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THE PLASTIC SURGERY FOUNDATION

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

Docket #FDA-2014-D-1856 (HCT/Ps)

Dear Madams and Sirs:

The American Society of Plastic Surgeons (ASPS) appreciates the opportunity to provide comments on the *Draft Guidance for Human Cells, Tissues, and Cellular and Tissue Based Products from Adipose Tissue* [hereafter "draft guidance"], published on December 24, 2014 by the Food and Drug Administration.

The ASPS is the largest association of plastic surgeons in the world, representing more than 7,000 members and 94 percent of all American Board of Plastic Surgery board-certified plastic surgeons in the United States. Plastic surgeons provide highly skilled surgical services that improve both the functional capacity and quality of life of patients. These services include the treatment of congenital deformities, burn injuries, traumatic injuries, hand conditions, and cancer. The ASPS promotes the highest quality patient care, professional and ethical standards, and supports education, research, and public service activities of plastic surgeons.

ASPS shares the FDA's commitment to providing patients with access to safe and effective treatments. Additionally, we respect the agency's tiered, risk-based framework to balance the need to protect patient safety with the need for therapeutic alternatives. It is in all our best interest to be certain that all HCT/Ps are appropriately regulated.

These shared objectives now prompt ASPS to submit these comments to express our serious concerns about the FDA's draft guidance.

For the reasons explained in more detail below, ASPS respectfully requests the FDA to:

- Expand its categorization of adipose tissue from exclusively structural to both structural and non-structural, depending on its intended use. This would reflect the many and often primary nonstructural functions of adipose-derived human cells, tissues, and cellular and tissue-based products or HCT/Ps. Treating all adipose HCT/Ps as structural would define minimal manipulation in terms of tissue or cell characteristics relevant to structural utility only. Where the intended use is not structural, however, it is not relevant, safe or even possible to assess the degree of manipulation of the HCT/P's biological characteristics if only structural characteristics are considered. This revision is further needed to satisfy the requirements of the same surgical exception under 21 CFR 1271.15(b), which many of our physicians rely on to provide our patients access to adipose-derived HCT/Ps.

- Regarding adipose tissue's structural functions, revise its position that de-cellularizing the adipose tissue necessarily diminishes its ability to perform its structural functions.

1. Regarding adipose tissue's structural functions, revise its position that fat grafting for the purpose of breast reconstruction constitutes non-homologous use simply because it does not restore the ability to lactate. This would reflect the fact that lactation is not the breast's sole or, for most of a woman's life, even its major function. Throughout a woman's adolescence and adulthood, the breast functions mainly as a secondary sex organ. Consequently, our surgeons do not perform breast reconstruction to re-establish a woman's ability to lactate. Adipose tissue is a natural component of breast tissue and, when used for reconstruction, performs the structural function of providing cushioning and support. In conjunction with improving physical appearance, breast reconstruction plays a therapeutic role in mitigating the adverse psychosocial sequela of mastectomy. Due to the importance of addressing a woman's emotional well-being, social functioning and psychosocial health, Federal law mandates insurance coverage of breast reconstruction following mastectomy.[1]

- Revise its position that stromal vascular fraction (SVF) involves more than minimal manipulation by recognizing that the SVF process primarily requires centrifugation and cell isolation – processes previously determined by the FDA to qualify for minimal manipulation.[2]

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I. Expand its categorization of adipose tissue from exclusively structural to both structural and non-structural, depending on its intended use.

FDA describes adipose tissue as "a connective tissue composed of clusters of adipocytes and other cells surrounded by a reticular fiber network and interspersed with small blood vessels, divided into lobes and lobules by connective tissue septa." It then defines adipose-derived HCT/Ps solely in terms of its structural function and, in doing so, ignores half of its previous definition of adipose tissue. The latter focuses exclusively on its "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" (emphasis added) when determining what qualifies as minimal manipulation.

