ALLIANCE OF
WOUND CARE
STAKEHOLDERS
POWER THROUGH COLLECTIVE ADVOCACY

April 29, 2013

Dr. Earl Berman
Cigna Government Services
Two Vantage Way
Nashville, TN 37228
Attn Medical Review

Submitted Electronically to Earl.Berman@cgsadmin.com

RE: Draft LCD - Application of Bioengineered Skin Substitutes: Ulcers (of Lower Extremities)

Dear Dr. Berman:

On behalf of the Alliance of Wound Care Stakeholders ("Alliance"), we are pleased to submit the following comments in response to Cigna Government Services ("CGS") draft LCD, "Application of Bioengineered Skin Substitutes: Ulcers (of Lower Extremities)". The Alliance is a nonprofit multidisciplinary trade association of health care professional and patient organizations whose mission is to promote quality care and access to products and services for people with wounds through effective advocacy and educational outreach in the regulatory, legislative, and public arenas. These comments were written with the advice of Alliance clinical specialty societies and organizations that not only possess expert knowledge in complex chronic wounds, but also in wound care research. A list of our members can be found at www.woundcarestakeholders.org. Our members not only treat patients but conduct clinical research on many of the products that are contained in this draft policy.

GENERAL COMMENTS

As stated in our specific comments below, the Alliance is concerned with CGS using the term "bioengineered skin substitutes" since it is not a technically accurate term and does not describe the technology that is either currently or will be in the marketplace. Instead, the Alliance recommends that CGS adopt the term "Cellular and/or tissue based products for wounds (CTPs)" which is accurate, broad, and inclusive of both current and future technology. The Alliance recently voted positively to accept adoption of this term; thus, we will be using the acronym "CTPs" instead of "skin substitutes in this document.

The Alliance recognizes the challenges and difficulties that the A/B MAC contractors such as CGS are facing in managing the LCD development process with new CTPs entering the marketplace. We know that CGS has attempted to establish a fair, balanced and accurate coverage policy and has taken into account the various forms of clinical evidence on which to

establish coverage for these important CTPs. However, this draft policy falls short and the Alliance has significant issues with this draft policy as our specific comments will reflect.

There are many new CTPs coming into the marketplace that are clinically efficacious as well as cost effective –yet this policy is limited in the products it does cover. While we appreciate that CGS has included all types of CTPS for coverage in their policy – including Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) - the Alliance would like to better understand the threshold for what is acceptable for clinical evidence submission in order for a product to be covered in the CGS policy. We would like to see more choices available to treat patients.

There are also several inconsistencies in the document that we have identified in our specific comments below. We believe that any inconsistencies need to be addressed and corrected prior to issuing this policy in final.

The Alliance is also concerned with how CGS has released this draft policy for comments. It is our understanding that the A/B MACs must have a public meeting. We did not see one posted on your website or communicated in any way to stakeholders. In addition, while CGS noted on the draft LCD that this policy was posted on March 13, 2013it was not posted to the public for comment until March 29, 2013. Therefore CGS did not adhere to the 45 day comment period. This policy is a significant departure from the previous CGS policy and the public should be afforded the full 45 days to comment. Thus, the comment period should actually end on May 13, 2013 and not April 29, 2013.

The following are our specific comments which are presented in the order of the draft LCD rather than in order of importance. Our format for addressing them is to state the issue, identify the language in the draft LCD, address our concerns and offer our recommendations. The issues are as follows:

SPECIFIC COMMENTS

The Term "Bioengineered Skin Substitute" is Clinically Inaccurate and Should be Replaced with the More Inclusive Descriptor "Cellular and/or Tissue Based Products for Wounds (CTPs)".

The Alliance is concerned with CGS using the term "bioengineered skin substitutes" since it is not a technically accurate term and does not describe the technology that is either currently or will be in the marketplace. Instead, the Alliance recommends that CGS adopt the term "Cellular and/or tissue based products for wounds (CTPs)" which does accurately describe and is broad and inclusive of both current and future technology. The Alliance recently voted positively on adoption of this term and, as mentioned above, we will be using the acronym "CTPs" when referring to Cellular and/or tissue based products for wounds in this document.

