



American Association of Tissue Banks® AATB TPG, LLC

June 17, 2022

Division of Dockets Management (HFA-305)
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

**In Re: Docket No. FDA-2021-N-1212, Wound Healing Scientific Workshop; Public Workshop;
Request for Comments**

Submitted electronically at www.regulations.gov

Dear Madams and Sirs:

The American Association of Tissue Banks (AATB or Association) and the American Association of Tissue Bank's Tissue Policy Group, LLC (AATB TPG or TPG) submit these comments related to a workshop of the Food and Drug Administration (FDA or Agency) related to wound healing and a request for further comments. These comments will focus on two key topics – (1) other FDA guidance which has an impact on wound care products and (2) responding to some direct questions from the FDA.

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.

Other FDA guidance. While the preliminary agenda acknowledged the FDA's [final](#) guidance titled *Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment, June 2006* (wound guidance), we wanted to ensure that you were also aware of other critical guidance related to the

regulation of certain wound products, especially the [final](#) guidance from June 2020 titled *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*. This latest guidance provides clarity on the Agency's thinking concerning the regulation of certain tissue products as it relates to wound covering. As the guidance explains, two key requirements for products to be regulated solely under PHS Act section 361 and 21 CFR 1271 as a "361 HCT/P" are that the product (1) be minimally manipulated and (2) be used in a homologous manner. 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. Namely, example 10-2 (copied in full below) details that amniotic membrane prepared in sheets is generally considered minimally manipulated, while example 11-2 (also copied in full below) notes that cellular removal can result in a minimally manipulated product. Finally, the final guidance clarifies in example 19-4 (copied in full below) that the amniotic membrane used as a cover is a homologous use. Not only is this framework consistent with at least [one](#) widely cited request for designation, but it is also consistent with recent Tissue Reference Group (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 has quoted certain TRG decisions in granting those codes. Recent codes have been granted for certain human cells, tissues, and cellular and tissue-based products (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, 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.

b. A manufacturer grinds and lyophilizes amniotic membrane and packages it as particles. The HCT/P generally is considered more than minimally manipulated because the processing alters 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.

a. Amniotic membrane is used for bone tissue replacement to support bone regeneration following surgery to repair or replace bone defects. This is not a homologous use because bone regeneration is not a basic function of amniotic membrane.

b. An amniotic membrane product is used for wound healing and/or to reduce scarring and inflammation. This is not homologous use because wound healing and reduction of scarring and inflammation are not basic functions of amniotic membrane.

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. Specifically, example 10-4 (copied in full below) clarifies that mechanical meshing and cryopreservation are appropriate product manipulations, while example 11-3 (also copied in full below) further clarifies that freeze-drying and decellularized dermis are also appropriate product manipulations. Finally, in example 20-1 (also copied in full 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).

1. 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.
2. A manufacturer processes skin by removing the epidermis and then grinding the dermis into particles. The HCT/P generally is considered more than minimally manipulated because the processing alters the original relevant characteristics of skin related 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.

b. An acellular dermal product is used for tendon replacement or repair. This is not homologous use because serving as a connection between muscle and bone is not a basic function of dermis.

Utilization data. In examining a Medicare Data Set utilizing outpatient patient care data from 2015-2019 concerning diabetic lower extremity ulcers, the majority of the patients received standard of care (70.5%), while approximately one-quarter (26.0%) received additional therapies to support or aid wound healing (e.g., amnion, PMA devices, or xenografts). Of the quarter who received additional therapies, 41% received an amniotic product, 5% received a skin substitute product, 17% received a PMA device [e.g., Integra® (Meshed) Dermal Regeneration Template, Apligraf®, or Dermagraft®], 14% received a 510(k) xenograft, and 23% received a combination of the above products or other products.

Recommendations as organizations representing product developers. Not only are HCT/Ps utilized as a cover for wounds (as “361 HCT/Ps”), but they can also be classified as medical devices or biological products. At this time, we are unaware of any HCT/Ps classified as drugs. While the source materials for these products are the same, the different processing steps and regulatory requirements can present different challenges, as further highlighted below.