Historical uses of adipose tissue. For more than a century, adipose tissue has been used for an array of therapeutic applications that do not cushion or support and, consequently, do not fit FDA's definition of the "main function" of adipose tissue. In many instances, the primary function of adipocytes, the reticular fiber network and small blood vessels in adipose tissue is biological and non-structural. A wide variety of therapies – many of which have been safely used for decades – fall squarely within FDA's definition of non-structural tissue because the HCT/P has "a systemic effect or is dependent upon the metabolic activity of living cells for its primary function.[3]"

- The use of fat grafting was first reported in 1893 when Gustav Neuber transplanted adipose from the arm to the lower orbit to in order to improve unsightly, depressed, adherent scars.[4] The fat graft served both structural and biological functions in releasing the adhesions with a good outcome.
- In 1910, Eugene Holländer was the first to describe fat grafting by injection in order to modulate scars specifically from the bone to the skin.[5]
- In 1912, Holländer published photographs of fat grafting by injection which was also done to modulate scars specifically from the bone to the skin. The pictures depicted the treatment of a breast and instructed the reader to sharply release the adhesions between the bone and skin in order to place fat and prevent recurrence.[6]
- In 1919, Erich Lexer published a two-volume book, which devoted 300 pages to fat grafting. He described fat grafting to the breast, and extensive use of fat grafting to aid in orthopedic procedures. He used fat grafts not only for cushioning and support, but also to improve gliding in tendon injuries during a tenolysis. This is not unlike the current treatment of Dupuytren's with infiltrated fat grafts at the same time as release of the adherent tissues.[7]
- In 1920, Sir Harold Gilles published a book based on his experiences in WWI entitled "Plastic Surgery of the Face based on selected cases of War Injuries of the Face". In the text, he discusses the healing ability of fat in many of the cases presented. He notes that for gashing wounds to the face involving mucosa, bone, nerves and skin, "[t]he good result obtained was due, I think, to the use of fat flaps."[8]
- In 1922, the literature introduces the use of fat grafts to repair intestinal ruptures, bladder, liver and uterine injuries.[9]
- In 1926, Conrad Miller described the use of fat grafts to treat 36 cases of cicatricial contracture of the face and neck with only "moderate shrinkage of the fat."[10] He also reported treating "two cases of very persistent parotid fistulas…which defied all other methods of treatment" with excellent results which he followed for five years.
- Thus, favorable outcomes in all of these studies (1893 – 1926) resulted from fat's transformational and therefore biological functions as opposed to its structural functions of providing cushioning and support.

Favorable outcomes in the germinal period of fat grafting (1893 – 1926) resulted from fat's transformational and, therefore, biological functions, in addition to its structural functions of providing cushioning and support. Fat grafting has long been used not just for filling or structure, but also for repair, and there is an extensive historical and contemporary body of evidence that supports the understanding that adipose tissue is a repair organ in the body.

Current applications. It is now well-established that adipose-derived HCT/Ps serve many biological, non-structural functions, including the following general purposes:

- Endocrine: "Adipose tissue is a complex, essential, and highly active metabolic and endocrine organ[11]"

- Immunity: "There has been much effort recently to define the role of adipocytokines, which are soluble mediators derived mainly from adipocytes (fat cells), in the interaction between adipose tissue, inflammation and immunity"[12]

- Regenerative capabilities: "White adipose tissue (WAT) is perhaps the most plastic organ in the body, capable of regeneration following surgical removal and massive expansion or contraction in response to altered energy balance"[13]

- Multipotency in situ, in vivo: "differentiation of locally available multipotent mesenchymal stromal cells into osteoblasts resulting in the calcification of extracellular matrix."[14]

Beyond these general purposes, adipose tissue – especially fat grafting – has been found to provide the following non-structural clinical benefits:

- Reversal or modulation of scarring.[15] Scar tissue is made up of a scaffold type of connective tissue known as collagen. As a wound heals, scar tissue forms. All scars contract over the first year and may form smooth, subtle changes in the skin. At times, however, wounds from burns, trauma, infection, or surgery (such as cleft lip surgery) [16] can result in thickened, overgrown and functionally restrictive scars. Fat grafting within and under these scars has restored normal contour and function, alleviating the need for riskier surgeries on these disabled patients. [17,18] In addition, the United States Department of Defense is investing heavily in research, at both the basic science and clinical level, exploring adipose-derived stem cells and fat transfer therapies for burn scar mitigation. This represents a nonstructural use supported by federal funding.

