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Standard Guide for Classification of Therapeutic Skin Substitutes[1]

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1. Scope

1.1 This guide defines terminology and provides classification for products that can be substituted for tissue grafts of human or animal tissue in medical and surgical therapies of skin lesions.

1.2 This guide provides a classification method for skin substitutes by comparing their clinical uses with those of conventional tissue grafts. However, skin substitutes may also have equivalent, superior, or inferior clinical properties in comparison to conventional tissue grafts. Clinical classification is independent of the materials and technology used to make a skin substitute, or whether its components include human or animal tissue or other biological or non-biological materials.

1.3 This guide also describes a nomenclature for systematic description of the technologies and components of skin substitutes that is independent of their clinical utilities. This systematic nomenclature is not intended to be prescriptive for product labeling, and it describes only the most salient characteristics of skin substitutes; the actual biological and clinical functions of skin substitutes 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.

1.4 This guide does not provide a correspondence between the skin substitute composition and the clinical classification. Also, more than one product may be suitable for each clinical use, and one product may have more than one clinical use.

1.5 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory 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

F2210 Guide for Processing Cells, Tissues, and Organs for Use in Tissue Engineered Medical Products

F2312 Terminology Relating to Tissue Engineered Medical Products

2.2 *Other Reference:*

Dorland's Illustrated Medical Dictionary, 29th Ed., W. B. Saunders Company, Philadelphia, 2000.

3. Terminology

3.1 *Skin Tissue Definitions:*

3.1.1 *dermal, adj*—pertaining to the dermis. **Dorland's**

3.1.1.1 *Discussion*—In this guide, to avoid confusion, "dermal" is preferred to be used to refer only to a patient's existing or regenerated tissue and not to dermal tissue when used as a component of a skin substitute. Exceptions are "dermal autograft" and "dermal autograft substitute."

3.1.2 *dermis, n*—the layer of the skin deep to the epidermis, consisting of a dense bed of vascular connective tissue. **Dorland's**

3.1.3 *epidermal, adj*—pertaining to or resembling epidermis. **Dorland's**

3.1.3.1 *Discussion*—In this guide, to avoid confusion, "epidermal" is used to refer only to the patient's existing or regenerated tissue and not to epidermal tissue used as a component of a skin substitute. Exceptions are "epidermal autograft" and "epidermal autograft substitute."

3.1.4 *epidermis, n*—the outermost and nonvascular layer of the skin. **Dorland's**

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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.

3.1.5 *skin, n*—the outer integument or covering of the body, consisting of the dermis and the epidermis, and resting upon the subcutaneous tissues. **F2312**

3.1.6 *tissue, n*—an aggregation of similarly specialized cells united in the performance of a particular function. In general, a tissue contains an extracellular matrix, in addition to specialized cells. **F2312**

3.2 *Skin Wound and Ulcer Definitions:*

3.2.1 *excised skin wound, n*—a full or deep partial thickness open skin wound that has been created by surgery and that is free of foreign matter, necrotic and devitalized tissue, and microbial contamination, has no punctuate bleeding, and is capable of engrafting a skin autograft. In addition, an excised skin wound should have a suitable contour such that the skin graft or skin graft substitute can adhere (such as by capillary attractive force) without significant air or fluid pockets between it and the underlying viable tissue.

3.2.2 *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**

3.2.3 *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. **F2312**

3.2.4 *open wound, n*—a wound that communicates with the atmosphere by direct exposure **F2312**

3.2.5 *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**

3.2.6 *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**

3.2.6.1 *decubitus ulcer, n*—an ulceration caused by prolonged pressure allowed to lie still in bed for a long period of time. Also known as *decubital ulcer*, *pressure sore*, *bed sore*. **Dorland's**

3.2.6.2 *diabetic foot ulcers, n*—an ulcer, usually of the lower extremities, associated with diabetes mellitus. **Dorland's**

3.2.6.3 *venous stasis ulcer, n*—ulceration due to venous stasis or insufficiency. Also know as *stasis ulcer*. **Dorland's**

3.2.7 *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. **F2312**

3.2.7.1 *Discussion*—In this guide, skin wounds include those caused by trauma, surgical incision, or surgical excision; skin lesion is the most general term, encompassing both skin ulcers and skin wounds. This guide makes no distinction among different types of ulcers (for example, decubitus ulcers, diabetic ulcers, venous stasis ulcers) which are a result of differing pathologies or conditions and for which different procedures and different types of skin substitute may be appropriate.

