Bio-engineered skin and soft tissue substitutes may be either acellular or cellular. Acellular products (i.e., cadaveric human dermis with cellular material removed) contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. Cellular products contain living cells such as fibroblasts and keratinocytes within a matrix. The cells contained within the matrix may be autologous, allogeneic, or derived from other species (e.g., bovine, porcine). Skin substitutes may also be composed of dermal cells, epidermal cells, or a combination of dermal and epidermal cells, and may provide growth factors to stimulate healing. Tissue-engineered skin substitutes can be used as either temporary or permanent wound coverings.

There are a large number of potential applications for artificial skin and soft tissue products. One large category is non-healing wounds, which potentially encompasses diabetic neuropathic ulcers, vascular insufficiency ulcers, and pressure ulcers. A substantial minority of such wounds do not heal adequately with standard wound care, leading to prolonged morbidity and increased risk of mortality. For example, non-healing lower extremity wounds represent an ongoing risk for infection, sepsis, limb amputation and death. Bio-engineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

Other situations in which tissue-engineered skin products might substitute for living skin grafts include certain post-surgical states such as breast reconstruction, in which skin coverage is inadequate for the procedure performed, or for surgical wounds in patients with compromised ability to heal. Certain primary dermatologic conditions that involve large areas of skin breakdown, such as bullous diseases, may also be conditions in which artificial skin products can be considered as substitutes for skin grafts.

Other situations in which bio-engineered skin products might substitute for living skin grafts include certain post-surgical states such as breast reconstruction, in which skin coverage is inadequate for the procedure performed, or for surgical wounds in patients with compromised ability to heal. Certain primary dermatologic conditions that involve large areas of skin breakdown,
such as bullous diseases, may also be conditions in which artificial skin products can be considered as substitutes for skin grafts. Acellular dermal matrix products are also being evaluated in the repair of other soft tissues including rotator cuff repair, following oral and facial surgery, hernias, and a variety of other conditions.

Regulatory Status

There are a large number of artificial skin products that are commercially available or in development. The following summary of commercially available skin substitutes describes those products that have substantial relevant evidence on efficacy. This list demonstrates the wide range of types of products available:

**Acellular Dermal Matrix**

Acellular dermal matrix products derived from donated human skin tissue are supplied by U.S. American Association of Tissue Banks (AATB) compliant tissue banks and Federal Drug Administration’s (FDA) guidelines. The processing removes the cellular components (i.e., epidermis and all viable dermal cells) that can lead to rejection and infection. Acellular dermal matrix products from human skin tissue are regarded as minimally processed and not significantly changed in structure from the natural material; the FDA classifies it as banked human tissue and therefore does not require FDA approval.

- **AlloDerm** is an acellular dermal matrix (allograft) tissue-replacement product that is created from native human skin and processed so that the basement membrane and cellular matrix remain intact. An injectable micronized form of AlloDerm (Cymetra) is also available.
- **AlloMax Surgical Graft** is an acellular non-cross-linked human dermis allograft.
- **DermaMatrix** is an acellular dermal matrix (allograft) derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation (MTF).
- **FlexHD** is an acellular hydrated dermis derived from donated human allograft skin. The Musculoskeletal Transplant Foundation acquires and processes the tissue.
- **Graftjacket Regenerative Tissue Matrix** is an acellular regenerative tissue matrix that has been processed from screened donated human skin supplied from U.S. tissue banks. The allograft is processed minimally to remove the epidermal and dermal cells while preserving dermal structure.

**PriMatrix** is a xenogeneic acellular dermal matrix processed from fetal bovine dermis. It is indicated through the U.S. Food and Drug Administration’s (FDA) 510(k) process for partial and fullthickness wounds; diabetic, pressure, and venous stasis ulcers; surgical wounds; and tunneling, draining, and traumatic wound.

**Amniotic Membrane**

Amniotic membrane is harvested immediately after birth, cleaned, sterilized, and either fresh frozen or dehydrated. Human amniotic membrane is considered to be minimally processed and not significantly changed in structure from the natural material; the FDA classifies it as banked human tissue and therefore, it does not require FDA approval. EpiFix and Amniofix are
commercially available sources of dehydrated human amniotic membranes. EpiFix is provided in sheets and Amniofix is an injectable form of micronized amniotic membrane. Other amniotic membrane products are AmnioClear, AmnioGraft, and Biodefense and BioDDryFlex

**Collagen Scaffold**

OASIS Wound Matrix is a xenogeneic collagen scaffold derived from porcine small intestinal mucosa. It was cleared by the FDA’s 510(k) process in 2000 for the management of partial and full-thickness wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds, trauma wounds, and draining wounds.

**Living Cell Therapy**

Apligraf is a bilayered living cell therapy composed of an epidermal layer of living human keratinocytes and a dermal layer of living human fibroblasts. It was FDA approved in 1998 for use in conjunction with compression therapy for the treatment of non-infected, partial and full-thickness skin ulcers due to venous insufficiency and in 2001 for full-thickness neuropathic diabetic lower extremity ulcers nonresponsive to standard wound therapy.

Dermagraft is composed of cryopreserved human-derived fibroblasts and collagen applied to a bioabsorbable mesh. Dermagraft has been approved by the FDA for repair of diabetic foot ulcers and for use in the treatment of wounds related to dystrophic epidermolysis bullosa.

OrCel is an absorbable allogeneic bilayered cellular matrix, made of bovine collagen, in which human dermal cells have been cultured. It was approved by the FDA pre-market approval for healing donor site wounds in burn victims and under a humanitarian device exemption (HDE) for use in patients with recessive dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites.

**Biosynthetic**

Biobrane/Biobrane-L is a biosynthetic wound dressing constructed of a silicon film with a nylon fabric partially imbedded into the film. The fabric creates a complex 3-dimensional structure of trilament thread, which chemically binds collagen. Blood/sera clot in the nylon matrix, adhering the dressing to the wound until epithelialization occurs.

This policy does not address products used in the treatment of burns, tendon/ligament repair or products supplied in an inpatient setting.

