



American Association of Tissue Banks®

February 23, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

In Re: Docket No. FDA-2014-D-1856-0001: Comments to the Draft Guidance Document Titled “Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry” (December 2014)

Submitted electronically at www.regulations.gov

Dear Madams and Sirs:

The American Association of Tissue Banks (AATB or Association) submits these comments to the draft guidance document titled “Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry” (December 2014) (hereinafter “draft adipose guidance document”).

The AATB is a professional, non-profit, scientific and educational organization. It is the only national tissue banking organization in the United States, and its membership totals **more than 125 accredited tissue banks and 650 individual members**. These banks recover tissue from more than **30,000 donors** and distribute in excess of **two and a half million allografts for more than one million tissue transplants performed annually in the U.S.** More than 90 percent of the human tissue distributed for these transplants comes from AATB-accredited tissue banks.

The Association was founded in 1976 by a group of doctors and scientists who had started in 1949 our nation’s first tissue bank, the United States Navy Tissue Bank. Recognizing the increasing use of human tissue for transplant, these individuals saw the need for a national organization to develop standards, promote ethics, and increase donations.

Since its beginning, the AATB has been dedicated to improving and saving lives by promoting the safety, quality, and availability of donated human tissue. To fulfill that mission, the **AATB publishes standards and accredits tissue banks, and certifies tissue bank personnel (as specialists)**. The Association also interacts with regulatory agencies and conducts educational meetings.

The AATB’s *Standards for Tissue Banking* contain extensive requirements for donor screening and testing to enhance safety and to avoid disease transmission. With the exception of ocular tissue, AATB-accredited institutions provide most of the commonly used structural tissues for clinical use

in the United States. Given that, the Association is, therefore, extremely interested in any Food and Drug Administration (FDA or agency) proposals potentially affecting the regulation of tissue products, including Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps).

Summary of Concerns

The AATB's concerns about the draft adipose guidance document are threefold. First, the AATB believes that the proposed approach to determining the original relevant characteristics of the tissue represents a significant departure from agency practice and existing regulation. Second, the agency's use of a draft guidance to implement what is essentially an overhaul of regulation in this field falls far short of the depth and breadth of public comment that is needed to ensure thoughtful regulation of tissue and avoid unintended consequences. Even within the limited period provided for comment, the AATB has identified issues with the draft guidance's unduly narrow view of the function of certain tissues, which will limit options for patients and surgeons (especially as it relates to breast reconstruction and augmentation, mesenchymal stem cells (MSCs) from adipose tissue, decellularization of adipose tissue, and cellular therapies). Finally, the AATB urges the FDA to provide additional clarification related to the draft guidance document issued that addresses exceptions to "same surgical procedure". These concerns and additional policy suggestions are described in more detail below.

I. THE DRAFT GUIDANCE DOCUMENT REPRESENTS A SIGNIFICANT DEPARTURE FROM AGENCY PRACTICE AND REGULATION IN THIS AREA.

In the draft adipose guidance document, the FDA defines adipose tissue and the agency's definition of its relevant characteristics. Per the guidance, the FDA generally considers adipose tissue to be a structural tissue, and its relevant characteristics for reconstruction, repair, or replacement relate to its utility to cushion and support the other tissues of the subcutaneous layer (subcutaneum) and skin. Importantly, this approach to determining the original relevant characteristics of the tissue represents an additional, significant departure from agency practice. For example, the FDA has provided examples of processing that amount to more than minimal manipulation of adipose tissue because such processing alters the relevant characteristics stated in the guidance. These include:

1. Processing to isolate non-adipocyte or nonstructural components from adipose tissue (with or without subsequent cell culture or expansion), because this processing entirely removes the connective tissue and structural components of the adipose tissue. For example, isolating stromal vascular fraction, a potential source of adipose-derived stromal/stem cells (MSCs), for clinical therapeutic purposes would be more than minimal manipulation.
2. Processing to remove cellular components to obtain the decellularized extracellular matrix portion of adipose tissue, because removal of these cells leaves very little bulk and alters the ability of the adipose tissue to provide cushioning and support. For example, by this logic, treating adipose with acid/detergent, washing, decellularizing, and grinding the tissue to obtain a homogenous fibrous tissue suspension would be more than minimal manipulation.

