



November 18, 2022

Meredith Loveless, MD
CGS Administrators, LLC
Attn: Medical Review
26 Century Blvd., Ste ST610
Nashville, TN 37214-3685

In Re: Proposed LCD – Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers (DL) (DL36690).

Submitted electronically at cmd.inquiry@cgsadmin.com

Dear Madams and Sirs:

The American Association of Tissue Banks (AATB or Association) and the American Association of Tissue Bank’s Tissue Policy Group (AATB TPG or TPG) submit these comments related to the proposed local coverage determination (LCD) referenced above. Our comments focus on four key areas:

- determination of which products are covered,
- requirements related to documentation from the Food and Drug Administration (FDA or Agency) Tissue Reference Group (TRG),
- restrictions on the number of applications, and
- restrictions on switching between skin substitutes.

The American Association of Tissue Banks (AATB) is a professional, non-profit, scientific, and educational organization. AATB is the only national tissue banking organization in the United States, and its membership totals more than 120 accredited tissue banks and over 6,000 individual members. These banks recover tissue from more than 58,000 donors and distribute in excess of 3.3 million allografts for more than 2.5 million tissue transplants performed annually in the US. The overwhelming majority of the human tissue distributed for these transplants comes from AATB-accredited tissue banks.

The AATB TPG includes Chief Executive Officers and senior regulatory personnel from U.S. tissue banks that process donated human tissue. The purpose of the TPG is to drive policy in furtherance of the adoption of laws, regulations, and standards that foster the safety, quality, and availability of donated tissue. The TPG’s membership is responsible for the vast majority of tissue available for transplantation within the U.S.

History of use. Certain wound-related “361 human cells, tissues, and cellular and tissue-based products,” or “361 HCT/Ps,” which include certain amnion, split-thickness skin, and

decellularized dermis products, per the FDA, have “utility to serve as a protective covering”¹ or “to serve as a barrier.”² Recognizing the need to assist individuals with severe burns, skin grafting was one of the first allografts. The use of allograft skin dates back to Reverdin in 1869 describing the use of skin grafting in clinical practice for the first time.³ George Pollock used his skin in addition to the patient’s skin to cover a burn in 1871.⁴ The first report of successful use of allograft skin to treat a burn was by Girdner in 1881.⁵ In 1903, Wentscher reported that allograft skin retained cellular viability after 3-14 days.⁶ James Barrett Brown, M.D. (1899-1971), with his work in the early 1930s, revolutionized the concepts of skin grafting.^{7,8} His work highlighted the nature of allografts – that split-thickness skin from the mother was completely absorbed within three weeks of being transferred to her severely burned son.⁹ Organizations, such as the Ancient Arabic Order of the Nobles of the Mystic Shrine – or Shriners – helped further the use of skin grafts to assist burn care for children for 50 years.¹⁰ As skin grafting became more common to save the life of burn patients, banking of skin paralleled the development of blood banks in the 1930s and gave way to the development of The Navy Tissue Bank in 1949. Thus, it is unsurprising that the human split-thickness skin and decellularized dermis are still used today for various applications, including diabetic foot ulcers^{11,12,13,14} and chronic wounds.¹⁵

¹ See Example 11-3 related to skin products with the FDA’s final guidance titled *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*.

² See Example 10-2 related to amniotic products within the FDA’s final guidance titled *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*.

³ Reverdin JL. Greffeepidermique, experiencefaite dans le service de M le docteur Guyon, a l’hopitalnecker. Bull Imp SocChir Paris. 1869;10:511-5

⁴ Pollock GD. Cases of skin grafting and skin transplantation. Trans Clin Soc Lond. 1871;4:37-54

⁵ Girdner JH. Skin-grafting with grafts taken from the dead subject. Med Record NY. 1881;20:119-20

⁶ Wentscher J. A further contribution about the survivability of human epidermal cells. Dtsch Z Chir. 1903;70:21-44.

⁷ Blair VB, Brown JB, Hamm WG. Early Cre of burs. JAMA 1932;98:1355-1359.

⁸ Blair VP, Brown JB. The use and uses of split thickness skin grafts of intermediate thickness. Surg Gynecol Obstet. 1928;98:82-97.

⁹ Ibid.

