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Food and Drug Administration
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**Docket No. FDA-2014-D-1856: Comments to the Draft Guidance Document Titled "Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry" (December 2014)**

Dear Sirs and Madams:

IFATS, the International Federation of Adipose Therapeutics and Sciences, was founded in 2003 by pioneering adipose stem cell biologists and clinician–scientists. Since that time, attendance at the IFATS annual meetings has grown by nearly ten-fold, drawing members from 40 countries in North America, Europe, Africa, the Middle East, Asia, Australia, and Central and South America. The IFATS annual meeting serves as a unique scientific forum that brings together basic scientists, clinicians, translational researchers, and regulatory and biotech representatives to discuss the latest advances in adipose tissue biology and therapeutics. IFATS is formally aligned with the prestigious journal, *Stem Cells,* where a number of the IFATS members serve on the journal's editorial board, as well as on the editorial board of its sister journal, *Stem Cells Translational Medicine*. Furthermore, in collaboration with the International Society for Cellular Therapy (ISCT), IFATS has provided the scientific community with a detailed description and definition of adipose derived cells (both stromal vascular fraction, or SVF, and adipose-derived stromal/stem cells, or ASCs) in a formal publication in *Cytotherapy.*[1] In addition to including leading basic adipose biologists from around the world, the IFATS membership also includes cardiologists, immunologists, neuroscientists, plastic and reconstructive surgeons, orthopedists, and vascular surgeons who are at the forefront of regenerative medical applications involving adipose tissue and cells. As such, IFATS has the necessary expertise to serve as a resource and think-tank for regulatory agencies examining the safety and efficacy of adipose tissue-related products and therapies. IFATS is committed to patient safety in the translation of new adipose therapies.

IFATS respectfully submits comments to the Draft Guidance Document Titled "Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry" (December 2014).

IFATS requests the FDA to reconsider three main points in the Draft Guidance document. These are 1) the categorization of adipose exclusively and/or primarily as structural; 2) the concept that decellularizing adipose tissue represents more than minimal manipulation; and, 3) the concept that adipose HCT/P's for breast applications would represent non-homologous use.

**Structural Classification of Adipose Tissue**

The FDA defines HCT/P as "Structural" or "Nonstructural" under 21 CFR 1271.10(a) as:

"4) Either:

i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function"

We request that the classification of adipose tissue be expanded from exclusively structural to include both structural and/or nonstructural use depending on the intended application. A rigid structural definition would focus solely on adipose tissue "*characteristics for reconstruction, repair, or replacement that relate to its utility to cushion and support the other tissues in the subcutaneous layer (subcutaneum) and skin.*" While this is an important element, there should be equal emphasis on both the structural and nonstructural functions of adipose tissue.

To this point, adipose tissue is a functional unit composed of different cell types, each of which has characteristic nonstructural functions. Cell types include adipocytes, stem and progenitor cells, granulocytes, monocytes, lymphocytes, endothelial cells, pericytes, and stromal cells.[1]

Moreover, adipose is a dynamic tissue in which resident cellular components contribute to nonstructural tissue healing and repair.[2]

We present examples of nonstructural properties of adipose tissue:

**Adipocytes Appear in Bone Marrow and Have Nonstructural Functions**

The FDA has exempted bone marrow and blood products from regulation under sections 351 and 361. That adipose tissue is present in bone marrow and serves numerous nonstructural functions has been well recognized for over four decades. These nonstructural functions include:[3]

a. Pre-adipocytes as mesenchymal cells in bone marrow
    i. Bone marrow contains a spectrum of mesenchymal cells, including pre-adipocytes. When exposed to certain cytokines, pre-adipocytes can differentiate into adipocytes, osteoblasts and chondrocytes depending on the organism's current needs. This is a nonstructural function.

b. Bone marrow adipocytes and lympho-hematopoiesis

i. Pre-adipocytes and adipocytes regulate lympho-hematopoiesis and enable the bone marrow microenvironment to regulate proliferation within blood cell lineages so as to favor erythropoiesis rather than myelopoiesis. This is a nonstructural function.

ii. Adipocytes also contain metabolic precursors and energy for the purpose of lympho-hematopoiesis. This physiologic process has nothing to do with providing cushioning and support and therefore is not properly described as a structural use of adipose cells. This is a nonstructural function.

