American Association of Tissue Banks®

September 8, 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) submit these requests regarding the local coverage determination (LCD) and its associated local coverage article (LCA) referenced above. The AATB and TPG are seriously concerned that the LCD and accompanying LCA will restrict access to critical allografts used in wound care. We therefore urge you to:

- Update the LCA to provide payment for appropriately regulated allografts in the Group 3 set of HCPCS codes considered "Non-Covered" 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 for manufacturers and tissue processors to obtain proof of regulatory status (i.e., Tissue Reference Group (TRG) letters), and only use such evidence to confirm regulatory compliance;
- Revise the application limit to be 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; and
- Postpone the proposed implementation date until at least January 1, 2024.

We further request a meeting at your earliest convenience – but prior to the September 17, 2023, implementation date – to discuss our concerns with the LCD.

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.

Concerns with covered vs. non-covered products: As noted in the November 18, 2022 letter from the AATB and TPG to CGS Administrators regarding the Proposed LCD (DL36690), the Food and Drug Administration (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 exclude 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 will therefore result in the discontinuation of Medicare coverage for numerous CTPs that play a significant role in the management of diabetic foot ulcers and venous leg ulcers.

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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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 the LCD and LCA. If CGS continues to require proof of FDA regulatory compliance for 361 HCT/Ps (i.e., a letter from the FDA Tissue Reference Group (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 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 Tissue Reference Group. 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 and is based on both the content of the 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 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.

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Impact on patients: Finally, we note that patient access to skin substitutes is particularly important given the disproportionate impact of diabetic foot ulcers and venous leg ulcers 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.

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Given our concerns with the determinations included in the LCD and accompanying LCA, we request a delay in implementation accompanied with a meeting at your earliest convenience – but prior to the September 17, 2023, implementation date, to discuss these issues further. Thank you for your consideration of these comments.

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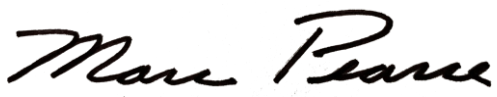

Marc Pearce
President & CEO
American Association of Tissue Banks

Doug Wilson
Chair
Tissue Policy Group

American Association of Tissue Banks®

September 8, 2023

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

Re: L36377, 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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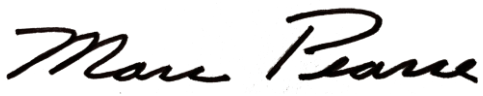

Marc Pearce
President & CEO
American Association of Tissue Banks

Doug Wilson
Chair
Tissue Policy Group

American Association of Tissue Banks®

September 8, 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

Dear Dr. Campos:

The American Association of Tissue Banks (AATB or Association) and the American Association of Tissue Banks' Tissue Policy Group (AATB TPG or TPG) submit these requests regarding the local coverage determination (LCD) and its associated local coverage article (LCA) referenced above. The AATB and TPG are seriously concerned that the LCD and accompanying LCA will restrict access to critical allografts used in wound care. We therefore urge you to:

- Update the LCA to provide payment for appropriately regulated allografts in the Group 3 set of HCPCS codes considered "Non-Covered" 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 for manufacturers and tissue processors to obtain proof of regulatory status (i.e., Tissue Reference Group (TRG) letters), and only use such evidence to confirm regulatory compliance;
- Revise the application limit to be 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; and
- Postpone the proposed implementation date until at least January 1, 2024.

We further request a meeting at your earliest convenience – but prior to the September 17, 2023, implementation date – to discuss our concerns with the LCD.

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.

Concerns with covered vs. non-covered products: As noted in the November 18, 2022 letter from the AATB and TPG to CGS Administrators regarding the Proposed LCD (DL36690), the Food and Drug Administration (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 exclude 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 will therefore result in the discontinuation of Medicare coverage for numerous CTPs that play a significant role in the management of diabetic foot ulcers and venous leg ulcers.

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.

Even if Novitas stands by the decision in the LCD to unilaterally reclassify wound coverings or barriers as categorically distinct from skin substitutes, we disagree that these allografts should be treated the same as wound dressings and excluded from receiving separate payment. Wound dressings are removed and replaced often, do not come into contact with the wound, and are often made using synthetic materials. In contrast, the human tissue-based wound coverings and barriers that are improperly excluded under this LCD are applied or fixated directly to the wound and remain there, naturally incorporating into the

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[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.0000000000009650

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[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

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[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.ijsu.2017.02.008. Epub 2017 Feb 14

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[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.

wound, until the health care provider determines that the wound has stopped progressing and another application is indicated. Given this important role and function, these allografts – and similar dermal allografts – are a critical component of effective wound management, including when they function as wound coverings or barriers (as considered by FDA), and should be eligible for separate Medicare payment.

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 the LCD and LCA. If Novitas continues to require proof of FDA regulatory compliance for 361 HCT/Ps (i.e., a letter from the FDA Tissue Reference Group (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 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 Tissue Reference Group. 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 and is based on both the content of the 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 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. As finalized, the LCDs indicate hard stops at 4 applications within 12 weeks in DFUs and VLUs with no meaningful flexibility. That may result 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 result in higher cost of treatment for patients who may then require additional and more complex treatment plans due to the non-resolution of their wound. 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 diabetic foot ulcers and venous leg ulcers 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.

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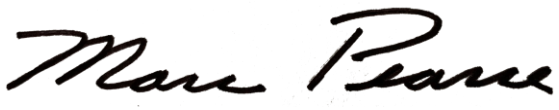
Given our concerns with the determinations included in the LCD and accompanying LCA, we request a delay in implementation accompanied with a meeting at your earliest convenience – but prior to the September 17, 2023, implementation date, to discuss these issues further. Thank you for your consideration of these comments.

Respectfully,



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