- Modulating pain. Adipose tissue has been shown to assist with reduction in pain associated with breast implants,[19] post-mastectomy,[20] lower back injuries,[21] or nerve or neuroma repair.[22]

- Reversal of damage done by therapeutic radiation. Radiation therapy is used extensively as an adjunct to cancer resection surgery. One in eight women is diagnosed with breast cancer and most require radiation therapy once the cancer is removed. The radiation damages the overlying skin, which becomes progressively tense, thickened and scarred. The radiated skin is often painful as well. Many surgeons have found that fat grafting reverses the skin damage caused by radiation making the skin soft, supple, and less painful. The fat grafting benefits to the skin permit breast reconstructive options that the women may not have available to her if poor quality radiated skin remains.[23,24,25,26,27,28]

  Adipose tissue is a vast reservoir of regenerative precursor cells with capabilities similar to those of bone marrow-derived stem cells.[29] Many studies have shown that fat can improve the quality of wound healing by through non-structural methods such as transdifferentiating into components of skin.[30,31,32,33,34] Specifically, Ebrahimian et al showed that fat therapy enhanced repair in radiated and non-irradiated mouse wounds,[34] and this was confirmed by Akita et al and Rigotti, clinically.[32,33] Improved skin quality has been subjectively observed in patients via fat grafting. This was affirmed experimentally by animal studies, which demonstrated increased neosynthesis of type I collagen.[35] Lastly, fat grafting has a potential for angiogenesis and cytokine production in pathologic tissue.[34,36]

- Treatment of bed sores. Bed ridden or debilitated patients, such as paraplegics or quadriplegics; occasionally suffer from pressure sores that may be as deep as the underlying bone. The local skin is chronically irritated and scarred making closure and healing nearly impossible without large operative procedures. Recurrent pressures are even more

complicated and patients are at risk of severe bone infection possibly leading to loss of the limb. Indeed, millions of patients have some type of chronic wound or ulcer that have significant problems healing, and this costs patients and society billions of dollars each year.

Fat grafting around the wound, under the edges of the pressure sore or ulcer or into the base of the wound has led to uncomplicated healing and reversal of the chronically inelastic skin surrounding the ulcer. This has resulted in improved quality of life for these patients with less surgical risk.[37] Current literature cites nonstructural modulation through neovascularization and increased dermal collagen production as the mechanisms through which fat grafts "rejuvenate" overlying skin and facilitate wound healing.[38,39,40] Furthermore, Prichard found that fat derived cells secrete a unique profile of pro-wound healing cytokines.[41]

- Vocal cord paralysis. There are a number of conditions that result in paralysis of vocal cords. Patients are stricken with a range of negative outcomes, from difficult to understand speech to a complete inability to speak. Fat grafting at the base of the vocal cords has been successful in restoring intelligible speech, permitting patients to resume better quality of life.[42,43,44] The nonstructural scar modulation of the vocal cord decreases fibrosis and restores mobility of the cords through collagen changes and angiogenesis.[45,46,47,48,49,50,51]

- Velopharyngeal insufficiency. Patients born with cleft lip and palates are typically operated upon within the first year of life. As many as 20% of these children will suffer from an inability to speak properly because the palate does not move as it should secondary to scarring and poor mobility.

  The child's speech is hypernasal (too much air leaks through their nose instead of through their mouth when they speak). The speech is difficult to understand, and the children are in speech therapy for years. Even with therapy, many children require another surgery to restore or just improve their speech. Fat grafting has helped many of these children achieve normal speech. The fat is grafted into the palate and the back of the throat (posterior pharyngeal wall), increasing mobility of the palate and permitting more air to be channeled out the mouth while the child talks. Fat grafting has been successful in preventing risky throat surgery as well as salvaging unsuccessful surgery to restore the child's normal speech. This has been demonstrated by nasoendoscopy, speech perceptual evaluation, and objective measurement of nasal airflow. Scar modulation is thought to be a contributing factor in the improvements identified with fat grafting in children with velopharyngeal insufficiency.[52,53,54]

- Scleroderma and systemic sclerosis. Scleroderma is a systemic disorder of the connective tissue that is characterized by fibro-proliferative disease and manifests as diffuse or localized fibrosis, vasculopathy, and immune abnormalities. Scleroderma may involve organ systems such as the cardiac, respiratory, gastro-intestinal, vascular, renal, subcutaneous tissue, and skin. The cutaneous manifestations include fibrosis, stiffness, joint contractures, finger ischemia, Raynaud's phenomenon, ulceration and pain.