In past practice, the FDA addressed questions of minimal manipulation on a case-by-case basis, assessing the intended use of a proposed HCT/P and the relevant characteristics of the product for these uses, to determine whether the processing has altered the original *relevant* characteristics to accomplish these intended uses, such that the processing amounts to minimal manipulation. In essence, what characteristics of a tissue are relevant depended in part on the tissue itself and in part on the intended use of the processed tissue. Under the approach outlined in the draft adipose guidance document, the FDA has intimated that specific tissues have specific relevant characteristics independent of their use. As such, it is likely that many HCT/Ps using adipose tissue will be considered more than minimally manipulated and, thus, subject to regulation beyond section 361 of the Public Health Service Act (PHS Act) and 21 CFR 1271, irrespective of how they are processed. As such, the draft adipose guidance document could render more HCT/Ps subject to regulation as drugs, devices, or biologics under section 351 of the PHS Act, the Food, Drug, and Cosmetic Act (FDCA), and the applicable regulations. These products would be subject to the more stringent regulatory requirements of these authorities, including premarket review requirements.

Based upon AATB's initial review of the draft adipose guidance document, it is apparent that the draft adipose guidance document raises important and complex issues of science and regulatory policy. We also believe that an interactive dialogue between interested parties and FDA could lead to significant improvements in the final version of this guidance. In addition, as further outlined below, we have serious concerns with the draft adipose guidance document because it may dramatically affect current medical practice related to breast reconstruction and augmentation, use of MSCs from adipose tissue, decellularization of adipose tissue, and the use of many cellular therapies utilizing adipose tissue. Finally, in light of the draft adipose guidance document further referencing the draft guidance document issued that addresses exceptions to same surgical procedure, we have additional suggestions to provide enhanced clarity regarding this exception.

II. THE AGENCY'S USE OF A DRAFT GUIDANCE TO OVERHAUL REGULATION OF ADIPOSE TISSUE LEAVES INSUFFICIENT TIME AND OPPORTUNITY FOR AFFECTED STAKEHOLDERS TO COMMENT.

Previously, the AATB submitted preliminary comments to the docket (attached) in which the Association requested that the FDA:

- (1) hold a public workshop on the draft adipose guidance document;
- (2) hold at least one meeting with the AATB on this topic; and
- (3) extend the comment period for the draft adipose guidance document by at least six months.

We appreciate the response from Dr. Midthun from February 10, 2014 in which the agency conveyed that it "would take the request for a public workshop into consideration." With respect to the meeting with AATB on the topic, the agency noted that it would be "inconsistent with FDA's existing process for the consideration of comments on draft guidance documents." Finally, with respect to the extension of the comment period, the agency denied the request for an extension

but noted that individuals could continue to submit comments to the docket after the comment period has closed and referred the AATB to a recent updated document on FDA's website¹ which stated that the FDA intends to invite comments on all related HCT/P guidance documents when it invites comments on the draft guidance document for homologous use. Overall, the AATB appreciates the positive response thus far (especially as it relates to the comment period) and hopes that the agency will opt to have a public workshop to further discuss these relevant issues.

Finally, despite the potential to provide comments to the docket at any time, the AATB has worked diligently to provide these more substantive comments by the initial February 23 deadline. These more substantial comments are still preliminary, due to the lack of time to prepare a more comprehensive response. However, these comments should provide the agency with a sense of the defective nature of the draft adipose guidance document and the need for more dialogue. As written, the implementation of the draft adipose guidance document will negatively impact the access to and delivery of health care to the public.

III. THE DRAFT GUIDANCE'S UNDULY NARROW VIEW OF THE FUNCTION OF CERTAIN TISSUES WILL LIMIT OPTIONS FOR PATIENTS AND SURGEONS.

As more fully outlined below, the AATB has concerns related to FDA's interpretation within this draft adipose guidance document, especially as it relates to breast reconstruction and augmentation, the use of MSCs from adipose tissue, decellularization of adipose tissue, and the ability to continue to provide cellular tissues from adipose. The AATB believes that the more appropriate "basic function" for determining homologous use of breast tissue would recognize the anatomical and secondary sexual (and aesthetic) characteristics of breast tissue and not limit such function and the homologous use solely to lactation. In addition, the AATB is very concerned with the FDA's inappropriate characterization of skin and believes that a more appropriate characterization would recognize that epidermis and dermis perform different functions within the human body. As such, the homologous use of dermis relates, at least in part, to its connective properties and ability to provide flexibility and strength. Finally, the AATB is concerned with the FDA's interpretation that the extraction of cell components from structural tissues like adipose tissue results in a more than minimally manipulated MSC product, while extraction of those same MSCs from nonstructural tissue (such as peripheral blood derived MSCs) may result in a minimally manipulated product. In addition, the AATB has concerns with the FDA's erroneous assessment that cells perform the primary function in a combination structural and nonstructural HCT/P -- a wholly new regulatory concept more suitable for regulation.