iii. Adipocytes contain cholesterol esters, triglycerides and lipoproteins which are essential to the synthesis of plasma membranes during blood cell development. This is a nonstructural function.

c. Bone marrow and extramedullary adipocytes and energy metabolism:

i. The energy reserves found in adipocytes assist in homeostatic control of temperature in the bone marrow microenvironment and throughout the body. This is a nonstructural function.

ii. Bone marrow and extramedullary adipocytes therefore contribute to the overall energy metabolism of the organism. This is a nonstructural function.

d. Bone marrow adipose tissue as an endocrine organ: [4]

i. Bone marrow adipose tissue (MAT) increases during caloric restriction (CR), is responsible for increased adipokine secretion, and alters skeletal muscle adaptation to CR. These and other observations identify MAT as an endocrine organ. This is a nonstructural function.

**Adipocytes and Adipose Stromal Cells within Adipose Tissue Depots Have Numerous Nonstructural Functions**

We recognize the structural (passive) Roles of adipose tissue, including:

- Insulation (subcutaneous fat)
- Mechanical (infrapatellar fat or Hoffa's fat pad of the knee joint)
- Space occupying (bone marrow fat in the elderly)[5]

However, the multiple nonstructural roles of adipose tissue cannot be ignored. From the first references of fat grafting in the world literature in the late 19th century, more than a century ago, surgeons recognized the value of fat for not only providing structure and cushioning, but also for the potential fat has to heal tissues into which it is grafted. In 1893 Gustav Neuber was the first to describe the use of fat grafts. He transplanted fat to the orbital region to heal the

adherent scarring which was the sequela of osteomyelitis. He noted the transformation of facial scarring to more normal appearing skin and subcutaneous tissues.[6]

In 1912, Holländer described the treatment of a breast scar with fat injections. He instructs the reader to sharply release the adhesions between the bone and skin and place fat to prevent the recurrence of the scarring.[7]

In 1926, Charles Conrad Miller[8] developed a new system for injection of fat grafts. Miller described 36 cases of correcting cicatricial contraction on the face and neck with only "moderate shrinkage of the fat. He reported treating with fat grafts "two cases of very persistent parotid fistulas…which defied all other methods of treatment—with excellent results" which he followed for over five years.

Favorable outcomes in the germinal period of fat grafting (1893 – 1926) resulted from fat's transformational nonstructural uses in addition to its structural uses to provide cushioning and support. Historically and currently, therefore, fat grafting has been used not just for filling or structure, but also for the nonstructural repair of the tissues into which it is placed.[8]

The scientific community has expanded the scope of its understanding of the diverse roles of adipose tissue.[9] A critical factor in shifting the scientific community's appreciation of the role of adipose tissue was the discovery of the first widely accepted adipokine, leptin, in the mid-1990's.[10] The realization that adipose tissue secreted proteins with systemic actions on hematopoietic, reproductive, metabolic, and other cells and tissues demonstrated unequivocally that it met the definition of a true "endocrine" organ.[11, 12]

**It is now well-recognized that the many nonstructural roles of adipose tissue include the following:**

Endocrine

- Glucose and lipid metabolism and control via adipokine secretion[13]
- Reproductive and endocrine control via adipokine secretion [14-16]
- Immunomodulatory and immunosuppressive systemic control via cytokine and protein factor secretion[17-22]

Paracrine

- Angiogenic control via vasculogenic cytokine secretion[22-26]
- Hematopoietic control via cytokine secretion locally and systemically[27]
- Neurogenesis via secretion of cytokine factors [28-34]

Hematopoietic potential of adipose stem cells in adipose depots

- Serving as a reservoir for hematopoietic and lymphoid progenitor cells similar to the bone marrow[18, 35, 36]
- Thermogenesis (brown and beige fat) [37-41]

- Energy reservoir (white adipose depots)[42,43]