**II. Criteria/Guidelines**

A. Allogeneic acellular dermal matrix products (i.e., AlloDerm, AlloMax) or Strattice is covered (subject to Limitations/Exclusions and Administrative Guidelines) in breast reconstructive surgery when one of the following criteria are met:

1. There is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required.
2. There are viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis.
3. The infra-mammary fold and lateral mammary folds have been undermined during mastectomy and re-establishment of these landmarks is needed.
B. Apligraf, Dermagraft or Epifix is covered (subject to Limitations/Exclusions and Administrative Guidelines) for the treatment of chronic, non-infected, full-thickness diabetic lower extremity ulcers when all of the following criteria are met:

1. The ulcers have not adequately responded after six weeks of standard wound therapy*.
2. The patient is on a comprehensive diabetic management program
3. Reduction in pressure on a foot ulcer has been accomplished with appropriate modalities.

C. Apligraf, Epifix or Oasis Wound Matrix is covered (subject to Limitations/Exclusions and Administrative Guidelines) for the treatment of chronic, non-infected, partial or full-thickness lower extremity skin ulcers due to venous insufficiency when all of the following criteria are met:

1. The ulcers have not adequately responded after six weeks of standard wound therapy*.
2. Compression bandages and/or graduated compression garments have been consistently applied; and
3. Leg elevation and exercise have been encouraged.

D. OrCel is covered (subject to Limitations/Exclusions and Administrative Guidelines) for the treatment of dystrophic epidermolysis bullosa.

* Standard wound therapy includes:

- Evaluation of wound with documentation of measurements (length, width and depth) at baseline and at least weekly by a licensed medical professional
- Application of moist topical dressings
- Debridement of necrotic tissue, if present
- Treatment of infection, if present
- Evaluation and provision of adequate nutrition
- Management of diabetes mellitus, if applicable
- Evaluation and management of peripheral artery disease, if applicable

III. Limitations/Exclusions

A. Bio-engineered skin and soft tissue substitutes have not been shown to improve health outcomes for all other conditions not listed under Criteria/Guidelines.

B. The following bio-engineered skin and soft tissue substitutes have not been shown to improve health outcomes, this includes, but is not limited to:

- Allopatch HD
- Alloskin AC
- Alloskin RT
- Amnioexcel or Biodexcel
- Amniomatrix or Biodmatrix
- Architect extracellular matrix
- Arthroflex
- Biodfence Dryflex
- Cymetra
- Excellagen
- E-Z Derm
- Flex HD
- Gammagraft
- Grafix core
- Grafix prime
- Graftjacket Express injectable (not applicable when used in tendon repair)
- Graftjacket Regenerative Tissue Matrix (not applicable when used in tendon repair)
- Hyalomatrix
- hMatrix
- MatriStem Micromatrix
- MatriStem Wound Matrix
- Mediskin
- Memoderm
- Neox
- Primatrix
- Repriza
- SurgiMend
- Talymed
- Tensix
- TissuMend
- XCM Biologic Tissue Matrix

IV. Administrative Guidelines

A. Precertification is required for the application of Apligraf, Dermagraft, OrCel, Epifix and Oasis. Complete HMSA’s Precertification request and mail or fax the form as indicated. Include the following information:

1. Clinical notes documenting patient’s compliance with a diabetic management program.
2. The exact location of the ulcer and initial ulcer size.
3. Duration and description of the standard treatments that were tried and failed.
4. Documentation of the presence of dystrophic epidermolysis bullosa if this is the indication.

B. Precertification is not required for acellular dermal matrixes or Strattice when used in breast reconstruction surgery. HMSA reserves the right to perform retrospective reviews using the above criteria to validate if services rendered met payment determination criteria.

C. Applicable HCPCS codes:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>Q4101</td>
<td>Apligraf, per sq. cm.</td>
</tr>
<tr>
<td>Q4102</td>
<td>Oasis wound matrix, per sq. cm.</td>
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Q4106  Dermagraft, per sq. cm.
Q4116  AlloDerm
Q4124  Oasis Ultra tri-layer wound matrix, per sq. cm.
Q4130  Strattice TM, per sq. cm.
Q4131  Epifix, per sq. cm.
Q4145  Epifix, injectable, 1 mg

D. HCPCS codes that do not meet payment determination criteria:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
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<tr>
<td>Q4107</td>
<td>Graftjacket, per sq. cm.</td>
</tr>
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<td>Q4110</td>
<td>PriMatrix, per sq. cm.</td>
</tr>
<tr>
<td>Q4111</td>
<td>GammaGraft, per sq. cm.</td>
</tr>
<tr>
<td>Q4112</td>
<td>Cymetra, injectable</td>
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<td>Q4113</td>
<td>Graftjacket Express, injectable, 1cc</td>
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<td>Q4117</td>
<td>Hyalomatrix, per sq. cm.</td>
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<td>Q4118</td>
<td>Matristem micromatrix, per sq.cm.</td>
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<td>Matristem wound matrix, per sq.cm.</td>
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<td>Talymed, per sq. cm.</td>
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<td>Unite Biomatrix, per sq. cm.</td>
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<td>Grafix core, per sq. cm.</td>
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<td>Q4136</td>
<td>EZ-derm, per sq. cm.</td>
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<td>Q4140</td>
<td>Biodfence, per square centimeter</td>
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<td>Q4141</td>
<td>Alloskin AC, per square centimeter</td>
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<td>Repriza, per square centimeter</td>
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<td>Q4147</td>
<td>Architect extracellular matrix, per square centimeter</td>
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<tr>
<td>Q4148</td>
<td>Neox 1k, per square centimeter</td>
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<tr>
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V. Rationale:

Breast Reconstruction

AlloDerm

Systematic Reviews: Two systematic reviews from 2012 found an increased rate of complications with acellular dermal matrix-assisted breast reconstruction. One meta-analysis of 16 retrospective studies found a higher likelihood of seroma (pooled odds ratio [OR]: 3.9; 95% CI: 2.4-6.2), infection (pooled OR: 2.7; 95% CI: 1.1-6.4) and reconstructive failure (pooled OR: 3.0; 95% CI: 1.3-6.8) when compared to breast reconstruction using traditional musculofascial flaps. Another meta-analysis that compared 19 studies using acellular dermal matrix (n=2,037) with 35 studies using submuscular reconstruction (n=12,847) found an increased risk of total complications (relative risk [RR]: 2.05; 95% CI: 1.55-2.70), seroma (RR: 2.73; 95% CI: 1.67-4.46), infection (RR: 2.47; 95% CI: 1.71-3.57), and reconstructive failure (RR: 2.80; 95% CI: 1.76-4.45) with acellular dermal matrix. These meta-analyses are limited by the poor quality of included studies and significant heterogeneity.