Finally, given the potential effect of the interpretation of the draft adipose guidance document on

¹Footnote 1 states the following: "Please note that when FDA issues for comment the draft guidance on homologous use, we also intend to specifically invite comments to FDA's public docket on the previously issued draft guidance documents on the following topics related to human cells, tissue, and cellular and tissue based products (HCT/Ps): minimal manipulation, HCT/Ps from adipose tissue, and same surgical procedure exception." See

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM431409.pdf>

the exception for the same surgical procedure, the AATB provides some additional suggestions for clarity: (1) that the HCT/P be used in a homologous manner to qualify for the exception to the same surgical procedure and (2) that an HCT/P must be regulated solely under section 361 of the PHS Act and 21 CFR 1271 to qualify for the exception.

A. Breast Reconstruction and Augmentation

Following a mastectomy or lumpectomy, there are various options for breast reconstruction. For a lumpectomy (or partial or segmental mastectomy), given the preservation of some breast tissue, the options primarily focus on the use of autograft flaps² (i.e., flaps from the patient's own body). All of these flap procedures utilize the woman's own vascularized tissue, along with her own adipose (i.e., fat) tissue, to help reconstruct the breast.

Following a mastectomy, there are three main options:

- (1) use of the autograft flap procedures (which, similar to the options for lumpectomy, involve a woman's own flaps composed of vascularized tissue and her own adipose tissue, but with different procedures given the amount of reconstruction required³);
- (2) implant-based methods, which tend to use allograft tissue (such as acellular dermal matrixes or ADMs), along with tissue expanders and saline or silicone implants; and
- (3) a combination of the autograft flap procedures with implant-based methods.

Each of these procedures may be complemented with fat grafting which consists of utilizing the patient's own adipose tissue for reinjection at the reconstruction site. This process helps to support the reshaping of the breast and may lead to greater patient satisfaction with respect to the aesthetic appearance of the reconstructed breast.

Unfortunately, the draft adipose guidance document calls into question the use of all of these procedures for breast reconstruction.

i. Use of Adipose Tissue for Flap Procedures

Specifically, with respect to the use of a woman's own adipose tissue (which is essential to any of the flap procedures, whether for lumpectomy or mastectomy), FDA's draft adipose guidance document states the following (from Example B-3) (emphasis added):

Adipose tissue is recovered and processed for injection into the breast, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent, for non-implant breast augmentation. The breast is composed of lobes of glandular tissue and branching ducts, interspersed with fat and ligaments that

²Those flap procedures include fasciocutaneous local tissue advancement flaps, breast parenchymal local flaps, and latissimus dorsi myocutaneous flaps. See <http://emedicine.medscape.com/article/1276001-overview>.

³Those other procedures include Transverse rectus abdominis myocutaneous or TRAM flap, latissimus dorsi flap, and deep inferior epigastric perforator or DIEP flap. Ibid.

support the breast and give it shape; and nerves, blood vessels, and lymphatic tissues. **The basic function of breast tissue is to produce milk (lactation) after childbirth. Because this is not a basic function of adipose tissue, using HCT/Ps from adipose tissues for breast augmentation would generally be considered a non-homologous use.**

Thus, as outlined in this example, any injection of adipose tissue (i.e., fat grafting) would require additional FDA regulation. In addition, while the example may be limited to the adipose tissue which is injected (as compared to potentially surgically implanted as part of a flap procedure), given the FDA's assessment that the basic function of the breast tissue is lactation, any utilization of adipose tissue (which cannot produce milk) would be a non-homologous use and, as such, would likely require additional FDA regulation.

This analysis of homologous use is based on a misapplication of the definition of homologous use found in 21 CFR 1271.3(c). The regulatory definition states that in order to be homologous use, the HCT/P must perform the same basic function or functions in the recipient as the tissue being implanted served in the donor. Adipose tissue is implanted in the recipient to provide additional padding, cushioning, and shape to the breast. These are the same functions adipose tissue serves in the donor, and breast reconstruction is therefore homologous use of adipose tissue.

If adipose tissue were being implanted to provide the patient with additional milk production capability, then this would clearly be a non-homologous use. It is quite clear, however, that adipose tissue is not used in breast reconstruction to provide milk production capability. Instead, adipose tissue is used in breast reconstruction for the clearly homologous (anatomical) purpose of providing additional padding, cushioning and shape to the breast. The use of adipose tissue in breast reconstruction or augmentation is to supplement existing adipose tissue by providing additional padding and cushioning. The breast is a structure which contains lobules which may or may not produce milk. Adipose tissue helps define the anatomical structure of the breast and pads and cushions the lobules.

The fact that adipose tissue does not produce milk is irrelevant to the question whether breast reconstruction is homologous use for adipose tissue. The definition of homologous use does not require that the recipient's tissue that is adjacent to the implant performs the same basic function as the implanted tissue in the donor. Thus, the draft adipose guidance document has turned the regulatory definition of homologous use upside down.