The Alliance submits that the term "skin substitute" is misleading and inaccurate to describe the products that are the subject of this LCD for the following reasons:

- This term is not used by either regulatory agency--FDA in its classification of these biologic products nor by CMS in its coding descriptors.
- The CMS division that addresses HCPCS coding for these biologic products abandoned the term "skin substitute" effective in 2010 when a manufacturer requested that CMS delete this term since it was an incorrect descriptor. The manufacturer stated at the 2010 CMS HCPCS Public Meeting that that this language was wrong since allografts are mislabeled as "skin substitutes." Allografts differ in structure, tissue origin, and in some cases differ from biologic products in terms of how they are approved by the FDA (human skin for transplantation not devices). CMS thus changed the descriptors and eliminated the term "skin substitutes" from all of its Q codes for these items.
- In addition, the Agency for Healthcare Research and Quality (AHRQ), in its 2011 draft technology assessment on skin substitutes stated that these products were not "skin substitutes."

In 2012, the Alliance embarked on a yearlong effort to determine an appropriate term. In order to achieve a fair and inclusive process for determining this new term, a workgroup of scientists, clinical organizations, and business entities was created from the Alliance to address this issue. Such diverse multidisciplinary clinical specialties societies as the American Podiatric Medical Association, Society of Vascular Medicine, American Society of General Surgeons, Association for the Advancement of Wound Care, American Professional Wound Care Association, American Board of Wound Management and the American Physical Therapy Association participated in this process.

The following were the criteria used to select the new term:

- be based on science
- be inclusive of all products in marketplace today with eye towards what is in the "pipeline"
- be neutral in regards to FDA--- nothing that would be offensive and not allow manufacturers to get their products approved in the future if needed
- ensure that all products are eligible for Medicare coverage as drugs and biologicals consistent with their USP monographs
- easily understood by clinicians
- easily linked to the existing CPT codes for the application of the products

The Alliance reviewed over 18 different names during this process and selected the term "Cellular and/or tissue based products for wounds (CTPs)" since it met the criteria listed above.

To further validate this point, page 4 of the draft LCD, CGS states, "The expectation is that the product itself will function as a permanent replacement for the lost or damaged skin, or as a facilitator for the development and/or growth of the patient's skin."

The Alliance has concerns with this sentence since it is not correct that CTPs function as a permanent replacement for the lost or damaged skin. None of the CTPs currently on the market or in the development

pipeline acts to fully replace skin. CTPs that are incorporated into the wound via degradation and remodeling clearly do not replace skin, but instead act by enabling repair/regeneration of the patient's own skin. There are four scientific articles which are attached that support deleting language that suggests that CTPs function as a "permanent replacement" for lost or damaged skin:

1. Hu S, Kirsner RS, Falanga V, Phillips T, Eaglstein WH. Evaluation of Apligraf® persistence and basement membrane restoration in donor site wounds: a pilot study. *Wound Repair Regen*. 2006 Jul-Aug;14(4):427-33. (Attachment 3)
   - Persistence: No persistence of Apligraf® DNA was found after week 4 (p. 429)
   - Conclusion: "Apligraf® DNA persisted in a minority of patients at 4 weeks in acute partial-thickness wounds. Apligraf' s®' success in speeding healing of acute wounds appears to be related to factors other than the persistence of donor DNA or effect on basement membrane restoration."

2. Marston WA, Hanft J, Norwood P, Pollak R. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care*. 2003; 26:1701-1705. (Attachment 4)
   - Statement regarding degradation/remodeling of product: "Dermagraft is a bio-engineered dermal substitute that laboratory data suggest has two principal modes of action. It provides living, human dermal fibroblasts that deposit matrix proteins and facilitate angiogenesis. It also provides a preformed collagen matrix, receptors, and bound growth factors that facilitate the migration of the patients' epithelial cells that close the wound." (p1704)

3. Veves A, Falanga V, Armstrong DG, Sabolinski ML. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care*. 2001; 24:290-295. (Attachment 5)
   - Statement regarding degradation/remodeling of product: "Living human skin equivalents (HSEs), which are produced by using tissue-engineering techniques, have been successful in treating chronic wounds, such as venous ulcers. Although their precise mode of action is not known, it is believed that they act by both filling the wound with extracellular matrix and inducing the expression of growth factors and cytokines that contribute to wound healing." (p290-291)

4. Falanga V, Sabolinski M. A bilayered living skin construct (APLIGRAF) accelerates complete closure of hard-to-heal venous ulcers. *Wound Repair Regen*. 1999; 7:201-207. (Attachment 6)
   - Statement regarding degradation/remodeling of product: "At this point, we still do not know whether the allogenic neonatal cells of Graftskin remain in the wound and for how long. It is likely that they are able to remain in the wound for some time, at least long enough to take over and produce the right signals and substances, or long enough to instruct the resident cells and restore their own program for proper wound healing." (p206)

As such, the Alliance recommends that CGS not utilize the term "skin substitute" in its policy and use the term "cellular and/or tissue based wound care products for wounds (CTPs)". We also recommend that CGS does not state that CTPs function as a permanent replacement for the lost or damaged skin.

