. This will include interactions with other products and with the recipient.

8.2 Tissue characterization (under jurisdiction of Subcommittee F04.42) is important for the final product configuration as well as component description (see 7.2). Tissue characterization methods will be applied to the construct, the product and their respective interfaces with each other and the patient tissues.

8.3 Structural characterization is important for the final product configuration as well as component description (see 7.3). Structural characterization methods will be applied to the construct, the product, and their respective interfaces with each other and the patient tissues.

8.4 Material-tissue interfaces and their modification can be characterized using imaging modalities, physico-chemical probes, and end-point methodologies. Thus, test methods to determine the therapeutic effect relative to the intended use would be developed. Testing for chemical modification of a biomolecule by the matrix could be performed in pre-clinical validation phase.

8.5 *Time-Varying Physical Properties*—Characterization of physical properties with time after exposure to patient tissues/

organs may be important. If the product is comprised of degradable materials understanding the rate of degradation is of key importance to monitoring its performance (under jurisdiction of Subcommittee F04.43). The degradation rate will be influenced by the material's characteristics, the patient's body contact region, and duration of exposure and of storage. Determination of the degradation rates and the necessity of specific rates to achieve tissue repair must be measurable with appropriate methodologies. Coordination with ISO 10993 biodegradation test requirements will be made.

9. Assessment (under jurisdiction of Subcommittee F04.47)

9.1 The purpose of Product Development/Preclinical Assessment subcommittee is to establish guidances, standards, and test methods for product development from *in vitro* safety testing through selection of appropriate animal models to demonstrate clinical effectiveness for specific medical applications.

9.2 Pre-clinical safety evaluations include assessment of toxicity, pyrogenicity, tumorigenicity, carcinogenicity, and immunogenicity. In addition to standardized testing used for biomaterials, TEMPs should be assessed using *in vitro* and *in vivo* tests that include cells and tissues that will be in physical contact with the TEMP and, where appropriate, with cells and tissues that will be affected by products that may be produced by the TEMP.

9.3 *In-vitro* tests include cell, tissue, and organ culture and use cellular, biochemical and molecular methods. *In vivo* assessment methods include histology/histomorphometry of implanted tissues and associated structures, tissues involved in immune response and detoxification, and target tissues of any products produced by the TEMP.

9.4 If the TEMP is intended to repair, regenerate, or substitute for a structural tissue or organ, mechanical and physical properties following treatment should be assessed.

9.5 Biochemical assessments should be used to determine that tissue function is acceptable. Molecular assessments should be used to determine if the phenotype of the tissue is maintained or restored. *In vivo* assessments should determine if host-dependent or time-dependent changes in the TEMP modify its effectiveness (for example, altered material properties such as shape, stiffness and porosity; fibrous encapsulation; scaffold degradation and bioactive factor release kinetics; cell death; or loss of a transgene).

9.6 Testing for pharmacokinetics and residence time of the biomolecule should be done, where appropriate.

9.7 Although these guidances, standards, and test methods are not definitively predictive of the human outcome, they may give some indication of product efficacy and risk to be expected. Standards that relate to specific medical applications are being developed where possible. The user of this classification should consult those preclinical assessment standards to determine their relevance for their product applications in human clinical studies.

9.8 Evaluation for articular cartilege assessment using animal models will be developed, as will test methods for asessment of bone graft substitutes (under jurisdiction of Subcommittees F04.47.06 and F04.47.01).

10. Normal Biology (under jurisdiction of Subcommittee F04.41)

10.1 The description of normal biological function for human tissues and organs aids in establishing the expected level of performance in the absence of the disease or bodily injury. While TEMPs may not fully restore the tissue or organ, these descriptions set a goal for a level of desirable function. Standards that describe the normal range of various parameters for each tissue and organ (see Fig. X2.1) will also help the clinicians understand how the TEMP performs relative to normal biology. For instance, this may be of particular importance when a TEMP is intended to alter the immune response, blood conditions, or tissue or organ appearance in certain disease states.

10.2 After implantation, the wound healing process can affect the expected normal biology. Distinctions in this regard need clarification and specification.

11. Delivery Systems (under jurisdiction of Subcommittee F04.46)

11.1 The purpose of TEMP Delivery Systems is to put into the appropriate place a product that will achieve a desired therapeutic effect to an appropriate therapeutic target (tissue or organ) for a specific duration. The materials, methods, and protocols used to accomplish this are critical elements of overall TEMP performance. The complexity of TEMPs means, however, that there are many modes of delivery that make up the overall system for getting a therapeutic effect to its proper target. The different modes of delivery are classified to assist the ongoing development of delivery standards, as well as their future use. Many TEMPs will contain multiple components. At least one of the components must be the therapeutic component, but there may be other components that provide complimentary functions, including those related to the delivery of the therapeutic component (and thus the therapeutic effect). The broadest classification of an overall delivery system is between (*1*) the systems used to deliver the entire TEMP to a specific site in a patient and (*2*) the components of the TEMP that affect the delivery of the therapeutic component. The former type is referred to as "Product Delivery Systems" and the latter as "Component Delivery Systems."

11.2 *Product Delivery Systems*—These are the technologies, procedures, and equipment used to deliver an entire TEMP, which might contain any combination of cells, tissues, biomolecules and biomaterials, to its intended site of action (*in vivo*, *ex vivo*, or *in vitro*, according to Fig. X2.1). In most cases, the site of action will be *in vivo* and typical modes of delivery include topical, injectable, implantable, and endoscopic. Issues such as invasiveness, sterility, product pretreatment, and duration of the procedure will be important.

11.3 *Component Delivery Systems*—These are components of a TEMP that have been designed to affect the delivery of the therapeutic component after the TEMP has been delivered via a Product Delivery System. Component Delivery Systems are further classified into two groups: delivery components that transport a therapeutic effect to the proper target tissue/organs (Therapeutic Target Delivery Systems) and components that