



# An ASTM Standard for Classification of Tissue Engineered Skin Substitutes

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# The Need for Consistent Classification

- **Regulatory Approval**
  - Food and Drug Administration
- **Reimbursement**
  - Centers for Medicare and Medicaid Services
  - Other payers
  - Coding (ICD-9-CM, CPT, Level II codes)
  - Groupings for Prospective Payment Systems
- **European Approvals and Reimbursements**



<b>Product</b>	<b>Agencies</b>	<b>Purpose or Use</b>
Premarket approvals and clearances	Food and Drug Administration	Assurance of safety and efficacy and accurate claims and labeling
Current Procedural Terminology (CPT) codes	American Medical Association	Coding for statistics and payment for medical procedures carried out by physicians
International Classification of Diseases, Clinical Modification (ICD-9-CM) codes	National Center for Health Statistics for diagnosis classifications and Centers for Medicare and Medicaid Services (CMS) for procedure codes	Coding for statistics and payment for hospital inpatient operations
HCPCS Level II codes	HCFA, the Health Insurance Association of America (HIAA), the American Dental Association (ADA) and the Blue Cross/Blue Shield Association (BCBSA).	Coding for categories not included in CPT codes
Diagnosis Related Groups (DRG)	CMS	Prospective Payment System classification that Medicare uses to pay hospitals for inpatient procedures
Ambulatory Payment Classes (APC)	CMS	Prospective Payment System classification that Medicare uses to pay physicians for outpatient procedures
“Grouper” software	3M Healthcare Information Systems	Software that aggregates diagnosis and procedure codes into DRG or APC classes used by hospitals, CMS, and other third party payers
Coding Clinic publications	American Hospital Association	Authoritative advice on appropriate coding
Medicare coverage decisions	CMS	Coverage decisions based on “reasonable and necessary” criteria
BCBS Technical Assessment	BCBS Association	Detailed reports on selected technologies

# Potential Uses of Standards



- Provide authoritative common conceptual framework for classification
- Harmonize the treatment of medical technologies among agencies
  - FDA approval, coverage decisions, informatics.
- Basis for standardized methodology for clinical assessment and for performance criteria

# Standard Guide for Classification of Skin Substitutes

- Defines terminology and provides a system of classification for products that can be substituted for human or animal skin in medical and surgical therapies
- Provides a foundation for future standards on clinical assessment, clinical performance, and preclinical assessment
- A prototype for standards for other innovative medical products

# Sources for Terminology



- Definitions should be meaningful to clinicians
- Mostly, terminology for the standard is derived from medical dictionary definitions
- Skin substitutes are classified by clinical utility only
  - Independent of technology
  - Components or their sources
  - Human or animal tissue, biological or non-biological

# Sources of Confusion for “Skin Substitutes”



- The variety of medical and surgical procedures that use wound covers and grafts
- Differences in outcome expectations for healing
  - “by first intention”
  - “by second intention”
- Differences in performance requirements among wound dressings, biological wound covers, and skin grafts

# Skin Substitute vs. Skin Replacement



- In the standard, “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,”
- “Substitute” is used only as a noun in the context of “substitute for skin graft”

# Skin Wound Physiology



- The clinical needs for skin substitutes are based on the physiology of the skin wound, which includes inflammation, wound contraction, and formation of granulation tissue.

# Wound inflammation



- 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).

# More Physiology



- **Wound contraction**
  - Shrinkage and spontaneous closure of open skin wounds
- **Granulation tissue**
  - Newly formed vascular tissue normally produced in the healing of wounds of soft tissue and ultimately forming the scar; it consists of small, translucent, red, nodular masses or granulations that have a velvety appearance
- **Scar**
  - Fibrous tissue replacing normal tissues destroyed by injury or disease

# Wound Outcomes



- **Wound contracture,**
  - a condition of fixed high resistance to passive stretch of muscle, skin or joints resulting from fibrosis and scarring of the skin and/or the tissues supporting the muscles or the joints
- **Scar**
  - fibrous tissue replacing normal tissues destroyed by injury or disease

# Healing



- **Healing by first intention**
  - Healing in which union or restoration of continuity occurs directly without intervention of granulations
- **Healing by second intention**
  - Union by closure of a wound with granulations which form from the base and both sides toward the surface of the wound

