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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

[1] This terminology 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] 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.

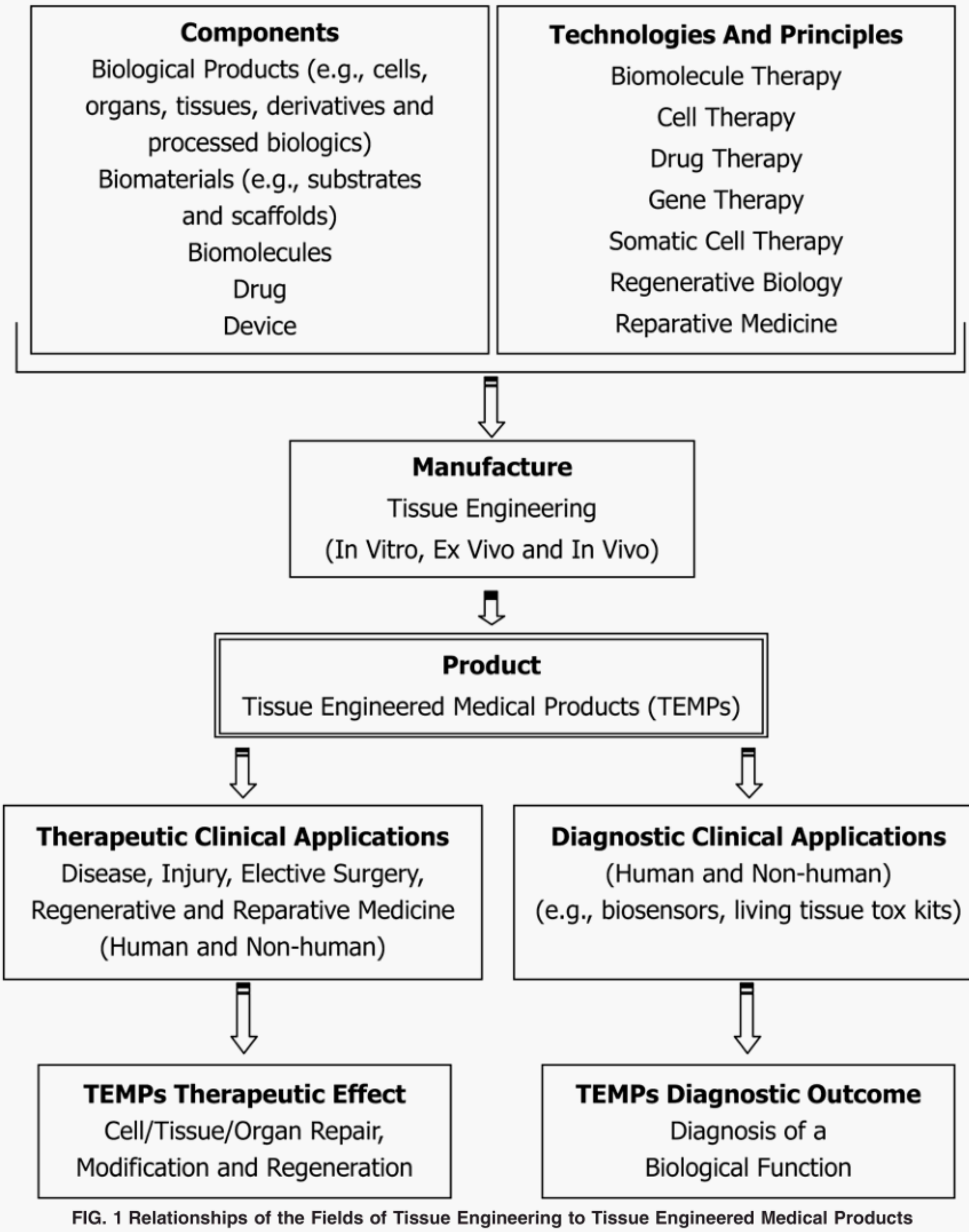

FIG. 1 Relationships of the Fields of Tissue Engineering to Tissue Engineered Medical Products

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.

and is composed chiefly of fibrous elements, proteins involved in cell adhesion, and glycosaminoglycans and other space-filling molecules. It serves as a scaffolding holding tissues together and its form and composition help determine tissue characteristics." (8) Extracellular matrix, a biological material or tissue derivative, may be used as a component of a TEMP.

femtolitre, *n*—a cubic micron; a measurement of cell volume.

full thickness skin autograft, *n*—a skin [auto]graft consisting of the epidermis and the full thickness of the dermis.

full-thickness skin wound, *n*—a skin wound with the loss of epidermis, and all of the dermis or at least the depth of dermis that includes most or all sources of epidermal cells from epidermal adnexae (glands and follicles).