Randomized Controlled Trials: In 2012, McCarthy et al. reported a multicenter blinded randomized controlled trial of AlloDerm in 2-stage expander/implant reconstruction. Seventy patients were randomized to AlloDerm acellular dermal matrix-assisted tissue expander/implant reconstruction or to submuscular tissue expander/implant placement. There were no significant differences between the groups in the primary outcomes of immediate postoperative pain (54.6 AlloDerm and 42.8 control on a 100-point visual analog score) or pain during the expansion phase (17.0 AlloDerm and 4.6 control), or in the secondary outcome of rate of tissue expansion (91 days AlloDerm and 108 days control) and patient reported physical well-being. There was no significant difference in adverse events, although the total number of adverse events was small. Phase 2 of the study will evaluate long-term outcomes.

Controlled Studies: Preminger and colleagues evaluated the impact of AlloDerm on expansion rates in immediate tissue expander/implant reconstruction in a retrospective matched cohort study. Forty-five patients had reconstruction with AlloDerm and 45 had standard reconstruction. Subjects were matched for expander size (+/-100 mL), history of irradiation, and indication for mastectomy.
There were no significant differences in initial filling volume, mean number of postoperative expansions, mean rate of postoperative tissue expansion, or in the incidence of postoperative complications. Aesthetic outcomes were not addressed. In 2008 Colwell and Breuing reported on 10 patients who had mastopexy with dermal slings, 5 patients were given AlloDerm and 5 were given autologous tissue. Patients maintained projection and breast base width after 6 months to 3 years.

Uncontrolled Studies: A number of case series have also demonstrated that this approach can provide tissue coverage of implants and tissue expanders. AlloDerm has been reported in nipple reconstructive surgery in a case series on 30 nipple reconstructive procedures performed at one institution. Use of AlloDerm has also been reported in a small series (n=3) to correct breast implant-related problems (malposition, symmastia, and rippling).

Breuning and Colwell reported on use of the AlloDerm hammock in 43 patients and 67 breasts in 2007. Indications for reconstructive surgery and use of the allograft were immediate expander-implant reconstruction (N=10), immediate silicone implant reconstruction (N=30), delayed expander-implant reconstruction (N=4), and revisional implant reconstruction for capsular contracture following capsulectomy (N=23). The article indicates that patients were included if AlloDerm was used in association with an implant or expander to reconstruct their breast. The authors reported that the AlloDerm hammock allowed complete coverage of the implant and symmetric positioning of the infra-mammary fold. In delayed reconstructions with existing skin redundancy at the mastectomy site, inferior epigastric tissue was recruited, and tissue expanders filled over 75% of the desired volume, thus decreasing the need for subsequent filling. One patient had implant extrusion and 2 had infections. No capsular contracture, hematoma, or seroma was observed at mean follow-up of approximately 1.5 years (range, 6 months to 3 years). The authors concluded that implant reconstruction with an inferolateral AlloDerm hammock facilitates positioning of the implant in immediate or revisional breast reconstruction and simplifies expander-implant reconstruction.

Thus, a number of case series have demonstrated that this approach can provide tissue coverage of implants and tissue expanders.

Other: Liu et al. reported postoperative complications in breast reconstruction with (n=266) or without (n=204) AlloDerm in 2011. Radiation therapy, body mass index (BMI), intraoperative use of tumescent solution, and medical comorbidities were similar between the 2 groups, but there were twice as many smokers and the implants were larger in the AlloDerm group. There was a trend for a higher rate of major infections that required prosthesis removal in the AlloDerm group (4.9% vs. 2.5%, p=0.172) and a statistically significant increase in overall wound infection rate (6.8% vs. 2.5%). The overall surgical complication rate was significantly higher in the AlloDerm group (19.5% vs. 12.3%). Multivariate analysis indicated that the use of acellular dermal matrix, smoking, higher BMI, higher initial volume, and bigger implant size were associated with a higher overall surgical complication rate. This study is limited by the retrospective analysis and differences between groups at baseline.

Bindingnavele et al. reviewed charts of 41 patients (65 breasts) who had staged breast reconstruction with acellular cadaveric dermis to report postoperative complication rates. Rates for wound infection, expander removal, hematoma, and seroma were 3.1%, 1.5%, 1.5%, and 4.6%,
respectively. The authors concluded that based on low rates of complications and good cosmetic outcomes, the technology should be in the repertoire of plastic surgeons, and that follow-up is required to evaluate long-term outcomes.

Strattice

Given the extensive data from case series as well as the clinical input obtained about the usefulness of this procedure in providing inferolateral support for breast reconstruction, use of AlloDerm may be considered medically necessary in breast reconstruction when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; when there is viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis’ or when the infra-mammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed. The expanding body of literature for Strattice as well as the wide acceptance of its use by the reconstructive surgery community make it a medically necessary alternative to AlloDerm under similar circumstances.

**Interpositional Graft after Parotidectomy**

AlloDerm

In 2003, Sinha et al. reported the use of AlloDerm acellular human dermal matrix as an interpositional physical barrier to prevent the development of Frey syndrome (gustatory sweating) after parotidectomy. Thirty patients were divided into 3 groups; it was not described if the assignments were randomized. One group underwent superficial parotidectomy with reconstruction of the defect with AlloDerm, a second group had superficial parotidectomy without placement of an interpositional barrier, and the third group underwent deep-plane rhytidectomy without disruption of the parotid fascia. At minimum 1-year follow-up, there was a subjective incidence of Frey syndrome in 1 patient treated with AlloDerm and 5 patients in group 2. The objective incidence of Frey syndrome, measured with the Minor starch-iodine test, was 2 patients treated with AlloDerm and 8 patients in group 2. None of the patients in group 3 who underwent deep-plane rhytidectomy without disruption of the parotid fascia had subjective or objective Frey syndrome. There were no adverse effects.