¹⁰ Čapek KD, Culnan DM, Desai MH, Herndon DN. Fifty Years of Burn Care at Shriners Hospitals for Children, Galveston. Ann Plast Surg. 2018;80(3 Suppl 2):S90-S94. doi:10.1097/SAP.0000000000001376

¹¹ Guo X, Mu D, Gao F. Efficacy and safety of acellular dermal matrix in diabetic foot ulcer treatment: A systematic review and meta-analysis. Int J Surg. 2017 Apr;40:1-7. doi: 10.1016/j.ijsu.2017.02.008. Epub 2017 Feb 14

¹² Cazzell S, Vayser D, Pham H, Walters J, Reyzelman A, Samsell B, Dorsch K, Moore M. A randomized clinical trial of a human acellular dermal matrix demonstrated superior healing rates for chronic diabetic foot ulcers over conventional care and an active acellular dermal matrix comparator. Wound Repair Regen. 2017 May;25(3):483-497. doi: 10.1111/wrr.12551. Epub 2017 Jun 12.

¹³ Reyzelman AM, Bazarov I. Human acellular dermal wound matrix for treatment of DFU: literature review and analysis. J Wound Care. 2015 Mar;24(3):128; 129-34. doi: 10.12968/jowc.2015.24.3.128.

¹⁴ Zelen CM., et al. An Aseptically Processed, Acellular, Reticular, Allogenic Human Dermis Improves Healing in Diabetic Foot Ulcers: A Prospective, Randomised, Controlled, Multi-Centre Follow-Up Trial. *Int Wound J*. 2018 Apr 22. doi: 10.1111/iwj.12920.

¹⁵ Walters J, Cazzell S, Pham H, Vayser D, Reyzelman A. Healing Rates in a Multicenter Assessment of a Sterile, Room Temperature, Acellular Dermal Matrix Versus Conventional Care Wound Management and an Active Comparator in the Treatment of Full-Thickness Diabetic Foot Ulcers. *Eplasty*. 2016;16:e10. Published 2016 Feb 4.

Similarly, the human amniotic membrane has been utilized to treat wounds for over a century. In 1910, Davis utilized the lining of the amniotic sac as a skin graft.¹⁶ In 1913, two additional studies were published related to the use of amnion for skin grafting.^{17,18} In 1940, DeRotth used chorion and amnion to treat eye wounds.¹⁹

FDA regulation of skin substitutes. In June 2020, the FDA issued [final](#) guidance from titled *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*. This guidance provides clarity on the Agency’s thinking concerning the regulation of certain tissue products when used as wound coverings. As the guidance explains, two key requirements for products to be regulated solely under Section 361 of the Public Health Service Act (“PHS Act”) and 21 CFR Part 1271 as a “361 HCT/P” are that the product (1) be minimally manipulated and (2) be intended for homologous use. Concerning wound care products, there are two primary product types this guidance addresses – amniotic membrane and various skin (i.e, split-thickness skin and decellularized dermis) products.

Amniotic membrane. In addition to clarifying that the amniotic membrane is considered a structural tissue (p. 9), the FDA provided several examples that may be relevant to your discussion regarding wounds. With respect to minimal manipulation, example 10-2 (a) (copied below) details that amniotic membrane prepared in sheets is generally considered minimally manipulated, while example 11-2 (also copied below) notes that cellular removal can result in a minimally manipulated product. With respect to intended use, the final guidance clarifies in example 19-4 (c) (copied below) that the amniotic membrane used as a cover is a homologous use. For conciseness, we have not included the non-minimally manipulated, non-homologous use examples.

This framework is consistent with at least [one](#) widely-cited request for designation and recent FDA TRG recommendations to our member tissue banks in the past several years. In addition, as part of the HCPCS [code review](#), the Centers for Medicare and Medicaid Services (CMS) has quoted certain TRG decisions in granting those codes. Recent codes have been granted for certain HCT/Ps (1) when intended to serve as a selective barrier and to protect wounds from the surrounding environment, and its use is “not intended for wound healing”, (2) that serve as a barrier and provide protective cover from the surrounding environment for acute and chronic wounds, and (3) when intended for “repair, reconstruction and replacement of the recipient’s tissue” and “as a covering.”

Example 10-2: Original relevant characteristics of amniotic membrane relating to its utility to serve as a barrier generally include the tissue’s physical integrity,

¹⁶ Davis JW. Skin transplantation with a review of 550 cases at the Johns Hopkins Hospital. Johns Hopkins Med J Hosp Rep 1910;15:307-96.

¹⁷ Stern M. The grafting of preserved amniotic membrane to burned and ulcerated surfaces, substituting skin grafts. J Am Med Assoc 1913;83:478-80.

¹⁸ Sabella N. Use of the fetal membranes in skin grafting. Medical Records NY 1913;83:478-80.