  The dense fibrotic skin in Scleroderma patients restricts movement of the digits and face. Fat grafting improves the quality and elasticity of their skin, restoring function and form. The

adipose tissue is grafted directly under the dermis working by autocrine and paracrine mechanisms to reverse constrictive, inelastic skin while improving blood supply and promoting the healing of ulcers. All of these nonstructural mechanisms of the fat grafting are the result of angiogenesis (new blood vessel formation), fibrosis modulation, and attraction of healing growth factors.[55,56,57,58,59]

- Treatment for Dupuytren's. Dupuytren's disease is characterized by progressive, contractile fibrosis of the fascia within the palm. Dense cords irreversibly force the fingers into the palm resulting in limited function of the hand. The fibrosis of Dupuytren's disease is similar to that of connective tissue disorders such as scleroderma, only much more dense and concentrated along the cords and nodules. The exact etiology of Dupuytren's disease is unknown, but is it widely believed that local tissue ischemia and subsequent fibrosis of the fascia is responsible for the development of the disease. The local tissue ischemia may be due to a variety of environmental and host factors producing oxygen free radicals which produce or proliferate fibroblasts into myofibroblasts which contract and orient along the lines of stress, which cause cords to contract the fingers but also result in further ischemia. This promotes a self-perpetuating cycle.

  For years adipose tissue has been successfully grafted into the cords following needle aponeurotomy. Contracted fingers are straightened and recurrence prevented because of the fat grating. It is felt that the fat grafting promotes nonstructural angiogenesis, decreases ischemia, and promotes a protective array of collagen that hinders the pathogenic fibrosis characteristic of Dupuytren's disease.[60,61,62,63,64]

- Treatment for Raynaud's phenomenon. Raynaud's phenomenon manifests as recurrent vasospasm of the fingers and toes and usually occurs in response to stress or cold exposure. After fat grafting, patients have improved symptomatology with evidence suggestive of measurably increased perfusion.[65]

Defining all use of adipose tissue as structural, despite its many nonstructural uses, is particularly problematic for two reasons: (1) It does not reflect biologic reality; and (2) It dramatically affects regulatory classifications.

The "structural" components of adipose tissue, such as reticular fiber network and interspersed blood vessels, have nonstructural functions. For instance, the extracellular matrix works as an extensive messaging system important in cell function and regeneration.[66] Most of the adipokines released by adipose tissue are released by the non-adipocyte fraction of adipose tissue.[67] The density of the capillary network in adipose tissue is not a structural feature, but is instead fat depot-dependent and reflects other functional/secretory aspects of adipose.[68]

The safety of adipose tissue transfer does not correspond to classifications of risk tiers as proposed by the FDA. ASPS has the accumulated experience of its thousands of members and has surveyed the issue of adipose tissue transfer. The results of this survey of the literature, as well as clinical practice, are summarized in a published document.[69] ASPS is conscious of the issue of safety and has already approved the implementation of an Adipose Tissue Transfer Registry.

Consigning all adipose functions to the structural track impedes FDA's risk based regulations from properly capturing and evaluating the potential risks or lack thereof of nonstructural therapies. Using an evaluative structure that is misaligned with the actual use may actually increase risk while reducing patient access to safe and effective therapies.

Put simply, categorizing adipose HCT/Ps as exclusively structural does not reflect biological reality. When used for nonstructural rather than structural purposes, the relevant characteristics of adipose HCT/Ps relate to key characteristics of nonstructural tissue, and therefore "include differentiation and activation state, proliferation potential, and metabolic activity," as opposed to "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." Only in this way can the degree of manipulation of adipose tissue and, therefore, the potential risk to patient safety, be properly identified and evaluated.

Therefore, given the non-structural and structural properties of adipose tissue, it is our position that the FDA would be better served acknowledging the complex biological characteristics of adipose tissue and not relying solely on its structural properties. This is particularly important because the reliance upon the structural properties alters the FDA's views on what constitutes minimal manipulation. And, for the application of the same surgical exception, we would encourage the FDA to examine issues related to both minimal manipulation and homologous use.

Definition of minimal manipulation. FDA's tiered, risk based regulatory framework evaluates the degree of minimal manipulation for one purpose: to promote patient safety by gauging the degree of risk and basing the degree of regulatory oversight on that level of risk. It logically follows that the degree of minimal manipulation – i.e., the degree of alteration of the HCT/P's relevant characteristics – must be evaluated in terms of how the HCT/P is processed for its intended purpose.

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 [are] dependent upon the metabolic activity of living cells for [their] primary function," minimal manipulation constitutes processing that does not alter "relevant biological characteristics…include differentiation and activation state, proliferation potential, and metabolic activity."