Cross-cutting themes

Regardless of the classification of HCT/Ps, we have recommendations for better collaboration between industry and the Agency in four areas – better utilization of real-world evidence (RWE), better delineation of the standard of care, development of additional efficacy endpoints, and

utilization of other methods to address bias (e.g., artificial intelligence and utilization of observer panels).

Better Utilization of Real-World Evidence. While we appreciate that the Agency has been working to enhance its guidance framework to provide additional clarity to the industry, at times, the focus has been too narrow. For instance, we previously provided comments to the [draft](#) guidance titled *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products* and the [draft](#) guidance titled *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products*. Specifically, we noted that both draft guidance documents were narrowly tailored in direct response to the Congressional directive under 505F of the Federal Food, Drug, and Cosmetic Act. While we appreciate that the Food and Drug Administration (FDA or Agency) needs to be responsive to Congressional intent, we simply note that the FDA has the general authority to issue guidance that is much more expansive in content, such as the August 2017 [final](#) guidance titled *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*. Given that broader agency authority, ***we look forward to working with you to help better define the appropriate real-world evidence for use to support the approval or clearance of certain HCT/Ps.***

In addition, we would note that, in analyzing real-world data (RWD) to develop RWE, a variety of statistical approaches may be utilized (e.g., propensity scoring, Cox regression analysis, etc.). There are advantages or disadvantages of the various approaches. For instance, propensity scoring may remove many subjects from the statistical analysis. A more appropriate statistical approach may be the Cox regression analysis, given that all patient data are in the analysis, which may provide better RWE. ***We encourage the FDA to afford flexibility in its regulatory framework to allow a sponsor to choose the statistical approach that is best designed for the RWD to obtain the most beneficial RWE.***

Concerning generalizability, the wound guidance notes in section II that “it is difficult to generalize results obtained from a trial conducted in subjects with one wound type to patients with another wound type.” However, the FDA did not also recognize another potential generalizability problem – issues that develop when the strict inclusion and exclusion criteria of a randomized clinical trial (RCT) result in a population that may not mimic the population of patients who will ultimately utilize these products. As such, ***we recommend that the FDA better outline how RWD/RWE could augment the RCT design to provide more generalizable results.***

Better Delineation of the Standard of Care. We appreciate that the Agency included within section IV.F of the wound guidance information related to standard care. As the final guidance notes “varying standard care procedures can confound the outcome of a clinical trial.” Since the finalization of that guidance, variation in standard care has increased. Thus, it would be helpful for the ***FDA to better delineate the current standard care (e.g., debridement, offloading) to assist with the development of the control arm.***

Development of Additional Efficacy Endpoints. As detailed in section IV.G of the wound guidance, traditional efficacy endpoints for wound healing studies generally include improved wound healing (i.e., the incidence of complete wound closure, accelerated wound closure, facilitation of wound closure, quality of healing, etc.) and improved wound care (i.e., treatment of wound infection, debridement, wound pain control). In addition, during the workshop, at least one Agency official noted that composite efficacy endpoints may be appropriate (e.g., decrease in the number of debridements or dressing burden coupled with decreased pain). ***We encourage the FDA to work with the industry to identify additional primary efficacy endpoints for wound studies.*** Those endpoints, which are clinically meaningful, may include partial wound area reduction (given that a reduction of less than 100% may still be clinically valuable), patient-centric outcomes (e.g., quality of life scores)(given that they help measure the patient’s ability to participate in activities of daily living), and others which may assist with capturing costs to the healthcare system as well as pain and suffering to patients (e.g., visits to the Emergency Room; number and duration of hospital stays; complications resulting from infections, such as including osteomyelitis and amputation, etc.).

