



November 7, 2023

Meredith Loveless, MD
Earl Berman, MD
CGS Administrators, LLC (CGS)
26 Century Boulevard
Suite ST610
Nashville, TN 37214

Re: L36690, A56696– Skin Substitute Grafts/Cellular and/or Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

Dear Drs. Loveless and Berman:

The American Association of Tissue Banks (AATB or Association) and the American Association of Tissue Banks' Tissue Policy Group (AATB TPG or TPG) write to thank you for withdrawing the local coverage determination (LCD) and its associated local coverage article (LCA) referenced above. As you know, the AATB and TPG are seriously concerned that implementation of the LCD and accompanying LCA would have significantly restricted patient access to critical allografts used in wound care. As you revise the LCD and LCA, we urge you to:

- Provide payment for appropriately regulated allografts to ensure patients have access to all appropriately regulated cellular and/or tissue-based products (CTPs) for diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs);
- Provide at least 18 months after finalization of an LCD for manufacturers and tissue processors to obtain proof of regulatory status (i.e., Tissue Reference Group (TRG) letters), before coverage and payment of any products are discontinued, and only use such evidence to confirm regulatory compliance; and
- Ensure any application limit is consistent with patients' clinical needs, as supported by clinical notes in each patient's chart based on the patient's condition, the type of wound (VLU vs DFU), and the medical judgement of the treating physician.

Additionally, we request that CGS Administrators include the AATB and TPG in any activities for which external expertise is required. This may include multijurisdictional meetings to review available evidence or to consider policies under development. AATB and TPG representatives have a deep understanding of the current landscape regarding CTPs, available literature, the Food and Drug Administration's (FDA's) regulatory framework, and CMS coding and coverage policies. Therefore, we would be ideally suited to contribute expertise to any deliberations addressing CTP coverage policy.

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 7,000 individual members. These banks recover tissue from more than 70,000 donors and distribute in excess of 3.3 million allografts for

more than 2.5 million tissue transplants performed annually in the U.S. 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.

We have further described our concerns below and are happy to meet with you to discuss in more detail.

Concerns with covered vs. non-covered products: As noted in our September 8, 2023 [letters](#) regarding the LCDs and LCAs, and the November 18, 2022 [letter](#) from the AATB and TPG to CGS Administrators regarding the Proposed LCD (L36690), the FDA issued [final guidance](#) in June 2020 titled *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*. The guidance clarified the Agency's thinking regarding the regulation of certain tissue products when used as wound coverings and, importantly, described how manufacturers/tissue processors of two primary product types – amniotic membrane and various skin (i.e., split-thickness skin and decellularized dermis) products – can legally market such tissues in compliance with the Agency's regulatory scheme for human cells, tissues, and cellular and tissue-based products (HCT/Ps).

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. The guidance notes that the Agency considers both amniotic membrane and skin to be structural tissues (p. 9) and provides examples of how the agency intends to interpret minimal manipulation and homologous use.

Specifically, in order for a structural tissue product to meet the requirements for regulation as a 361 HCT/P with respect to minimal manipulation, the processing must not alter the relevant characteristics of the tissue, relating to the tissue's utility for reconstruction, repair, or replacement. To meet the requirements for homologous use, the guidance specifies that an HCT/P is intended "*...for homologous use when it is used to repair, reconstruct, replace, or supplement:*

- *Recipient cells or tissues that are identical (e.g., skin for skin) to the donor cells or tissues, and perform one or more of the same basic functions in the recipient as the cells or tissue performed in the donor; or*
- *Recipient cells or tissue that may not be identical to the donor's cells or tissues, but that perform one or more of the same basic functions in the recipient as the cells or tissue performed in the donor."*

