Designation: F2211 – 13

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

This standard is issued under the fixed designation F2211; 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 CFR Parts 16 and 1270 and 21 CFR Parts 207, 807, and 1271.

1.3 This standard does not purport to address specific components covered 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:*[2]

F2027 Guide for Characterization and Testing of Raw or Starting Biomaterials for Tissue-Engineered Medical Products

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

F2131 Test Method for ***In Vitro*** Biological Activity of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2) Using the W-20 Mouse Stromal Cell Line

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

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]

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.

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

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

(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**).[5]

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 X2.2 for examples of each of the human systems). Examples of product applications under development are given in X2.4.

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, 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 may be used as support structures or delivery systems for therapeutic cells or biomolecules (**2**). Raw materials, referred to as substrates, may be formed or processed into scaffolds to provide load-bearing capacity, or a framework 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

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

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 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 F2131) 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 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 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. 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

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 cartilage assessment using animal models will be developed, as will test methods for assessment of bone graft substitutes.

10. Normal Biology

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

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 control the delivery of the therapeutic effect to the target (Therapeutic Effect Delivery Systems).

11.3.1 *Therapeutic Target Delivery Systems*—These are materials, methods or mechanisms used to enhance the transport of the therapeutic component to its intended target (for example, nanoparticles that have been surface-modified to bind

to the surface receptors of specific cells), to contain the therapeutic component at the target (for example, a scaffold containing BMP that gels around a bone fracture), or to protect the therapeutic component at the target site (for example, a permselective encapsulation membrane to protect transplanted cells from a patient's immune system). Important issues for these delivery systems include: delivery efficiency, stability (for example, of materials or material-therapeutic binding), material strength, permselectivity, molecular-weight cut-off, and device dimensions and configuration.

11.3.2 *Therapeutic Effect Delivery Systems*—There are mechanisms and material properties that are used to control the (mass) transport of a therapeutic effect between a therapeutic component and its target tissue/organ. For example, the permeability of a porous membrane or the degradation dynamics of a bioresorbable polymer scaffold can be varied to achieve a specific delivery rate of a therapeutic cell, biomolecule, or biomaterial. A more complex example of a Therapeutic Effect Delivery System is a vascularized interface between transplanted cells (secreting a therapeutic protein) and a circulatory system of a diabetic.

11.4 *Encapsulation Systems*—Transplanted cells (for example, xenogeneic or allogeneic) can be isolated from the immune system of the recipient of the tissue by enclosing the cells in a natural or synthetic polymer. Isolation of the tissue in polymer capsules also facilitates the eventual removal of the tissue from the host. Encapsulation systems are very complex and may require all of the modes of delivery described above. This is one of the reasons that encapsulation systems are the focus of tissue engineering standards development and why we highlight these systems in this document.

11.4.1 For instance, it is expected that the implantation of microcapsules, beads or tubes of cell-containing polymer will require new standardized surgical instruments and implantation protocols, particularly considering the variety of implant sites that are envisioned (for example, intraperitoneal for islets, intracranial for dopamine-secreting cells). The polymer membrane surrounding the cells must be strong enough to contain the cells, ideally at a specific site, and permeable to nutrients and waste products. The membrane must also, however, control (limit) the mass transport of immune components (immunoglobin, complement) into the capsule and the permeation of encapsulated cell antigens out of the capsule.

11.4.2 Many applications (for example, the encapsulation of insulin secreting islets) may also require an additional delivery system to enhance the transport of insulin and nutrients (for example, oxygen) between the encapsulated cells and the circulatory system. The cell encapsulation guideline outlines the important issues common to all encapsulation systems. Encapsulation systems are often classified based on: (*1*) membrane material (for example, alginate, agarose, polyacrylates, modified PEG); (*2*) Configuration of device (for example, spherical capsules, hollow fibres, planar devices, blood-contacting versus diffusion devices), membrane formation mechanism (for example, drop formation, coating methods, extrusion, *in-situ* polymerization), and cell types (for example, islets, hepatocytes, genetically engineered, and so forth). Specific test methods, guidelines, and standard practices will continue to be developed based on these typical distinctions.

12. Microbiological Safety and Adventitious Agents

12.1 The safety from contamination by potentially infectious adventitious agents is important in the development of all TEMPs as well as their components. Animal products could transmit disease via viruses and prions, for example, transmissible spongioform encephalopathy, and so forth. Standards developed will be designed to identify the requirements intended to prevent the introduction, transmission, and spread of transmissible disease through the use of tissue engineered medical products by helping to ensure the following:

12.1.1 That the products do not become contaminated during manufacturing;

12.1.2 That the products do not serve as a nidus for infection during clinical use; and,

12.1.3 That the products do not significantly impair immunological or biological function either through design failures or improper manufacturing.

12.1.4 That the cell source be free of contaminating agents prior to manufacturing.

12.1.5 That the products do not contain infectious agents capable of infecting humans or human cells. In the case of endogenous retroviruses, the products should not produce infectious virus.