A 2008 publication from Asia compared use of allogeneic acellular dermal matrix (RENOV) in 168 patients who had superficial or partial parotidectomy. Sixty-four patients received an acellular dermal matrix and 104 patients had superficial or partial parotidectomy alone. The size of the graft depended on the amount of tissue required to restore the normal facial contour. The method of assignment to the 2 groups was not described. At a median follow-up of 16 months (range, 11-27), the subjective incidence of Frey syndrome was 2% in the acellular dermal matrix group compared with 61% in controls. Objective assessment, performed in 30 patients randomly selected from each group, found an incidence of Frey syndrome in 2 patients (7%) treated with acellular dermal matrix and 24 patients (80%) in the control group. One patient in the acellular dermal matrix group and 18 patients in the control group developed a parotid fistula.

DermaMatrix
DermaMatrix is an acellular dermal matrix that differs from AlloDerm in several ways; it can be stored at room temperature (vs. refrigerated), it has a shelf-life of 3 years (vs. 2 years), and it can be rehydrated in 3 minutes (vs. 30 minutes).

Athavale et al. evaluated complications of AlloDerm and DermaMatrix in a retrospective review of 100 patients treated between 2001 and 2009 at a single U.S. institution. Exclusion criteria for the study included presence of malignancy on final surgical pathology report, incomplete medical records, previous history of radiation therapy to the head and neck region, and additional procedures to the region of the parotid gland. Initially, only AlloDerm was used; this changed to a 20/80 ratio of AlloDerm/DermaMatrix due to more readily available stock of DermaMatrix. Complications were defined as any outcome that required procedural intervention for resolution (seroma/sialocele formation, infected fluid collection, and/or serosanguinous fluid collection). The authors identified 8 complications in 31 DermaMatrix implants (26%) compared with 5 complications in 69 AlloDerm implants (7%). The complication rate did not differ for total parotidectomies but was higher for DermaMatrix compared to AlloDerm for subtotal parotidectomies (37% vs. 8%). Nearly half of all complications were seroma/sialocele formation.

Randomized, double-blind, controlled trials with longer follow-up are needed to evaluate this procedure.

**Surgical Repair of Hernias**

**AlloDerm**

Gupta et al. compared the efficacy and complications associated with the use of AlloDerm and Surgisis bioactive mesh in 74 patients who underwent ventral hernia repair in 2006. The first 41 procedures were performed using Surgisis Gold 8-ply mesh formed from porcine small intestine sub-mucosa, and the remaining 33 patients had ventral hernia repair with AlloDerm. Patients were seen 7-10 days after discharge from the hospital and at 6 weeks. Any signs of wound infection, diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm mesh resulted in 8 hernia recurrences (24%). Fifteen of the AlloDerm patients (45%) developed a diastasis or bulging at the repair site. Seroma formation was only a problem in two patients.

In 2007, Espinosa-de-los-Monteros and colleagues retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases. They reported a significant decrease in recurrence rates when human cadaveric acellular dermis was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias. However, no differences were observed when adding human cadaveric acellular dermis as an overlay to patients with large-size hernias treated with underlay mesh.

A 2013 study compared AlloDerm with FlexHD for complicated hernia surgery. From 2005 to 2007, AlloDerm was used to repair large (>200 cm2) symptomatic complicated ventral hernia that resulted from trauma or emergency surgery (n=55). From 2008 to 2010, FlexHD was used to repair large complicated ventral hernia in patients meeting the same criteria (n=40). The 2 groups were comparable at baseline. At one-year follow-up, all of the AlloDerm patients were diagnosed with hernia recurrence (abdominal laxity, functional recurrence, or true recurrence) requiring a second
repair. Eleven patients (31%) in the FlexHD group required a second repair. This comparative study is limited by the use of nonconcurrent comparisons, which is prone to selection bias and does not control for temporal trends in outcomes.

The limited evidence available at this time does not support the use of AlloDerm in hernia repair.

**Laryngoplasty**

There are several reports with short-term follow-up of micronized AlloDerm (Cymetra) injection for laryngoplasty. In 2005, Milstein et al. reported mean 11.2 month follow-up (range, 1 to 35 months) of Cymetra injection in 20 patients with unilateral vocal-fold paralysis. Pre- and post-operative digital voice samples and video stroboscopy were rated on a 4-point scale by a panel of 3 voice experts who were blinded to the pre- or postoperative status. Compared with preoperative measures, Cymetra improved voice quality (from 3.23 to 1.65), glottal closure (from 3.21 to 1.42), and degree of vocal-fold bowing (from 2.38 to 1.36). Quality-of-life measures and patients’ self-perceptions of vocal quality were also improved. In 5 patients (25%), the effect was temporary, and in 8 patients (40%) who had follow-up of 1 year or longer, the improvement was maintained. Longer-term study in a larger number of patients is needed to determine the durability of this procedure and to evaluate the safety of repeat injections.

**Tympanoplasty**

Vos et al. reported a retrospective non-randomized comparison of AlloDerm versus native tissue grafts for type I tympanoplasty in 2005. Included in the study were 108 patients (25 AlloDerm, 53 fascia reconstruction, and 30 fascia plus cartilage reconstruction) treated between 2001 and 2004. One surgeon had performed 96% of the AlloDerm tympanoplasties. Operative time was reduced in the AlloDerm group (82 minutes for AlloDerm, 114 minutes for fascial cases, and 140 minutes for fascia plus cartilage). There was no significant difference in the success rate of the graft (88% for AlloDerm, 89% for fascia grafts, 96.7% for cartilage plus fascia). There was no significant difference in hearing between the groups at follow-up (time not specified). Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure.

