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Standard Guide for Classification of Cellular and/or Tissue-Based Products (CTPs) for Skin Wounds[1]

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1. Scope

1.1 This guide defines terminology for description of cellular and/or tissue-based products (CTPs) for skin wounds. CTPs are defined primarily by their composition and comprise cells and/or the extracellular components of tissue. CTPs may contain cells (viable or nonviable), tissues, proteins, and other materials for which there is a rationale for benefit beyond that achievable with conventional wound coverings. CTPs may additionally include synthetic components. Whether an individual CTP is capable of promoting wound healing must be determined by adequate evidence and is beyond the scope of this standard.

1.2 This guide also describes a classification and nomenclature for CTPs based on their composition. This systematic nomenclature is not intended to be prescriptive for product labeling, and it describes only the most salient characteristics of these products; the actual biological and clinical functions can depend on characteristics not recognized in the nomenclature, and it should be understood that two products that can be described identically by the nomenclature should not be presumed to be identical or have the same clinical utility.

1.3 This guide defines CTP-related terminology in the context of skin wounds. However, this guide does not provide a correspondence between the CTP composition and its clinical use(s). More than one product may be suitable for each clinical use, and one product may have more than one clinical use.

1.4 *This standard does not purport to address safety concerns with the use of CTPs. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

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

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

F2311 Guide for Classification of Therapeutic Skin Substitutes

F2312 Terminology Relating to Tissue Engineered Medical Products

F2739 Guide for Quantitating Cell Viability Within Biomaterial Scaffolds

3. Terminology

3.1 *Skin Tissue Definitions:*

3.1.1 *dermal, adj*—pertaining to the dermis (**1**).[3]

3.1.2 *dermis, n*—the layer of the skin deep to the epidermis, consisting of a dense bed of vascularized connective tissue (**1**).

3.1.3 *dermoepidermal junction (DEJ), n*—distinct anatomic zone between the epidermis and dermis that facilitates adherence between the two layers; contains laminin, collagen type VII, collagen type IV, and tenascin C (**2**).

3.1.4 *epidermal, adj*—pertaining to or resembling epidermis (**1**).

3.1.5 *epidermis, n*—the outermost and nonvascularized layer of the skin (**1**).

3.1.6 *extracellular matrix, n*—a structural and functional entity produced by cells that surrounds and supports cells and

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

regulates cell communication. Typical components are collagens, adhesive glycoproteins, glycosaminoglycans, and proteoglycans (**3**).

3.1.7 *skin, n*—the outer integument or covering of the body, consisting of the dermis and the epidermis, and resting upon the subcutaneous tissue. (**F2312**)

3.1.8 *tissue, n*—an aggregation of similarly specialized cells united in the performance of a particular function. A tissue contains an extracellular matrix in addition to specialized cells (**F2312**)

3.2 *Skin Wound and Ulcer Definitions:*

3.2.1 *acute wound, n*—a wound that normally proceeds through an orderly and timely reparative/regenerative process that results in sustained restoration of anatomic and functional integrity (**4**).

3.2.2 *arterial ulcer, n*—ulceration due to peripheral arterial disease (**5**).

3.2.3 *burn, n*—injury to tissues caused by contact with heat, chemicals, electricity, friction, or radiant and electromagnetic energy (**1**).

3.2.4 *chronic wound, n*—a wound that has failed to proceed through an orderly and timely process to produce anatomic and functional integrity, or proceeded through the repair process without establishing a sustained anatomic and functional result (**4**).

3.2.5 *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). (**F2312**)

3.2.6 *lesion, n*—any pathological or traumatic discontinuity of tissue or loss of function of a part. (**F2312**)

3.2.7 *mixed arterial-venous ulcer, n*—an ulceration due to a combination of chronic venous insufficiency and arterial disease (**5**).

3.2.8 *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. (**F2312**)

3.2.9 *scar, n*—fibrous tissue replacing normal tissues destroyed by injury or disease. (**F2312**)

3.2.10 *surgical wound, n*—a wound created as the result of a surgical procedure.

3.2.11 *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. (**F2312**)

3.2.12 *pressure ulcer, n*—localized injury to the skin and/or underlying tissue usually over a bony prominence as a result of pressure, or pressure in combination with shear and/or friction. Also known as *decubital ulcer*, *decubitus ulcer*, *pressure sore*, *bed sore* (**6**).

3.2.13 *diabetic ulcer, n*—an ulcer, usually of the lower extremities and particularly of the foot, associated with diabetes mellitus (**1**).

3.2.14 *venous leg ulcer, n*—ulceration on the leg due to chronic venous insufficiency. Also known as venous stasis ulcer or venous insufficiency ulcer (**5**).

3.2.15 *wound, n*—a disruption of normal anatomic structure and function of a tissue or organ. Also known as *injury* or *trauma*(**4**).

3.2.15.1 *Discussion*—In this guide, skin wounds include those caused by burns, trauma, surgical incision, or surgical excision, in addition to ulcers associated with underlying chronic conditions. This guide makes no distinction among different types of ulcers, which are a result of differing pathologies or conditions and for which different procedures and different types of CTPs may be appropriate.

3.3 *Wound Healing Physiology Definitions:*

3.3.1 Acute wound healing of skin typically proceeds in a sequential series of steps that overlap in time: hemostasis, inflammation, new tissue formation (re-epithelialization, granulation tissue formation, neovascularization), and tissue remodeling (wound contraction and extracellular matrix reorganization). Each of these steps is characterized by dynamic, reciprocal interactions among cells, extracellular matrix, and the cellular microenvironment. In contrast, chronic wounds do not proceed normally through these healing steps but instead exhibit numerous abnormalities as a result of underlying pathobiology (**7, 8**).