Utilization of Artificial Intelligence to Address Bias. We appreciate that section IV.D of the wound guidance provided an initial framework for wound assessment and qualification (i.e., use of photographs and molds), with an additional statement in section IV.C encouraging the utilization of a blinded assessment by a third-party evaluator. In the intervening sixteen years since the release of the final wound guidance, there have been considerable developments in imaging technology coupled with artificial intelligence. And, these advancements provide opportunities to standardize assessments while reducing bias. Therefore, ***we recommend that the Agency detail its expectations regarding the validation process for artificial intelligence and advanced imaging technologies*** to help encourage the utilization of such advancements in future wound studies, potentially replacing the need for a blinded assessment by a third-party evaluator.

Utilization of Observer Panels. Within the wound guidance in section IV.C, the Agency acknowledged that wound care studies cannot be blinded in a meaningful way, leaving all of those studies open to criticism of potential bias. To help compensate for that deficiency, a variety of tools may be utilized including an observer-blinded trial (which may be difficult if there are remnants of the observed product within the wound bed during observation) and a observer panels (which the FDA has utilized in reviews with some success). ***We request that the Agency clarify that observer panels are an appropriate trial design to address potential bias in wound care studies.***

“361 HCT/Ps”

As detailed above, “361 HCT/Ps,” which include certain amnion, split-thickness skin, and decellularized dermis products, can be utilized as a wound cover. As such, these products are instrumental to current wound care treatment programs and have a long history of use. 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.¹ George Pollock used his own skin in addition to the patient's own skin to cover a burn in 1871.² The first report of successful use of allograft skin to treat a burn was by Girdner in 1881.³ In 1903, Wentscher reported that allograft skin retained cellular viability after 3-14 days.⁴ James Barrett Brown, M.D. (1899-1971), with his work in the early 1930s, revolutionized the concepts of skin grafting.^{5,6} 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.⁷ 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.⁸ 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 not surprising that the human split-thickness skin and decellularized dermis are still utilized today for various applications, including diabetic foot ulcers^{9,10,11} and chronic wounds.¹²

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.¹³ In 1913, two additional studies were published related to the use of amnion for skin grafting.^{14,15} In 1940, DeRotth utilized chorion and amnion together to treat eye wounds.¹⁶ As a result of these studies and others, doctors continue to utilize amnion for a variety of wound applications.

¹ Reverdin JL. Greffeepidermique, experiencefaitedans le service de M le docteurGuyon, a l'hospitalnecker. Bull Imp SocChir Paris. 1869;10:511-5

² Pollock GD. Cases of skin grafting and skin transplantation. Trans ClinSocLond. 1871;4:37-54

³ Girdner JH. Skin-grafting with grafts taken from the dead subject. Med Record NY. 1881;20:119-20

⁴ Wentscher J. A further contribution about the survivability of human epidermal cells. Dtsch Z Chir. 1903;70:21-44.

⁵ Blair VB, Brown JB, Hamm WG. Early Cre of burs. JAMA 1932;98:1355-1359.

⁶ Blair VP, Brown JB. The use and uses of split thikness skin grafts of intermediate thickness. Surg Gynocol Obstet. 1928;98:82-97.

⁷ Ibid.

⁸ 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

⁹ 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

¹⁰ 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.

¹¹ 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.

¹² 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.

¹³ Davis JW. Skin transplantation with a review of 550 cases at the Johns Hopkins Hospital. Johns HopkinsMed J Hosp Rep 1910;15:307-96.

¹⁴ Stern M. The grafting of preserved amniotic membraneto burned and ulcerated surfaces, substituting skin grats.J Am Med Assoc 1913;83:478-80.

¹⁵ Sabella N. Use of the fetal membranes in skin grafting. Medical Records NY 1913;83:478-80.

¹⁶ De Rotth A. Plastic repair of conjunctival defects with fetal membranes. Arch Ophthalmol 1940;23:522-5.