3.3 *Wound Healing Physiology Definitions:*

3.3.1 *Discussion*—In 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 (see 6.3.1). Wound closure "by approximating the wound edges or performing a skin autograft" is "healing by first intention," and wound closure by "allowing spontaneous healing from the edges" is "healing by second intention."

3.3.2 *devitalized, n*—deprived of vitality or life. **Dorland's**

3.3.3 *engraftment, n*—incorporation of grafted tissue into the body of the host. **F2312**

3.3.4 *[graft] take, n*—engraftment. **F2312**

3.3.5 *granulations, n*—granulation tissue.

3.3.6 *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**

3.3.7 *heal, v*—to restore wounded parts or to make healthy. **F2312**

3.3.8 *healing, n*—the restoration of integrity to injured tissue. **F2312**

3.3.9 *healing by first intention, n*—healing in which union or restoration of continuity occurs directly without intervention of granulations. **F2312**

3.3.10 *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. **F2312**

3.3.11 *hypercatabolism, n*—abnormally increased catabolism. **Dorland's**

3.3.12 *necrotic, n*—characterized by the sum of the morphological changes indicative of cell death and caused by the progressive degradative action of enzymes. **Dorland's**

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

3.3.14 *primary wound closure, n*—wound closure by approximating wound edges or performing a skin graft (healing by first intention).

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

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

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

3.3.18 *skin replacement, n*—the permanent replacement of lost or diseased skin with healthy skin.

3.3.19 *tissue regeneration, n*—healing in which lost tissue is replaced by proliferation of cells, which reconstruct the normal architecture. **F2312**

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

3.3.21 *wound closure, n*—the provision of an epithelial cover over a wound. It can be accomplished by approximating wound edges, performing a skin graft, or allowing spontaneous healing from the edges. **F2312**

3.3.22 *wound closure immediate physiological response, n*—an immediate restoration of some of the physiological functions of skin by a skin graft or skin substitute that is demonstrated by an immediate reduction in wound inflammation, pain, and fluid loss. Granulation tissue is not formed and wound contraction does not occur. In the case of a large wound, the open wound systemic physiological response is also reduced.

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

3.3.24 *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.

3.3.24.1 *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," because that definition does not address fibrosis and scarring in skin. **F2312**

3.3.25 *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 *Graft Definitions:*

3.4.1 *allograft, n*—a graft of tissue between individuals of the same species but of disparate genotype. Called also allogeneic graft and homograft.[3] **F2312**

3.4.2 *autograft, n*—a graft of tissue derived from another site in or on the body of the organism receiving it. **F2312**

3.4.3 *conventional graft, n*—fresh or frozen graft tissue, not otherwise processed.

3.4.4 *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. **F2312**

3.4.5 *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. **F2210**

3.4.6 *epidermal autograft, n*—an autograft consisting primarily of epidermal tissue, including keratinocyte stem cells, but with little dermal tissue.[5] **F2312**

3.4.7 *full thickness skin autograft, n*—a skin [auto]graft consisting of the epidermis and the full thickness of the dermis. **F2312**

3.4.8 *graft, n*—any tissue or organ for implantation or transplantation. **F2312**

3.4.9 *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. **F2210**

3.4.10 *recipient, n*—the individual or organism into whom materials are grafted or implanted. **F2210**

3.4.11 *split thickness skin autograft, n*—a skin [auto]graft consisting of the epidermis and a portion of dermis. **F2312**

3.4.12 *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. Some (but not all) forms of transplantation are regulated by the U.S. Food and Drug Administration (FDA) under 21 CFR Parts 16 and 1270 (1) and 21 CFR Parts 207, 807, and 1271 (2). **F2210**

3.4.13 *xenocultured cell, n*—a cell that is a xenotransplantation product.

3.4.13.1 *Discussion*—Xenografts and xenotransplantation products comprise overlapping but not congruent groups of skin substitutes. Autograft, allograft, and xenograft are traditional terms to describe tissue used in surgical procedures. Because autograft involves the harvesting of the patient's own tissue, care is taken to preserve its viability. However, allograft and xenograft are not necessarily alive and may have been frozen for storage. Skin substitutes may combine attributes of autograft, allograft, xenograft, and xenotransplantation product, depending on the origin of cells or tissues used in their manufacture, and whether these components are alive or not. For example, a skin substitute consisting of viable autologous epidermal cells grown on a feeder layer of metabolically active, non-replicating murine cells may be both autologous and a xenotransplantation product.

