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

This standard is issued under the fixed designation F3163; 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~~ Scope*

1.1 This guide defines terminology for description of cellular and/or tissue-based products (CTPs) for skin wounds. CTPs are ~~defined primarily~~ TEMPs (tissue-engineered medical products) that are primarily defined 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.~~ viable and/or nonviable human or animal cells, viable and/or nonviable tissues, and may include extracellular matrix components. 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~~ categories and ~~nomenclature~~terminology for CTPs based on their composition. This systematic ~~nomenclature~~categorization 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,~~categorization and it should be understood that two products that can be described identically by the ~~nomenclature~~categorization 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 guide 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 involved in the development of said products in accordance with applicable regulatory guidance documents and in implementing this guide to evaluate the cellular and/or tissue-based products for wounds.

1.5 *This standard does not purport to address ~~safety concerns with the use of CTPs.~~ 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~~ safety, health, and ~~health~~environmental practices and determine the applicability of regulatory limitations prior to use.*

1.6 *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.*

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

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***A Summary of Changes section appears at the end of this standard**

2. Referenced Documents

2.1 *ASTM Standards:*[2]

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

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

F2311 Guide for Classification of Therapeutic Skin Substitutes (Withdrawn 2017)[3]

F2312 Terminology Relating to Tissue Engineered Medical Products

F2739 Guide for Quantifying Cell Viability and Related Attributes within Biomaterial Scaffolds

3. Terminology

3.1 *Skin Tissue Definitions:*

3.1.1 *dermal, adj*—pertaining to the dermis (**1**).[4]

3.1.2 *dermis, n*—the layer of the skin ~~deep to~~ underneath 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 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~~a level of organization in multicellular organisms consisting of a group of structurally and functionally related cells and extracellular matrix. (**F2312**)

3.2 *Skin Wound and Ulcer Definitions:*[5]

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~~also referred to ~~peripheral~~as ~~*arterial disease*~~*ischemic ulcer,* is caused by poor perfusion (delivery of nutrient-rich blood) to the lower extremities (**5, 6**).

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**).

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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 last approved version of this historical standard is referenced on www.astm.org.

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

[5] 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.

3.2.5 *diabetic leg or foot ulcer, n*—a break of the skin of the foot that includes minimally the epidermis and part of the dermis and involves infection, ulceration, or destruction of tissues of the foot associated with neuropathy and/or peripheral artery disease in the lower extremity of a person with (a history of) diabetes mellitus (**5, 6**).

3.2.6 *full-thickness skin wound, n*—a skin wound with the loss of or penetration through the 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)~~

3.2.7 *ischemic ulcer, n*—see *arterial ulcer*.

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

3.2.9 *mixed arterial-venous ulcer, n*—an ulceration due to a combination of chronic venous insufficiency and arterial disease (**57**).

3.2.10 *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)~~

3.2.11 *pressure injury/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. Also known as *decubital ulcer*,*decubitus ulcer*,*pressure sore*, or *bed sore*(**8**).

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

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

3.2.14 *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).~~

3.2.15 *venous leg ulcer, n*—~~ulceration~~ a local defect on the leg due to chronic venous insufficiency. Also known as a venous stasis ulcer or a venous insufficiency ulcer (**5, 6**).

3.2.16 *wound, n*—~~a~~ an acquired 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~~**9, 810**).

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];~~(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.[6]

~~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~~**11**).

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

[6] 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.

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.~~a synthetic or natural substance or composite used for a biological or biomedical application. **(F2312)**

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

3.5.9 *cell, n*—the smallest structural and functional unit of ~~an~~ a eukaryotic organism. Typically, cells are microscopic and consist of cytoplasm and a nucleus enclosed in a membrane (~~10~~12).

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.~~cell that expresses similar genes. ~~**(F2311)**~~

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

3.5.13 *cellular and/or tissue-based ~~product (CTP),~~products (CTPs), 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.~~ TEMPs (tissue-engineered medical products) that are primarily defined by their composition and comprise viable and/or nonviable human or animal cells, viable and/or nonviable tissues, and may include extracellular matrix components. CTPs may additionally include synthetic components.~~Whether~~[7] ~~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,~~to: single sheets, multilayer sheets, ~~3-dimensional~~three-dimensional constructs, particles ~~(e.g., ~~(for example, 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~~ensure that it is ~~non-viable.~~nonviable. ~~**(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

[7] Guidance regulated by (*1*) CBER under Section 361 of the PHS Act and 21 CFR Part 1271, (*2*) CBER as drugs, devices, and/or biological products subject to Section 351 of the PHS Act and/or the Act and applicable regulations in Title 21 of the CFR, or (*3*) CDRH under the FD&C Act as a medical device.

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*~~*nonviable 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)~~ a substance in order to change or preserve it. In this standard, processed is used to refer to tissue (as in processed tissue) (~~10~~12).

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 cells, including whether or not it is ~~a/an~~an impervious solid, impervious membrane, porous membrane, ~~open cell~~ open-cell porous foam, ~~non-woven~~nonwoven fiber, woven fabric, or cell-permeable gel. ~~(F2311)~~

3.5.32 *stem cell, n*—a cell that can replicate itself and produce cells that take on more specialized functions (~~11~~13).

3.5.32.1 *Discussion*—
The working definition of a stem cell includes self-renewal and the ability to differentiate into several cell types. There are also aspects of clonality and potency. Stem cells can be derived from early embryos after the formation of the blastocyst or from fetal, postnatal, or adult sources and can include induced pluripotent stem cells.