GDF, *n*—growth and differentiation factor.

gel, *n*—the three-dimensional network structure arising from intermolecular polymer chain interactions.

DISCUSSION—Such chain interactions may be covalent, ionic, hydrogen bond, or hydrophobic in nature. See also Terminology F1251.

genetic material, *n*—is nucleic acid (either deoxyribonucleic acid or ribonucleic acid).

DISCUSSION—Genetic material is also known as DNA, RNA, genetic element, gene, factor, allele, operon, structural gene, regulator gene, operator gene, gene complement, genome, genetic code, codon, anticodon, messenger RNA (mRNA), transfer RNA (tRNA), ribosomal extrachromosomal genetic element, plasmagene, plasmid, transposon, gene mutation, gene sequence, exon, intron (modified version, (9)). Genetic material may be used as a component of a TEMP.

gene therapy, *n*—"is a medical intervention based on modification of the genetic material of living cells. Cells may be modified *ex vivo* for subsequent administration or may be altered *in vivo* by gene therapy products given directly to the subject. When the genetic manipulation is performed *ex vivo* on cells that are then administered to the patient, this is also a type of somatic cell therapy. The genetic manipulation may be intended to prevent, treat, cure, diagnose, or mitigate disease or injuries in humans." (5). Gene therapy technologies can be applied in tissue engineering to generate TEMPs.

gene therapy products, *n*—"are defined for the purpose of this statement as products containing genetic material administered to modify or manipulate the expression of genetic material or to alter the biological properties of living cells." (5).

genetically modified, *vt*—referring to cells, tissues, and organs of any origin that have an altered or modified genetic content.

graft, *n*—any tissue or organ for implantation or transplantation.

graft take, *n*—engraftment.

granulations, *n*—granulation tissue.

granulation tissue, *n*—the newly formed vascular tissue normally produced in the healing of wounds of soft tissue and ultimately forming the cicatrix [scar]; it consists of small, translucent, red, nodular masses or granulations that have a velvety appearance.

heal, *v*—to restore wounded parts or to make healthy.

healing, *n*—the restoration of integrity to injured tissue.

DISCUSSION—In the surgical wound closure, an important distinction is made according to whether the surgeon expects the healing to be accomplished by granulation tissue. This distinction is made because in the normal physiology of wound healing, granulation tissue matures into scar with wound contracture, which is an undesirable outcome. Wound closure "by approximating the wound edges or performing a skin autograft" is called "healing by first intention," and wound closure by "allowing spontaneous healing from the edges" is called "healing by second intention."

healing by first intention, *n*—healing in which union or restoration of continuity occurs directly without intervention of granulations.

healing by second intention, *n*—union by closure of a wound with granulations which form from the base and both sides toward the surface of the wound.

hydrocolloid, *n*—a water-soluble polymer of colloidal nature when hydrated.

immobilization, *n*—the entrapment of materials, such as cells, tissues, or proteins within, or bound to, a matrix.

implantation, *n*—the procedure of inserting materials such as a cell(s), tissue(s), or organ(s) for therapeutic purposes. Synonym: *graft* or *grafting*. TEMPs may be applied to a recipient by implantation or grafting.

in-process control, *n*—monitoring and, if necessary, adjustments performed to ensure that the process conforms to its specification. The control of the environment or equipment may be part of in-process control.

lesion, *n*—any pathological or traumatic discontinuity of tissue or loss of function of a part. In this guide, "skin lesion" is intended to encompass skin wounds and skin ulcers (8).

maintenance therapy, *n*—therapy of chronically ill patients that is aimed at keeping the pathology at its present level and preventing exacerbation.

manufacture, *v*—"any or all steps in the recovery, screening, testing, processing, storage, labeling, packaging or distribution of any human cellular or tissue-based product." (10).