However, as noted above, to retain the “361 HCT/P” status, the products can only have a manufacturer’s objective intent as a wound cover. Thus, any other intended uses would require FDA review or approval. Given that there is no current Agency framework for the utilization of RWE to add an intended use to a “361 HCT/P”, there are no real incentives for innovation or gathering additional evidence related to the potential benefit of HCT/Ps. ***Therefore, we urge the Agency to provide a framework to allow “361 HCT/Ps” to utilize RWE/RWD to expand homologous uses.***

Medical devices

Concerning devices, we have two issues we would like to further discuss; namely, pre-clinical animal studies, and the use of RWE to expand indications.

Animal studies. The traditional device framework requires that animal studies be included as part of the pre-clinical evaluation of new class II and class III medical devices. Within the wound space, there are limited animal models for certain product indications (e.g., diabetes foot ulcer, with no suitable way to model a foot ulcer in an animal). When that product is an HCT/P (and not a traditional device material such as synthetics), there are additional complications in using euthymic animals (i.e., immunocompetent animals), including that a xenogeneic response may not be indicative of human incompatibility. ***We request that the FDA work with the industry to better detail animal models for HCT/Ps involved in wound care studies.***

Use of RWE to expand indications. In the draft guidance titled *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products*, the FDA outlined the type of RWE to help support the approval of a new indication for a drug already approved under section 505(c) of the FD&C Act or to help support postapproval study requirements. ***While we appreciate this additional clarification for drugs/biologics, it would also be helpful to receive similar guidance concerning devices.***

Biological products

We want to highlight seven areas for future collaboration related to HCT/Ps that may require a Biologics License Application (BLA): pooling, retention samples, sterility testing, potency testing, identity, required clinical studies, and biocompatibility requirements.

Pooling. We recognize the limitation detailed under 21 CFR 1271.220(b), which states that “[h]uman cells or tissue from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.” We understand the concerns that resulted in the implementation of this regulation, however, in certain cases, the benefit of patient access to pooled products may outweigh the risk of pooling. Regulations currently allow for an exemption or alternative granted by the Director of CBER. Considering advancements in donor screening and testing processes, traceability controls, and digital records, risks associated with pooling may be minimized to safe thresholds in certain cases. Additionally, industry-wide bioburden controls have

been shown effective in reducing bacterial transmission. Furthermore, many products are terminally sterilized providing a level of viral inactivation for increased risk reduction. While we recognize FDA's resource constraints, we ask that ***FDA develop guidance or frequently asked questions (FAQs) related to the FDA's expectations for pooling risk/benefit analyses and a risk management framework for HCT/Ps requiring a BLA.*** We can confirm that tissue banks would be interested in contributing to this effort if the FDA wishes to engage the industry in this activity.

Retention samples. Currently, with pooling restrictions, "351 HCT/Ps" and "361 HCT/Ps" are produced in single donor lots. This results in a limited amount of product available from each lot for release testing, retains, and patient use. With the additional requirements for release testing and retains for "351 HCT/Ps", the amount of product available for patient access can be significantly reduced, and in some cases, would not be feasible in terms of product production. We are aware of CBER suggesting options, such as using process by-products to meet testing and retain requirements, but this may not be acceptable in many cases. With pooled products, lot sizes would be larger and more products from each lot would be available for release testing, retains, and distribution for patient access. Without the option of pooling, for some "351 HCT/Ps", the amount of product required for testing and retains can be prohibitive, reducing the amount of product available for patients to an unacceptable level. ***We recommend FDA establish a framework for pooling that allows processors to meet standard testing and retains requirements with sufficient additional products available for patient use.***

Sterility testing. The AATB and the TPG are heartened by the flexibility provided under 21 CFR 610.12(h)(2) that states: *A manufacturer is not required to comply with the sterility test requirements if the Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research, as appropriate, determines that data submitted in the biologics license application or supplement adequately establish that the route of administration, **the method of preparation, or any other aspect of the product** precludes or does not necessitate a sterility test to assure the safety, purity, and potency of the product.* (Emphasis added.) In light of that flexibility, ***we urge the FDA to clarify that any HCT/P that has been terminally sterilized to a validated Sterility Assurance Level (SAL) of 10^{-6} in conformity with ISO 11137 Parts 1 & 2 "Radiation Sterilization of Healthcare Products" would not require sterility testing on individual lots.*** We recommend this clarification based on Recognized Consensus Standards, the mathematical limitation of sterility testing of a terminally sterilized product, the potential for inaccurate results due to cross-contamination, and greater harmonization of requirements across Centers within the FDA.