In addition, such an interpretation of the "basic function" of breast tissue (only for lactation) is inconsistent with other governmental positions which support breast augmentation or breast reconstruction in women who are not likely to rely upon such breast tissue for lactation, including coverage of breast reconstruction surgeries in women who are post-menopausal⁴ as well as coverage of breast augmentation coverage for transgendered individuals.^{5,6} Finally, it is

⁴<http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=64&ncdver=1&bc=AgAAQAAAAAAAA&>

⁵<http://kaiserhealthnews.org/news/with-coverage-through-obamacare-transgender-woman-opts-for-surgery/>

inconsistent with Federal law (Public Law 105-277), which requires insurance coverage for breast reconstruction post-mastectomy or lumpectomy irrespective of the woman's childbearing status.⁷

Contrary to FDA's assertion, given that not all women have children, not all women who have children breastfeed, and that the lack of being able to breastfeed is likely not the rationale for why women are opting for breast reconstruction, FDA has an inappropriately narrow scope of the "basic function" of breast tissue. If, however, FDA were to take a more reasoned position related to the "basic function or functions" of breast tissue by recognizing that adipose tissue is the major contributor for volume and shape of the breast⁸ and that breast tissue is a secondary sex organ, then FDA could easily ascertain that adipose tissue for use in breast reconstruction is appropriate. Further, the AATB also notes that the FDA's determination related to "homologous use" is a departure from previous agency interpretations. Under the Good Tissue Practices (GTP) Final Rule, the FDA indicated that the determination of homologous use and the regulations would focus "on the objective intent of the HCT/P's manufacturer for a nonhomologous use," and agreed with commenters that such uses would normally be determined "narrowly" and "by the promotion, labeling, and objective intent of the manufacturer⁹." However, under this new interpretation, the agency's determination is not narrowly tailored but broadly applied. **Thus, under the current guidance document, FDA is inappropriately limiting the use of all flap procedures (which rely upon adipose tissue), as well as any injected adipose tissue, for breast reconstruction procedures.**

ii. Use of Acellular Dermal Matrices (ADMs) for Implant-based Reconstruction

For women who have undergone mastectomies who opt to have breast reconstructive surgery, with increasing frequency, surgeons are electing to use ADMs to assist with implant-based primary breast reconstruction. Of the approximately 95,000 breast reconstructions performed in the United States in 2013, about 68,000 (roughly 72%) were tissue expander-implant-based breast reconstructions.¹⁰ The introduction of ADM has provided surgeons with alternative means of obtaining sufficient soft tissue to cover the tissue expander or implant, thereby alleviating some complications. Several authors, including Salzberg¹¹ and Spear,^{12,13} have reported enhanced outcomes, citing increased fill volumes and improved aesthetic outcomes. According to a recent

⁶http://www.washingtonpost.com/national/health-science/ban-lifted-on-medicare-coverage-for-sex-change-surgery/2014/05/30/28bcd122-e818-11e3-a86b-362fd5443d19_story.html

⁷Women's Health and Cancer Rights Act of 1998, PL 105-277.

⁸<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749276/>

⁹See 66 FR 5447, at 5458 and 5459.

¹⁰American Society of Plastic Surgeons: Reconstructive Breast Surgery Statistics 2013. Available at <http://www.plasticsurgery.org/Documents/news-resources/statistics/2013-statistics/reconstructive-procedures-demographics.pdf>. Accessed 11 September 2015.

¹¹Salzberg CA. Nonexpansive immediate breast reconstruction using human acellular tissue matrix graft (AlloDerm). *Ann Plast Surg.* Jul 2006;57(1):1-5.

¹²Spear SL, Parikh PM, Reisin E, Menon NG. Acellular dermis-assisted breast reconstruction. *Aesthetic Plast Surg.* May 2008;32(3):418-25.

¹³<http://www.plasticsurgery.org/news/past-press-releases/2014-archives/acellular-dermal-matrix-techniques-successful-in-breast-reconstruction-revision-surgery.html>

review article,¹⁴ principal advantages include the potential enhancement of cosmesis in breast reconstruction, amelioration of late or irradiation-induced contracture, improved long-term correction of complications following aesthetic revisionary surgery and cost-savings imparted by the direct-to-implant breast reconstruction model.

Despite the clinical relevance of ADMs for breast reconstruction surgery, as part of the *Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Consideration* (draft minimal manipulation guidance),¹⁵ the FDA states that the “main function” of skin is that it “provides a barrier to retain moisture and protect from infection and/or the **external** environment” (emphasis added). Given that ADMs are derived from a layer of skin (i.e., dermal layer) and that its use for breast reconstruction is internal to the human body, the draft guidance calls into question the use of ADMs for breast reconstruction.