**Diabetic Lower Extremity Ulcers**

Apligraf

In 2001, Veves and colleagues reported on a randomized prospective study on the effectiveness of Graftskin (Apligraf), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers. The study involved 24 centers in the US, 208 patients were randomly assigned to ulcer treatment either with Graftskin (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical debridement and adequate foot off-loading, was provided in both groups. Graftskin was applied at the beginning of the study and weekly thereafter for a maximum of 4 weeks (maximum of five applications) or earlier if complete healing occurred. At the 12-week follow-up visit, 63 (56%) Graftskin-treated patients achieved complete wound healing compared with 36 (38%) in the control group (p=0.0042). The Kaplan-Meier median time to complete closure was 65 days for Graftskin, significantly lower than the 90 days observed in the control group (p=0.0026). The rate of adverse reactions was similar between the two groups with the exception of osteomyelitis and lower-limb amputations, both of which were less frequent in the Graftskin group. The authors
concluded that application of Graftskin for a maximum of 4 weeks resulted in a higher healing rate when compared with state-of-the-art treatment and was not associated with any significant side effects. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf (Graftskin), in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management.

In 2010, Steinberg and colleagues reported on a study of 72 subjects from Europe and Australia that assessed the safety and efficacy of Apligraf in the treatment of non-infected diabetic foot ulcers. The design and patient population of this study were similar to the 208-subject US study (described above) which led to FDA approval of Apligraf for the treatment of diabetic foot ulcers. For these studies, subjects with a non-infected neuropathic diabetic foot ulcer present for at least two weeks were enrolled in these prospective, multicenter, randomized, controlled, open-label studies that compared Apligraf use in conjunction with standard therapy (sharp debridement, standard wound care, and off-loading) against standard therapy alone. Pooling of data was performed because of the similarity and consistency of the two studies. Efficacy and safety results were consistent across studies independent of mean ulcer duration that was significantly longer in the European study (21 months, compared to 10 months in the U.S. study). Reported adverse events by 12 weeks were comparable across treatment groups in the two studies. Efficacy measures demonstrated superiority of Apligraf treatment over control treated groups in both studies. Combining the data from both studies, 55.2% (80/145) of Apligraf subjects had complete wound closure by 12 weeks, compared to 34.3% (46/134) of control subjects (p=0.0005), and Apligraf subjects had a significantly shorter time to complete wound closure (p=0.0004). The authors concluded that both the EU and US studies exhibited superior efficacy and comparable safety for subjects treated with Apligraf compared to control subjects, and the studies provide evidence of the benefit of Apligraf in treating DFU.

In 2010, Kirsner and colleagues reported on analysis of 2,517 patients with diabetic neuropathic foot ulcers who were treated between 2001 and 2004. The study was a retrospective analysis using a wound-care database; the patients received advanced biological therapy i.e., Apligraf (446 patients), Regranex, or Procuren. In this study, advanced biological therapy was used, on average, within 28 days from the first wound clinic visit and associated with a median time to healing of 100 days. Wounds treated with engineered skin (Apligraf) as the first advanced biological therapy were 31.2% more likely to heal than wounds first treated with topical recombinant growth factor (p<0.001), and 40.0% more likely to heal than those first treated with platelet releasate (p=0.01). Wound size, wound grade, duration of wound, and time to initiation of advanced biological therapy affected the time to healing.

Dermagraft
A pivotal multi-center FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft or control. Over the course of the 12-week study patients received up to 8 applications of Dermagraft. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. At 12 weeks, the median percent wound closure for the Dermagraft group was 91% compared to 78% for the control group. Ulcers treated with Dermagraft closed significantly faster than ulcers treated with conventional therapy. No serious adverse events were attributed to Dermagraft. Ulcer infections developed in 10.4% of the
Dermagraft patients compared to 17.9% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft-treated group (19% vs. 32.5%).

**EpiFix**

EpiFix is an amniotic membrane extracellular collagen allograft comprised of an epithelial layer and two fibrous connective tissue layers. Amniotic membrane is banked human tissue regulated by the AATB and FDA. Four growth factors are present in EpiFix including epidermal growth factor (EGF), transforming growth factor - β (TGF-β), fibroblast growth factor (FGF) and platelet derived growth factor A & B (PDGF A & B). It is proposed to promote cellular migration to enhance soft tissue repair in acute and chronic wounds free of necrotic tissue and infection; partial- and full-thickness wounds; venous, diabetic, pressure, and chronic vascular ulcers. Epifix comes in a wide variety of sizes eliminating waste and reducing cost.

Clinical trials reported ninety percent of wounds treated exhibited 100% uptake of the amniotic membrane graft without rejection after 1 week. An average of 50 percent reduction of wound volume and size was proven by weekly measurements. Clinical pain, signs of infection, and drainage post application was noticeably less among amniotic membrane graft patients. Postoperative course and maintenance is simple and direct, which allowed for better compliance.

A single site industry sponsored prospective, randomized comparative parallel study of amniotic membrane vs. standard management in the treatment of diabetic ulcers was published by Zelen C. in 2012. It was terminated early due to dramatic and significant improved outcomes in the Epifix group. At 6 weeks the Epifix arm had a 92% wound healing rate compared to only 8% for the conventional treatment arm. Though the authors conclude that further expanded studies should be considered, they point out that the dramatic improvement in outcomes coupled with the cost effective characteristic of the product already make it a viable clinical option for diabetic ulcers.

**GraftJacket Regenerative Tissue Matrix**

Brigido et al. reported a small (n=40) randomized pilot study of GraftJacket compared with conventional treatment for chronic non-healing diabetic foot ulcers in 2004. Control patients received conventional therapy with debridement, wound gel with gauze dressing, and off-loading. GraftJacket patients received surgical application of the scaffold using skin staples or sutures and moistened compressive dressing. A second graft application was necessary after the initial application for all patients in the GraftJacket group. Preliminary 1 month results showed that after a single treatment, ulcers treated with GraftJacket healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs. 15%), width (50% vs. 23%), area (73% vs. 34%) and depth (89% vs. 25%). All of the grafts incorporated into the host tissue.

