Adipose Tissue Regulation in the United States

Deborah L. Griffin, MSc, Manager, QA/RA for Cellular Therapies
University of Pittsburgh Cancer Institute
Pittsburgh, PA, USA

Lynn O’Donnell, PhD, Associate Professor, Director, Cell Therapy Laboratory
The Ohio State University, Division of Hematology and James Cancer Hospital
Columbus, OH, USA

Currently, the recovery, processing, and implantation of autologous adipose tissue is considered by the FDA to be human cells, tissues, or cellular and tissue-based products (HCT/Ps) as defined by 21 CFR 1271, which requires registration with the FDA and manufacturing in compliance with Good Tissue Practices (GTPs). Moreover, the FDA position is that processing of adipose tissue for many indications “alters the relevant characteristics of the adipose tissue relating to the tissue’s utility for reconstruction, repair, or replacement” and for many indications (e.g., breast augmentation, osteoarthritis, gum recession) “do not meet the definition of homologous use in 21 CFR 1271.3(c).” Such HCT/Ps are regulated as both drugs and biological products, thus requiring demonstration of safety and efficacy, a biologic license application (BLA) or Investigational New Drug (IND) application for use in humans, and manufacturing under current Good Manufacturing Practices (cGMPs). In the past year, there have been a number of warning letters by the FDA and a response from the adipose tissue medical community refuting the FDA’s jurisdiction over the use of autologous adipose tissue.

Adipose Warning letters in 2012

Last year, the FDA issued four warning letters related to adipose tissue transplantation. One letter was related to the creation and marketing of a device to collect and/or isolate adipose stem cells where the FDA asserts that the company is marketing the device for indications for which it does not have clearance, such as the “enhancement of male pectorals”.

The other three warning letters were related to processing of adipose tissue for aesthetic purposes as well: IntelliCell Biosciences, Inc. Warning Letter, Thomas E Young, LLC Warning Letter, CellTex Warning Letter. One of the Warning Letters noted that the IntelliCell product has a YouTube video promoting the use of the “autologous homologous” IntelliCell product. The purpose of the letters is two-fold. First, they notify the facility of the formal regulatory status of their product and the FDA’s rationale and authority (i.e., laws and regulations) for that designation. Second, they outline some of the specific deviations that were found to be present at the facility and were presented in the Form FDA 483, Inspectional Observations, at the completion of the inspection. In these cases, the processing citations were all very similar and primarily related to documentation and the lack of formal, written procedures for a wide array of processes. Of particular interest are the statements that the sites specifically lack “having written procedures designed to prevent microbial contamination of drug products purporting to be sterile” and appropriate validation of sterilization process for aseptic processing. None of the three sites were found to be testing the adipose tissue for sterility prior to administration to patients. Unfortunately, the redactions in the Warning Letters do not allow for analysis, as one letter states that 6 of X patients receiving the product experienced adverse reactions, including, but not limited to “fever, redness, soreness, cyst formation, mastitis, and infection”. Was this 100% of the recipients or 1%? Documentation of equipment and facility conditions, batch
records and labeling were also significant deficiencies. For those of us who work in FACT-accredited facilities, the lack of documentation of these adipose processing facilities is astonishing.

General Review of Adipose Regulations in the US

The FDA states that adipose tissue falls under 21 CFR 1271 regulations for human cells, tissues, and cellular- and tissue-based products. The Small Entity Guidance for regulation of HCT/Ps, as published in 2007, and the cGTP Guidance, published in 2011, do not specifically exclude adipose tissue in the examples of tissues and cells that are exempt from 21 CFR 1271, nor do they establish whether adipose tissue is regulated solely as an HCT/P or also as a drug and biologic, as these must really be determined on an individual basis.

In 2006, The New England Journal of Medicine published an article by Dina Gould Halme, Ph.D., and David A. Kessler, M.D., reviewing the “recent” regulations for stem cell based therapy in the US, an article which still holds up today. Included in the posting of this article is a tab listing the articles referencing Halme and Kessler, with a huge variety of content covering media and culture conditions, unproven therapies and stem cell tourism, and both adipose tissue and adipose-derived stem cells. A 2012 article by Douglas Sipp and Leigh Turner in Science deals with the issue more broadly but reiterates the FDA’s regulation of stem cell therapy products as drug products, and touches upon Global Challenges, which will be the topic of an upcoming Telegraft article.

A recent Google search for “Autologous Adipose Tissue Regulation” returned more than 2.8M results. Wading through the plethora of websites can be confusing, as the word “regulation” also results in scholarly articles dealing with up- or down-regulation of adipose genes/proteins as well as patent filings! Articles document the use of autologous adipose stem cells in a variety of indications ranging from the obvious repair of soft tissue defects in plastic surgery and bone regeneration to improvement of neurological deficits and treatment of urinary incontinence. The sheer number of indications and types of processing is staggering.

Rebuttals and Counterpoints

Of course, there is another side to the FDA’s position, and many articles have been published that refute the FDA’s purview for regulating adipose tissue processing. While not intended to be a thorough review of that position, I mention a couple of references here as a starting point for interested readers. A particularly beefy and well-referenced article, written by professors at Boston College Law School, maintains that autologous stem cell therapies are equivalent to practice of medicine and should not be regulated as biological drug products. The article discusses the founding and the original purpose of the FDA, beginning with the Biologics Act of 1902 to establish the basis for the FDA’s jurisdiction. The article then builds the argument that the FDA was specifically excluded from governing the practice of medicine, but that the FDA, once it defines a particular item as a drug, now maintains regulation over that item. A discussion of the Regenexx case, an analysis of the jurisdiction of the FDA, and a comparison to the European Commission’s Advanced Therapies Regulations rounds out the remainder of the article. Another thoughtful article in the Journal of Translational Medicine, although loaded with inflammatory language, discusses how the regulations are “stifling” medical advancements and is worth reading for their perspective.
More to Come…

The FDA has taken legal action against some of these facilities, and those court cases are likely to drag on for years. Another noteworthy story is that of ongoing civil litigation being brought forth by six patients in California with the assertion that a Seoul-based company (RNL Bio) misled patients by making claims that the therapies had far-reaching effectiveness. This question of how cellular therapy products, in particular autologous products, are regulated has become a big topic for the field of cellular therapy as a whole, as well as for ISCT in particular as this debate is now taking place in many regions around the world. For example, ISCT Australia / New Zealand Vice President Dominic Wall recently wrote of Australia’s decision to exempt from their new tissue regulations all autologous cellular therapy products as the practice of medicine (see September 2012 Telegraft). This particular debate, which is exemplified by what is happening today with adipose tissue in clinics all over the world, is tightly connected to larger debates on cell therapy medical tourism and balancing access to innovative medical care with preventing unethical use of unproven therapies. Indeed, ISCT will continue to be active in these matters, and there will be at least two sessions on these topics at the ISCT Annual Meeting in Auckland in a couple of weeks. Master Class 2 "Access to Unproven Cell Therapies" (Tuesday April 23, 5 - 6 pm), chaired by ISCT President Kurt Gunter, will have three global perspectives on the topic by leaders in the field, while Quality and Operations Track 6 "Roundtable Debate: Pros and Cons in the Cellular Therapy Field" (Wednesday April 24, 10:45 am – 12:15 pm) will give all session attendees an opportunity to offer their opinion and debate openly in a small group setting the issue of autologous cell therapy regulation.

References