3.4.14 *xenograft, n*—a graft of tissue transplanted between animals of different species. Called also heterograft, heterologous graft and heteroplastic graft. A xenograft is not necessarily a xenotransplantation product (3.4.16), and vice versa. **F2312**

3.4.15 *xenotransplantation, n*—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,

[3] It should be understood that an allograft substitute or autograft substitute may include animal components which cause it to be also a xenotransplantion product according to 3.4.16.

[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.*, 23, 2002, pp. 327-332; and Kagan, R. J., Invited editorial, *J Burn Care Rehabil.*, 23, 2002, pp. 326.

tissues, or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues or organs.[6]

3.4.16 *xenotransplantation product, n*—live cells, tissues, or organs used in xenotransplantation.[7]

3.5 *Other Wound Cover Definitions:*

3.5.1 *dressing, n*—any of various materials utilized for covering and protecting a wound. **F2312**

3.5.2 *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.**F2312**

3.5.3 *wound cover, n*—a dressing, skin graft, or skin substitute.

3.6 *Skin Substitute Components and Processes:*

3.6.1 *acellular scaffold, n*—a scaffold without primary or cultured cells.

3.6.2 *allogeneic or allogenic, adj*—from cells, tissues, and organs in which the donor and recipient are genetically different individuals of the same species. Synonyms: *allograft* and *homograft*. **F2210**

3.6.3 *autologous, adj*—from cells, tissues, and organs in which the donor and recipient is the same individual. Synonyms: *autogenous*, *autograft*, or *autotransfusion*, a *self-to-self graft*. **F2210**

3.6.4 *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**

3.6.5 *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. **F2312**

3.6.6 *cell culture, n*—the *in vitro* growth or maintenance of cells. **F2210**

3.6.7 *cell type, n*—a distinct morphological or functional form of cell.

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

3.6.9 *cultured cells, n*—cells propagated by cell culture.

3.6.10 *extracellular matrix, n*—any material produced by cells and excreted to the extracellular space within the tissues. It takes the form of both ground substance and fibers and is composed chiefly of fibrous elements, proteins involved in cell adhesion, and glycosaminoglycans and other space-filling molecules.

3.6.11 *killed cell, n*—a cell that has been subjected to conditions that assure that it is non-viable.

3.6.12 *live cell, n*—a viable cell.

3.6.13 *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.

3.6.14 *natural materials, n*—synthesized or produced by living cells. **F2027**

3.6.15 *non-viable cell, n*—a cell not meeting one or more of the criteria for viability given in 3.6.23.

3.6.16 *primary cells, n*—dispersed cells derived directly from fresh tissue.

3.6.17 *proliferation competent cell, n*—viable cell capable of continued growth and replication under appropriate culture or *in vivo* conditions.

3.6.18 *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**

3.6.19 *scaffold architecture, n*—macrostructure characteristics of a scaffold biomaterial that determines its permeability to cells, including whether or not it is an impervious solid, impervious membrane, porous membrane, open cell porous foam, non-woven fibers, woven fabric, cell-permeable gel.

3.6.20 *skin substitute format, n*—the overall shape of the skin substitute, such as sheet, multilayer sheet, particles, granules, pellet, spheroid, cylinder, and so forth

3.6.21 *syngeneic, adj*—from cells, tissues, and organs in which the donor has an unreactive genotype with the recipient. Synonyms: *syngraft*, *isograft*, *isogeneic*, or *isogenic*. **F2210**

3.6.22 *synthetic biomaterial, n*—a chemically synthesized biomaterial.

3.6.23 *viable cell, n*—a cell capable of metabolic activity that is structurally intact with a functioning cell membrane.

3.6.24 *xenogeneic or xenogenic, n*—from cells, tissues, and organs in which the donor and recipient belong to different species. Synonyms: *xenogenous*, *heterogeneic*, or *heterologous*. **F2210**

3.7 *Medical and Surgical Procedures:*

3.7.1 *debridement, n*—the removal of foreign material and devitalized or contaminated tissue from or adjacent to a traumatic or infected lesion until surrounding healthy tissue is exposed. **Dorland's**

3.7.2 *dressing therapy, n*—application of wound dressing in direct contact with wound tissue or lesion. Wound dressing therapy may be used to protect an open skin wound or skin ulcer during healing by second intention and in therapy of non-healing ulcers that is aimed at promoting natural wound closure and/or tissue repair or at keeping the pathology at its present level and preventing exacerbation.