Provision of Specific Criteria for Coverage is Necessary

Your current policy for CTPs was well written and was in a format that was easy to follow and understand. We have often referred to your policy as one that was that standard which others should follow when submitting comments to other contractors. The Alliance would have preferred if CGS would have maintained the previous policy and included any modifications to that policy (such as changing the terminology used to describe these products and provide more information regarding the coverage it will use for determining coverage) instead of rewriting the policy.

That being said, the Alliance appreciates that CGS has attempted to provide criteria it will use for determining coverage for any CTP so as to guide the wound care community in its research and publication efforts. The draft policy states, "we have determined to cover those which we are satisfied have achieved at least a threshold minimum of literature supporting their efficacy". However, the policy does not indicate what the minimum threshold is and whether companies that are seeking coverage will have to meet the same or greater threshold. While we believe that there are areas that still need to be clarified in this policy, providing information to the wound care community regarding the type of information CGS is seeking in order for products to be considered for coverage is necessary. This will allow for a more transparent process for manufacturers when submitting their product for coverage.

The Alliance believes that evidence can be established for coverage not only through RCTs but also through a combination of retrospective clinical studies (relevant since the populations of patients that demonstrate a need for the products in question would be *eliminated* in many and most RCTs), scientific evidence and expert knowledge. This approach is consistent with the widely accepted definition of evidence based medicine but also adopted by the newly created important organization Patient Centered Outcomes Research Institute (PCORI). We believe that payers should cover these CTPs if the manufacturers provide clinical evidence in peer reviewed journals showing positive outcomes of their products without regard of how they are regulated by the FDA—Class II, III or HCT/Ps. There are examples of A/B MAC policies [NHIC, WPS and Noridian] which have applied this approach and have broader product coverage of CPT products, some with additional indications for wounds with deeper tissue exposure of muscle, tendon and bone, not provided by this draft coverage policy.

In addition to our general comments, we recognize the challenges and difficulties that CGS is facing in managing the LCD development process with new CTPs entering the marketplace. However, your current policy would make it easier for CGS to accept new products without having to reissue your LCD everytime a new CTP is approved for coverage. The format of the current policy with "general indications and limitations to Medicare coverage and payment" and applied "to all materials and services related to skin substitute/replacement" with the more specific coverage information pertaining to the individual CTPs are included in the local coverage articles (LCAs) – which is very beneficial. This type of format should be advantageous to CGS since the contractor would not need to revise its LCD every time it makes the decision to cover a new CTP; it could merely write a new LCA.

Recommendation: The Alliance would like to recommend that CGS retain the format of its current LCD. Specifically, the section "general indications and limitations to Medicare coverage and payment" should be more general and applied "to all materials and services related to skin substitute/replacement". Then, as with the current LCD, the Alliance recommends that the more specific coverage information pertaining to the individual CTPs be included in the LCAs.

LCD only Pertains to Lower Extremity Wounds

Issue: The title of the draft LCD - Application of Bioengineered Skin Substitutes: Ulcers (Lower Extremities) is significantly different than CGS's previous policy title—"Biologic Products for Wound Treatment and Surgical Interventions." Instead of having a broad focus, it now has a narrow one of ulcers of the lower extremity. The policy has gone from surgical procedures to ulcers of the lower extremity. This policy is no longer inclusive of how and where these products are applied.

Language in the Policy: The Policy Title is "Application of Bioengineered Skin Substitutes: Ulcers (of lower extremity).

Concerns: The Alliance is concerned that in this draft policy the coverage of CTPs are limited to lower extremity wounds. This is a clear departure from the previous LCD and therefore it is unclear whether other wound types will be covered by CGS. Previously, CGS covered acute postoperative wounds, deep tissue reconstruction and/or replacements or burns in this policy. We question whether they would still be covered based on medical necessity. If not, your beneficiaries with these other wounds will be denied access to these state-of-the-art products.