In 2009, Reyzelman et al. reported an industry-sponsored multicenter randomized study that compared a single application of GraftJacket versus standard of care in 86 patients with diabetic foot ulcers. Offloading was performed using a removable cast walker. Ulcer size at presentation was 3.6 cm2 in the GraftJacket group and 5.1 cm2 in the control group. Eight patients, 6 in the study group and 2 in the control group, did not complete the trial. At 12 weeks, complete healing was observed in 69.6% of the GraftJacket group and 46.2% of controls. After adjusting for ulcer size at presentation, a statistically significant difference in non-healing rate was calculated, with
odds of healing 2.0 times higher in the study group. Mean healing time was 5.7 weeks versus 6.8 weeks for the control group. The authors did not report if this difference was statistically significant. The median time to healing was 4.5 weeks for GraftJacket (range, 1 – 12) and 7.0 weeks for control (range 2 – 12). Kaplan-Meier survivorship analysis for time to complete healing at 12 weeks showed a significantly lower non-healing rate for the study group (30.4%) compared with the control group (53.9%). The authors commented that a single application of GraftJacket, as used in this study, is often sufficient for complete healing. This study is limited by the small study population, differences in ulcer size at baseline, and the difference in the percentage of patients censored in each group. Questions also remain about whether the difference in mean time to healing is statistically or clinically significant. Additional trials with a larger number of subjects are needed to evaluate if GraftJacket Regenerative Tissue Matrix improves health outcomes in this population.

**Oasis Wound Matrix**

Niezgoda and colleagues compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS Wound Matrix, an acellular wound care product, versus Regranex Gel. This was an industry-sponsored randomized controlled multicenter trial conducted at 9 outpatient wound care clinics and involved 73 patients with at least 1 diabetic foot ulcer. Patients were randomized to receive either Oasis Wound Matrix (n=37) or Regranex Gel (n=36) and a secondary dressing. Wounds were cleansed and debrided, if needed, at a weekly visit. The maximum treatment period for each patient was 12 weeks. After 12 weeks of treatment, 18 (49%) Oasis-treated patients had complete wound closure compared with 10 (28%) Regranex-treated patients. Oasis treatment met the non-inferiority margin, but did not demonstrate that healing in the Oasis group was statistically superior (p=0.055). Post-hoc subgroup analysis showed no significant difference in incidence of healing in patients with type 1 diabetes (33% vs. 25%) but a significant improvement in patients with type 2 diabetes (63% vs. 29%). There was also an increased healing of plantar ulcers in the Oasis group (52% vs. 14%). These post-hoc findings are considered hypothesis generating. Additional study with a larger number of subjects is needed to evaluate the effect of Oasis treatment in comparison with the current standard of care.

**PriMatrix**

In 2011, Karr published a retrospective comparison of PriMatrix (a xenograft fetal bovine dermal collagen matrix) and Apligraf in 40 diabetic foot ulcers. The first 20 diabetic foot ulcers matching the inclusion and exclusion criteria for each graft were compared. Included were diabetic foot ulcers of 4 weeks’ duration, at least 1 sq. cm and depth to subcutaneous tissue, healthy tissue at the ulcer, adequate arterial perfusion to heal, and able to off-load the diabetic ulcer. The products were placed on the wound with clean technique, overlapping the edges of the wound, and secured with sutures or staples. The time to complete healing for PriMatrix was 38 days with 1.5 applications compared to 87 days with 2 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

**Lower Extremity Ulcers due to Venous Insufficiency**
Apligraf

Falanga and colleagues reported a multicenter randomized trial of Apligraf (human skin equivalent) in 1998. A total of 293 patients with venous insufficiency and clinical signs of venous ulceration were randomized to compression therapy alone or compression therapy and treatment with Apligraf. Apligraf was applied up to a maximum of 5 (mean 3.3) times per patient during the initial 3 weeks. The primary endpoints were the percentage of patients with complete healing by 6 months after initiation of treatment and the time required for complete healing. At 6 months’ follow-up, the percentage of patients healed was increased with Apligraf (63% vs. 49%) and the median time to complete wound closure was reduced (61 vs. 181 days). Treatment with Apligraf was found to be superior to compression therapy in healing larger (>1000 mm²) and deeper ulcers and ulcers of more than 6 months’ duration. There were no symptoms or signs of rejection and the occurrence of adverse events were similar in both groups. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf (Graftskin), in conjunction with good local wound care, met the TEC criteria for the treatment of venous ulcers that fail to respond to conservative management.

Dermagraft

Dermagraft is a living cell therapy composed of cryopreserved human fibroblasts cultured on a bioabsorbable mesh. Dermagraft has been approved by the FDA for repair of diabetic foot ulcers. Use of Dermagraft for venous ulcers is an off-label indication. In 2013, Harding el al. reported an open-label multi-center randomized controlled trial that compared Dermagraft plus compression therapy (n=186) versus compression therapy alone (n=180). The study had numerous inclusion/exclusion criteria that restricted the study population to patients who had nonhealing ulcers with compression therapy but had capacity to heal. Intent-to-treat analysis revealed no significant difference between the 2 groups in the primary outcome measure, the proportion of patients with completely healed ulcers by 12 weeks (34% Dermagraft vs. 31% control). Pre-specified subgroup analysis revealed a significant improvement in the percent of ulcers healed for ulcers of 12 months or less in duration (52% vs. 37%) and for ulcers of 10 cm or less (47% vs. 39%). There were no significant differences in the secondary outcomes of time to healing, complete healing by week 24, and percent reduction in ulcer area.

Oasis Wound Matrix

In 2005, Mostow et al. reported an industry-sponsored multicenter (12 sites) randomized trial that compared weekly treatment with Oasis Wound Matrix versus standard of care in 120 patients with chronic ulcers due to venous insufficiency that were not adequately responding to conventional therapy. Healing was assessed weekly for up to 12 weeks, with follow-up performed after 6 months to assess recurrence. After 12 weeks of treatment, there was a significant improvement in the percentage of wounds healed in the Oasis group (55% vs. 34%). After adjusting for baseline ulcer size, patients in the Oasis group were 3 times more likely to achieve healing than those in the standard care group. Patients in the standard care group whose wounds did not heal by the 12th week were given the option to cross over to Oasis treatment. None of the healed patients treated with Oasis wound matrix and seen for the 6-month follow-up experienced ulcer recurrence.
A research group in Europe has described two comparative studies of the Oasis matrix for mixed arterial/venous and venous ulcers. In a 2007 quasi-randomized study, Romanelli et al. compared the efficacy of two extracellular matrix-based products, Oasis and Hyaloskin (extracellular matrix with hyaluronic acid). A total of 54 patients with mixed arterial/venous leg ulcers were assigned to the two arms based on order of entry into the study; 50 patients completed the study. Patients were followed up twice a week and the dressings were changed more than once a week only if necessary. After 16 weeks of treatment, complete wound closure was achieved in 82.6% of Oasis-treated ulcers compared with 46.2% of Hyaloskin-treated ulcers. Oasis treatment significantly increased the time to dressing change (mean of 6.4 vs. 2.4 days), reduced pain on a 10 point scale (3.7 vs. 6.2) and improved patient comfort (2.5 vs. 6.7).