Potency testing. When describing the potency testing requirements for BLA products, representatives for CBER have stated that ideally, a potency assay will represent the product's mechanism of action (MOA), which may be very complex. Further, bioassays may be time-consuming and have variability. Sometimes a single assay alone is not sufficient, and the MOA may never be known. The development of a bioassay is an iterative process. A successful potency assay is based on what FDA thinks is a reasonable MOA proposal. Despite best efforts, often, the package

insert for an approved biologic will indicate that the MOA has not been identified or is unknown. While the determination of the MOA is not a requirement, a final potency test is required, but the potency test, in effect, relies in part upon determining the MOA. Additionally, the potency test must be developed and validated in concert with other tests and studies (e.g., stability studies, lot release studies, and comparability). In light of this interactive and iterative process, it would be helpful to receive a decision from CBER related to the adequacy of a product's potency assessment as early in the BLA process as possible. ***We ask that CBER develop additional guidance related to best practices for potency assessment development and commit to earlier and frequent interaction with Sponsors to provide constructive feedback and confirmation of appropriate potency activities and decisions.***

Identity. 21 CFR 610.14 Identity addresses the requirements for identity testing of the contents of a final container of each filling of each lot of "351 HCT/Ps". Identity may be established through various methods, including the physical or chemical characteristics of the product. It is understood that the identity requirements for a "351 HCT/P" are in addition to the special controls applicable for "361 HCT/Ps" in 21 CFR 1271.250, 1271.270, and 1271.290, for Labeling, Records, and Tracking. Given the ambiguity regarding what additional identity tests would be relevant for HCT/Ps, which have much different physical and chemical characteristics than the products defined as biological products in 21 CFR 600.3 (*any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man*), ***we ask that CBER develop additional guidance related to best practices for "351 HCT/P" identity test requirements and commit to earlier and frequent interaction with Sponsors to provide constructive feedback and confirmation of appropriate identity testing activities and decisions.***

Required clinical studies. In the FDA's 1998 guidance titled *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, the FDA notes that "[t]he usual requirement for more than one adequate and well-controlled investigation reflects the need for independent substantiation of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness." Especially for products that may have been on the market before the close of the recent enforcement discretionary period and for products in which there are minor differences between the HCT/P that requires a BLA versus a "361 HCT/P", ***we urge the Agency to consider the body of evidence in totality so that any required prospective clinical trials are narrowly focused*** on the key evidence gaps. We appreciate that the Agency has taken a similar tack with the recent approval of [STRATAGRAFT](#) (as discussed within the workshop), and we urge the Agency to continue this approach. The Agency has made significant strides in guiding the use of real-world evidence to support regulatory decision making; we recommend further collaboration with the industry to tease out the nuances of real-world data available for human tissues previously marketed solely for homologous uses ("361 HCT/Ps").

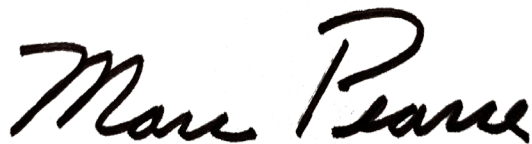
Biocompatibility requirements. While we appreciate the Agency's focus on ensuring that products utilized in the wound care space are biocompatible, ***we urge the Agency to employ flexibility with***

respect to the biocompatibility testing requirements, due to the limitations in testing human tissue in euthymic animals, given that it will likely result in a xenogenic response, especially if the the HCT/P contains cells.

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We hope that you will find this information useful in your deliberations. In addition, **we request a virtual meeting to further discuss these critical issues**. The AATB and the TPG stand ready and willing to assist the FDA with its deliberations in any way that you deem appropriate.

Respectfully,

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

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