Perspectives on the FDA Draft Guidances for Use of Adipose Tissue

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In response to claims made by some physicians, clinics, and medical companies advertising the unsubstantiated beneficial effects of autologous stem cell therapies, the US Food and Drug Administration (FDA) published 3 draft "guidances" in the Federal Register, between 2007 and 2014, related to the use of aspirated fat and its constituents. The last set of guidances relevant to aspirated fat were the subject of public hearings in September, 2016. These guidances are nonbinding interpretations of federal regulations already on the books. While nonbinding, in their final iteration, they provide insight into how the FDA will interpret existing regulations. Unfortunately, while each guidance has attempted to further clarify the one before, the result has been to make all of them more difficult to assess. The guidances under scrutiny seem to interpret the federal code in a way that would require some clinicians who use human cells, tissues, and cellular- and tissue-based products (HCT/Ps) derived from adipose tissue to register and report as manufacturers.[1]

Essentially, the FDA proposes to prohibit the separation and reinjection of the stromal vascular fraction (SVF) of adipose tissue, even in procedures within the same patient. However, upon closer examination, what the guidances really do is to obfuscate the issue and open the door to further misinterpretation, including the possibility of disallowing simple fat injections for a variety of reconstructive and aesthetic procedures for which they have been studied extensively, used for years, and shown to be safe.

Board-certified plastic surgeons share the US FDA's commitment to provide patients with access to safe and effective treatments. In addition, we respect the agency's tiered, risk-based decision framework, which is intended to balance the need for protecting patient safety with the need for therapeutic alternatives.[2] The FDA is to be commended for undertaking the onerous task of providing regulatory guidelines for the medical use of HCT/Ps. Unfortunately, the recent FDA guidances have the possible unintended consequence of depriving patients in need of certain reconstructive and aesthetic treatments of an inexpensive and useful tool with proven safety and results.

In a recent article in *Mayo Clinic Proceedings*, Dr Turner[3] focuses on several concerns related to the misuse and marketing of adipose-derived autologous stem cell treatments. While plastic surgeons support evidence-based use of stem cell therapies, we agree that the commercial use of these products needs to be further investigated and regulated as necessary to ensure patient safety and efficacy. The FDA's current regulatory language, however, lacks the required specificity to provide meaningful guidance to healthcare professionals.

In a joint position statement on stem cells and fat grafting, the American Society of Plastic Surgeons (ASPS) and the American Society for Aesthetic Plastic Surgery (ASAPS) state their commitment "to patient safety, advancing the quality of care, innovative treatments and

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practicing medicine based upon the best available scientific evidence."[4] The position statement makes clear that these 2 professional organizations strongly support a more evidenced-based practice for the use of stem cells both in reconstructive and aesthetic plastic surgery procedures. ASPS and ASAPS also share concern regarding unsubstantiated claims of improved results with stem cell therapy in traditional procedures such as facelifts and breast augmentation.[5] To further address the science in this field, the Plastic Surgery Foundation established the General Registry of Autologous Fat Transfer (GRAFT) and is currently collecting data.

The above positions do not, however, mean that plastic surgeons believe *any* regulation is *good* regulation. The draft guidance documents issued by the FDA to regulate adipose-derived autologous stem cell interventions have the potential to produce many consequences that negatively affect patient care. Such consequences may include denial of appropriate treatment, delay of treatment, increased costs, and unnecessary burdens placed upon the treating physician.

All fractionated fat cell treatments should not be painted with the same brush. Put differently, by failing to delineate the specific HCT/Ps subject to regulation, adipose cells (one of the components) would be subject to the same restrictions as other components such as stem cells. Inevitably, the fat cell therapies used in reconstructive and aesthetic procedures which have been detailed in hundreds of clinical and investigative articles might no longer be a legal option. Indeed, the "baby" will have been thrown out with the bathwater.

Definition of "Sizing" and Other Minimal Manipulations

The FDA draft guidance outlines the circumstances under which establishments and healthcare professionals that manufacture and use HCT/Ps derived from adipose tissue may qualify for a Section 1271.15(b) exemption.[1] Section 1271.15(b) states, "You are not required to comply with the requirements of this part if you are an establishment that removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure." The FDA includes within this exemption "autologous cells or tissues that are removed from an individual and implanted into the same individual without intervening processing steps beyond rinsing, cleansing, or sizing, or certain manufacturing steps" explicitly because "[these cells or tissues] raise no additional risks of contamination and communicable disease transmission beyond that typically associated with surgery" and would remain in their "original form."