In a 2010 trial, Romanelli et al. compared Oasis with a moist wound dressing in 23 patients with mixed arterial/venous ulcers and 27 patients with venous ulcers. The study was described as randomized, but the method of randomization was not described. After the 8-week study period, patients were followed up monthly for 6 months to assess wound closure. Complete wound closure was achieved in 80% of the Oasis-treated ulcers at 8 weeks compared to 65% of the standard of care group. On average, Oasis-treated ulcers achieved complete healing in 5.4 weeks as compared with 8.3 weeks for the standard of care group. Treatment with Oasis also increased the time to dressing change (5.2 vs. 2.1 days) and the percentage of granulation tissue formed (65% vs. 38%).

**Epifix**

In 2012, Hanumanthappa et al published the results of a prospective comparative study comparing healing rates for venous stasis ulcers in an Epifix group vs. a saline soaked gauze group. Both groups were placed in compression stockings. Measured outcomes were rate of granulation, epithelialization, amount of exudate, and infection rate. The Epifix group showed statistically significant improved outcomes in each of the 4 measured categories. The authors concluded that widespread availability, low cost, ease of use, safety, and demonstrated efficacy made the use of Epifix a superior alternative of recalcitrant venous stasis ulcers.

**PriMatrix**

In 2011, Karr published a retrospective comparison of PriMatrix and Apligraf in 28 venous stasis ulcers. The first 14 venous stasis ulcers matching the inclusion and exclusion criteria for each graft were compared. Included were venous stasis ulcers of 4 weeks’ duration, at least 1 sq. cm and depth to subcutaneous tissue, healthy tissue at the ulcer, adequate arterial perfusion to heal, and able to tolerate compression therapy. The products were placed on the wound with clean technique, overlapping the edges of the wound, and secured with sutures or staples. The time to complete healing for PriMatrix was 32 days with 1.3 applications compared to 63 days with 1.7 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

**Section Summary.**

Randomized controlled trials have demonstrated the efficacy of Apligraf and Oasis Wound Matrix and Epifix over the standard of care. Use of these products may be considered medically necessary for lower extremity ulcers due to venous insufficiency. In a moderately large randomized controlled
trial, Dermagraft was not shown to be more effective than controls in the primary or secondary end points for the entire population and was slightly more effective than controls (an 8%-15% increase in healing) only in subgroups of patients with ulcer duration of 12 months or less or size of 10 cm or less. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

**Dystrophic Epidermolysis Bullosa**

OrCel is approved by a HDE for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites. As this is a rare disorder, it is unlikely that there will be randomized controlled trials to evaluate if OrCel improves health outcomes for this condition.

**Summary**

Bio-engineered skin and soft tissue substitutes are being evaluated for a variety of conditions. Overall, the number of bio-engineered skin and soft tissue substitutes is large but the evidence is limited for any specific product. Relatively few products have been compared with the standard of care, and then only for some indications. A few comparative trials have been identified for use in lower extremity ulcers (diabetic or venous). In these trials, there is a roughly 15% to 20% increase in the rate of healing. Several other products/indications are supported by either clinical input or by an FDA HDE.

**Breast Reconstruction**

Given the extensive data from controlled cohorts and case series, as well as the clinical input obtained about the usefulness of this procedure in providing inferolateral support for breast reconstruction, use of acellular dermal matrixes or Strattice may be considered medically necessary in breast reconstruction when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; when there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis, or when the infra-mammary fold and lateral mammary folds have been undermined during mastectomy and re-establishment of these landmarks is needed.

**Interpositional Graft after Parotidectomy**

Two lower quality controlled trials were identified that demonstrated a reduction in the incidence of Frey syndrome with use of an interpositional acellular dermal matrix graft. Neither study described the method of group assignment or blinding of patients and assessors. In addition, clinical input regarding the use of an interpositional spacer after parotidectomy was not uniform. Therefore, bio-engineered skin and soft tissue substitutes are considered investigational to fill in contour defects and prevent Frey syndrome after parotidectomy.

**Fistula Repair**

One randomized controlled trial was identified that used an acellular dermal matrix product that has not been cleared for marketing in the U.S. Therefore, the use of this product for fistula repair is no covered.

**Surgical Repair of Hernias**
The limited evidence available does not support the efficacy of any tissue-engineered skin substitute for surgical repair of hernias. Therefore, this use is not covered.

**Laryngoplasty**

The effect of micronized AlloDerm (Cymetra) in laryngoplasty has been reported in case series. Longer term controlled study in a larger number of patients is needed to determine the durability of this procedure and to evaluate the safety of repeat injections.

**Tympanoplasty**

AlloDerm has been compared with native tissue grafts in a non-randomized controlled study. There was no significant difference in the success rate of the graft (88% for AlloDerm, 89% for fascia grafts, 96.7% for cartilage plus fascia), and there was no significant difference in hearing between the groups at follow-up. Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure.

**Diabetic Lower Extremity Ulcers**

Randomized controlled or comparative trials have demonstrated the efficacy of Apligraf, Dermagraft and Epifix over the standard of care. Use of these products may be considered medically necessary for the treatment of diabetic lower extremity ulcers. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

**Lower Extremity Ulcers due to Venous Insufficiency**

Randomized controlled or comparative trials have demonstrated the efficacy of Apligraf, Epifix and Oasis Wound Matrix over the standard of care. Use of these products may be considered medically necessary for lower extremity ulcers due to venous insufficiency. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

**Dystrophic Epidermolysis Bullosa**

OrCel has received approval via a Humanitarian Device Exemption (HDE). As this is a rare disorder and it is unlikely that there will be randomized controlled trials, this product is considered medically necessary for this indication.