A more accurate moniker for the described function of “skin” would be “epidermis,” given that it is the epidermal layer of the skin that such function is describing, while dermis (or the second layer of the skin) has different functionality. In particular, the dermis is not responsible for providing a barrier to retain moisture and protect from infection or the external environment. Rather, the dermis is “the sensitive connective tissue layer of the skin located below the epidermis, containing nerve endings, sweat and sebaceous glands, and blood and lymph vessels,¹⁶” which (according to the Merck manual¹⁷), provides flexibility and strength. Therefore, the function, at least in part, for dermis relates to its connective properties and ability to provide flexibility and strength. By using this definition of function for dermis, not only would the draft guidance have a better scientific underpinning but it would also ensure that patients are still able to obtain access to ADMs as a breast reconstruction option.

As highlighted above, the draft adipose guidance and draft minimal manipulation guidance documents call into question ALL breast reconstruction procedures. As such, **unless the FDA significantly revises the draft adipose guidance document, women that choose reconstruction after mastectomy or lumpectomy will have reduced access to current surgical procedures that help to restore both physical and emotional well-being after a breast cancer diagnosis.**

B. MSCs from Adipose Tissue

The draft adipose guidance document states the following (emphasis added): “Adipose tissue is sometimes processed by various means (e.g., enzymatic digestion, mechanical disruption, etc.) to isolate the non-adipocyte or nonstructural components of adipose tissue. In some instances, these non-adipocyte or nonstructural components are cultured and expanded. **Processing to isolate**

¹⁴<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3383551/>

¹⁵<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm427795.htm>

¹⁶The American Heritage® Medical Dictionary Copyright © 2007, 2004 by Houghton Mifflin Company. Published by Houghton Mifflin Company. All rights reserved.

¹⁷http://www.merckmanuals.com/home/skin_disorders/biology_of_the_skin/structure_and_function_of_the_skin.html

non-adipocyte or nonstructural components from adipose tissue (with or without subsequent cell culture or expansion) is generally considered more than minimal manipulation. This is because the connective tissue and structural components of the adipose tissue are entirely removed from the non-adipocyte or nonstructural isolates, thereby altering the original relevant characteristics relating to the tissue's utility for reconstruction, repair, or replacement."

The FDA's interpretation that the extraction of cell components from adipose tissue results in a more than minimally manipulated product, as well as a product which is ineligible for the exception to "same surgical procedure," is especially concerning as it is related to the extraction of MSCs. By way of background, MSCs are found in virtually all organs of the body. Bone marrow-derived MSCs (BM-MSCs) were discovered first, and the bone marrow was considered the main source of MSCs for clinical application.¹⁸ Subsequently, MSCs have been isolated from various other sources with the adipose tissue, serving as one of the alternatives to bone marrow. Adipose tissue-derived MSCs (ASCs) can be more easily isolated; this approach is safer, and also, considerably larger amounts of ASCs can be obtained compared with the bone marrow. Despite minor differences between these MSC populations, ASCs seem to be as effective as BM-MSCs in clinical application, and, in some cases, may be better suited than BM-MSCs.¹⁹

Therefore, despite the fact that MSCs, whether they are derived from cord blood, peripheral blood, adipose, amnion, or other sources are (by definition) the same, FDA's interpretation is that the extraction of cell components from adipose tissue (because those are classified solely as structural tissues) results in a more than minimally manipulated MSC product, while extraction of those same MSCs from peripheral blood (which are classified solely as nonstructural tissues) results in a potentially minimally manipulated product. For reasons which are unclear from a scientific perspective, FDA seems to be creating a regulatory hurdle for adipose-derived MSCs (requiring them to be regulated as more than 361 HCT/Ps), while simultaneously allowing peripheral blood derived MSCs (at least under certain conditions) to be regulated as 361 HCT/Ps. It is unclear as to why FDA believes that, from a regulatory standpoint, the source of the MSCs is most important, rather than the "relevant biological characteristics" (the key regulatory requirement for nonstructural tissues).

Thus, for a newly emerging technology – adipose tissue, FDA is by guidance narrowing the regulatory definition of minimal manipulation and not allowing "cell separation" to be considered minimal manipulation for this HCT/P form. And, by doing so, FDA is inappropriately limiting the appropriate clinical application of those products. This approach is questionable as a matter of administrative law, absent notice and comment rulemaking, and is bad policy as well.

¹⁸Note: The AATB acknowledges that, per 21 CFR 1271.3(d)(4), "Minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow)" is not considered a 361 HCT/P and is, instead, receives oversight from the Health Resources and Services Administration. However, it is important, in this context, to highlight the similarities of MSCs, despite their origin and regulatory framework.