Unfortunately, even when CTPs are in compliance with the FDA's regulatory scheme under the PHS Act and 21 CFR Part 1271, the LCD and accompanying LCA would have excluded many CTPs from separate coverage and payment based on a determination that the CTPs are considered wound coverings or

wound dressings, rather than skin substitutes. We disagree with this distinction and contend that many of the CTPs excluded from coverage based on information that the products serve as barriers or skin coverings are – in fact – skin substitutes. These allografts are often provided in the form of a sheet that is anchored to the wound with sutures, adhesive strips, or other similar mechanisms and provides “scaffolding” of the wound site by providing a temporary extracellular matrix framework for new skin cells to attach and grow into during the healing process, even if their primary purpose is to serve as a barrier or covering. Numerous studies have demonstrated this scaffolding effect of the extracellular matrix framework.^{1,2,3} The LCD’s exclusion of allografts designated as wound coverings or wound dressings would have therefore resulted in the discontinuation of Medicare coverage for numerous CTPs that play a significant role in the management of DFUs and VLUs.

It is important to note that CTPs – *including* barriers and wound coverings – are key medical products that play an important role in the treatment of wounds. Numerous published peer-reviewed prospective multicenter randomized control trials support the use of CTPs in the treatment of DFUs and VLUs versus standard of care (SOC); SOC includes treating wounds with actual supplies categorized under A codes [such as collagen alginates (A6010)] rather than skin substitutes categorized under Q

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Additionally, we are aware that language used in TRG letters is not standardized, but that contractors' coverage determinations for individual products are based on both the content of each applicant's submission and the TRG's interpretation of the submission contents at the time of the Agency's review. Should CGS continue to require that a TRG letter must be furnished for coverage, we urge you to use the TRG letter only to verify that a CTP is appropriately regulated as a 361 HCT/P, not to determine that a CTP may or may not be marketed or used for specific intended uses based on the language FDA includes in the TRG letter.

Concerns with application limit: The AATB understands that the "default" limitation on the number of applications was based on published clinical evidence for a number of products that were used to heal small chronic wounds (i.e. less than 4 sq cm). However, there are many chronic wounds that will require more than four (4) applications to heal (i.e., larger and more complex wounds), so we believe there needs to be consideration that such large and complex wounds would require more than four (4) applications to ensure healing. We suggest that the number of applications be supported by clinical notes in the patient's chart based on the patient's condition, the type of wound (VLU vs DFU), and the medical judgement of the treating physician. As always local A/B MACs may perform post-payment review, at their discretion, to ensure provider documentation of medical necessity for the treatment of their wound(s) is contained within the patient's clinical record. The rescinded LCD indicated hard stops at 4 applications within 12 weeks in DFUs and VLUs with no meaningful flexibility. Such a requirement, if implemented, may have resulted in providers stopping treatment at those limits to the detriment of the beneficiaries who need it most: those with large and/or complex wounds, over long durations, and/or patients who are immunocompromised or have severe co-morbidities. In fact, restricting the number of applications could have resulted in higher cost of treatment for patients who may then require additional and more complex treatment plans due to the non-resolution of their wounds. We believe that providers should have the CTPs available to them to heal chronic wounds and retain the ability to provide the level of care based on each patient's specific need, including for larger and more complex, chronic wounds.

Impact on patients: Finally, we note that patient access to skin substitutes is particularly important given the disproportionate impact of DFUs and VLUs on racial and ethnic minority populations. Latinos, African Americans, and Native Americans in particular have the highest incidence of foot ulcers in the United States, and limiting access to these important wound care products may lead to greater disparities and worse outcomes for patients. We urge you to consider these populations as you revise your coverage policies.

Thank you for your consideration of these comments.

Respectfully,

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Marc Pearce
President & CEO
American Association of Tissue Banks

A handwritten signature in black ink that reads "Doug Wilson". The signature is written in a cursive, flowing style.

