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Standard Terminology Relating to Tissue Engineered Medical Products[1]

This standard is issued under the fixed designation F2312; 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 terminology defines basic terms and presents the relationships of the scientific fields related to Tissue Engineered Medical Products (TEMPs). Committee F04 has defined these terms for the specific purpose of unifying the language used in standards for TEMPs.

1.2 The terms and relationships defined here are limited to TEMPs. They do 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 The terms and nomenclature presented in this standard are for the specific purposes of unifying the language used in TEMP standards and are not intended for labeling of regulated medical products.

1.4 *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, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.5 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *Government Documents:*[2]

21 CFR Parts 16 and 1270 Human Tissues, Intended for Transplantation (July 29, 1997)

21 CFR Parts 207, 807, and 1271 Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing (January 19, 2001)

3. Significance and Use

3.1 The need for standards regarding TEMPs has also prompted a need for definitions. This terminology sets forth definitions of the most commonly used terms and specifies the relationship among the sciences and components applied in tissue engineering to develop TEMPs. Use of these terms and an understanding of these relationships will unify the ASTM TEMPs standards with a common language such that the users of these standards can understand and interpret the standards more precisely. Terms specific to a TEMP standard will also be defined within the respective standard as appropriate.

3.2 *Defining Terms*—Terms are defined with a broad scope to encompass these new products known as TEMPs. For instance, the definition for somatic cell therapy as stated in the "Guidance for Human Somatic Cell Therapy and Gene Therapy" (**1**)[3] is recognized in this terminology. However, for the purposes of TEMPs that contain cells, we have added the definition of "cell" which is much broader and not limited to the use of living cells.

3.3 *Clinical Effects of TEMPs*—The users of this terminology should note that terms used regarding the clinical effects of TEMPs, for instance, "modify or modification" of the patient's condition, may also be interpreted to "enhance, augment, transform, alter, improve, or supplement." Similarly, "repair" may also serve to mean "restore."

3.4 The diagram in Fig. 1 shows the relationships of components of TEMPs and of the fields of science (for example, technologies and principles) used in tissue engineering to create TEMPs. Certain TEMPs may be tissue engineered or produced *in vitro* by using specific components and sciences to create an off-the-shelf TEMP for the users. Other TEMPs may by design require the users to place the components inside the patient, (that is, *in vivo*) to rely upon the patient's regenerative potential to achieve the product's primary intended purpose. The expectation of a TEMP used for therapeutic clinical applications is to have a therapeutic effect, specifically to repair, modify or regenerate the recipient's cells, tissues, and organs or their structure and function. Such a TEMP may be used for human and non-human applications. In

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[2] 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.