Coverage Guidance- Coverage Indications, Limitations and/or Medical Necessity Indications- Vague or Inappropriate Language in Indications For Use

Issue: While the Alliance agrees with most of the language contained in the indications for use, we have concerns regarding vague or inappropriate language used for allowing coverage of CTPs. The two concerns are as follows:

1. **Language in the Policy:** For purposes of this LCD, conservative measures include but are not limited to:

   - Elimination of edema
   - Elimination of underlying cellulitis, osteomyelitis or other infection
   - Appropriate debridement of necrotic tissue
   - For diabetic foot ulcers appropriate non weight bearing and or off loading pressure
   - For venous status ulcers standard compression therapy
   - Provision of appropriate wound environment to promote wound healing**.**

   Note: documentation must indicate that these conditions have been successfully treated and resolved prior to skin substitute treatment

Concerns: The Alliance's **c**oncern specifically lies with the language in the note and specifically that "these conditions have been successfully treated and resolved". While some of the listed conditions (edema, infection and remove necrotic tissue) can be treated and resolved, the other conditions are ongoing treatments that support the healing process.

Recommendations: The Alliance recommends that the language simply read, "For purposes of this LCD, conservative measures include but are not limited to" and that CGS eliminate the language in the notes which states "these conditions have been successfully treated and resolved" prior to the LCD becoming final.

2. **Language in the Policy:** Only apply skin substitutes to wounds with adequate circulation/oxygenation to support tissue growth/wound healing as evidenced by physical examination (presence of acceptable peripheral pulses and or ankle brachial index (ABI) of no less than 0.65).

   Concerns: The Alliance maintains that the language which requests the "presence of acceptable peripheral pulses" is not only vague, but there is no clinical evidence which supports it. As such, the Alliance would like to request that CGS provide the clinical findings which support the presence of acceptable peripheral pulse.

   Recommendations: The Alliance recommends that CGS eliminate "presence of acceptable peripheral pulses" from the draft LCD before it becomes final as it is vague and there is no clinical evidence which supports it.

Indications and Limitations for Coverage of Products

1. **Issue**: Within this section of the draft LCD, CGS separates out each of the products that are covered and provides their indications for use. However the language contained in this section is not consistent. If CGS decides to keep this section in the policy, the Alliance believes that the language needs to be consistent with the FDA labeling for these products and therefore changed prior to the policy becoming final.

Language in the Draft LCD:

First CGS states:

Limitations for use:

There should be no fewer than two weeks between applications for venous stasis ulcers and there should be no fewer than three weeks between applications for neuropathic diabetic foot ulcers. More frequent applications should be documented in the patient's medical records.

Treatment of any ulcer will typically last no more than twelve weeks.

Then CGS goes on to state:

Apligraf® (Q4101) Indications:
• Full-thickness neuropathic diabetic foot ulcer
• Venous stasis ulcer

Apligraf® (Q4101) Limitations:
• Apligraf® is limited to five applications per ulcer, though more than three applications to a single wound are usually unnecessary
- Medicare does not cover continued reapplication of Apligraf when the treatment is unsuccessful after 30 days of treatment

• Medicare does not cover retreatment of an ulcer following an unsuccessful course of treatment.
• Medicare does not cover retreatment of a successfully-treated, healed ulcer.

Oasis® (Q4102; Q4124) Indications:
• Neuropathic diabetic foot ulcer.
• Venous stasis ulcer.

Oasis® (Q4102; Q4124) Limitations:
• Medicare payment for Oasis® is limited to12 weeks of therapy per ulcer.
• Medicare does not covered continued reapplication of Oasis when the treatment is unsuccessful after 30 days of treatment
• Medicare does not cover retreatment of an ulcer following an unsuccessful course of treatment.
• Medicare does not cover retreatment of a successfully-treated, healed ulcer.

Dermagraft® (Q4106) Indications:
• Full thickness diabetic foot ulcers

Dermagraft® (Q4106) Limitations:

• Studies have documented that, for Q4106, survival of the dermal substitute decreases significantly when the 24 steps noted in the FDA labeling are not followed. Therefore, the 24 steps must be followed and documented.
• Frequency is limited to 8 applications per ulcer.
• Medicare does not cover continued reapplication of Dermagraft for the same ulcer if satisfactory and reasonable healing progress is not noted after 12 weeks of treatment.
• Medicare does not cover continued reapplication of Dermagraft when the treatment is not successful after 30 days of treatment.
• Medicare does not cover retreatment of an ulcer following an unsuccessful course of treatment.
• Medicare does not cover retreatment of a successfully-treated, healed ulcer.

GraftJacket® (Q4107) Indications:
- Full-thickness diabetic foot ulcers
- Patient does not have a current HbA1C reading exceeding 12%

- Underlying disease process(es) contributing to the ulcer, e.g., diabetes, is adequately treated and documented; and
- Ulcers located on the foot or toes and are free of infection, redness, drainage, underlying osteomyelitis, surrounding cellulitis, tunnels or tracts, eschar or any necrotic material that could interfere with the adherence of GRAFTJACKET® and the process of wound healing.