In both instances, what qualifies as "relevant characteristics" should depend on whether the intended use is structural or nonstructural. Therefore, when adipose tissue is used for one of its many nonstructural functions, its "relevant biological characteristics…include differentiation and activation state, proliferation potential, and metabolic activity." Treating all adipose HCT/Ps as structural would define minimal manipulation in terms of tissue or cell characteristics relevant to structural utility. Where the intended use is not structural, however, it is not relevant, safe or even possible to assess the degree of manipulation of the HCT/P's biological characteristics if only structural characteristics are considered. Consequently, characterizing all adipose tissue as

structural even when its function has nothing or little to do with support and cushioning means that the definition of minimal manipulation literally does not fit the tissue processing being evaluated.

Focusing exclusively on structural utility would not only contradict the regulatory definition of homologous use, given that FDA defines "homologous use" as *"an HCT/P that performs the same **basic function or functions** in the recipient as in the donor".*[70] *(emphasis added)* but also defeat the fundamental purpose for evaluating the degree of manipulation at all: maximizing patient safety by minimizing risk. Applying the structural definition of minimal manipulation to nonstructural uses defeats this purpose by increasing risk and jeopardizing patient access to safe and effective nonstructural therapies. This is especially concerning because, as previously detailed, many nonstructural treatments have been used for decades or longer, and often carry less risk than alternative treatments.

Application of Same Surgical Procedure Exception. To qualify for the "same surgical procedure" exception to regulation under 21 CFR 1271.15(b), the HCT/P must otherwise meet the definition of a 361 HCT/P in that it must be, among other things, minimally manipulated and for homologous use. As previously explained, subjecting all adipose tissue to the definition of structural tissue precludes virtually all nonstructural uses from qualifying as being minimally manipulated.

Insisting that all adipose tissue be evaluated as structural tissue even when used for nonstructural purposes would completely prohibit patient access to adipose-derived HCT/P therapies that are used for the same basic albeit nonstructural purpose in both donor and recipient, and minimally manipulated in terms of the original biological characteristics relevant to that nonstructural purpose. According to the draft guidance in its current form, this ban would apply even for autologous minimally manipulated and homologous therapies.

Therefore, the ASPS requests the FDA revise the draft guidance to reflect the following:

- **Because intended uses of adipose tissue can be both structural and biological, adipose tissue may be categorized as either structural or biological based on its intended use.**

- **Minimal manipulation for both structural and nonstructural adipose HCT/Ps should be evaluated in terms of the original characteristics that are relevant to the structural or nonstructural nature of the intended use.**

II. Revise its position that de-cellularizing the adipose matrix necessarily diminishes its ability to perform its structural functions

Regarding adipose tissues' structural functions, we respectfully request the FDA to revise its position that de-cellularizing the adipose matrix significantly alters its ability to perform its structural functions. The key to understanding the structural properties of adipose tissue is appreciating the anatomy. Adipose tissue is composed of lipid containing cells, which are supported within an extensive skeletal framework of fibrous tissue. These rich, collagenous bands form an interconnecting network that is the basis for the structural properties of adipose tissue and

does not depend on the presence of cells or lipid.[71] Moreover, these fibrous bands have significant biomechanical properties of tensile strength and elasticity, both important for padding and cushioning.[72]

To suggest that removing the cellular component or the lipid component of adipose tissue obviates its structural capability ignores the critical importance of the collagen matrix skeleton. Indeed, a number of investigators[73,74] have demonstrated that adipose tissue can be de-cellularized, as has been done with dermis, bone, and other tissues regulated as HCT/P products, and the adipose tissue will retain its structural properties. These products can be hydrated in saline solution and injected to add padding and cushioning to soft tissues. De-cellularization of allogeneic adipose tissue are essential to insure the safety of the resulting matrix and minimize potential immune response upon implantation.[75,76] The resulting matrix maintains it original structural and conductive properties and contains the endogenous proteins that facilitate and support host cell infiltration.[77] In that form, the matrix still supports the function of cushioning.[7,78,79]

There is a strong analogy between bone being processed into demineralized bone matrix, dermal tissues being processed into acellular dermal matrix (ADM), and adipose tissue being processed into an adipose derived matrix. Bone undergoes grinding, de-lipidization, de-cellularization, disinfection and de-mineralization. Dermal matrix undergoes de-cellularization, de-lipidization, disinfection, and grinding. Adipose tissue undergoes mechanical reduction (grinding), de-lipidization, de-cellularization, and cleaning or disinfection. All result in a particulate form that retains the endogenous matrix proteins and micro structure that allows for host cell infiltration and have been safely used to benefit patients for over a decade.[80]

Additionally, determining that de-cellularized 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."[81]

Therefore, the ASPS requests the FDA revise the draft guidance to reflect the fact that de-cellularization of adipose tissue for a structural use does not result in more than minimal manipulation.