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

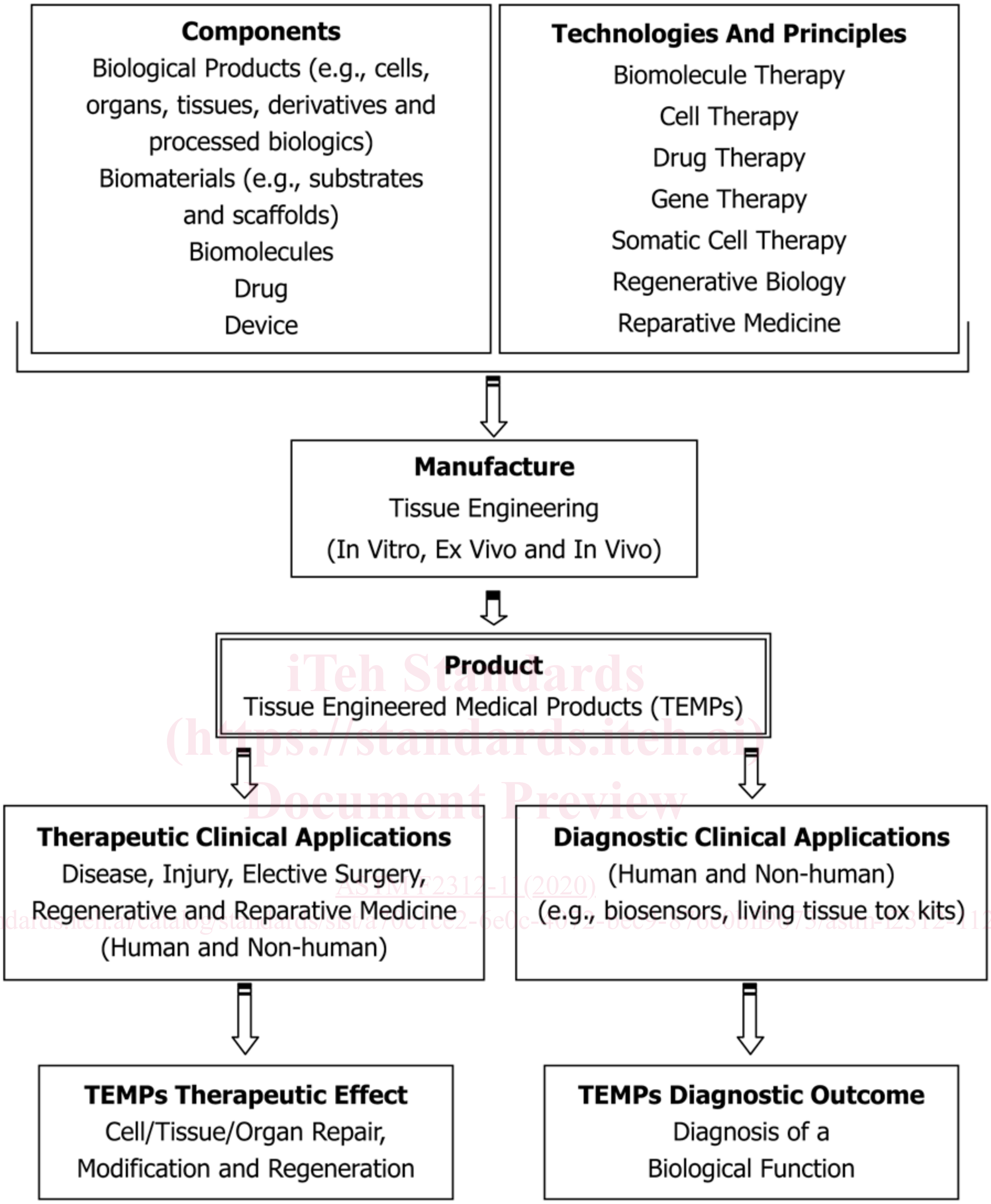
Components
Biological Products (e.g., cells, organs, tissues, derivatives and processed biologics)
Biomaterials (e.g., substrates and scaffolds)
Biomolecules
Drug
Device
Technologies And Principles
Biomolecule Therapy
Cell Therapy
Drug Therapy
Gene Therapy
Somatic Cell Therapy
Regenerative Biology
Reparative Medicine
Manufacture
Tissue Engineering
(In Vitro, Ex Vivo and In Vivo)
Product
Tissue Engineered Medical Products (TEMPs)
Therapeutic Clinical Applications
Disease, Injury, Elective Surgery, Regenerative and Reparative Medicine (Human and Non-human)
Diagnostic Clinical Applications
(Human and Non-human)
(e.g., biosensors, living tissue tox kits)
TEMPs Therapeutic Effect
Cell/Tissue/Organ Repair, Modification and Regeneration
TEMPs Diagnostic Outcome
Diagnosis of a Biological Function

FIG. 1 Relationships of the Fields of Tissue Engineering to Tissue Engineered Medical Products

other applications, a TEMP may be used in diagnostic clinical applications, or both, to achieve an investigative outcome of the function of the cells, tissues, and organs.

4. Terminology

adventitious agents, *n*—an unintentionally introduced microbiological or other infectious contaminant. In the production of TEMPs, these agents may be unintentionally introduced into the process stream or the final product, or both.

alginate, *n*—polysaccharide obtained from some of the more common species of marine algae, consisting of an insoluble mix of calcium, magnesium, sodium, and potassium salts.

DISCUSSION—Alginate exists in brown algae as its most abundant polysaccharide, mainly occurring in the cell walls and intercellular spaces of brown seaweed and kelp. Alginate's main function is to contribute to the strength and flexibility of the seaweed plant. Alginate is classified as a hydrocolloid. The most commonly used alginate is sodium alginate. Sodium alginate and, in particular, calcium cross-linked alginate gels are used in Tissue Engineered Medical Products (TEMPs) as biomedical matrices, controlled drug delivery systems, and for immobilizing living cells.

allogeneic or allogenic, *adj*—cells, tissues, and organs in which the donor and recipient are genetically different individuals of the same species. Synonyms: *allograft* and *homograft*.

allograft, *n*—a graft of tissue between individuals of the same species but of disparate genotype. Called also *allogeneic graft* and *homograft*.