3.7.3 *excision, n*—the surgical procedure to prepare a wound to accept a skin graft. The result of the procedure is an excised skin wound (see 3.2.1). Excision encompasses any

[6] This definition is intended to be consistent with that of the United States Public Health Service (USPHS) and the United States Food and Drug Administration. See http://www.fda.gov/CBER/xap/xap.htm and http://www.fda.gov/CBER/gdlns/clinxeno.htm.

[7] See http://www.fda.gov/CBER/gdlns/clinxeno.htm.

debridement necessary to remove foreign material, devitalized tissue or contaminated tissue.[8]

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

3.7.5 *sharp debridement, n*—debridement accomplished by incising tissues with a sharp edge. **Dorland's**

3.7.6 *skin allograft therapy, n*—the treatment of a skin lesion by the temporary topical application of skin allograft or skin allograft substitute that is aimed at promoting tissue repair and wound closure.

3.7.7 *skin replacement, n*—the therapeutic outcome of successful skin replacement surgery.

3.7.8 *skin replacement surgery, n*—surgery that permanently replaces lost skin with healthy skin. **F2312**

3.7.9 *skin xenograft therapy, n*—the treatment of a skin lesion by the temporary topical application of skin xenograft that is aimed at promoting tissue repair and wound closure. **F2312**

4. Significance and Use

4.1 As much as possible, terminology contained herein is based on medical dictionary definitions.

4.2 This guide provides nomenclature and classifications to accurately and unambiguously describe tissue engineered skin substitutes as well as their clinical functions. These classification systems and their nomenclature are not intended to be prescriptive for product labeling or advertising.

4.3 In this guide, "replacement" and "substitute" have different meanings, although they can be used synonymously in ordinary English. "Skin substitute," which is defined in 3.5.2, is a tissue-engineered medical product that a physician or surgeon can use in a medical or surgical procedure. "Skin replacement," which is defined in 3.7.7, is the therapeutic outcome of successful skin replacement surgery, but this is only one of several clinical uses for skin substitutes.

4.4 Skin substitutes are used in different medical settings and by different medical and surgical specialties. In order to help clarify the clinical applications of skin substitutes, a discussion of common medical and surgical procedures that use conventional skin tissue grafts (autograft and fresh or frozen allograft and xenograft) is provided in Section 6. This discussion is intended provide context for understanding the categories of Section 7, which model clinical uses of skin substitutes by comparison with the uses of conventional skin grafts. However, the procedures, circumstances, and surgical intentions in section are not intended to limit the possible uses of skin substitutes, nor is the classification in section intended to limit the uses of skin substitutes to only those uses of conventional skin graft tissues.

[8] This definition is intended to be consistent with the usage of plastic, reconstructive and burn surgeons, who typically accomplish excision with the aid of a dermatome. Some other medical specialties may use excision interchangeably with sharp debridement; however, a wound created by sharp debridement is not necessarily capable of accepting a skin autograft.

5. Cell Viability

5.1 Some skin substitutes 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.

5.2 Because of the heterogeneity and dynamics of cell populations, the contributions of cells to the clinical utility of skin substitutes 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.

5.3 This guide suggests five basic levels of viability for cell populations in tissue engineered medical products:

5.3.1 *Proliferation Competent Cells*—At least a portion of the cells of a population of viable cells are capable of further growth and replication *in vivo* or *in vitro*.

5.3.2 *Viable Cells*—A large portion of cells in the population are 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.

5.3.3 *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. A tissue subjected to freezing and thawing (without cryoprotection) would be presumed to contain non-viable cells.

5.3.4 *Killed Cells*—All cells in the population are definitively not carrying out metabolic functions and do not demonstrate membrane functions. A heat or radiation sterilized tissue would contain killed cells.

5.3.5 *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.

5.4 *Examples:*

5.4.1 Cultured epidermal autograft 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" if they have the capability of engraftment when grafted onto an excised wound. To function as a permanent epidermis, however, the cell population must also be "replication competent."

5.4.2 Cultured allogeneic fibroblast sheet that has been demonstrated in clinical trials to require that 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."

5.4.3 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 substituting for a skin allograft by providing temporary wound closure when placed on an excised burn wound. This cell population would be considered "non-viable."

5.4.4 Porcine tissue is treated to remove most cells and lyophilized. However, the extracellular matrix retains growth factors that may contribute to clinical function. This tissue would be termed "acellular."