12.2 Standards/guidance will be developed for prevention of contamination at critical control points: materials source/procurement, material processing, and final end product, including shipping and storage.

12.3 Application of sterilization methods may be difficult when dealing with living cells and tissues, requiring development of innovative approaches and verification methods.

12.4 The cell source should be free of contaminating agents prior to manufacturing.

13. Clinical Trials

13.1 Clinical trials for TEMPs pose additional considerations relevant to human ethics. In some clinical conditions there is the difficulty of treating some patients with an approved control therapy that may be considered inadequate. Certain areas call for precise surrogate end points and will be delineated by the standards.

13.2 Evaluation of clinical trial data will aid the developer in further product development, study design and problems with the selection of the intended use.

13.2.1 Clinical outcomes definitions for the critical areas appropriate for each product type and target population will be determined based on prior experiences with classical medical products and applied where appropriate to TEMPs.

13.2.2 Statistical evaluations, epidemiological, and post-market surveillance provide increased assurances of the continued safety and performance of the product.

14. Keywords

14.1 biomaterials; biomolecules; cells; classification; TEMPs; tissue-engineering

APPENDIXES

(Nonmandatory Information)

X1. RATIONALE

X1.1 The legislation [Food and Drug Administration Modernization Act of 1997 (P.L. 105-115), which amends section 514 of the Food, Drug, and Cosmetic Act (21 U.S.C. 514(c))] has promulgated the implementation of consensus standards for the Center for Devices and Radiological Health, , allowing the product sponsor to self-declare conformance to specific standards. (**3**) The use of consensus standards is designed to will result in improvements in the regulatory process with consistency among product reviews and speed of submission preparations and of reviews.

X1.2 The use of consensus standards in the international area will have added value in the global marketplace and thus these standards would have impact on the global economy and health care. This will require harmonization of the strategy for development and regulation by global groups, but anticipates the by-product of buy-in due to participation of multinationals in the consensus process.

X2. BACKGROUND

X2.1 Background of Tissue Engineering

X2.1.1 Tissue engineering is a newly developing field of technology that has been previously defined. The group attending the first meeting on Tissue Engineering in 1988 (**4**) defined tissue engineering as the "application of the principles and methods of engineering and the life sciences toward the fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes that restore, maintain, or improve tissue function." Tissue Engineered Medical Products are those protocols and products developed for use in the human body as biological substitutes to restore, maintain, or improve tissue function. "Implied in the above is the essence of tissue engineering: the use of living cells, alone or together with either natural or synthetic extracellular components, in the development of implantable parts or devices for the restoration or replacement of function." (**5**)

X2.1.2 Tissue engineering is part of the new science of regenerative biology and medicine (**6**). Regenerative biology seeks to understand how some body tissues are replaced naturally, through the study of a variety of animal models, including lower vertebrates such as amphibians that are strong regenerators.

X2.1.3 Regenerative medicine seeks to apply this understanding to restore the structure and function of damaged human tissues that do not naturally regenerate, using three techniques. The first is the transplantation of replacement cells into sites of injury or disease (cell therapy). The second is to induce regeneration *in situ* by the pharmacological suppression of inhibitory factors or supplying factors that stimulate regeneration (drug/gene therapy), or both. Tissue engineering is the third approach, and involves the construction *in vitro* of bioartificial tissues by seeding cells into scaffolds of artificial or natural materials, then using them as extracorporeal devices or implanting them into the body (combination device and biologic therapy).

X2.1.4 TEMPs may be a cell-biomaterial construct or a drug-cell formulation that is topically applied, implanted, injected, or used as an *ex vivo* device (**7**).

X2.1.5 Recently, many insights into the existence of stem/progenitor cells within the adult body has prompted work on regenerative biology (**8**), with expectation for a newly emerging field of regenerative medicine. There is the likelihood that both approaches will eventually be used to result in medical products for restoration of tissue.

X2.2 Human Systems

X2.2.1 *Human Organ/Tissue Systems of the Human Body*—Many but not all organ/tissues or components have been represented here as examples within each system.

X2.2.2 *Cardiovascular System*—Heart, valves, arterial and venous blood vessels, and microvasculature and cardiac muscle.

X2.2.3 *Digestive System*—Oral cavity, tongue, teeth, salivary glands, pharynx, tonsils, esophagus, stomach, small intestine, colon, pancreas [exocrine functions], biliary tract, gall bladder, liver, appendix, recto-anal canal.

X2.2.4 *Endocrine System*—Pancreas/islets (endocrine function), pituitary, parathyroid, thyroid, adrenal and pineal body.

X2.2.5 *Hematopoietic System*—Blood and bone marrow, lymph nodes, spleen, thymus, lymphatic vessels.

X2.2.6 *Integumentary System*—Skin (epidermis and dermis), hair, nails, sweat glands, sebaceous glands.