Most surgeons would agree that fat grafts harvested with syringe aspiration or conventional liposuction need processing to separate the aqueous fluid fraction and oil, thus limiting the reinjected lipoaspirate to fat. Surgeons frequently use centrifugation to separate the fat cells from the aqueous and oil components of the suspension. One of the examples that the FDA guidelines provide mentions centrifugation of the lipoaspirate at low speed, and subsequent resuspension, as being acceptable. Thus, centrifugation *should* be considered a method of sizing but the statement referencing this in the guidance documents lacks the clarity upon which to confidently ascertain exemption from the rule.

Definition of "Structural Tissue"

The FDA defines adipose tissue as a "connective tissue that stores energy in the form of lipids, insulates the body, and provides cushioning and support for subcutaneous tissues and internal organs." This definition makes adipose a structural tissue and thus, according to the guidances, restricts its use. Yet the FDA's interpretation does not reflect biologic reality. It is well established that adipose-derived HCT/Ps serve many nonstructural, cellular functions, including as endocrine organs,[6] soluble mediators in immunity,[7,8] regenerative organs,[9] modulators of scarring,[10,11] and pain reducers.[12] Because adipose tissue has both nonstructural and structural properties, the FDA should acknowledge these complex biologic characteristics and not rely solely on a structural definition for its guidance.

Definition of "Homologous Use of Adipose Tissue"

In order to best explain the quagmire that the FDA has seemingly created with its ambiguous guidances, their potential impact on breast reconstructive procedures provides an excellent "looking glass," understanding that these same definitions and prohibitions would apply to virtually all other uses of fat injections in aesthetic and reconstructive surgery. Homologous use of adipose tissue is defined by the FDA as occurring when "the tissue used for the repair, reconstruction, replacement or supplementation of a recipient's cells or tissues performs the same basic function or functions in the recipient as the donor." The FDA guidance states that fat grafting during breast reconstruction is a use of adipose tissue different from that of the breast's primary function, lactation; consequently, in this context, fat grafting would be a nonhomologous use and the fat no longer a HCT/P.

The FDA's should reconsider its position on fat grafting for breast reconstruction. Clearly, lactation is not the breast's sole function. Throughout a woman's adolescence and adulthood, the breast functions mainly as a secondary sex organ. Ironically, according to the FDA definition, a

reconstructed breast is not really a breast at all. It would potentially be informative for the individuals responsible for the FDA's definition of a *breast* to interview a number of women who have undergone reconstruction. Although these women have a structure that does not lactate and is insensate, they most certainly would consider it their breast. The additional fat to smooth contours and increase volume is not substituting for a lactating breast (the original structure) but rather is a structural enhancement to a reconstructed breast. The loss of a breast may lead to feelings of decreased femininity and to psychosocial concerns.[13-15] Besides improving appearance, breast reconstruction has a therapeutic role in mitigating the possible adverse psychosocial sequelae of mastectomy and federal law mandates insurance coverage of breast reconstruction after mastectomy.[16] For some patients, fat grafting provides an important option for reconstructing the breast and treating other conditions that occur after mastectomy, such as reversing damage caused by therapeutic radiation and reducing breast implant and postmastectomy pain.

In 2007, an ASPS task force studying fat grafting to the breast determined that complication rates associated with this procedure were no greater and most likely lower than the risks typically associated with plastic surgery procedures. On the basis of this evidence, the task force concluded that autologous fat grafting was safe for breast surgery.[17] The procedure is widely accepted as an effective and reliable method for restoring volume and contour irregularities in the reconstructed breast.[18-21]

CONCLUSIONS

Caught in the FDA's wide-thrown regulatory net is a long history of safe and effective use of adipose tissue in nonstructural, fat-grafting therapies.[22,23] For the past 15 years, physicians have routinely used autologous fat transplants for soft-tissue augmentation, including breast reconstruction and augmentation,[5-8] as well as for facial reconstruction in HIV-compromised individuals, trauma patients, and in a variety of other instances where volume enhancement is needed. Inappropriate uses of stem cells and fat grafting, as well as unsubstantiated claims of efficacy, deserve the FDA's attention and regulation. However, unintended consequences of the agency's faulty guidances could prevent thousands of patients from being offered safe and proven treatment options.

The FDA must be a credible arbiter in sorting out the facts and fiction of stem cell therapies. Rather than attempting to define the complex matrix of adipose tissue in a manner that fails to pass scientific scrutiny, the agency should simply state its intent to regulate its use for purposes not supported by substantial evidence-based research. It behooves each of us, just as our professional societies do, to pay close attention to these periodic guidances and respond in the public domain as necessary. Hopefully, our collective voices will be sufficient to protect our patients' interests as we strive to offer them the safest and most effective therapies to optimize their aesthetic and reconstructive outcomes.

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