6. Medical and Surgical Therapies for Skin Lesions and Wounds

6.1 This discussion of medical and surgical therapies describes wound healing and skin grafting procedures using conventional skin autograft, allograft, and xenograft. It is intended to provide a context for describing the essential properties required for products to function as substitutes for conventional skin grafts in these procedures. (However, skin substitutes can have novel clinical utilities that can not be accomplished by conventional skin substitutes.)

6.2 *The Natural Healing Process of Partial Thickness Wounds:*

6.2.1 Partial thickness wounds are capable of spontaneous healing with good outcome if not too deep. (Healing and therapy of deep partial thickness wounds is essentially the same as for full thickness wounds.) However, dressing therapy or allograft therapy can be capable of increasing the rate of healing and minimizing the risk of infection or scar.

6.3 *The Natural Healing Process of Full Thickness Wounds:*

6.3.1 The natural healing process for full thickness wounds is an example of healing by second intention.

6.3.2 The immediate physiological response to an untreated, debrided, or excised full thickness open skin wound (such as open wounds covered by dressings) includes wound inflammation, edema, and fluid loss. For wounds of large area, there may also be a systemic physiological response characterized by fever, hypercatabolism, and an increased vulnerability to infection. Following the immediate physiological response, tissue repair replaces lost dermal tissue by a fibrous scar that is produced from granulation tissue.

6.3.3 If the wound is contracted enough by the dermal tissue repair process, the wound is closed by regenerated epidermis created by migration and proliferation of epidermal tissue from the wound margins. In addition to the partial or complete immobilization of joints, wound contracture and the formation of scar tissue can result in chronic fragility of the overlaying epidermal tissue, discomfort, and unacceptable cosmetic appearance.

6.3.4 Systemic physiology during natural healing of full thickness wounds: A full or partial thickness open skin wound that is too large in surface area to be promptly closed by wound contraction and epidermal migration from the margin may be accompanied by continued life threatening systemic physiological responses.

6.4 *Skin Replacement Surgery (Skin Grafts):*

6.4.1 Skin lesions that are not expected to heal spontaneously with good clinical outcome and in a reasonable time may be treated by skin replacement surgery. Skin replacement surgery an example of healing by first intention that is used when an open skin wound is too large to close by apposition of the edges. Skin replacement surgery is a two-step procedure:

6.4.1.1 *Excision*—The first step in skin replacement therapy is surgical excision of the lesion resulting in an excised skin wound (3.2.1).

6.4.1.2 *Wound Closure by Skin Autograft*—The second step in skin replacement therapy is the application of skin autograft (full thickness or split-thickness) or skin autograft substitute to the excised skin wound. The physiological response of an excised skin wound to skin autograft comprises two phases: *(1)* a wound closure immediate physiological response followed by *(2)* permanent engraftment of the skin graft tissue and permanent wound closure. The result of skin replacement surgery is healing by first intention in which the lost skin is permanently replaced by intact healthy skin, with normal tissue architectures of both dermis and epidermis (without significant scar or contracture).

6.4.2 *Alternative Wound Closure Procedures Used in Skin Replacement Surgery:*

6.4.2.1 *Temporary Wound Closure with Skin Allograft or Skin Xenograft*—When skin autograft is not immediately available for use in skin replacement surgery, a skin allograft, skin xenograft or skin allograft substitute may be applied to the excised skin wound for temporary wound closure. The physiological response of an excised skin wound to skin allograft or xenograft is a wound closure immediate physiological response. However permanent engraftment does not occur. Skin replacement surgery is then completed in a future surgical procedure to remove the skin allograft or xenograft and apply a skin autograft to the previously excised wound. (Note that while both skin allograft and skin xenograft can be used for temporary wound closure, there may be clinical differences. Allograft may engraft temporarily before being immunologically rejected. Xenograft usually does not engraft, but also may not maintain wound closure as long as allograft.)

6.4.2.2 *Wound Closure by Epidermal Autograft*—Freshly excised skin wounds and excised skin wounds that have been treated with by allograft, xenograft, or by dermal regenerative autograft substitute can be closed by epidermal autograft. The physiological response of these wounds to epidermal autograft is a wound closure immediate physiological response followed by permanent epidermal tissue engraftment and permanent wound closure.

6.5 *Reconstructive Surgery Using Dermal Autograft:*

6.5.1 Dermal autograft can be surgically implanted in reconstructive procedures for tissue augmentation or reinforcement and will permanently engraft when implanted in a closed wound environment, such as under skin or in internal tissue.