III. Homologous Structural Uses of Fat Grafting for Breast Reconstruction

In Example B-3 of the Draft Guidance, adipose injection into the breast is declared non-homologous use because "[t]he 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."

This statement is biologically inaccurate for several reasons:

- Lactation is only a function of the breast during a very limited period following childbirth. In contrast, throughout a woman's adolescence and adulthood, the breast's main function is that of a secondary sex organ.
- Adipose tissue, which is present in breast tissue, is not injected to the breast to assist in the production of milk, but to preserve the structure and function of a secondary sex organ.
- Structural replacement of the interspersed adipose tissue in the breast therefore constitutes homologous use.
- The loss of breast tissue after cancer has considerable psychosocial implications.[82]

Clinicians have used fat for the treatment of tissue deficiencies and contour abnormalities for over a century. For the past 15 years, physicians have routinely used autologous fat transplantation for soft-tissue augmentation, including breast reconstruction and augmentation.

In 2007, an ASPS Task Force determined that complication rates associated with fat grafting (specifically to the breast) are no greater – and are most likely lower - than the risks typically associated with surgery. Based on this evidence, the Task Force concluded that autologous fat grafting is safe.[83] In a recent survey, seventy percent of U.S. plastic surgeons have used fat grafting techniques for breast operations, but they are more likely to use it for breast reconstruction rather than cosmetic breast surgery.[84] Eighty-eight percent of plastic surgeons who currently perform fat grafting to the breast said they use fat grafting for breast reconstruction techniques, and often apply fat grafting along with implants or flap procedures. The surgeons found fat grafting particular useful for improving the shape of the breast, including reconstruction after "lumpectomy" for early-stage breast cancer.[85]

Fat grafting for breast reconstruction has been used safely for decades and for many patients provides the only remaining option for reconstructing the breast and treating other post-mastectomy conditions, such as reversing damage caused by therapeutic radiation[86] and reducing implant breast pain and post-mastectomy pain.[87] In recognition that breast reconstruction plays an essential role in both physical and psychological healing following mastectomy, federal law mandates health insurers to pay for breast reconstruction,[88] and states have also enacted separate legislation to further clarify coverage.[89] Given that, the vast majority of insurance companies cover the procedure.[90,91,92,93,94,95]

Characterizing fat grafting for breast reconstruction as non-homologous use will bring this procedure within the scope of section 351 and prevent it from qualifying for the same surgical procedure exemption. The practical reality of requiring clinicians to bear the many costs of complying with section 351's requirements, especially with regard to premarket approval, is that women will be deprived of a longstanding and safe procedure.[96] Women often require or strongly prefer using their own tissue to restore an essential part of their body. The draft guidance in its current form would deprive women of this important option for post-mastectomy breast reconstruction.

With regard to women who have exhausted alternative therapies, the draft guidance would essentially force them to bear the scars and enduring pain of a life-threatening disease. This conflicts with the safety record for using a woman's own fat to replace adipose tissue and otherwise reconstruct and support the breast while restoring its function as a secondary sex organ.[97]

For these reasons, ASPS respectfully requests the FDA revise the draft guidance to categorize fat grafting for the purpose of breast reconstruction as a structural use as homologous rather than non-homologous.

IV. Revise its position that stromal vascular fraction (SVF) involves more than minimal manipulation by recognizing that the SVF process primarily requires centrifugation and cell isolation

As part of the draft guidance document, the FDA provides two examples which reference stromal vascular fraction. In the first example,[98] FDA asserts that due to enzymatic digestion and mechanical disruptions to isolate cellular components, stromal vascular fraction is considered more than minimally manipulated. In contrast, in the second example,[99] FDA acknowledges that centrifugation followed by re-suspension in a sterile saline solution would result in a HCT/P eligible for the same surgical exception. Given that processing involving centrifugation using similar tissue is considered minimal manipulation, the key concern for the FDA seems to be the enzymatic digestion.