¹⁹ De Rotth A. Plastic repair of conjunctival defects with fetal membranes. Arch Ophthalmol 1940;23:522-5.

tensile strength, and elasticity.

a. A manufacturer processes amniotic membrane to preserve it and package it in sheets. The HCT/P generally is considered minimally manipulated because the processing does not alter the original relevant characteristics of the HCT/P relating to its utility to serve as a barrier.

Example 11-2: Original relevant characteristics of the amniotic membrane related to its utility to serve as a barrier generally include its physical integrity, tensile strength, and elasticity. A manufacturer processes amniotic tissue to remove the chorion and other cells. The HCT/P generally is considered minimally manipulated because the processing does not alter the original relevant characteristics of the HCT/P relating to its utility to serve as a barrier.

Example 19-4: The basic functions of amniotic membrane include serving as a selective barrier for the movement of nutrients between the external and in utero environment, protecting the fetus from the surrounding maternal environment, and serving as a covering to enclose the fetus and retain fluid in utero.

c. An amniotic membrane product is applied to the surface of the eye to cover or offer protection from the surrounding environment in ocular repair and reconstruction procedures. This is homologous use because serving as a covering and offering protection from the surrounding environment are basic functions of amniotic membrane.

Split-Thickness Skin/Decellularized Dermis. Similar to amniotic membrane, the FDA guidance acknowledges that skin is considered a structural tissue (p. 9) and then provides several key examples related to how skin/dermis is regulated under the “361 HCT/P” framework. With respect to minimal manipulation, example 10-4 (a) (copied below) clarifies that mechanical meshing and cryopreservation are appropriate product manipulations, while example 11-3 (also copied below) further clarifies that freeze-drying and decellularizing dermis are also appropriate product manipulations to be considered a 361 HCT/P. With respect to homologous use, in example 20-1 (a) (also copied below), the guidance details the appropriate uses of the dermis, namely, to support, protect, reinforce, or cover.

Example 10-4: The original relevant characteristics of skin relating to its utility to serve as a protective covering generally include its large surface area, keratinized, water-resistant epithelial layer (epidermis), and dense, strong, and flexible connective tissue layer (dermis).

a. A manufacturer processes skin by mechanical meshing and cryopreservation and packages it in sheets as meshed skin. The HCT/P generally is considered minimally manipulated because the processing does not alter the original relevant characteristics of the skin relating to its utility as a protective covering.

Example 11-3: The original relevant characteristics of skin relating to its utility to serve as a protective covering generally include its large surface area, keratinized, water-resistant epithelial layer (epidermis), and dense, strong, and flexible

connective tissue layer (dermis). A manufacturer processes skin to remove epidermis and freeze-dries and packages the remaining connective tissue, as decellularized dermis. The HCT/P generally is considered minimally manipulated because the processing does not alter the original relevant characteristics of the HCT/P relating to its utility to serve as a protective covering.

Example 20-1: The basic functions of skin include covering, protecting the body from external force, and serving as a water-resistant barrier to pathogens or other damaging agents in the external environment. The dermis is the elastic connective tissue layer of the skin that covers, provides support and protects the body from mechanical stress.

a. An acellular dermal product is used for supplemental support, protection, reinforcement, or covering for a tendon. This is homologous use because in both anatomic locations, the dermis provides support and protects the soft tissue structure from mechanical stress.

Concerns with covered vs. non-covered products: Given this historical and regulatory background, we are concerned that the draft LCD arbitrarily provides coverage for some “361 HCT/Ps” but doesn’t include other, similar products. This is especially true of amniotic membrane in sheet form as well as certain decellularized dermis products, as noted above. As such, *all amnion products in sheet form and split-thickness skin/decellularized dermis products when labeled and marketed as wound coverings or barriers should be considered in compliance with relevant FDA regulations, should not require a TRG letter, and should be covered under the LCD.*

Further, given some confusion within the reimbursement community, we also want to note that, per the FDA regulation of “361 HCT/Ps”, the FDA has stated that “wound healing” claims are not appropriate for amnion products. It is important to understand that despite this FDA claims limitation, these products are a critical component of effective wound care and are appropriately used “on label” as a “wound covering” under this proposed LCD/LCA.

Concerns with FDA TRG documentation requirement: The draft LCD notes that “for skin substitutes classified as HCT/Ps, a letter from the FDA indicating that the HCT/P has met regulatory guidance is acceptable evidence of the FDA regulatory compliance for HCT/Ps regulated under section 361 of the Public Health Service Act and/or the Federal Food, Drug, and Cosmetic Act.” The draft LCD also states that “it is recommended that the manufacturer of the particular skin substitute graft or CTP product obtain the appropriate information and send to the MAC along with evidence-based literature, if available. Once this information has been received by the MAC, the product will be considered for coverage and placed into the appropriate Code Group in the associated article.” This follows other CMS actions in recent years tying reimbursement status to TRG letters. Tissue banks are complying with such requests, but we are concerned that such documentation requirements are contrary to the intent of FDA regulations, may unnecessarily burden FDA staff, and may result in disruption of care for patients who need such products.