6.6 *Treatments for Partial Thickness Ulcers and Burns:*

6.6.1 *Debridement*—Ulcers can be treated by debridement before initiating a dressing, xenograft, or allograft therapy or during replacement of the dressing or graft.

6.6.2 *Adjunct Therapies*—The healing of ulcers can also be promoted by adjunct therapies directed to the underlying causes of the ulcer.

6.6.3 *Dressing Therapy*—Dressing therapy does not always achieve optimal healing of partial thickness skin wounds or skin ulcers.

6.6.4 *Skin Xenograft Therapy*—Skin xenograft therapy can produce therapeutic responses such as a reduction in inflammation or pain, resolution of infection, or an induction/acceleration of tissue repair and wound closure, in comparison with a dressing therapy.

6.6.5 *Skin Allograft Therapy*—Skin allograft therapy can produce therapeutic responses such as a reduction in inflammation or pain, resolution of infection, or an induction/acceleration of tissue repair and wound closure, in comparison with a dressing therapy.

7. Classification of Skin Substitutes by Clinical Use

7.1 These classes represent ideal properties of skin substitutes that enable them to be used as substitutes for natural tissues in medical procedures. Performance standards for products to be classified by this guide are outside of the scope of this guide.

7.2 *Skin Substitutes Used in Healing by Second Intention:*

7.2.1 *Skin Allograft Substitute for Skin Allograft Therapy*—A skin allograft substitute for skin allograft therapy, when applied to a skin lesion such as a skin ulcer or a partial thickness skin wound, produces a therapeutic response such as reduced inflammation or pain, resolution of infection, or induction or acceleration of healing, in comparison with a dressing therapy.

7.3 *Skin Substitutes Used in Skin Replacement Surgery:*

7.3.1 *Skin Allograft Substitute for Skin Replacement Surgery*—A skin allograft substitute for skin replacement surgery, can be applied to an excised skin wound and produces an immediate wound closure physiological response but does not permanently engraft. To complete the skin replacement surgery, a future surgical procedure is performed to remove the allograft substitute and replace it by a skin autograft or skin autograft substitute.

7.3.2 *Skin Autograft Substitute*—When applied to an excised skin wound, a skin autograft substitute produces an immediate wound closure physiological response followed by permanent engraftment, tissue regeneration of both dermis and epidermis, and permanent wound closure. A skin autograft substitute necessarily includes viable epidermal cells.

7.3.3 *Dermal Regenerative Autograft Substitute*—When applied to an excised skin wound, a dermal regenerative autograft substitute produces an immediate wound closure physiological response followed by permanent engraftment and regeneration of an autologous dermal tissue that is capable of engrafting an epidermal autograft. To complete the skin replacement surgery, a future surgical procedure is performed to apply an epidermal autograft or epidermal autograft substitute for permanent wound closure.

7.3.4 *Epidermal Autograft Substitute*—A substitute for epidermal autograft, when applied to an excised skin wound or regenerated dermal tissue, produces a wound closure immediate physiological response followed by epidermal tissue engraftment and permanent wound closure.

7.4 *Skin Substitutes used in Reconstructive Surgery:*

7.4.1 *Dermal Autograft Substitute*—A dermal autograft substitute permanently engrafts when implanted in a closed wound in or under dermis or in other connective tissue.

8. Nomenclature for Skin Substitute Composition

8.1 *Global Properties of Skin Substitutes:*

8.1.1 Skin substitute formats are overall shapes, which are typically sheets, multilayered sheets, particles, or granules.

8.1.2 Skin substitute sterility may be designated as sterile or aseptic (aseptically processed).

8.1.3 If the skin substitute is a xenotransplantation product as defined by the current U.S. Public Health Service definition, "xenotransplantation" should be included in the name. For example, see 8.4.10.

8.1.4 The nomenclature does not necessarily describe all characteristics that contribute to clinical function of a skin substitute. Products that can be identically named by this nomenclature should not be presumed to be similar in clinical function.

8.1.5 All terminology should be used in conformance with regulatory requirements.

8.2 *Components of Skin Substitutes*—Key skin substitute components are the cells and scaffolds. A component or its descriptors should be included in the name either if it is believed to contribute to clinical properties, if it is useful for describing the skin substitute, if it is useful for distinguishing it from other similar products, or if it is required by the syntax.

