Designation: F 2311 – 03

Standard Guide for Classification of Therapeutic Skin Substitutes[1]

This standard is issued under the fixed designation F 2311; 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 guide defines terminology and provides a system of classification for products that can be substituted for human or animal skin grafts (or grafts of the dermal or epidermal component tissues of skin) in medical and surgical therapies. This guide is intended to include (or be expandable to) possible future tissue engineered skin technology that could provide novel or superior therapeutic properties to those of natural skin grafts.

1.2 As much as possible, terminology is based on medical dictionary definitions.

1.3 Substitutes for skin grafts are classified by clinical utility only; the classification is independent of the technology used to make a skin substitute, its components, or whether the sources of components include human or animal tissue or other biological or non-biological materials.

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 and health practices and determine the applicability of regulatory requirements prior to use.*

2. Terminology

2.1 *Definitions:*

2.1.1 *tissue, n*—an aggregation of similarly specialized cells united in the performance of a particular function. **Dorland's**[2]

2.1.2 *skin, n*—the outer integument or covering of the body, consisting of the dermis and the epidermis, and resting upon the subcutaneous tissues. **Dorland's**

2.1.3 *Skin Lesions:*

2.1.3.1 *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. **Dorland's**

2.1.3.2 *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. **Dorland's**

2.1.3.3 *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).

2.1.3.4 *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.

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

2.1.3.6 *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. **Dorland's**

2.1.4 *Skin Wound Physiology:*

2.1.4.1 *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. **Dorland's**

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

2.1.4.3 *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.)

2.1.4.4 *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. **Dorland's**

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

Current edition approved Sept. 10, 2003. Published November 2003.

[2] Dorland, WAN, *Dorland's Illustrated Medical Dictionary*, 29th Ed., W. B. Saunders Company, Philadelphia, 2000.

2.1.4.5 *granulations, n*—granulation tissue.

2.1.4.6 *scar, n*—fibrous tissue replacing normal tissues destroyed by injury or disease. **Stedman's**[3]

2.1.5 *Skin Wound Closure and Healing:*

2.1.5.1 *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. **Churchill's**[4]

2.1.5.2 *heal, v*—to restore wounded parts or to make healthy. **Dorland's**

2.1.5.3 *healing, n*—the restoration of integrity to injured tissue. **Dorland's**

2.1.5.4 *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 (see 4.1.2). 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. **Dorland's**

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. **Dorland's**

2.1.5.5 *tissue regeneration, n*—healing in which lost tissue is replaced by proliferation of cells, which reconstruct the normal architecture. **medweb**[5]

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

2.1.6 *Therapies for Skin Wounds and Ulcers*:

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

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

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

2.1.7 *Biomaterials and Grafts:*

2.1.7.1 *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. **Dorland's**

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

2.1.7.3 *graft, n*—any tissue or organ for implantation or transplantation. **Dorland's**

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

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

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

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

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

2.1.7.9 *epidermal autograft, n*—an autograft consisting primarily of epidermal tissue, including keratinocyte stem cells, but with little dermal tissue.[7]

2.1.7.10 *dermal autograft, n*—a skin [autograft] from which epidermis and subcutaneous fat have been removed; used instead of fascia[8] in various plastic [surgery] procedures. **Dorland's**

2.1.7.11 *engraftment, n*—incorporation of grafted tissue into the body of the host. **Dorland's**

2.1.7.12 *graft take, n*—engraftment.

2.1.7.13 *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.

3. Significance and Use

3.1 This guide is intended to provide the foundation of standards for clinical assessment, clinical performance, and preclinical assessment of substitutes for skin grafts.

3.2 This guide is intended to aid accurate claims and labeling for the clinical utilities of substitutes for skin grafts in regulatory reviews.

3.3 In this guide, "replacement" and "substitute" have different meanings, although they can be used synonymously in ordinary English. "Replacement" is used only as an adjective in the context of "skin replacement surgery," which is

[3] Stedman, T. L., *Stedman's Medical Dictionary*, 27th Ed., Lippincott Williams & Wilkins, Philadelphia, 2000.