3.3.2 *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. (**F2312**)

3.3.3 *heal, v*—to restore wounded parts or to make healthy. (**F2312**)

3.3.4 *healing, n*—the restoration of integrity to injured tissue. (**F2312**)

3.3.5 *necrotic, adj*—characterized by the sum of the morphological changes indicative of cell death and caused by the progressive degradative action of enzymes (**1**).

3.3.6 *scar, n*—fibrous tissue replacing normal tissues destroyed by injury or disease. (**F2312**)

3.3.7 *tissue regeneration, n*—healing in which lost tissue is replaced by migration, differentiation, and proliferation of cells that deposit new extracellular matrix with normal architecture, function, and appearance.

3.3.8 *tissue repair, n*—healing in which lost tissue is replaced by a fibrous scar, which is produced from granulation tissue. (**F2312**)

3.3.9 *wound contraction, n*—the shrinkage and spontaneous closure of open skin wounds. (**F2312**)

3.3.10 *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.

3.3.10.1 *Discussion*—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," (1) because that definition does not address fibrosis and scarring in skin. (F2312)

3.3.11 *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. 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. (F2312)

3.4 *Wound Cover Definitions:*

3.4.1 *dressing, n*—any of various materials utilized to cover and protect wounds. (F2312)

3.4.2 *surgical dressing, n*—any of various materials utilized to cover and protect wounds following surgical procedures or debridement of any type.

3.5 *CTP Components and Methods:*

3.5.1 *acellular scaffold, n*—a scaffold without primary or cultured cells. (F2311)

3.5.2 *allogeneic or allogenic, adj*—from cells, tissues, and organs in which the donor and recipient are genetically different individuals of the same species. (F2311)

3.5.3 *autologous, adj*—from cells, tissues, and organs in which the donor and recipient is the same individual. (F2311)

3.5.4 *bioactive agent, n*—any molecular component that elicits a tissue or cell response.

3.5.5 *biocompatible, adj*—the ability of a material to perform with an appropriate host response in a specific situation (9).

3.5.6 *biological, adj*—synthesized or produced by living cells.

3.5.7 *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. (F2312)

3.5.8 *biosynthetic, adj*—partly synthesized or produced by living cells and partly chemically synthesized.

3.5.9 *cell, n*—the smallest structural and functional unit of an organism. Typically, cells are microscopic and consist of cytoplasm and a nucleus enclosed in a membrane (10).

3.5.10 *cell culture, n*—the *in vitro* growth or maintenance of cells. (F2311)

3.5.11 *cell type, n*—a distinct morphological or functional form of cell. (F2311)

3.5.12 *cellular, adj*—containing viable (living) cells.

3.5.13 *cellular and/or tissue-based product (CTP), n*—a product defined primarily by its composition, comprising cells and/or the extracellular components of tissue. CTPs may contain cells (viable or nonviable), tissues, proteins, and other materials for which there is a rationale for benefit beyond that achievable with conventional wound coverings. CTPs may additionally include synthetic components. Whether an individual CTP is capable of promoting wound healing must be determined by adequate evidence and is beyond the scope of this standard.

3.5.14 *cellular therapy, n*—a treatment containing viable (living) cells.

3.5.15 *cellularized scaffold, n*—a scaffold that has been seeded with viable cells. The seeded scaffold may or may not be further cultured. (F2311)

3.5.16 *CTP product format, n*—the overall shape or appearance of the CTP, which includes, but is not limited to, single sheets, multilayer sheets, 3-dimensional constructs, particles (e.g., powders), granules, gels, sprays, pellets, spheroids, cylinders, and so forth.

3.5.17 *cultured cells, n*—cells propagated by cell culture. (F2311)

3.5.18 *decellularized scaffold, n*—an acellular scaffold formed by removing the cells from an extracellular matrix by chemical and physical treatments. (F2311)

3.5.19 *devitalized scaffold, n*—a tissue-derived scaffold containing killed cells and no viable cells.

3.5.20 *differentiated cell, n*—cell with morphological and metabolic characteristics of a specialized type.

3.5.21 *extracellular matrix architecture, n*—structural characteristics of an extracellular matrix.

3.5.22 *killed cell, n*—a cell that has been subjected to physical or chemical conditions that assure that it is non-viable. (F2311)

3.5.23 *live cell, n*—a viable cell. (F2311)

3.5.24 *metabolically active, adj*—capable of catalyzing all of the chemical transformations and transport processes typical of living organisms, including anabolism and catabolism. Metabolic processes typically transform small molecules, but also include macromolecular processes such as DNA repair and replication, protein synthesis and degradation, and membrane transport. (F2311)

3.5.25 *natural materials, n*—synthesized or produced by living cells. (F2027)

3.5.26 *non-viable cell, n*—a cell that does not meet the definition of viability specified in 3.5.35. (F2311)

3.5.27 *primary cells, n*—dispersed cells derived directly from fresh tissue. (F2311)

3.5.28 *processed, adj*—characterized by a series of mechanical or chemical operations on (something) in order to change or preserve it. In this standard, processed is used to refer to tissue (as in processed tissue) (10).

3.5.29 *proliferation competent cell, n*—cell capable of replication.

3.5.30 *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. (F2150)

3.5.31 *scaffold architecture, n*—macrostructural characteristics of a scaffold biomaterial that determines its permeability to