¹⁹<http://www.ncbi.nlm.nih.gov/pubmed/22468918>

C. Decellularizing Adipose Tissue

Unfortunately, as part of the draft adipose guidance document, the FDA states that “[a]dipose tissue may also be processed to remove cellular components to obtain the decellularized extracellular matrix portion of adipose tissue.

Adipose tissue is a loose fibrous connective tissue that occupies the space between organs and tissues and provides structural and metabolic support. After the removal of the adipocytes that reside in the matrix, the framework of fibrous tissue of structural collagenous proteins that was originally surrounding the cells is maintained and continues to provide structure, support and cushioning.^{20,21} For allogeneic transplantation, cell removal is essential to insure safety of the resulting matrix and is a process that has been routinely performed with other tissues regulated as HCT/P such as dermis and bone. Multiple reports in literature demonstrate that decellularization of adipose tissue minimizes the potential of immune response upon implantation and provides a matrix that is safe and retains the essential endogenous proteins for host cell attachment and infiltration.^{22,23} The resulting adipose matrix preserves its structural, conductive properties and can be injected or implanted to add padding and cushioning to soft tissues.^{24,25,26} Adipose tissue processed this way generally is considered more than minimally manipulated because removal of the cells leaves very little bulk and alters the ability of the adipose tissue to provide cushioning and support.”

The AATB has serious concerns with these statements. Determining that decellularized adipose tissue is more than minimally manipulated is incongruous with other existing acellular tissues currently recognized as 361 HCT/Ps. The processing required to remove lipids and cells from adipose is similar to the processing of acellular dermal matrix. And, the FDA acknowledges in a separate draft guidance document that “extraction or separation of cells from structural tissue in which the remaining structural tissue’s relevant characteristics relating to reconstruction, repair, or replacement remain unchanged generally would be considered minimal manipulation.²⁷”

²⁰Lockwood TE. Superficial fascial system (SFS) of the trunk and extremities: a new concept. *Plast Reconstr Surg*. 1991 Jun;87(6):1009-18.

²¹ Song AY, Askari M, Azemi E, Alber S, Hurwitz DJ, Marra KG, Shestak KC, Debski R, Rubin JP. Biomechanical properties of the superficial fascial system. *Aesthet Surg J*. 2006 Jul-Aug;26(4):395-403.

²²Flynn LE. The use of decellularized adipose tissue to provide an inductive microenvironment for the adipogenic differentiation of human adipose-derived stem cells. *Biomaterials*. 2010 Jun;31(17):4715-24.

²³Brown BN, Freund JM, Han L, Rubin JP, Reing JE, Jeffries EM, Wolf MT, Tottey S, Barnes CA, Ratner BD, Badylak SF. Comparison of three methods for the derivation of a biologic scaffold composed of adipose tissue extracellular matrix. *Tissue Eng Part C Methods*. 2011 Apr;17(4):411-21.

²⁴ Wu I, Nahas Z, Kimmerling KA, Rosson GD, Elisseeff JH. An injectable adipose matrix for soft-tissue reconstruction. *Plast Reconstr Surg*. 2012 Jun;129(6):1247-57.

²⁵ Omid E, Fuetterer L, Reza Mousavi S, Armstrong RC, Flynn LE, Samani A. Characterization and assessment of hyperelastic and elastic properties of decellularized human adipose tissues. *J Biomech*. 2014 Nov 28;47(15):3657-63.

²⁶ Wang L, Johnson JA, Zhang Q, Beahm EK. Combining decellularized human adipose tissue extracellular matrix and adipose-derived stem cells for adipose tissue engineering. *Acta Biomater*. 2013 Nov;9(11):8921-31.

²⁷<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm427692.htm>

The draft guidance states that when cells are isolated from structural tissue, the definition of minimal manipulation applicable to structural tissue should be applied to the cells. Thus, according to the draft guidance in example 10-1,²⁸ if cells are isolated from adipose tissue, and the cells are intended to be the HCT/P, the cells are more than minimally manipulated because removing the cells alters the remaining adipose tissue's ability to provide cushioning and support. Evidently, according to the draft guidance, the only cells that could be considered minimally manipulated are derived from structural tissue with original characteristics that are not altered by the cell isolation or are derived from nonstructural tissue. No scientific basis for this limitation on the kinds of cells that may be considered minimally manipulated is provided. Moreover, this is an entirely new limitation added to the regulations that should not be implemented via a guidance document.