DISCUSSION—For TEMPs, manufacture is expanded to include production of products *in vitro* or *in vivo*. TEMPs may also include the use of non-human cellular or tissue-based materials in any manufacturing steps.

microorganism, *n*—bacteria, fungi, yeast, mold, viruses, and other infectious agents. However, it should be noted that not all microorganisms are infectious or pathogenic.

natural materials, *n*—synthesized or produced by living cells.

micron (μ), *n*—0.001 mm, also known as a micrometre; measurement of cell diameter.

open wound, *n*—a wound that communicates with the atmosphere by direct exposure.

partial thickness skin wound, *n*—a skin wound with the loss of the epidermis and part of the dermis, but retaining a layer of viable dermal tissue that includes the sources of epidermal cells from which the wound can heal spontaneously by epidermal tissue regeneration.

pores, *n*—an inherent or induced network of channels and open spaces within an otherwise solid structure.

porometry, *n*—the determination of the distribution of pore diameters relative to direction of fluid flow by the displacement of a wetting liquid as a function of pressure.

porosimetry, *n*—the determination of pore volume and pore size distribution through the use of a nonwetting liquid (typically mercury) intrusion into a porous material as a function of pressure.

porosity, *n*—property of a solid which contains an inherent or induced network of channels and open spaces.

DISCUSSION—Porosity can be measured by the ratio of pore (void) volume to the apparent (total) volume of a porous material and is commonly expressed as a percentage.

processed biologics, *n*—cells, tissues, or organs that have undergone manipulation for use in the manufacture of TEMPs; processing here extends beyond the minimal manipulation or processing as it is applied in the field of structural, reproductive and metabolic tissue transplantation (11). A processed biologic may be used as a component of a TEMP.

primary healing, *n*—healing by first intention.

primary wound closure, *n*—wound closure for healing by first intention.

processing, *vt*—any activity performed on cells, tissues, and organs other than recovery, such as preparation and preservation for storage and packaging.

processing materials, *n*—any item or material that is not a component of the TEMP and is in contact with the cells, tissues, and organs during processing.

pyrogen, *n*—any substance that produces fever.

raw count, *n*—the enumeration of the cell population not corrected for coincidence.

recipient, *n*—the individual or organism into whom materials are grafted or implanted.

recovery, *n*—the obtaining of cells or tissues which may be used for the production of TEMPs.

reprocessing, *vt*—the reworking of cells, tissues, and organs of unacceptable quality from a defined stage of processing, so that the quality may be rendered acceptable by one or more additional operations.

regenerative biology, *n*—the scientific discipline that endeavors to understand how tissues and organs are replaced naturally. The principles of regenerative biology can be applied in tissue engineering to generate TEMPs.

regenerative medicine, *n*—a branch of medical science that applies the principles of regenerative biology to specifically restore or recreate the structure and function of human cells, tissues, and organs that do not adequately regenerate.

reparative medicine, *n*—a branch of medical science whereby clinicians use surgical methods to repair or modify the structure and function of patient's cells, tissues, or organs. The principles of reparative medicine can be applied in tissue engineering to generate TEMPs.

rhBMP, *n*—recombinant human bone morphogenetic protein.

ruggedness, *n*—the degree of reproducibility of the same sample under a variety of normal conditions; for example, different operators.

scaffold, *n*—a support, delivery vehicle, or matrix for facilitating the migration, binding, or transport of cells or bioactive molecules used to replace, repair, or regenerate tissues.

scar, *n*—fibrous tissue replacing normal tissues destroyed by injury or disease.

secondary healing, *n*—healing by second intention.

secondary wound closure, *n*—wound closure for healing by second intention.

size thresholds, *n*—the instrument's lower and upper size settings for the particular cell population; adjustable "size gate." Cells or fragments outside the size settings are excluded from the analyses.

skin, *n*—the outer integument or covering of the body, consisting of the dermis and the epidermis, and resting upon the subcutaneous tissues (8).

skin allograft therapy, *n*—the treatment of skin wound or skin ulcer by the temporary topical application of skin allograft(s).

skin replacement surgery, *n*—surgery that permanently replaces lost skin with healthy skin.

skin substitute, *n*—a biomaterial, engineered tissue, or combination of biomaterials and cells or tissues that can be substituted for a skin allograft, a skin autograft, an epidermal autograft, or a dermal autograft in a clinical procedure.

solubility, *n*—a measure of the extent to which the material can be dissolved.