First, we note that FDA’s regulation of HCT/Ps is a “risk-based, flexible regulatory [framework](#)” whereby “361 HCTP/s” are relatively low-risk products that, so long as they follow certain requirements, do not require premarket approval from the FDA to prove or “establish compliance” with the relevant regulations. By requiring TRG letters for reimbursement, the draft LCD (and related CMS actions) increase the burden on FDA staff and limit access to therapies – some of which are already on the market – for patients who need them. Further, by requiring TRG opinions to substantiate Section 361 HCT/P status, CMS is imposing a burdensome regulatory requirement that is not even otherwise required by FDA, the agency that directly regulates such products. The TRG recommendation was intended by FDA to be an elective process, but it is being expanded under the proposed LCD into a mandatory step in coverage.

Additionally, the reliance on FDA TRG letters is potentially problematic because the FDA TRG process is not streamlined, and it may take an inordinate amount of time to receive a final TRG letter. (Based on our internal analysis, in some cases it takes over 300 days to receive a final TRG letter.) ***If this policy is included in the final LCD as proposed, products should be covered for at least eighteen months to account for the delay that may occur while manufacturers secure TRG letters.*** Additionally, some skin substitute products (such as sheet products from amniotic membrane and split-thickness skin/decellularized dermis products) should not require a TRG letter because, as noted in the section above, FDA typically considers them minimally manipulated and for homologous use.

Finally, AATB has noted that the MAC is arbitrarily making coverage decisions based on minor differences in the content of TRG letters. These differences may be a reflection of the evolving language that FDA uses in the letters, and not necessarily a change in how FDA is regulating the products in question. To be clear, for a product to qualify as a “361 HCT/P”, it must meet the criteria for homologous use and minimal manipulation. Therefore, if the LCD requires a TRG letter, then all products with TRG letters affirming appropriate regulation should be treated equally and continue to be covered, regardless of statements made by FDA in the letter.

Concerns regarding limited number of product applications: The draft LCD allows for up to four product applications; however, we believe four applications may be insufficient and ***recommend changes so that the allowable number of applications is consistent with the instructions for use for such product.*** The number of allowable product applications should not be an arbitrary number; it should be based on the individual product and the professional judgement of the patient’s health care provider assessing the wound.

Concerns related to switching skin substitute graft products during treatment: We are concerned that switching skin substitute graft products in a 12-week episode of skin replacement surgery for wound care would generally not be considered medically reasonable and necessary under the LCD, except in rare cases (which the draft LCD notes may be considered on appeal when the medical necessity of the change is clearly documented in the medical record). In such rare cases when the wound closure process has stalled and a provider seeks to switch to another covered product, the appeal process could waste valuable healing time which is particularly a concern for diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) that can be exceptionally difficult to heal. In addition, wound care products that originate from similar tissue can have

different effects on a wound. Nevertheless, the proposed LCD maintains a limitation against repeat application of skin substitute grafts when a previous application was unsuccessful. Rather than mandating the abandonment of treatment with any alternative skin substitute, it is important that the LCD allow alternative skin substitutes to continue to be covered to help the wound close because, as the proposed LCD recognizes, there are data comparing skin substitutes that demonstrate differences in healing time (see Sanders et al. and Harding et al). Without the ability to switch skin substitute graft products, patients may be severely limited in treatment options for their nonhealing DFUs and VLUs. ***We recommend deferring to the professional judgement of the provider on whether it is medically necessary to switch to another covered product.***

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We hope that you will find this information useful in your deliberations. The AATB and the TPG stand ready and willing to assist CGS Administrators LLC with its deliberations in any way that you deem appropriate.

Respectfully,



Marc Pearce
President & CEO
American Association of Tissue Banks



Joe Yaccarino
Chair
Tissue Policy Group

The American Association of Tissue Banks

The American Association of Tissue Banks (AATB) is a professional, non-profit, scientific, and educational organization. AATB is the only national tissue banking organization in the United States, and its membership totals more than 120 accredited tissue banks and over 6,000 individual members. These banks recover tissue from more than 58,000 donors and distribute in excess of 3.3 million allografts for

more than 2.5 million tissue transplants performed annually in the US. The overwhelming majority of the human tissue distributed for these transplants comes from AATB-accredited tissue banks.

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