Promoting Lactation

- Fat serves as an energy reservoir and nutrient supply for breast epithelial cells. Adipose tissue in the breast undergoes profound changes during pregnancy and parturition in younger females. As pregnancy progresses, the breast epithelium proliferates in a branching manner to occupy the majority of the adjacent adipose tissue and stroma. At parturition, the epithelial cells draw on the lipid reserves of adipocytes within immediate proximity and secrete these nutrients into the milk available to the newborn infant during suckling. As long as the mother continues to breast feed the infant, the epithelial cells remain viable and active; however, if suckling is discontinued for periods of 24 to 48 hours, the epithelial cells undergo rapid apoptosis, leaving pre-adipocytes and adipocytes as the predominant cell within the breast parenchyma. While the presence and organization of epithelial cells within the breast tissue provide it with a unique architecture, the mammary adipocytes themselves show remarkable similarity to adipocytes from elsewhere in the body. Thus, the mammary fat pad displays homology to other adipose tissue depots.[44]

Regenerative Function

- Fat tissue is a source of local and circulating multipotent progenitor cells capable of repairing and regenerating damaged tissues such as irradiated skin, alleviating fibrotic changes, improving mobility and vitality, and repairing structures such as hair follicles and lymphatics.[45-47]
- Multipotent progenitor cells may be recruited for repair and regeneration of ischemic damage induced by acute myocardial infarction.[48]
- The adipose mesenchymal stem cells also are present in a perivascular position, and serve as progenitors of cells which contribute to vascular network formation and vascular structures.[49-52] As such, the adipose mesenchymal stem cells are located in a position and serve a role shared by mesenchymal stem cells located in nearly all body tissues[53], and their provision to a range of tissues to enhance vascularity or perfusion constitutes the provision of a cell which is precisely homologous to that already present in the tissue.
- Adipose mesenchymal stem cells induce a monocyte/macrophage phenotype switch from M1 to M2 macrophages, contributing to improved infarct healing postacute myocardial infarction. [54]

**Additional specific examples of adipose tissue's nonstructural uses:**

1) Modulation of scarring
   a) Treating old burn scars [55-57]
   b) Release of adherent scarring/fasciotomies [58]
   c) Modulation of scarring in primary cleft lip repair[59]
2) Reversal of damage caused by therapeutic radiation [60-63]
   *For BOTH*
   a) Structural (filling tissue defect) uses, and
   b) Nonstructural tissue repair and regenerative uses [60]
3) Treating acute thermal injury [64, 65]
4) Treating Pain
   a) Mitigating implant breast pain[66]
   b) Improving post-mastectomy pain [67-69]
   c) Improving lower back pain[70]
   d) Nerve or neuroma repair[71, 72]
5) Healing ulcers
   a) Treating pressure sores[73]
   b) Treating chronic non-healing anal fissures and associated stenosis [74]
6) Treating vocal fold paralysis [75-77]
7) Treating velopharyngeal insufficiency [78]
8) Treating scleroderma and systemic sclerosis[79]
9) Treating Dupuytren's disease of the hand [80, 81]
10) Treating Raynaud's phenomenon: After fat grafting, there is improved symptomatology with evidence suggestive of measurably increased perfusion [82]
11) Improving tendon repair
   a) Use of adipose tissue to assist in tenolysis for foot and hand tendon adherence[83]
   b) Treating adherent tendons and joints in burn patients with fat graft[84]
12) Preventing osseous reunion of skull defects [85]
13) Improving the quality of skin[86]

**The Impact of Categorizing Adipose as Exclusively Structural**

Defining all use of adipose tissue as structural despite its many nonstructural uses is particularly problematic in terms of:

1. Defining minimal manipulation
2. Determining homologous use
3. Applying section 351's "same surgical procedure" exception

**Minimal Manipulation**

21 CFR 1271.3(f) distinguishes minimal manipulation of structural tissue from minimal manipulation of nonstructural cells and tissues.

- Minimal manipulation of structural tissue consists of processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.

- For cells and nonstructural tissues that have "a systemic effect or is dependent upon the metabolic activity of living cells for its primary function," minimal manipulation constitutes processing that does not alter "relevant biological characteristics."

Treating all adipose HCT/Ps solely as structural would define minimal manipulation in terms of tissue or cell characteristics relevant to structural properties only. As clearly demonstrated by the many nonstructural uses presented above, applying the concept of minimal manipulation based on cushioning and padding has no relevance when the intended use is nonstructural. Failing to evaluate the characteristics that the FDA has deemed relevant to non-structural use would consequently prevent the proper assessment of risk for application of the tissue. For nonstructural adipose therapy, this could potentially increase risk while simultaneously restricting patient access to therapies.