[4] *Churchill's Illustrated Medical Dictionary*, Churchill Livingstone, New York, 1989.

[5] Hiley, P., and Barber, P. C., *General Pathology (Pathology Foundation Course)*, Chapter 3, Healing and Repair, Department of Pathology, University of Birmingham, U.K., http://medweb.bham.ac.uk/http/depts/path/Teaching/foundat/repair/healing.html.

[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 guide is intended to classify skin substitutes by clinical equivalency, and not by composition, the dictionary definition is used, for this guide 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.

[7] 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., 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 Rehibil*, 23, 2002, pp. 326.

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

defined in 2.1.6.3. "Substitute" is used only as a noun in the context of "skin substitute," which is defined in 2.1.7.13.

4. Normal Physiology of Skin Wound Healing

4.1 *Normal Physiology of Healing by Second Intention of Full Thickness Skin Wounds*:

4.1.1 The immediate physiological response to a full thickness open skin wound includes wound inflammation, edema, and fluid loss. For wounds of large area, there may also be a systemic physiological response characterized by fever, hypercatabolic metabolism, and an increased vulnerability to infection. Such a wound is life threatening.

4.1.2 Following the immediate physiological response, tissue repair replaces lost dermal tissue by a fibrous scar that is produced from granulation tissue.

4.1.3 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.

4.1.4 Systemic physiology during healing by second intention: 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.

4.1.5 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.

4.2 *Skin Replacement Surgery*:

4.2.1 *Definitions*:

4.2.1.1 *clean surgical skin wound, n*—a full or partial thickness skin wound that is created by surgical excision or incision and that is free of necrotic tissue, without significant bleeding, and without significant microbial contamination. For example, see ICD-9-CM procedure code 86.22[9] for surgical excision.

4.2.1.2 *dermal tissue engraftment, n*—engraftment of dermal tissue resulting in reestablishment of vascular connections with cellular and extracellular matrix remodeling in the dermis.

4.2.1.3 *epidermal tissue engraftment, n*—engraftment of an epidermal autograft by a process of epidermal tissue regeneration resulting in a confluent epidermis and permanent wound closure. (Epidermal appendages such as hair are not regenerated.)

4.2.1.4 *wound closure immediate physiological response, n*—an immediate restoration of some of the physiological functions of skin 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.

4.2.2 Skin lesions (including open skin wounds created by surgical excision or incision procedures that are too large to close by apposition of the edges) that are not expected to heal spontaneously with good clinical outcome and in a reasonable time may be treated by skin replacement surgery.

4.2.3 Skin replacement surgery is a two-step procedure:

4.2.3.1 The first step of skin replacement surgery is surgical excision of the lesion and any necrotic tissue or microbial contamination, resulting in a clean surgical skin wound.

4.2.3.2 The second step in skin replacement surgery is the application of skin autograft to the clean surgical skin wound.

(1) The physiological response to skin autograft (full thickness or split-thickness) applied to a clean surgical skin wound comprises a wound closure immediate physiological response followed by dermal tissue engraftment and epidermal tissue engraftment. The result 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).

(2) Dermal tissue engraftment during skin replacement surgery with skin autograft may be differentiated from dermal tissue regeneration ("lost tissue is replaced by proliferation of cells") because autograft replaces the lost tissue without a significant increase in the quantity of dermis.

4.2.3.3 When skin autograft is not immediately available for use in skin replacement surgery, a skin allograft or skin xenograft may be applied to the clean surgical skin wound for temporary wound closure. (Note that skin allograft has superior temporary wound closure properties to those of skin xenograft.)

(1) The application of skin allograft or skin xenograft to a clean surgical skin wound results in an immediate wound closure physiological response. However the wound closure is temporary because permanent dermal tissue engraftment and epidermal tissue engraftment do not occur.

(2) Skin replacement surgery is then completed by surgical removal of the skin allograft or xenograft and the application of a skin autograft.

4.3 Other medical and surgical procedures that utilize skin grafts:

4.3.1 *Wound Closure by Epidermal Autograft*:

4.3.1.1 In some situations in which skin autograft is not available, wound closure by epidermal autograft is an alternative to skin replacement surgery.