# Tissue Regeneration vs. Tissue Repair



- **Tissue regeneration**
  - Healing in which lost tissue is replaced by proliferation of cells which reconstruct the normal architecture
- **Tissue repair**
  - Healing in which lost tissue is replaced by a fibrous scar, which is produced from granulation tissue

# Dressings and Grafts



- **Dressing**
  - any of various materials utilized for covering and protecting a wound.
- **Graft**
  - any tissue or organ for implantation or transplantation
- **Engraftment**
  - incorporation of grafted tissue into the body of the host

# Grafts



- **Xenograft**

- a graft of tissue transplanted between animals of different species

- **Allograft**

- graft of tissue between individuals of the same species but of disparate genotype

- **Autograft**

- graft of tissue derived from another site in or on the body of the organism receiving it

# Skin Autografts



- **Skin allograft**
  - An allograft consisting of intact viable or non-viable epidermal and dermal tissue
- **Skin autograft**
  - An autograft consisting of intact viable epidermal and dermal tissue
- **Epidermal autograft**
  - An autograft consisting of epidermal tissue, with little or no dermal tissue
- **Dermal autograft**
  - Skin autograft from which epidermis and subcutaneous fat have been removed; used instead of fascia in various plastic [surgery] procedures

# Physiology of Dressing vs. Skin Graft



- A graft is capable of creating an immediate wound closure physiological response that immediately restores some of the physiological functions of skin. This physiological response 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. This immediate behavior of a skin graft applies to xenograft, allograft, and autograft, although the effect of xenograft is short lived.

# Engraftment of Autograft and Allograft



- Engraftment is incorporation of grafted tissue into the body of the host
- The engraftment of the dermal tissue of an allograft or autograft results in reestablishment of vascular connections with cellular and extracellular matrix remodeling in the dermis
- The engraftment of allograft is only temporary, and is followed by immunological rejection
- Only the engraftment of autograft is permanent.

# Physiology of Healing by Second Intention



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

# Skin Replacement Surgery



- Skin wounds that are too large to close by apposition of the edges and that are not expected to heal spontaneously with good clinical outcome may be treated by skin replacement surgery
- Skin replacement surgery is a two-step procedure
  - 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
  - The second step in skin replacement surgery is the application of skin autograft to the clean surgical skin wound

# Skin Autograft Physiology



- 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).

# Use of Allograft in Skin Replacement Surgery



- 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.
  - The application of skin allograft or skin xenograft to a clean surgical skin wound results in a wound closure immediate physiological response. However the wound closure is temporary because permanent dermal tissue engraftment and epidermal tissue engraftment do not occur.
  - Skin replacement surgery is then completed by surgical removal of the skin allograft or xenograft and the application of a skin autograft.

# Skin Allograft Therapy



- 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.

# Skin Substitute



- 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.

# Classification of Skin Substitutes



- Based on a comparison of the skin substitute to the skin graft that it substitutes for.
  - Substitute for skin allograft for skin allograft therapy
  - Substitute for skin allograft for skin replacement therapy
  - Substitute for skin autograft for skin replacement therapy.
  - Substitute for epidermal autograft for permanent wound closure
  - Substitute for dermal autograft for reconstructive surgery procedures.

# Examples



Class	Description	Examples
1	<u>Substitute for skin allograft for skin allograft therapy</u>	Human foreskin fibroblasts cultured <i>in vitro</i> in or on a matrix when used to treat a skin ulcer.
2	<u>Substitute for skin allograft for skin replacement therapy</u>	Human foreskin fibroblasts cultured on an occlusive membrane.
3	<u>Substitute for skin autograft for skin replacement therapy</u>	Bilayer of porous collagen-glycosaminoglycan copolymer and silicone membrane, when used in conjunction with an epidermal autograft; cultured bilayer of autologous fibroblasts and keratinocytes.
4	<u>Substitute for epidermal autograft for permanent wound closure</u>	Sheet of cultured autologous keratinocytes.
5	<u>Substitute for dermal autograft for reconstructive surgery procedures</u>	Decellularized human dermis