DISCUSSION—In the context of collagen, refers to the dissociation of the fibrillar aggregates of collagen molecules into a solution. Native Type I collagen which is soluble in dilute acids, but not soluble in neutral pH conditions is termed "insoluble" or "acid soluble" while simple aggregates of non-fibrillar collagen soluble in neutral salt solutions are termed "neutral salt soluble" . Post translational surface charge modifications may alter the solubility of collagen in neutral pH condition.

somatic cell, *n*—is any cell other than a germ or stem cell. Somatic cells may be used as a component of a TEMP.

somatic cell therapy, *n*—"is the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries in humans by the administration of autologous, allogeneic, or xenogeneic cells that have been manipulated or altered *ex vivo*. Manufacture of products for somatic cell therapy involves the *ex vivo* propagation, expansion, selection, or pharmacologic treatment of cells, or other alteration of their biological characteristics." (5). For the purposes of TEMPs somatic cell therapy technologies can be applied in tissue engineering to generate TEMPs, for human and non-human use.

somatic cell therapy products, *n*—" are defined as autologous (that is, self), allogeneic (that is, intra-species), or xenogeneic (that is, inter-species) cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics *ex vivo* to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries." (5) Somatic cell therapy products may be used as a component of a TEMP.

split thickness skin autograft, *n*—a skin [auto]graft consisting of the epidermis and a portion of dermis.

stem cells, *n*—progenitor cells capable of self-replication, proliferation, and differentiation.

sterilization, *n*—the destruction or removal of all microorganisms in or about an object, as by, chemical agents, electron beam, gamma irradiation, ultraviolet (UV) exposure, or filtration.

substrates, *n*—raw or virgin materials that will ultimately be used in tissue-engineered medical products for growth, support, or delivery of cells or biomolecules.

suspension, *n*—the dispersion of a solid through a liquid with a particle size large enough to be detected by purely optical means.

syngeneic, *n*—cells, tissues, and organs in which the donor has an unreactive genotype with the recipient. Synonyms: *syngraft*, *isograft*, *isogeneic*, or *isogenic*.

tissue, *n*—an aggregation of similarly specialized cells united in the performance of a particular function.

tissue engineering, *vivon*, *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 diagnoses as diagnostics.

DISCUSSION—The various principles 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 and biology, surgical reparative methods and technologies can used to create traditional devices and biologics. Tissue engineering could be applied to create products for non-human use as well.

tissue engineered medical product (TEMP), *n*—a medical product that repairs, modifies or regenerates the recipient's cells, tissues, and organs or their structure and function, or both.

DISCUSSION—TEMPs derive their therapeutic potential from various components used alone or used in various combinations. Components may be biological products (that is, cells, organs, tissues, derivatives, and processed biologics), biomaterials (that is, substrates and scaffolds), biomolecules, devices, and drugs. TEMPs may be used *in vivo*, *ex vivo*, or *in vitro* for treatment of disease and injuries and for elective surgery or for diagnostic means. TEMPs are unique from conventional organ transplants in that they exclude biologics used for immediate transplantation or immediate preservation for later transplantation.

tissue regeneration, *n*—healing in which lost tissue is replaced by proliferation of cells, which reconstruct the normal architecture.

tissue repair, *n*—healing in which lost tissue is replaced by a fibrous scar, which is produced from granulation tissue.

transplantation, *n*—for therapeutic purposes, the process of implanting in one part, cells, tissue(s), or organ(s) taken from another part or from another individual.

DISCUSSION—Transplantation in this sense is regulated by the U.S. Food and Drug Administration (FDA) under 21 CFR Parts 16 and 1270 and 21 CFR Parts 207, 807, and 1271.

ulcer, *n*—a local defect, or excavation of the surface of an organ or tissue, which is produced by the sloughing of inflammatory necrotic tissue.

wound, *n*—an injury or damage, usually restricted to those caused by physical means with disruption of the normal continuity of structures. Called also injury and trauma.

wound closure, *n*—the provision of an epithelial cover over a wound; it can be accomplished by approximating wound edges, performing a skin [auto]graft, or allowing spontaneous healing from the edges.

wound contraction, *n*—the shrinkage and spontaneous closure of open skin wounds.

wound contracture, *n*—a condition of fixed high resistance to passive stretch of muscle, skin or joints resulting from fibrosis and scarring of the skin or the tissues supporting the muscles or the joints, or both. (This definition is a modification of Dorland's definition of contracture, "a condition of fixed high resistance to passive stretch of muscle, resulting from fibrosis of the tissues supporting the muscles or the joints, or disorders of the muscle fibers," because that definition does not address fibrosis and scarring in skin (8).)

wound inflammation, *n*—a localized protective response elicited by injury or destruction of tissues, which serves to destroy, dilute, or wall off (sequester) both the injurious agent and the injured tissue.