APA bead, *n*—alginate-poly-L-lysine-alginate bead.

autograft, *n*—a graft of tissue derived from another site in or on the body of the organism receiving it.

autologous, *adj*—cells, tissues, and organs in which the donor and recipient is the same individual. Synonyms: *autogenous*, *autograft*, or *autotransfusion*, a *self-to-self graft*.

bioactive agents, *n*—any molecular component in, on, or with the interstices of a device that is intended to elicit a desired tissue or cell response.

DISCUSSION—Growth factors, antibiotics, and antimicrobials are typical examples of bioactive agents. Device structural components or degradation byproducts that evoke limited localized bioactivity are not included.

biocompatibility, *n*—a material may be considered biocompatible if the materials perform with an appropriate host response in a specific application.

biological product, *n*—"any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man." **(2)**.

DISCUSSION—The term analogous product is interpreted to encompass somatic cell and gene therapy **(3)**. A biological product may be used as a component of a TEMP. For the purposes of TEMPs, these biological products may be of any origin (that is, organism), tissue type, developmental stage, and may be living, non-living, and genetically or otherwise modified.

biomaterial, *n*—any substance (other than a drug), synthetic or natural, that can be used as a system or part of a system that treats, augments, or replaces any tissue, organ, or function of the body.

biomolecule, *n*—a biologically active peptide, protein, carbohydrate, vitamin, lipid, or nucleic acid produced by and purified from naturally occurring or recombinant organisms, tissues or cell lines or synthetic analogs of such molecules. A biomolecule may be used as a component of a TEMP.

biomolecule therapy, *n*—the use of biomolecules to repair, modify, or regenerate the recipient's cells, tissues, or organs or their structure and function, or both. Biomolecule therapy technologies can be applied in tissue engineering to generate TEMPs.

cell, *n*—"the smallest structural unit of an organism that is capable of independent functioning, consisting of one or more nuclei, cytoplasm, and various organelles, all surrounded by a semipermeable cell membrane" **(4)**.

DISCUSSION—Cells are highly variable and specialized in both structure and function, though all must at some stage synthesize proteins and nucleic acids, use energy, and reproduce. A cell or cells may be of any origin (that is, organism), tissue type, developmental stage, and may be living, non-living, and genetically or otherwise modified. Cells may be used as a component of a TEMP.

cell culture, *n*—the *in vitro* growth or maintenance of cells.

cell therapy, *n*—the administration of cells (any kind and form) to repair, modify or regenerate the recipient's cells, tissues, and organs or their structure and function, or both. Cell therapy technologies can be applied in tissue engineering to generate TEMPs.

channelyzer, *n*—a pulse height analyzer; places voltage pulses into appropriate size bins for the size distribution data.

chitosan, *n*—a linear polysaccharide consisting of β(1→4) linked 2-acetamido-2-deoxy-D-glucopyranose (GlcNAc) and 2-amino-2-deoxy-D-glucopyranose (GlcN). Chitosan is a polysaccharide derived by *N*-deacetylation of chitin.

coincidence, *n*—more than one cell transversing the aperture at the same time.

collagen, *n*—Type I collagen is a member of a family of structural proteins found in animals.

DISCUSSION—Type I collagen is part of the fibrillar group of collagens. It derives from the COL1A1 and COL1A2 genes, which express the alpha chains of the collagen. All collagens have a unique triple helical structure configuration of three polypeptide units known as alpha-chains. Proper alignment of the alpha chains of the collagen molecule requires a highly complex enzymatic and chemical interaction *in vivo*. As such, preparation of the collagen by alternate methods may result in improperly aligned alpha chains and, putatively, increase the immunogenicity of the collagen. Collagen is high in glycine, L-alanine, L-proline, and 4-hydroxyproline, low in sulfur, and contains no L-tryptophan. Natural, fibrillar Type I collagen is normally soluble in dilute acids and alkalis. When heated (for example, above approximately 40°C), collagen is denatured to single alpha chains (gelatin). At each end of the chains are short non-helical domains called telopeptides, which are removed in some collagen preparations. Through non-covalent interactions with sites on adjacent helixes, fibrillogenesis is achieved. Subsequently, non-reducible cross-links are

formed. Type I collagen can be associated with Type III and Type V collagen and also with the other non-collagenous proteins like elastin and other structural molecules like glycosaminoglycans and complex lipoproteins and glycoproteins.