GraftJacket® (Q4107) Limitations:
- Medicare payment for GraftJacket® is limited to 1 application per ulcer.
  Note: Treatment with Graftjacket® is usually expected to last no more than twelve (12) weeks and to involve a maximum of two applications for any ulcer that initially qualifies for treatment.
- Medicare does not cover retreatment of an ulcer following an unsuccessful course of treatment.
- Medicare does not cover retreatment of a successfully treated, healed ulcer.

PriMatrix® (Q4110) Indications:
- Partial and full-thickness wounds

PriMatrix® (Q4110) Limitations:
- adequate arterial blood supply as evidenced by ankle-brachial index (ABI) of 0.65 or greater in limb undergoing the procedure
- Full thickness ulcers of at least 3 weeks in duration and which extend through dermis
- Medicare does not cover retreatment of the same ulcer using PriMatrix ® following an unsuccessful course of treatment.
- Medicare does not cover retreatment of a successfully treated, healed ulcer.

Theraskin® (Q4121) Indications:
- Ulcers located on foot and toes
- free of infection, redness, drainage, underlying osteomyelitis, surrounding cellulitis, tunnels and tracts, eschar or any necrotic material

Theraskin® (Q4121) Limitations:
- adequate arterial blood supply as evidenced by ankle-brachial index (ABI) of 0.65 or greater in limb undergoing the procedure
- full thickness ulcers of at least 3 weeks in duration and which extend through dermis
- Medicare does not cover retreatment of the same ulcer using Theraskin ® following an unsuccessful course of treatment.
- Medicare does not cover retreatment of a successfully treated, healed ulcer.

Concerns: The Alliance's concerns are that the manner in which CGS describes the limitations for use are not consistent for all of the CTPs—some are applications per ulcer versus others are weeks of use. For instance, Apligraf describes applications per ulcer, Oasis describes 12 weeks of therapy, while Primatrix does not provide any specific limitations on the number of applications. This inconsistency will cause confusion in the clinical community and needs to be uniform.

Furthermore, Alliance believes CGS made a typographical oversight error. Theraskin is currently covered by CGS under its existing LCD and LCA for treatment of both DFUs and VLUs, however, the draft LCD only includes TheraSkin treatment for DFUs.

Recommendations: The Alliance recommends that CGS eliminate the language that states, "There should be no fewer than two weeks between applications for venous stasis ulcers and there should be no fewer than three weeks between applications for neuropathic diabetic foot ulcers. More frequent applications should be documented in the patient's medical records" and "Treatment of any ulcer will typically last no more than twelve weeks." Furthermore, the Alliance recommends that the language regarding the number of applications should read:

The number of applications per ulcer is based on the FDA labeling and clinical evidence in published clinical trials for the product.

Finally, the Alliance recommends that prior to release of a final policy, CGS should consider an indication correction for Theraskin along with clinical evidence from the manufacturer to support DFU, VLU, and other indications as suggested in their package label.

2. **Issue**: An additional issue within this section pertains to the language that retreatment of a successfully healed ulcer is not covered nor is retreatment of an ulcer following an unsuccessful course of treatment. This is hugely problematic as patients can - down the road - develop another ulcer in the same location or can have further breakdown OR can be placed on another type of product after an unsuccessful course of treatment on one type of product.

   Language in the Policy: Retreatment of an ulcer following an unsuccessful course of treatment is not covered. Retreatment of a successfully treated healed ulcer is not treated.

   Recommendations: The Alliance does not agree with the language as drafted in this policy as it is not appropriate to eliminate coverage for a Medicare beneficiary if they have further breakdown after a successful treatment of a wound or if a particular product was tried unsuccessfully on a patient and the clinician determines that another product may be used to help heal the wound. We therefore recommend that this language be eliminated from the policy as it is not clinically sound.

Missing ICD-9 Codes

Issue: In reviewing the draft LCD, the Alliance notes that there are several ICD-9 codes that should have been included in this policy but are missing. These diagnosis codes identify other clinical conditions that cause an ulcer of the lower extremity besides varicose veins.

Recommendation: The Alliance recommends that CGS include the ICD-9 codes provided below prior to the LCD becoming final:

459.31 Chronic venous hypertension with ulcer
459.33 Chronic venous hypertension with ulcer and inflammation
459.81 Venous insufficiency, NOS

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On behalf of the Alliance of Wound Care Manufacturers, we appreciate the opportunity to submit these comments. If you have any questions of would like further information, please do not hesitate to contact me.

Sincerely,

Marcia Nusgart R.Ph.
Executive Director