8.2.1 *Cellular Components of Skin Substitutes:*

8.2.1.1 Cellular components are differentiated by tissue of origin, species, cell type, viability, processes employed (for example, primary cells, cultured cells), any genetic modification or other manipulation, and viability. Each of these principal cell attributes should be identified. Each term in the description describes a characteristic of the cell: the terms do not modify each other and the order of terms in the syntax is only a recommendation.

8.2.1.2 Xenogeneic cells should be further differentiated by specific species (for example, porcine, bovine).

8.2.2 *Scaffold Components of Skin Substitutes:*

8.2.2.1 Scaffolds are structural components of the skin substitute that viable cells grow in or on. They also provide mechanical stability or occlusion. Natural substrates are a chemically complex extracellular matrix that is extracted from tissue by reductive processes (for example, decellularized dermis). Scaffolds can also be constructed from chemically characterized natural substrates (for example, purified collagen) or can be constructed from synthetic substrates.

8.2.2.2 The source of acellular tissue should be identified by species (for human source specify autogeneic or allogeneic; for xenogeneic source, bovine, porcine, and so forth) and tissue (for example, dermis, small intestinal submucosa).

8.2.2.3 Purified natural materials should be identified by species, tissue, and biochemical component (for example, collagen).

8.2.2.4 Synthetic biomaterials should be identified by common chemical name (for example, silicone, polyester).

8.2.2.5 *Scaffold Architectures*—Foams are presumed porous to cells, fibrous refers to non woven fibers, and fabrics are woven fibers. Scaffolds may also be impervious. Materials are presumed to be non-rigid unless otherwise specified. Foams are presumed to be open cell, unless otherwise specified.

8.3 *Syntax:*

8.3.1 The components, form, and sterility are specified with this syntax:

{cellular component(s) or acellular or blank} {in or blank} {scaffold(s) or blank} {format}, {sterility}

8.3.2 Each relevant cellular component can be specified with this syntax:

{ [viability] [process] [sex] [species] [tissue origin] [type] }

8.3.2.1 Typical choices for viability: replication-competent, viable, non-viable.

8.3.2.2 Typical choices for process: primary, cultured, xenocultured.

8.3.2.3 Sex is specified only if relevant to clinical utility: male, female.

8.3.2.4 Typical choices for cells from human and other species: autogeneic, allogeneic, porcine, bovine.

8.3.2.5 Typical choices for tissue origin of cells: dermis, epidermis, mucosal, endothelium.

8.3.2.6 Typical choices for cell type: keratinocyte, fibroblast, endothelial cell.

8.3.3 Scaffolds made from synthetic biomaterials are specified with this syntax:

{ [biomaterial] [architecture] scaffold }

8.3.4 Scaffolds made from natural biomaterials are specified with this syntax:

{ [chemical processing] [species] [tissue origin] [biochemical] [architecture] scaffold }

8.3.5 Products consisting of only natural scaffolds (without cells) are specified in this format:

{ acellular [chemical processing] [species] [tissue origin] [biochemical] [architecture] scaffold }

8.3.6 Typical choices for scaffold components:

8.3.6.1 Typical choices for synthetic biomaterials: polylactide, silicone, collagen.

8.3.6.2 Typical choices for natural biochemicals: collagen, chondroitin sulfate.

8.3.6.3 Typical choice for chemical processing: crosslinked.

8.3.6.4 Typical choices for species for natural scaffolds or biomaterials: human, bovine, porcine, shark.

8.3.6.5 Typical choices for tissue origin of natural scaffolds or biomaterials: dermis, small intestinal submucosa, pericardium, dura mater, fascia lata, demineralized bone, cartilage, tendon.

8.3.6.6 Typical choices for scaffold architecture: impervious solid, sponge, fibrous, fabric, porous membrane, impervious membrane, gel.

8.3.7 Typical choices for skin substitute format include: sheet, bilayer sheet, multilayer sheet, particles.

8.3.8 Typical choices for skin substitute sterility: sterile, aseptic.

8.4 *Examples of Skin Substitute Nomenclature That Could be Used to Describe Some Commercially Available Skin Substitutes:*

8.4.1 Acellular porcine small intestinal submucosa scaffold sheet, sterile.

8.4.2 Acellular bovine dermis scaffold sheet, sterile.

8.4.3 Acellular human dermis scaffold sheet, sterile.

8.4.4 Acellular crosslinked bovine tendon collagen and shark cartilage chondroitin sulfate foam scaffold sheet, sterile.

8.4.5 Acellular crosslinked bovine tendon collagen and shark cartilage chondroitin sulfate foam and impervious silicone membrane scaffold bilayer sheet, sterile.