By way of background, SVF is freshly isolated heterogeneous cell fraction, which could be derived from native adipose tissue or liposuction aspirates. SVF could be derived from both the fatty and fluid portions of liposuction aspirates after enzymatic digestion during centrifugation. Basically, SVF is what remained in the pellet after removal of the blood and fat components. It is a very crude and heterogeneous mix of multiple cell populations with different degrees of maturity and function.

Based on the method of adipose tissue processing, cellular composition of SVF can vary significantly. Most sources indicate that adipose-derived stromal (stem) cells represent up to 10% (2-10%) of SVF.[100] Endothelial cells (mature and progenitors) could represents anything from 7%[101] up to ~30%[102] of SVF. CD34+ cells are present at large numbers and could compose up to 63% of SVF.[103]

The assertion that processing adipose tissue changes the relevant characteristics of SVF does not reflect biologic reality.

- Isolating SVF from adipose tissue does not alter the relevant biological characteristics. The relevant biological characteristics of every single cell component of SVF are manifest "in situ" and after isolation.[104]
- The phenotype of SVF cells do not change during the process of enzyme digestion and isolation. Rather, the phenotype changes during cell culture (which is not used for SVF), described as a "dynamic phenotype."[105]

- Adipose tissue releases stromal cells into the circulation in vivo, not just during enzymatic digestion.[106]
- Cell separation, whether by collagenase or by a chemical signal ("mobilization"), does not alter the relevant biologic characteristics of bone marrow cells, precursor cells or the various SVF cell types. Collagenase digestion of tissue is a time honored way of isolating cells for the purpose of studying their normal function.
- Previously, the FDA acknowledged that cell separation is a form of minimal manipulation.[107] Therefore, it is unclear why the FDA would indicate that this general process is not appropriate for adipose tissue.

Similar to fat grafting for breast reconstruction, characterizing SVF as more than minimal manipulation will bring this procedure within the scope of section 351 and prevent it from the qualifying for the same surgical procedure exemption. The practical reality of requiring clinicians to bear the many costs of complying with section 351's requirements, especially with regard to premarket approval, is it could limit patient access to facial scar treatments,[108] facilitation of tolerance in rheumatic disease,[109] and therapeutic neovascularization for relieving ischemia and preventing fat absorption in an autologous manner.[110]

Given that SVF involves centrifugation and cell isolation, the FDA should revise its position that stromal vascular fraction (SVF) involves more than minimal manipulation.

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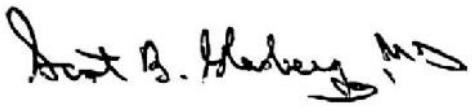
The ASPS appreciates the opportunity to offer these comments and looks forward to working with the FDA. ASPS has in the past met with representatives of the Center for Biologics Evaluation and Research (CBER) to review current trends in plastic surgery research and development of new therapies, and discuss the regulatory issues involved. **We respectfully request the opportunity to meet with CBER again to further discuss this draft guidance.** In particular, we believe a meeting with CBER's Director, Karen Midthun, would be particularly productive, given the large impact that this draft guidance can have for plastic surgeons. **In addition, given the potentially broad implications this guidance document may have, we also request that you hold a public meeting on this draft guidance document.**

Should you have any questions about our comments, please contact Catherine French, ASPS Health Policy Manager, at cfrench@plasticsurgery.org or 847.981.5401.

Sincerely,



Scot B. Glasberg, MD
President, American Society of Plastic

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

[2]As part of the final rule establishing the framework for the regulation HCT/Ps, the FDA included the following examples of minimal manipulation as part of the preamble (emphasis added): "At this time, examples of HCT/P's that we consider to be minimally manipulated include those that have been subjected to the following procedures: Density gradient separation; selective removal of B-cells, T-cells, malignant cells, red blood cells, or platelets; **centrifugation**; cutting, grinding, or shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or irradiation; **cell separation**; lyophilization; cryopreservation; or freezing." See http://www.fda.gov/OHRMS/DOCKETS/98fr/011901a.htm.

[3]http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm427795.htm

[4] Neuber, F., *Fettransplantation.* Bericht über die Verhandlungen der Deutschen Gesellschaft für Chirurgie. Zbl Chir, 1893. **22**: p. 66.

[5]Holländer E. Uber einen Fall von fortschreitenden Schwund des Fettgewebes und seinen kosmeti- schen Ersatz durch Menschenfett. Munch Med Wchschr 1910; 57:1794–5.