DISCUSSION—It is characterized in the acute form by the classical signs of pain (dolor), heat (calor) redness (rubor), swelling (tumor), and loss of function (functio laesa). Histologically, it involves a complex series of events, including dilation of arterioles, capillaries, and venules, with increased permeability and blood flow; exudation of fluids, including plasma proteins; and leukocytic migration into the inflammatory focus.

xenogeneic or xenogenic, *n*—cells, tissues, and organs in which the donor and recipient belong to different species. Synonyms: *xenogenous*, *heterogeneic*, or *heterologous*.

xenograft, *n*—a graft of tissue transplanted between animals of different species. Called also heterograft, heterologous graft and heteroplastic graft.[6]

xenotransplantation, *n*—any procedure that involves the transplantation or infusion into a human recipient of either *(1)* live cells, tissues, or organs from a nonhuman animal source or *(2)* human body fluids, cells, tissues, or organs that have had *ex vivo* contact with live nonhuman cells, tissues, or organs.

5. Organ and Tissue Systems of the Human Body

NOTE 1—Organs and tissues collectively interact as systems to achieve a common purpose. To unify the ASTM standards with a common language, ten (10) human body organ/tissue systems have been identified based on basic histology tissue and organ classifications (**12**, **13**). Examples of the organs, tissues or other elements in each system have been represented here.

5.1 *Cardiovascular System*—(for example, heart, valves, arterial and venous blood vessels and microvasculature and cardiac muscle).

5.2 *Digestive System*—(for example, 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).

5.3 *Endocrine System*—(for example, pancreas/islets [endocrine function], pituitary, parathyroid, thyroid, adrenal and pineal body).

5.4 *Hematopoietic System*—(for example, blood and bone marrow, lymph nodes, spleen, thymus, lymphatic vessels).

5.5 *Integumentary System*—(for example, skin [epidermis and dermis], hair, nails, sweat glands, sebaceous glands).

5.6 *Musculoskeletal System*—(for example, tendons, ligaments, bone structures, cartilage structures [elastic, hyaline, fibrous cartilage], bone [compact and spongy], skeletal, smooth muscles).

5.7 *Nervous System*—(that is central/peripheral autonomic and somatic nervous systems) (for example, spinal cord, ganglion, brain [ex. cerebellum, cerebrum, nuclei, glia, astrocytes, oligodendrocytes], eyes, inner ear [somatic sensory systems], all neuronal phenotypes, nerve fibers, and Schwann cells.

5.8 *Respiratory System*—(for example, nasal cavity and sinuses, trachea, larynx, lungs).

5.9 *Reproductive System*—(for example, male reproductive parts may be ducts, sex glands [ex. prostate], testes, epididymis, penis; female reproductive parts may be mammary glands and nipples, ovary, uterus, vagina, uterine tubes and in cases of pregnancy, the placenta).

5.10 *Urinary System*—(for example, kidneys, bladder, urethra, ureter).

6. Keywords

6.1 tissue engineered medical products, (TEMPs); tissue engineering

[6] Note that the United States Public Health Service (USPHS) and the United States Food and Drug Administration define "Xenotransplantation" more broadly as "any procedure that involves the transplantation, implantation, or infusion into a human recipient of either *(a)* live cells, tissues, or organs from a nonhuman animal source, or *(b)* human body fluids, cells, tissues, or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues or organs." Because this terminology is intended to classify skin substitutes by clinical equivalency, and not by composition, the dictionary definition is used, for this terminology only. It should be understood that an allograft or autograft substitute may include animal components which cause it to be also a xenotransplant by the Food and Drug Administration definition.

APPENDIX

(Nonmandatory Information)

X1. RATIONALE

X1.1 Purpose

X1.1.1 Because there is a need for standards related to the developing field of TEMPs (**14**), the participants of the F04.41 subcommittee have chosen to define specific terms related to TEMPs. These definitions are intended to unify the ASTM standards with a common language such that the users of these standards can understand and interpret the standards more precisely. Each of the other subcommittees will define their respective terms within their documents for particular applications.

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