Thus, once again, FDA is narrowing the regulatory definition of minimal manipulation and not allowing “cell separation” to be considered minimal manipulation for this HCT/P form. Therefore, for all of the reasons we have detailed above, **the AATB requests that the FDA revise its position that removal of cellular components from adipose tissue is considered more than minimal manipulation.**

D. Cellular Tissues

In parsing the phrasing of the draft adipose guidance document, the AATB has concluded that the FDA's intent is that products which contain both structural tissues as well as cells²⁹ are generally considered more than minimally manipulated because the HCT/P is dependent upon the metabolic activity of living cells for its primary function. This is primarily elucidated from question D in the adipose guidance document³⁰ examining questions related to whether stem cells

²⁸“Original relevant characteristics of adipose tissue, a structural tissue, to pad and cushion against shocks generally include its bulk and lipid storage capacity. A manufacturer recovers adipose tissue by tumescent liposuction and processes the adipose tissue to isolate cellular components, commonly referred to as stromal vascular fraction, which is considered a potential source of adipose-derived stromal/stem cells. The HCT/P generally is considered more than minimally manipulated because the processing breaks down and eliminates the structural components that provide cushioning and support, thereby altering the original relevant characteristics of the HCT/P relating to its utility for reconstruction, repair, or replacement.”

²⁹Note: Such cells are not from the original structural tissue but another tissue source, given that FDA's draft guidance states that “[s]tructural tissue is composed of structural components and cells, and those cells are part of the structural tissue. . . .”

³⁰If the HCT/P from adipose tissue has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and is not intended for autologous use or use by a first- or second-degree blood relative, then it does not meet the criteria in 21 CFR 1271.10(a) for regulation solely under section 361 of the PHS Act and the regulations in Part 1271. Autologous use is the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered (21 CFR 1271.3(a)).

Example D-1: Adipose tissue is recovered from an unrelated allogeneic donor. Stem cells are isolated from that adipose tissue and seeded onto a bone scaffold for repair of pathologically or surgically created bony voids. The manufacturer advertises the stem cells as contributing to the primary function of filling, augmenting, or repairing the bone void by giving rise to osteoblasts, which mineralize the allograft and increase its durability; this function depends on the metabolic activity of the cells. The HCT/P from adipose tissue is dependent upon the metabolic activity of living cells for its described primary function of repairing the bone void and it is not intended for autologous use or allogeneic use in a first- or second-degree blood relative. Therefore, the HCT/P would generally be considered not to meet the criteria in 21 CFR 1271.10(a) for regulation solely under section 361 of the PHS Act and the regulations in Part 1271.

from adipose tissue (cells) seeded onto a bone scaffold (structural tissue) would give rise to a more than minimally manipulated HCT/P. Despite the FDA's conclusion, the mere presence of the cells does not necessarily mean that the HCT/P is dependent upon the metabolic activity of the living cells for its primary function. Rather, depending on the HCT/P, the cells may be supporting the primary function of the scaffolding (e.g., bone regrowth). Further, this statement is contradictory to agency practice, given that the following tissue products containing live cells and a structural component have been safely regulated as 361 HCT/Ps for decades: fresh and cryopreserved skin used for burn patients; fresh cartilage grafts used for repair of cartilage defects; osteoarticular (OA) allografts used in limb preservation procedures and cancellous bone containing live cells. More recently, subsequent to discussions with the FDA related to an Untitled Letter (issued in October 2013³¹), according to an SEC filing,³² Osiris is currently marketing a 361 HCT/P Ovation OS,³³ which includes structural components (i.e., bone matrix), as well as nonstructural components (i.e., bone supportive growth factors, viable MSCs and osteoblasts, and growth factors). **The statement that the cells perform the primary function in a combination structural and nonstructural HCT/P is a wholly new regulatory concept that should be more explicitly explained via regulation if that is the FDA's intent.**

IV. THE FOOD AND DRUG ADMINISTRATION SHOULD PROVIDE ADDITIONAL CLARIFICATION RELATED TO THE EXCEPTION TO SAME SURGICAL PROCEDURE.

Previously, the AATB commented on the FDA's guidance document titled *Draft Guidance for Industry: Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception*³⁴ (draft same surgical guidance document). However, in further reviewing the draft adipose guidance document (which also discusses the exception to same surgical procedure), we request additional clarifications regarding the exception.