8.4.6 Non-viable cultured allogeneic dermis fibroblasts in polyamide/collagen fiber scaffold and silicone impervious membrane scaffold bilayer sheet, sterile.

8.4.7 Viable cultured allogeneic dermis fibroblasts in polyglactin woven fiber scaffold sheet, sterile.

8.4.8 Viable cultured allogeneic epidermis keratinocytes and allogeneic dermis fibroblasts in bovine tendon collagen gel scaffold bilayer sheet, aseptic.

8.4.9 Viable cultured allogeneic dermis fibroblasts and allogeneic epidermis keratinocytes in bovine tendon collagen foam scaffold and porous membrane scaffold bilayer sheet, aseptic.

8.4.10 Replication competent xenocultured autogeneic epidermis keratinocytes sheet, aseptic.

8.4.11 Replication competent cultured autogeneic epidermis keratinocytes and autogeneic dermis fibroblasts in bovine dermis collagen and shark cartilage chondroitin sulfate porous foam scaffold bilayer sheet, aseptic.

9. Keywords

9.1 skin graft; skin substitutes; surgery; tissue engineering; tissue regeneration; wound healing

APPENDIX

(Nonmandatory Information)

X1. EXAMPLES

X1.1 The examples shown in Table X1.1 are drawn from products commercially available (or pre-commercial). They are intended to be illustrative; this list is not meant to exclude from consideration other products or procedures for using them.

TABLE X1.1 Examples of Skin Substitutes Classified by Clinical Use

Clause	Clinical Utility Classification	Clinical Procedure Example	Medical or Surgical Objective
6.1.1	Skin Allograft Substitute for Skin Allograft Therapy	A partial thickness burn is covered with skin substitute and dressings until healed.	Faster healing and less scarring than treatment with non-biologic alternatives
		Devitalized tissue is removed from a diabetic ulcer or venous ulcer by sharp debridement. The skin substitute is placed on the wound and covered with a dressing for a week. The dressing and skin substitute are removed and the wound is debrided by lavage with a jet of saline and a fresh skin substitute is applied. This process is repeated until the wound is completely healed.	Complete healing of a lesion that has failed to close for months or years.
6.2.1	Skin Allograft Substitute for Skin Replacement Surgery	A full thickness burn is excised and hemostasis obtained. The skin substitute is cut to fit the wound, fixed in place and covered with dressings. In a separate procedure several weeks later, the skin substitute is removed and a split thickness autograft is applied and covered with dressings until the wound is completely healed.	After removal, the wound bed is viable and capable of accepting the autograft. Ultimate results equivalent to autograft applied to freshly excised wound.
6.2.2	Skin Autograft Substitute	Full thickness burn is excised and hemostasis obtained. Frozen allograft is cut to fit the wound, fixed in place and covered by a dressing. A biopsy of healthy skin is obtained at the same time and the keratinocytes and fibroblasts from it are seeded on a biomaterial sponge and grown by tissue culture to create a bilayer of autogeneic keratinocytes and fibroblasts. Several weeks later, the allograft is removed from the wound and the cultured skin substitute is cut to fit the wound, fixed in place (fibroblast side in contact with the wound) and covered with dressing until the wound is completely healed. During healing, the skin substitute is infused with a medium containing cell nutrients and antibiotics.	Healthy skin without scar or contracture or the loss of significant dermal tissue at a donor site.
6.2.3	Dermal Regenerative Autograft Substitute	Full thickness wound is excised and hemostasis obtained. The skin substitute is cut to fit the wound, fixed in place and covered with dressings. In a separate procedure several weeks later the silicone sheet is removed and an epidermal autograft is applied over regenerated dermis and covered with dressings until with wound is completely healed.	Healthy skin without scar or contracture or the loss of significant dermal tissue at a donor site.
6.2.4	Epidermal Autograft Substitute	Full thickness burn is excised and hemostasis obtained. Frozen allograft is cut to fit the wound, fixed in place and covered by a dressing. A biopsy of healthy skin is obtained at the same time and the keratinocytes from it are expanded by tissue culture. Several weeks later, the allograft is removed and the wound is covered with sheets of the cultured keratinocytes and covered with dressings until healed.	Permanent wound closure without the loss of significant tissue at a donor site.
6.2.6	Dermal Autograft Substitute	The wound is excised and hemostasis obtained. The skin substitute is applied and secured to the wound. The skin substitute is covered with a skin flap and covered with dressings until healed.	Tissue augmentation.

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