combination product, *n*—as defined in 21 CFR § 3.2(e), the term combination product includes: (*1*) A product comprised of two or more regulated components, that is, drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (*2*) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (*3*) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, for example, to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (*4*) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect." Furthermore, "many somatic cell products administered to patients will be combinations of a biological product and a device or of a drug, a biological product, and a device." (**5**). The term "combination product" may apply to TEMPs.

corrected count, *n*—the cell count corrected for coincidence.

cross-contamination, *n*—the unintended presence of a cell or a material with another cell or material.

degree of deacetylation, *n*—the fraction or percentage of glucosamine units (GlcN: deacetylated monomers) in a chitosan polymer molecule.

depolymerization, *n*—reduction in length of a polymer chain to form shorter polymeric units. Depolymerization may reduce the polymer chain to oligomeric or monomeric units, or both.

dermal autograft, *n*—a skin [autograft] from which epidermis and subcutaneous fat have been removed; used instead of fascia[4] in various plastic [surgery] procedures.

device, *n*—"an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article...intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals,...which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." Devices are "intended to affect the structure or any function of the body." (Section 201(h)(1) (**6**)).

DISCUSSION—Device Criteria: "A liquid, powder, or other similar formulation intended only to serve as a component, part or accessory to a device with a primary mode of action that is physical in nature" (**7**). A device may be used as a component of a TEMP.

disinfection, *n*—the destruction or reduction of pathogenic and other kinds of microorganisms by thermal or chemical means (for example, alcohol, antibiotics, germicides).

donor, *n*—a living or deceased organism who is the source of cells or tissues, or both, for research or further processing for transplantation in accordance with established medical criteria and procedures.

dressing, *n*—any of various materials utilized for covering and protecting a wound.

drug, *n*—"articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." Drugs are "intended to affect the structure or any function of the body of man or other animals." (Section 201(g)(1) (**6**)).

DISCUSSION—Drug Criteria: "A liquid, powder, tablet or other similar formulation that achieves its primary intended purpose through chemical action within or on the body, or by being metabolized" (**7**). A drug may be used as a component of a TEMP.

drug therapy, *n*—is the delivery of drug(s) that stimulate a specific physiologic (metabolic) response. Drug therapy technologies can be applied in tissue engineering to generate TEMPs.

electrolyte, *n*—diluent, offering slight conductivity, in which cells are suspended.

encapsulation, *n*—a procedure by which biological materials, such as cells, tissues, or proteins, are enclosed within a microscopic or macroscopic semipermeable barrier.

engraftment, *n*—incorporation of grafted tissue into the body of the host.

endotoxin, *n*—pyrogenic high molar mass lipopolysaccharide (LPS) complex associated with the cell wall of gram-negative bacteria.

DISCUSSION—Though endotoxins are pyrogens, not all pyrogens are endotoxins. Endotoxins are specifically detected through a Limulus Amebocyte Lysate (LAL) test.

epidermal autograft, *n*—an autograft consisting primarily of epidermal tissue, including keratinocyte stem cells, but with little dermal tissue.[5]

extracellular matrix, *n*—"(ECM), any material produced by cells and excreted to the extracellular space within the tissues. It takes the form of both ground substance and fibers

[4] "a sheet or band of fibrous tissue such as lies deep to the skin …" (Dorland's).

[5] For practical details, see Fang , P., Engrav, L. H., Gibran, N. S., Horani, S., Kiriluk, D. B., Cole, J. K., Fleckman, P., Heimbach, D. M., Gauer, G. J., Matsumura, H., and Warner, P., "Dermatome Steeing for Autografts to Cover Integra®," *J Burn Care Rehabil*, Vol 23, 2002, pp. 327–332; and Kagan, R. J., Invited editorial, *J Burn Care Rehibil*, Vol 23, 2002, p. 326.