[6]Holländer E. Die kosmetische Chirurgie. In: Joseph M, editor. Handbuch der Kosmetik. Leipzig (Germany): von Veit; 1912. pp. 689–90, 708

[7]Lexer E. Die freien Transplantationen. Stuttgart (Ger- many): Enke; 1919–1924.

[8](see Appendix A) Gillies HD. Plastic Surgery of the Face. London: Frowde, Hodder, Stoughton; 1920.

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

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[90]While it does not specifically mention fat grafting, the following coverage notes that liposuction (the first step for fat grafting) is allowed "to achieve breast symmetry" – the main rationale for fat grafting. https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/BreastReconstruction_CD.pdf

[91]Following Medically Necessary removal of all or part of a breast, we cover reconstruction of the breast, surgery and reconstruction of the other breast to produce a symmetrical appearance, and treatment of physical complications, including lymphedemas. http://info.kaiserpermanente.org/info_assets/child_health_plan/pdfs/membership_agreement_eoc.pdf.

[92]Reconstruction of the affected and the contralateral unaffected breast following a medically necessary mastectomy is considered a relatively safe and effective noncosmetic procedure. Accordingly, program payment may be made for breast reconstruction surgery following removal of a breast for any medical reason. http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=64&ncdver=1&bc=AgAAQAAAAAAA&

[93]Harvesting (via of lipectomy or liposuction) and grafting of autologous fat as a replacement for implants for breast reconstruction, or to fill defects after breast conservation surgery or other reconstructive techniques, is considered medically necessary. http://www.aetna.com/cpb/medical/data/100_199/0185.html

[94]Reconstructive surgery refers to surgical procedures and other techniques, undertaken in the context of breast cancer, to rebuild breast contour and, when necessary, reconstitute the areola and nipple. https://www.caresource.com/documents/breast-reconstruction-surgery-following-mastectomy/

[95]Restoration of a normal breast form through breast reconstruction is performed for patients undergoing mastectomy or lumpectomy. The manner of breast reconstruction is an individualized decision between the patient and their physician. https://my.cigna.com/teamsite/health/provider/medical/procedural/coverage_positions/medical/mm_0178_coveragepositioncriteria_breast_reconstruction_follow_mast_lump.pdf

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[98]Example A-1: Adipose tissue is recovered by tumescent liposuction. The adipose tissue undergoes processing or manipulation (e.g., enzymatic digestion, mechanical disruption, etc.) to isolate cellular components, commonly referred to as stromal vascular fraction, which is considered a potential source of adipose-derived stromal/stem cells for clinical therapeutic uses. This processing breaks down and eliminates the structural components that function to provide cushioning and support, thereby altering the original relevant characteristics of the HCT/P relating to its utility for reconstruction, repair, or replacement. Therefore, based on the definition of minimal manipulation for structural tissue, this processing would generally be considered more than minimal manipulation.

[99]Example A-1: Adipose tissue is recovered by tumescent liposuction. The lipoaspirate is centrifuged at a low speed before blood and extracellular fluid are decanted. The remaining adipose tissue is resuspended in sterile saline. Because nothing else is added to the adipose tissue, and only minor handling is performed (e.g., no steps were taken to isolate stem cells from the lipoaspirate, commonly referred to as stromal vascular fraction), the adipose tissue would remain a connective tissue composed of clusters of adipocytes and other cells surrounded by a reticular fiber network and interspersed small blood vessels. It is then re-injected into the subcutaneous space of the same patient from whom it was removed, in a single operation or in a limited number of predetermined operations in order to achieve the intended effect. We generally would consider the establishment manufacturing this HCT/P from adipose tissue to meet the exception under 21 CFR 1271.15(b), and the establishment would not be required to comply with the requirements in 21 CFR Part 1271.

[100]http://onlinelibrary.wiley.com/doi/10.1002/jcp.20636/abstract

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[107]At this time, examples of HCT/P's that we consider to be minimally manipulated include those that have been subjected to the following procedures: Density gradient separation; selective removal of B-cells, T-cells, malignant cells, red blood cells, or platelets; centrifugation; cutting, grinding, or shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or irradiation; cell separation; lyophilization; cryopreservation; or freezing. See http://www.fda.gov/OHRMS/DOCKETS/98fr/011901a.htm.

[108] http://www.ncbi.nlm.nih.gov/pubmed/24406591

[109] http://www.ncbi.nlm.nih.gov/pubmed/20537320

[110] http://www.ncbi.nlm.nih.gov/pubmed/21393582