3.5.33 *syngeneic, adj*—from cells, tissues, and organs in which the donor has a genotype unreactive with the recipient. Also known as *syngraft*,*isograft*,*isogeneic*, or *isogenic*. ~~(F2311)~~

3.5.34 *synthetic, adj*—chemically synthesized. ~~(F2311)~~

3.5.35 *viable cell, n*—a cell capable of metabolic activity that is structurally intact with a functioning cell membrane. **(F2739)**

3.5.36 *xenogeneic or xenogenic, adj*—from cells, tissues, and organs in which the donor and recipient belong to different species. Synonyms: *xenogenous*,*heterogeneic*, or *heterologous*. ~~(F2311)~~

3.6 *Medical and Surgical Procedures:*

3.6.1 *autolysis, n*—~~removal of devitalized tissue using~~ destruction of cells and/or tissues by the body's own enzymes (~~12~~14).

3.6.2 *biological debridement, n*—therapy using living organisms to digest necrotic tissue and pathogens (~~12~~14).

3.6.3 *debridement, n*—the removal of foreign material and devitalized or contaminated tissue from or adjacent to a traumatic or infected wound until surrounding healthy tissue is exposed (1).

3.6.4 *enzymatic debridement, n*—debridement using enzymatic preparations (~~12~~14).

3.6.5 *maintenance therapy, n*—therapy of chronically ill patients that is aimed at keeping the pathology at its present level and preventing exacerbation. ~~(F2312)~~

3.6.6 *mechanical debridement, n*—use of mechanical methods to ease removal of the surface eschar and debris (~~12~~14).

3.6.7 *medical debridement, n*—removal of fibrin, devitalized epidermis and/or dermis, exudate, debris, and/or biofilm from wounds in which tissue removal does not extend into subcutaneous tissue, muscle, bone, etc. (~~13~~15).

3.6.8 *surgical debridement, n*—removal of devitalized tissue from wounds that includes subcutaneous tissue (includes epidermis and dermis, if performed), muscle (includes epidermis, dermis, and subcutaneous tissue, if ~~performed)~~performed), and/or bone (includes epidermis, dermis, subcutaneous tissue, muscles, and/or fascia, if performed) (~~13~~15).

3.6.9 *surgical site preparation (for skin wounds), n*—surgical preparation or creation of the recipient site by excision of open skin wounds, burn eschar, or scar (including subcutaneous tissues), or incisional release of scar contracture to prepare a clean and viable wound surface for placement of a CTP (~~14~~5).

~~**4. Cell Viability**~~

~~4.1 Cell viability is a critical concept for CTPs in skin wounds, as some of these products derive clinical utility from constituent cell populations. Cell populations can be unambiguously distinguished by parameters such as cell type (for example, fibroblast, keratinocyte), species, and genetic origin, but within a population category the cells can vary substantially with respect to metabolic activities, membrane integrity, degree of differentiation, the ability of the cells to further grow and proliferate, and/or other properties. *In vivo*, the cell populations are usually in a steady state with respect to these properties; however, *ex vivo*, the cell populations may also be in a dynamic state, for example, decreasing viability over time (F2311).~~

~~4.2 Due to the heterogeneity and dynamics of cell populations, the contributions of cells to the clinical utility of cellular therapies result from ensemble statistics of heterogeneous and changing cell populations. Thus, categories used in the nomenclature, such as "metabolically active," and "viable," are abstractions for which precise operational definitions or specific methodologies for measurement are outside of the scope of this guide (F2311).~~

~~4.3 This guide suggests five basic levels of viability for cell populations in CTPs:~~

~~4.3.1 *Acellular*—Free of intact cells and not carrying out any metabolic reactions. A scaffold made from biomaterials or made by extracting killed cells from tissue would be acellular (F2311).~~

~~4.3.2 *Killed Cells*—The cell population has been treated so that all cells in the population are unable to carry out metabolic functions and do not demonstrate membrane functions. A heat or radiation sterilized tissue would contain killed cells (F2311).~~

~~4.3.3 *Non-Viable Cells*—The cell population is not capable of carrying out all metabolic and membrane functions, although it may demonstrate some metabolic functions for a period of time and a portion of the cells may demonstrate membrane function for a period of time (F2311).~~

~~4.3.4 *Viable Cells*—A large portion of cells in the population is capable of carrying out all of the metabolic reactions and membrane functions typical of live cells of the cell type, according to one or more assays and observations (F2311).~~

~~4.3.5 *Proliferation Competent Cells*—At least a portion of the cells of a population of viable cells is capable of further growth and replication *in vivo* or *in vitro* (F2311).~~

~~4.4 *Examples:*~~

~~4.4.1 Cultured epidermal cells consisting of a sheet of cultured autologous keratinocytes. This cell population typically consists of a mixture of replicating cells and differentiating cells that are not capable of further replication. The differentiating cells would be considered "viable" (F2311).~~

~~4.4.2 A cultured allogeneic fibroblast sheet that has been demonstrated in clinical trials to require a defined fraction of the cells to be viable using a specific assay(s) for metabolic or membrane function. Replication, however, is either not assayed or does not contribute to clinical function. This cell population would be termed to be "viable" (F2311).~~

~~4.4.3 A cultured allogeneic fibroblast sheet is frozen; when thawed, its cells no longer are viable according to a specific assay of membrane function. However, the sheet is capable of successfully behaving like a dermal allograft by providing temporary wound closure when placed on an excised burn wound. This cell population would be considered "non-viable" (F2311).~~