Doug Wilson
Chair
Tissue Policy Group



November 7, 2023

Alicia Campbell, MD
First Coast Service Options (FCSO)
P.O. Box 3425
Mechanicsburg, PA 17055

Re: L363377, A57680 – Skin Substitute Grafts/Cellular and/or Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

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Doug Wilson
Chair
Tissue Policy Group



November 7, 2023

Claudia Campos, MD, FACP
Novitas Solutions, Inc. (Novitas)
2020 Technology Parkway
Suite 100
Mechanicsburg, PA 17050

Re: L35041, A54117 – Skin Substitute Grafts/Cellular and/or Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

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- Provide payment for appropriately regulated allografts to ensure patients have access to all appropriately regulated cellular and/or tissue-based products (CTPs) for diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs);
- Provide at least 18 months after finalization of an LCD for manufacturers and tissue processors to obtain proof of regulatory status (i.e., Tissue Reference Group (TRG) letters), before coverage and payment of any products are discontinued, and only use such evidence to confirm regulatory compliance; and
- Ensure any application limit is consistent with patients' clinical needs, as supported by clinical notes in each patient's chart based on the patient's condition, the type of wound (VLU vs DFU), and the medical judgement of the treating physician.

Additionally, we request that Novitas include the AATB and TPG in any activities for which external expertise is required. This may include multijurisdictional meetings to review available evidence or to consider policies under development. AATB and TPG representatives have a deep understanding of the current landscape regarding CTPs, available literature, the Food and Drug Administration's (FDA's) regulatory framework, and CMS coding and coverage policies. Therefore, we would be ideally suited to contribute expertise to any deliberations addressing CTP coverage policy.

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 7,000 individual members. These banks recover tissue from more than 70,000 donors and distribute in excess of 3.3 million allografts for more than 2.5 million tissue transplants performed annually in the U.S. 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.

We have further described our concerns below and are happy to meet with you to discuss in more detail.

Concerns with covered vs. non-covered products: As noted in our September 8, 2023 [letters](#) regarding the LCDs and LCAs, and the November 18, 2022 [letter](#) from the AATB and TPG to CGS Administrators regarding the Proposed LCD (L36690), the FDA issued [final guidance](#) in June 2020 titled *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*. The guidance clarified the Agency's thinking regarding the regulation of certain tissue products when used as wound coverings and, importantly, described how manufacturers/tissue processors of two primary product types – amniotic membrane and various skin (i.e., split-thickness skin and decellularized dermis) products – can legally market such tissues in compliance with the Agency's regulatory scheme for human cells, tissues, and cellular and tissue-based products (HCT/Ps).

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. The guidance notes that the Agency considers both amniotic membrane and skin to be structural tissues (p. 9) and provides examples of how the agency intends to interpret minimal manipulation and homologous use.

Specifically, in order for a structural tissue product to meet the requirements for regulation as a 361 HCT/P with respect to minimal manipulation, the processing must not alter the relevant characteristics of the tissue, relating to the tissue's utility for reconstruction, repair, or replacement. To meet the requirements for homologous use, the guidance specifies that an HCT/P is intended "*...for homologous use when it is used to repair, reconstruct, replace, or supplement:*

- *Recipient cells or tissues that are identical (e.g., skin for skin) to the donor cells or tissues, and perform one or more of the same basic functions in the recipient as the cells or tissue performed in the donor; or*
- *Recipient cells or tissue that may not be identical to the donor's cells or tissues, but that perform one or more of the same basic functions in the recipient as the cells or tissue performed in the donor."*

Unfortunately, even when CTPs are in compliance with the FDA's regulatory scheme under the PHS Act and 21 CFR Part 1271, the LCD and accompanying LCA would have excluded many CTPs from separate coverage and payment based on a determination that the CTPs are considered wound coverings or wound dressings, rather than skin substitutes. We disagree with this distinction and contend that many of the CTPs excluded from coverage based on information that the products serve as barriers or skin

coverings are – in fact – skin substitutes. These allografts are often provided in the form of a sheet that is anchored to the wound with sutures, adhesive strips, or other similar mechanisms and provides “scaffolding” of the wound site by providing a temporary extracellular matrix framework for new skin cells to attach and grow into during the healing process, even if their primary purpose is to serve as a barrier or covering. Numerous studies have demonstrated this scaffolding effect of the extracellular matrix framework.^{1,2,3} The LCD’s exclusion of allografts designated as wound coverings or wound dressings would have therefore resulted in the discontinuation of Medicare coverage for numerous CTPs that play a significant role in the management of DFUs and VLUs.