All other uses of the tissue-engineered skin substitutes do not meet payment determination criteria.

**Practice Guidelines and Position Statements**

Review of the literature for 2013 guidelines from the American Society of Plastic Surgeons (ASPS) found that evidence suggests that the use of acellular dermal matrix, although increasingly common in postmastectomy expander/implant breast reconstruction, can result in increased risk of complications in the presence of certain risk factors. (59) The ASPS notes that cellular dermal matrix is currently used to increase soft tissue coverage, support the implant pocket, improve contour and reduce pain with expansion. However, evidence to support these improved surgical outcomes are limited. Some evidence suggests that use of acellular dermal matrix is associated
with increased postoperative complications, specifically related to infection and seroma. Overall, the ASPS found that evidence on acellular dermal matrix products in postmastectomy expander/implant breast reconstruction is varied and conflicting, and gave a Grade C recommendation based on level III evidence that surgeons should evaluate each clinical case individually and objectively determine the use of acellular dermal matrix.

In 2006, the American Society of Plastic Surgeons (ASPS) endorsed guidelines from the Wound Healing Society on the treatment of arterial insufficiency ulcers. The guidelines state that extracellular matrix replacement therapy appears to be promising for mixed ulcers and may have a role as an adjuvant agent in arterial ulcers, but further study is required. (Level IIIC) “Despite the existence of animal studies, case series, and a small number of random control trials to support biomaterial use for pressure ulcers, diabetic ulcers, and venous ulcers; there are no studies specifically on arterial ulcers. Therefore, studies in arterial ulcers must be conducted before the recommendation can be made.”

The ASPS endorsed guidelines from the Wound Healing Society on the treatment of venous ulcers in 2006. The guidelines state that various skin substitutes or biologically active dressings are emerging that provide temporary wound closure and serve as a source of stimuli (e.g., growth factors) for healing of venous ulcers. Guideline #7b.1 states that there is evidence that a bilayered artificial skin (biologically active dressing), used in conjunction with compression bandaging, increases the chance of healing a venous ulcer compared with compression and a simple dressing (Level I).

The ASPS also endorsed guidelines from the Wound Healing Society on the treatment of diabetic ulcers in 2006. The guidelines state that healthy living skin cells assist in healing diabetic foot ulcers by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed. Guideline #7.2.2 states that living skin equivalents may be of benefit in healing diabetic foot ulcers. (Level I)

The 2007 guidelines from the ASPS on chronic wounds of the lower extremity state that maintaining a moist environment, while simultaneously removing soluble factors detrimental to wound healing might logically provide optimal conditions for wound healing. Classic dressings include gauze, foam, hydrocolloid, and hydrogels. Fluid-handling mechanisms include absorption, gelling, retention and vapor transmission. Bioactive dressings include topical antimicrobials, bioengineered composite skin equivalent, bilaminar dermal regeneration template, and recombinant human growth factor.

The 2011 Guidance from the United Kingdom’s National Institute for Health and Clinical Excellence recommends not to use dermal or skin substitutes for the inpatient management of diabetic foot problems, unless part of a clinical trial.

The 2006 guidelines on diabetic foot disorders from the American College of Foot and Ankle Surgeons (ACFAS) state that bioengineered tissues have been shown to significantly increase complete wound closure in venous and diabetic foot ulcers. Tissue-engineered skin substitutes can function both as biologic dressings and as delivery systems for growth factors and extracellular matrix components through the activity of live human fibroblasts contained in their dermal elements. Currently, two bioengineered tissues have been approved to treat diabetic foot ulcers in
the U.S. Apligraf and Dermagraft; both have demonstrated efficacy in randomized, controlled trials. Apligraf has been shown to significantly reduce the time to complete wound closure in venous and diabetic ulcers. Regenerative tissue matrix (GraftJacket) is a new therapy used in diabetic foot ulcers, although it had not undergone any randomized clinical trials at the time of this guideline. This allograft skin is minimally processed to remove epidermal and dermal cells while preserving the bioactive components and structure of dermis. This results in a framework that supports cellular repopulation and vascularization.

The 2012 guidelines from the Infectious Diseases Society of America (IDSA) state that for selected diabetic foot wounds that are slow to heal, clinicians might consider using bioengineered skin equivalents (weak recommendation, moderate evidence) growth factors (weak, moderate), granulocyte colony stimulating factors (weak, moderate), hyperbaric oxygen therapy (strong, moderate), or negative pressure wound therapy (weak, low). (66) It is emphasized that none of these measures have been shown to improve resolution of infection and that they are expensive, not universally available, may require consultation with experts, and reports supporting their utility are mostly flawed.

A 2012 Technology Assessment from the Agency for Healthcare Research and Quality (AHRQ) does not make a formal recommendation for bioengineered skin and soft tissue substitutes. (1) The Assessment notes that autologous tissue grafting is an invasive and painful procedure and often the extent of damaged skin is too large to be covered by autologous tissue graft alone. A variety of skin substitutes and alternatives are designed to replace the damaged epithelial and dermal layers of skin, and many of the conditions and biological factors needed in the healing process may be provided by the substitute skin products.

Medicare National Coverage

Centers for Medicare and Medicaid Services (CMS) has issued the following national coverage determination: Porcine (pig) skin dressings are covered, if reasonable and necessary for the individual patient as an occlusive dressing for burns, donor sites of a homograft, and decubiti and other ulcers.

Beginning in 2014, CMS will not distinguish between different skin substitutes and will classify them as either high cost or low cost. CMS will package skin substitutes of the same class into the associated surgical procedures for hospital outpatient departments and ambulatory surgical centers. A separate payment might be made if the item is furnished on a different date of service as the primary service.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.
This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References


45. Shah, AP. EpiFix, Human Amniotic Membrane Allograft for Treatment in Diabetic Wound Care Management. Clinical Symposium on Advances in Skin & Wound Care, 2010