In both the draft adipose guidance document and the draft same surgical guidance document, FDA states that the exception applies if establishments meet these three criteria:

- (1) Remove and implant the HCT/Ps into the same individual from whom they were removed (autologous use);
- (2) Implant the HCT/Ps within the same surgical procedure; and
- (3) The HCT/Ps remain "such HCT/Ps;" they are in their original form.³⁵

We would like the FDA to clarify that an HCT/P must be used in a homologous manner to qualify for the exception to the same surgical procedure. The criteria do not explicitly state that the HCT/P must be used in a homologous manner. This is particularly relevant with respect

³¹<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/UntitledLetters/ucm371540.htm>

³²http://www.getfilings.com/sec-filings/131021/OSIRIS-THERAPEUTICS-INC_8-K/

³³<http://www.osiris.com/ovationOS>

³⁴<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm419911.htm>

³⁵Ibid.

to the use of adipose tissue and applications which would fall within the exception. As part of the adipose draft guidance document, as mentioned above, the FDA had indicated that the use of adipose tissue to treat bone and joint disease³⁶ as well as breast augmentation³⁷ is considered non-homologous use. But, the FDA has not clarified whether homologous use is a requirement for the exception, even if it is a requirement for an HCT/P to be regulated solely under section 361 of the PHS Act and 21 CFR 1271 (361 HCT/P). And, we request that the agency explicitly do so.

In addition, we would like the FDA to clarify that an HCT/P must be regulated solely under section 361 of the PHS Act and 21 CFR 1271 to qualify for the exception to same surgical procedure. Again, the exception does not explicitly require that the HCT/P be regulated solely as a 361 HCT/P. However, one could potentially interpret the specified exceptions outlined under 21 CFR 1271.15 (including the same surgical exception) to only apply to HCT/Ps otherwise solely regulated under 21 CFR 1271. Thus, we request that the agency explicitly provide that the exception to same surgical procedure only applies to 361 HCT/Ps.

V. RECOMMENDATIONS AND CONCLUSION

As previously noted, the AATB has concerns related to FDA's interpretation within this draft adipose guidance document, especially as it relates to breast reconstruction and augmentation, the use of MSCs from adipose tissue, decellularization of adipose tissue, and the ability to continue to provide cellular tissues from adipose. Specifically, the AATB believes that the more appropriate "basic function" for determining homologous use of breast tissue would recognize the anatomical and secondary sexual characteristics of breast tissue, the current presence of adipose tissue within the breast, and not limit such function and the homologous use solely to lactation.

In addition, the AATB is very concerned with the FDA's inappropriate characterization of skin and believes that a more appropriate characterization would recognize that epidermis and dermis perform different functions for the human body. The AATB is also concerned with the FDA's interpretation that the extraction of cell components from structural tissues like adipose tissue results in a more than minimally manipulated MSC product and one that is not eligible for the exception to same surgical procedure, while extraction of those same MSCs from nonstructural tissue (such as peripheral blood derived MSCs) may result in a minimally manipulated product which is also eligible for the exception. The AATB has additional concerns with the FDA's erroneous assessment that cells perform the primary function in a combination structural and

³⁶Example B-2: Adipose tissue is recovered and processed for use, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent, to treat bone and joint disease. Because adipose tissue does not perform this function in the donor, using HCT/Ps from adipose tissue to treat bone and joint disease is generally considered a non-homologous use.

³⁷Example B-3: Adipose tissue is recovered and processed for injection into the breast, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent, for non-implant breast augmentation. The breast is composed of lobes of glandular tissue and branching ducts, interspersed with fat and ligaments that support the breast and give it shape; and nerves, blood vessels, and lymphatic tissues. The basic function of breast tissue is to produce milk (lactation) after childbirth. Because this is not a basic function of adipose tissue, using HCT/Ps from adipose tissues for breast augmentation would generally be considered a non-homologous use.

nonstructural HCT/P -- a wholly new regulatory concept more suitable for regulation.

Given the potential effect of the interpretation of the draft adipose guidance document on the exception to same surgical procedure, the AATB also requests that the FDA clarify that, to qualify for the exception, an HCT/P must be: (1) used in a homologous manner and (2) regulated solely under section 361 of the PHS Act and 21 CFR 1271.

Finally, we believe that an interactive dialogue between interested parties and the FDA could lead to significant improvements in the final version of each guidance document.

For these reasons, we re-iterate our previous request that the FDA hold a public workshop on the draft guidance documents, as well as maintain the FDA's previous commitment to provide an additional comment period for all HCT/P-related draft guidance documents as part of the agency's release of the draft homologous use guidance document.

The AATB stands ready and willing to assist the FDA with its deliberations in any way that the agency deems appropriate.

Respectfully,

A handwritten signature in blue ink, appearing to read "Frank S. Wilton".

Frank S. Wilton
Chief Executive Officer

Cc: Margaret Hamburg, MD; Karen Midthun, MD; Celia Witten, MD, PhD; Mary Malarkey; Lori J. Churchyard; Melissa Segal; Angela Krueger; Leigh Hayes; Pauline Cottrell

Attachment: Previous letter