It is important to note that CTPs – *including* barriers and wound coverings – are key medical products that play an important role in the treatment of wounds. Numerous published peer-reviewed prospective multicenter randomized control trials support the use of CTPs in the treatment of DFUs and VLUs versus standard of care (SOC); SOC includes treating wounds with actual supplies categorized under A codes [such as collagen alginates (A6010)] rather than skin substitutes categorized under Q

¹ Dasgupta, Anouska PhD^{*}; Orgill, Dennis MD, PhD^{†‡}; Galiano, Robert D. MD[§]; Zelen, Charles M. DPM[¶]; Huang, Yen-Chen PhD^{*}; Chnari, Evangelia PhD^{*}; Li, William W. MD[¶]. A Novel Reticular Dermal Graft Leverages Architectural and Biological Properties to Support Wound Repair. *Plastic and Reconstructive Surgery - Global Open* 4(10):p e1065, October 2016. | DOI: 10.1097/GOX.0000000000001065.

² David Dolivo, Ping Vie, Chun Hou, Yingxing Li, Abigail Phipps, Thomas Mustoe, Seok Hong, Robert Galiano. Application of decellularized human reticular dermal allograft dermal matrix promoted rapid re-epithelialization in a diabetic murine excisional wound model, *Cytotherapy*, Published Jan 8, 2021, <https://doi.org/10.1016/j.jcyt.2020.11.009>

³ Sabol TJ, Tran GS, Matuszewski J, Weston WW. Standardized reporting of amnion and amnion/chorion allograft data for wound care. *Health Sci Rep.* 2022;5(5):e794. Published 2022 Aug 23. doi:10.1002/hsr2.794

codes.^{4,5,6,7,8,9,10,11,12,13} We encourage you to cover all allografts that meet applicable regulatory requirements, including those allografts considered a wound covering or barrier by the FDA, and defer to the professional judgement of the patient's health care provider assessing the wound to determine which allograft is most appropriate for the individual and each clinical application.

Concerns with TRG letter requirement: As noted above, the AATB and TPG believe all allografts that are in compliance with relevant FDA regulations should be covered by a revised LCD and LCA. If Novitas continues to require proof of FDA regulatory compliance for 361 HCT/Ps (i.e., a letter from the FDA TRG), the AATB and TPG believe that sufficient time should be given for manufacturers/tissue processors to acquire those letters and the CTPs should be covered while manufacturers/tissue processors work to obtain them. Specifically, we believe that a transition period is needed under which CTPs without a TRG

⁴ DiDomenico LA, Orgill DP, Galiano RD, et al. Use of an aseptically processed, dehydrated human amnion and chorion membrane improves likelihood and rate of healing in chronic diabetic foot ulcers: A prospective, randomised, multi-centre clinical trial in 80 patients. *Int Wound J.* 2018;15(6):950-957. doi:10.1111/iwj.12954

⁵ Zelen CM, Orgill DP, Serena T, Galiano R, Carter MJ, DiDomenico LA, Keller J, Kaufman J, Li WW. A prospective, randomized, controlled multicenter clinical trial examining healing rates, safety and cost of closure of an acellular reticular allogenic human dermis versus standard of care in the treatment of chronic diabetic foot ulcers. *Int Wound J.* 2016 Apr 12 doi: 10.1111/iwj.12600

⁶ Serena, Thomas E. M.D.; Orgill, Dennis P. M.D., Ph.D.; Armstrong, David G. D.P.M., M.D., Ph.D.; Galiano, Robert D. M.D.; Glat, Paul M. M.D.; Carter, Marissa J. Ph.D.; Kaufman, Jarrod P. M.D.; Li, William W. M.D.; Zelen, Charles M. D.P.M. A Multicenter, Randomized, Controlled, Clinical Trial Evaluating Dehydrated Human Amniotic Membrane in the Treatment of Venous Leg Ulcers. *Plastic and Reconstructive Surgery* 150(5):p 1128-1136, November 2022. | DOI: 10.1097/PRS.00000000000009650