**Homologous Use**

The FDA defines homologous use as serving the same basic function in the recipient as in the donor. Thus, to qualify as homologous use under this definition, adipose tissue that serves a nonstructural function in the donor must be used for that same basic purpose in the recipient. The Draft Guidance, however, would again use a structural definition that does not fit nonstructural use. This would preclude all nonstructural uses from qualifying as homologous even though they would otherwise fit FDA's definition of homologous.

**Same Surgical Procedure Exception**

To qualify for the "same surgical procedure" exception to section 351, the HCT/P must be both minimally manipulated and for homologous use.

As previously explained, subjecting all adipose tissue to the definition of structural tissue would seem to preclude virtually all nonstructural uses from qualifying as minimally manipulated and for homologous use. This would restrict patient access to therapies that are, in fact, minimally manipulated when evaluated in terms of characteristics relevant to intended use, and used for a homologous nonstructural purpose.

**Decellularized Adipose Tissue and Minimal Manipulation**

Even when adipose tissue is classified as structural, the concept that decellularizing the tissue alters its ability to perform its structural functions and constitutes more than minimal manipulation is unfounded. While adipose tissue is recognized as containing adipocytes, much of the structure of the tissue is imparted by a dense and interconnected framework of fibrous tissue. This fibrous skeleton imparts structural properties irrespective of the presence of cells or lipid [87]and demonstrate notable biomechanical properties of tensile strength and elasticity, both important for padding and cushioning.[88] This collagen skeleton within adipose tissue remains after cells are removed, and multiple reports[89-93] have demonstrated that de-cellularized adipose tissue retains structural properties and can be injected to impart padding and cushioning of soft tissues. Moreover, the processing of dermis to an acellular form, a well-recognized HCT/P, is comparable to the process of removing cells from adipose tissue. Since decellularization of dermis is regulated under section 361, decellularization of adipose tissue should also be regulated under section 361.

**Special Considerations for Adipose Tissue and Homologous Use relative to Breast Applications**

In Example B-3 of the Draft Guidance, application of adipose based HCT/Ps to the breast is declared non-homologous use because "*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 general be considered a non-homologous use*. " While lactation is a function of the breast, this narrow classification ignores the function of the breast as a secondary sex organ and vital component of a woman's body image. Indeed, lactation is only utilized in women who have children, and for a limited time span. The important role of the breast as a secondary sex organ is recognized by federal legislation and mandates a woman's right to breast reconstruction after mastectomy. Importantly, breast reconstruction is often performed in post-menopausal women who will not need to lactate. Additionally, breast reconstruction after mastectomy restores the breast mound but never results in the ability to lactate, and this procedure is commonly performed by transferring adipose tissue flaps. Additionally, fat grafting for breast reconstruction is now a common clinical practice. When considering that the breast is largely composed of fat tissue, applying fat based HCT/Ps to restore breast shape should be clearly considered homologous use.

Importantly, a very common and state-of-the-art method of breast reconstruction involves autologous free tissue flap transfer (free flap breast reconstruction).[94-96] These tissue flaps are completely removed from the body before implanting, and would therefore be considered an HCT/P. By classifying adipose based tissues as non-homologous when applied to the breast, an entire class of Centers for Medicare & Medicaid Services (CMS) approved breast reconstruction procedures would be at risk for not complying with the same surgical procedure exception. Additionally, this would be in opposition to federal legislation that recognizes a woman's right to breast reconstruction after mastectomy by mandating insurance coverage for the procedures described above.

IFATS wishes to thank the FDA for the opportunity to comment on this draft guidance document. As a multidisciplinary scientific society composed of adipose stem cell biologists and clinician–scientists, we would like the opportunity to engage in dialogue with the FDA. We respectfully request that representatives of the FDA, including the Director of CBER, meet with members of IFATS to further discuss issues surrounding the advancement of adipose based therapies.

**Respectfully Submitted by IFATS**


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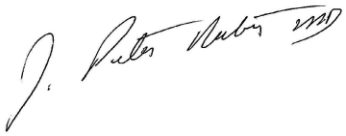

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