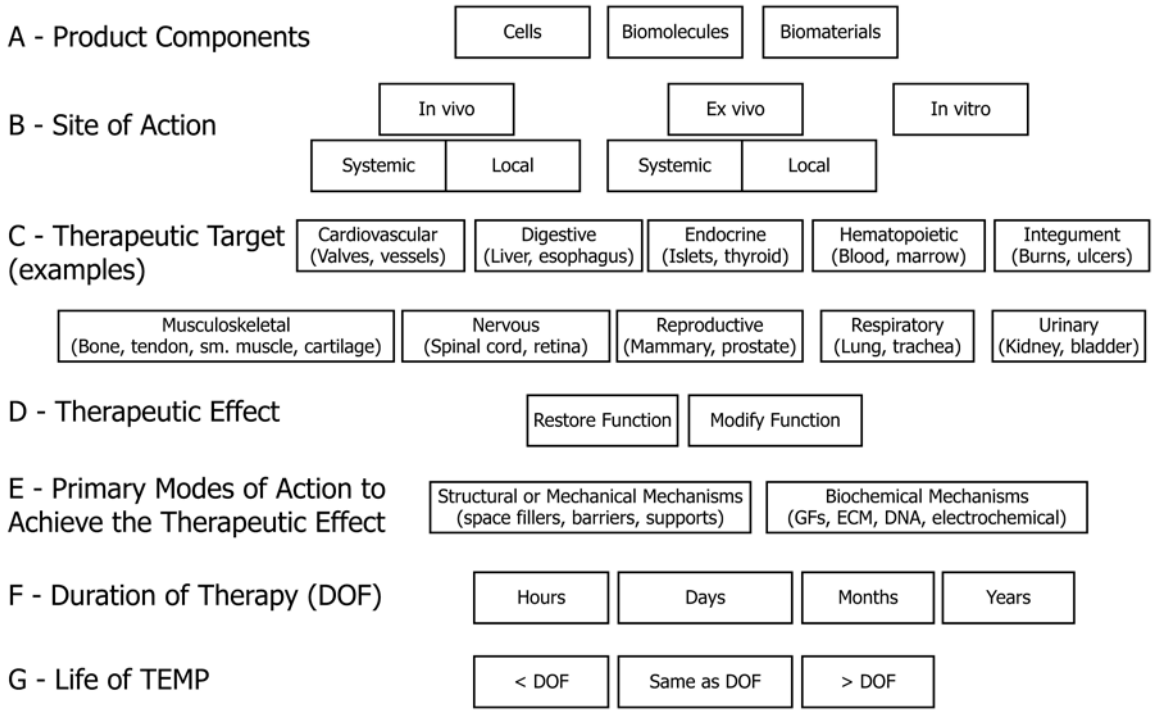

FIG. X2.1 Aspects of TEMPs

X2.2.7 *Musculoskeletal System*—Tendons, ligaments, bone structures, cartilage structures (elastic, hyaline, fibrous cartilage), bone (compact and spongy), skeletal, smooth muscles.

X2.2.8 *Nervous System*—Spinal cord, ganglion, brain (for example, cerebellum, cerebrum), eyes, inner ear (sensory systems), nerve fibres, and nerve bodies of any type.

X2.2.9 *Respiratory System*—Nasal cavity and sinuses, trachea, larynx, lungs.

X2.2.10 *Reproductive System*—Male: ducts, sex glands (for example, prostate), testes, epididymis, penis; Female: mammary gland and nipples, ovary, uterus, vagina, uterine tubes and in cases of pregnancy, the placenta.

X2.2.11 *Urinary System*—Kidneys, bladder, ureters, urethra.

X2.3 Aspects of TEMPs

X2.3.1 See Fig. X2.1 for aspects of TEMPs.

X2.4 TEMPs Examples

X2.4.1 The following are examples, which include but are not limited to, product applications under development that are included within the purview of the ASTM TEMPs activity for which standards may be developed:

X2.4.1.1 Encapsulated pancreatic islet cells for insulin delivery,

X2.4.1.2 Scaffolds that incorporate bone morphogenetic protein for bone regeneration,

X2.4.1.3 Cartilage synthesized by chondrocyte seeded scaffolds,

X2.4.1.4 Cell-seeded matrices for tendon repair,

X2.4.1.5 Dental materials that deliver a drug and guide tissue repair,

X2.4.1.6 Use of stem cells as sources of cell populations for tissue or organ repair,

X2.4.1.7 Mesenchymal stem cells for bone, cartilage, and tendon repair,

X2.4.1.8 Skeletal and smooth muscle gene therapy,

X2.4.1.9 Nerve guidance channels for peripheral nerve regeneration,

X2.4.1.10 Xenogeneic encapsulated cells for central nervous system drug delivery,

X2.4.1.11 Cultured cells for wound and burn dressings,

X2.4.1.12 Cells and scaffolds for epidermal and dermal grafts, and

X2.4.1.13 Microfiltration for hepatocyte entrapment for extracorporeal liver function.

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