⁷ Zelen CM, Gould L, Serena TE, Carter MJ, Keller J, Li WW. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. *Int Wound J.* 2015;12(6):724-732. doi:10.1111/iwj.12395

⁸ Tettelbach W, Cazzell S, Reyzelman AM, Sigal F, Caporusso JM, Agnew PS. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. *Int Wound J.* 2019;16(1):19-29. doi:10.1111/iwj.12976

⁹ Glat, Paul, et al. "Placental membrane provides improved healing efficacy and lower cost versus a tissue-engineered human skin in the treatment of diabetic foot ulcerations." *Plastic and Reconstructive Surgery Global Open* 7.8 (2019).

¹⁰ 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.ijssu.2017.02.008. Epub 2017 Feb 14

¹¹ 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.

¹² 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.

¹³ 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.

letter should continue to be covered for at least eighteen months to account for the time it takes for companies to prepare TRG submissions and the delay that may occur while manufacturers/tissue processors secure such letters and the volume of work for the FDA TRG. This timeline is based on our internal analysis that, in some cases, it takes more than 300 days to receive a final TRG letter under TRG's current workload; an increased workload would further exacerbate delays.

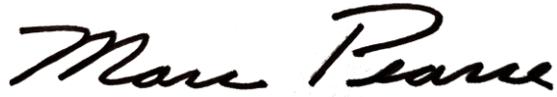
Additionally, we are aware that language used in TRG letters is not standardized, but that contractors' coverage determinations for individual products are based on both the content of each applicant's submission and the TRG's interpretation of the submission contents at the time of the Agency's review. Should Novitas continue to require that a TRG letter must be furnished for coverage, we urge you to use the TRG letter only to verify that a CTP is appropriately regulated as a 361 HCT/P, not to determine that a CTP may or may not be marketed or used for specific intended uses based on the language FDA includes in the TRG letter.

Concerns with application limit: The AATB understands that the "default" limitation on the number of applications was based on published clinical evidence for a number of products that were used to heal small chronic wounds (i.e. less than 4 sq cm). However, there are many chronic wounds that will require more than four (4) applications to heal (i.e., larger and more complex wounds), so we believe there needs to be consideration that such large and complex wounds would require more than four (4) applications to ensure healing. We suggest that the number of applications be supported by clinical notes in the patient's chart based on the patient's condition, the type of wound (VLU vs DFU), and the medical judgement of the treating physician. As always local A/B MACs may perform post-payment review, at their discretion, to ensure provider documentation of medical necessity for the treatment of their wound(s) is contained within the patient's clinical record. The rescinded LCD indicated hard stops at 4 applications within 12 weeks in DFUs and VLUs with no meaningful flexibility. Such a requirement, if implemented, may have resulted in providers stopping treatment at those limits to the detriment of the beneficiaries who need it most: those with large and/or complex wounds, over long durations, and/or patients who are immunocompromised or have severe co-morbidities. In fact, restricting the number of applications could have resulted in higher cost of treatment for patients who may then require additional and more complex treatment plans due to the non-resolution of their wounds. We believe that providers should have the CTPs available to them to heal chronic wounds and retain the ability to provide the level of care based on each patient's specific need, including for larger and more complex, chronic wounds.

Impact on patients: Finally, we note that patient access to skin substitutes is particularly important given the disproportionate impact of DFUs and VLUs on racial and ethnic minority populations. Latinos, African Americans, and Native Americans in particular have the highest incidence of foot ulcers in the United States, and limiting access to these important wound care products may lead to greater disparities and worse outcomes for patients. We urge you to consider these populations as you revise your coverage policies.

Thank you for your consideration of these comments.

Respectfully,

A handwritten signature in black ink that reads "Marc Pearce". The letters are cursive and fluid.

Marc Pearce
President & CEO
American Association of Tissue Banks

A handwritten signature in black ink that reads "Doug Wilson". The letters are cursive and fluid.

Doug Wilson
Chair
Tissue Policy Group