4.3.1.2 The surgical procedure is identical to that of skin replacement surgery, except that in the second step (4.2.3.2) the clean surgical wound is closed with epidermal autograft instead of skin autograft.

4.3.1.3 The physiological response to epidermal autograft applied to a clean surgical skin wound is epidermal tissue engraftment and wound closure.

4.3.1.4 Because epidermal autograft does not replace lost dermal tissue, the mechanical functions of dermis are not restored and scar and contracture may occur, as well as chronic fragility of the epidermis.

4.3.2 *Reconstructive Surgery Procedures Utilizing Dermal Autograft*:

4.3.2.1 Dermal autograft can be surgically implanted in various reconstructive procedures for tissue augmentation or reinforcement. Dermal autograft can permanently engraft, but

[9] *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM), Department of Health and Human Services, National Center for Health Statistics (NCHS), 1998.

dermal autograft does not create wound closure. Thus, it is implanted in or under dermis or in other internal tissue.

4.3.3 *Skin Xenograft Therapy*:

4.3.3.1 The application of skin xenograft to a skin lesion such as a skin ulcer or a partial thickness skin wound can produce therapeutic responses such as reduced inflammation or pain, resolution of infection, or induction or acceleration of healing, in comparison with a maintenance therapy.

4.3.4 *Skin Allograft Therapy*:

4.3.4.1 The application of skin allograft to a skin lesion such as a skin ulcer or a partial thickness skin wound can produce therapeutic responses such as reduced inflammation or pain, resolution of infection, or induction or acceleration of healing, in comparison with a maintenance therapy.

5. Classification of Skin Substitutes by Clinical Use

5.1 *Substitute for Skin Allograft for Skin Allograft Therapy*—A substitute for skin allograft 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 maintenance therapy.

5.2 *Substitute for Skin Allograft for Skin Replacement Surgery*—A substitute for skin allograft for skin replacement surgery, when applied to a clean surgical skin wound, produces an immediate temporary wound closure physiological response.

5.3 *Substitute for Skin Autograft for Skin Replacement Surgery*—A substitute for skin autograft for skin replacement surgery, when applied to a clean surgical skin wound, produces a wound healing by first intention, including a wound closure immediate physiological response and the permanent replacement of the lost skin with intact healthy skin, with normal tissue architectures of both dermis and epidermis.

5.4 *Substitute for Epidermal Autograft for Permanent Wound Closure*—A substitute for epidermal autograft for permanent wound closure, when applied to a clean surgical skin wound, produces a wound closure immediate physiological response and in permanent wound closure by epidermal tissue engraftment and regeneration.

5.5 *Substitute for Dermal Autograft for Reconstructive Surgery Procedures*—A substitute for dermal autograft for reconstructive surgery procedures engrafts when implanted in or under dermis or in other internal tissue.

6. Keywords

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

APPENDIX

(Nonmandatory Information)

X1. EXAMPLES OF SUBSTITUTES FOR SKIN GRAFTS

X1.1 These examples are drawn from products currently available commercially (or pre-commercially). They are intended to be illustrative; this list is not meant to exclude from consideration other products.

Classification	Description	Examples
5.1	Substitute for skin allograft for skin allograft therapy	Human foreskin fibroblasts cultured *in vitro* in or on a matrix when used to treat a skin ulcer.
5.2	Substitute for skin allograft for skin replacement therapy	Human foreskin fibroblasts cultured on an occlusive membrane.
5.3	Substitute for skin autograft for skin replacement therapy	Bilayer of porous collagen-glycosaminoglycan copolymer and silicone membrane, when used in conjunction with an epidermal autograft; cultured bilayer of autologous fibroblasts and keratinocytes.
5.4	Substitute for epidermal autograft for permanent wound closure	Sheet of cultured autologous keratinocytes.
5.5	Substitute for dermal autograft for reconstructive surgery procedures	Decellularized human dermis

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(**3**) Schulz, J. T. 3rd, Tompkins, R. G., and Burke, J. F., "Artificial Skin," *Annu Rev Med*, 51, 2000, pp. 231-44.