

Stem Cell Letter Could Signal New FDA Enforcement Trend

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The U.S. Food and Drug Administration has sent a warning letter covering three physician-operated stem cell treatment centers in California, Florida and New York asserting that the centers have unlawfully recovered and processed adipose (fat) tissue to perform stem cell therapy and deviated from current good manufacturing practice (CGMP) and current good tissue practice (CGTP) in doing so. The issuance of a warning letter in these circumstances is significant because it may signal a departure from the FDA's past practice of less strict regulatory enforcement against practitioners of stem cell therapies.

The procedure at issue is relatively common. The physician uses a needle to remove adipose tissue from the patient, isolates the stromal vascular fraction (SVF) of the tissue and implants the SVF autologously, meaning back into the same patient. One of the most common therapies of this type is a relatively simple office procedure in orthopedic and rehabilitation medicine; the physician obtains SVF from the patient and injects it back into a surgical or arthritic joint, in an effort to promote the repair and replacement of diseased cartilage.

In this particular warning letter, the FDA indicates that the treatment centers were obtaining and using autologous SVF to perform intravenous or intrathecal (spinal) injections, or for nasal or oral nebulization. The FDA notes that the treatment centers were using these procedures to treat a variety of serious conditions such as Parkinson's, multiple sclerosis and cerebral palsy. From the letter, it does not appear that the FDA cited the centers for performing stem cell procedures in the context of joint conditions.

Under federal regulations, adipose tissue and SVF constitute a "human cell, tissue or cellular and tissue based product" (HCT/P). HCT/Ps may be regulated in one of two ways under the Public Health Service (PHS) Act and enabling regulations. The product may be subject to Section 351 of the PHS Act, in which case it must undergo the extensive premarket approval process of a Biological License Application (BLA).

However, the product may be subject to certain exceptions, in which case it is regulated under Section 361 of the PHS Act, which exempts it from the BLA premarket approval process. Exceptions exist for (i) “minimal manipulation” of the HCT/Ps, (ii) putting the HCT/Ps to “homologous use” and (iii) harvesting and implantation of autologous HCT/Ps during the “same surgical procedure.” The FDA has issued three guidances in recent years discussing how these exceptions might or might not apply in specific contexts. But as a practical matter, the FDA appeared to be exercising a relatively high degree of enforcement discretion, for the most part pursuing only the more egregious cases.

Based on this recent warning letter, it appears the FDA may be changing its approach. In the warning letter, the FDA states that its enforcement action is based on its finding that at least two of the exceptions to Section 351 regulation do not apply. The FDA first concludes that the adipose tissue is more than “minimally manipulated” in the procedure at issue because the “processing alters the original relevant characteristics relating to the tissue’s utility for reconstruction, repair or replacement.” The FDA further concludes that the procedure is not putting the adipose tissue to “homologous use” because the SVF “is not intended to perform the basic function or functions of adipose tissue, which generally is to cover, connect or cushion.”

As noted above, there is a third exception to Section 351 regulation for HCT/Ps that are removed and transplanted back into the same patient during a single surgical procedure. In its guidance, the FDA has stated its intention to apply this exception where the HCT/Ps are not subjected to “intervening steps beyond rinsing, cleansing, or sizing, or certain manufacturing steps.” The FDA’s stated reasoning is that such limited procedures “raise no additional risks of contamination and communicable disease transmission beyond that typically associated with surgery.”^[1] Based on the warning letter’s description of IV or intrathecal injection and nasal or oral nebulization, it appears that the cited procedures may not involve harvesting and implantation in the same procedure, in which case this exception would be inapplicable. The FDA also cites CGMP and CGTP violations relating to such issues as contamination, record keeping and labeling, which also may have been a factor in the FDA’s approach in this case.

Many practitioners and organizations currently practice various forms of stem cell therapies using SVF derived from adipose tissue. As noted above, one of the most common uses of this procedure is in orthopedic and rehabilitation medicine for surgical or arthritic joints. To date, there appear to be few if any peer-reviewed, evidence-based studies reporting the success of this procedure to statistical significance. As a practical matter, payers are continuing to decline coverage on the ground that the procedure is experimental. However, anecdotal reports of success using this procedure are commonplace.

On balance, while this recent warning letter raises the possibility that the FDA may be taking a more aggressive enforcement approach with regard to stem cell therapy, questions still remain regarding how far the FDA will undertake enforcement activity in this area in particular circumstances, not least of which is in the popular orthopedic/rehabilitation field.

An interesting trend, which has continued in this warning letter, is the use of CGMP violations and other process violations as grounds for action. In many cases, these determinations have been made in the context of the issuance of letters to manufacturers of products about which the FDA is known to be skeptical.

In a broader context, this development is of a piece with a number of recent policy reversals by the FDA toward more restrictive regulation in a variety of innovative therapeutic initiatives. There is speculation that the agency is attempting to conclude rulemaking in a number of topics in anticipation both of a

potential change in party and enactment by Congress of the 21st Century Cures Act. The former could affect regulatory priorities and approaches. The latter, if it proceeds on its present path, would profoundly affect both the type of data the FDA will have to consider when evaluating such therapies, and in many cases change the outcome of the FDA's evaluation of therapies.

In the near term, it seems clear that if the FDA does proceed to increase enforcement in this area, which is of great interest to both practitioners and patients, it is almost certain that there will be a vigorous response from the various stakeholders.

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[1] FDA, Same Surgical Procedure Exception Under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception, at 3 (Draft Guidance for Industry October 2014).

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