

September 1, 2016

Robert M. Califf, M.D.
Commissioner
10903 New Hampshire Ave.
Silver Spring, MD 20993
Docket No. FDA-2015-D-3719

Dear Dr. Califf:

Thank you for the opportunity to comment on Docket No. FDA-2015-D-3719: Draft Guidances Relating to the Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products. The American Thoracic Society (ATS) has been closely following the development of cell-based therapeutic modalities for respiratory diseases such as COPD and cystic fibrosis. As patient access to safe and effective cell and tissue-based therapies strongly depends on FDA regulatory requirements, we find of particular interest the new FDA draft guidances for industry. We specifically refer to “Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products”, “Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations”, “Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products”, and “Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception” documents that are currently available for public deliberation.

In general, we consider the new guidances to be helpful by clarifying key definitions such as “homologous use”, “minimal manipulation” and “surgical exemption” and by removing vulnerable “gray areas” in the existing FDA regulations that have allowed for the appearance of hundreds of US clinics (Knoepfler and Turner, *Cell Stem Cell*, 2016; Berger et al, *Cell Stem Cell*, 2016) offering unregulated and unproven stem cell-based therapies. Despite the non-binding nature of the guidances, they may encourage systematic regulatory actions regarding this type of “clinic” outfits, which will be welcomed by our professional society. We provide detailed comments for each guidance below.

1) “Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products”

Title 21 of the Code of Federal Regulations (CFR) Part 1271 defines, among others, the criteria that exempt human cells, tissues, and cellular and tissue-based products (HCT/Ps) from the requirements of section 351 of the PHS Act (regulation as drug or device including pre-market review). One of the criteria, namely “minimal manipulation” had not been clearly defined in the past and this has been used as a “loophole” for outfits that offer unregulated cell based-therapies for various ailments, including lung diseases.



There are several examples of structural and non-structural tissue manipulation in this guidance and we believe the more relevant ones to tissue/cell products for lung diseases are Points 10 and 12. The ATS agrees with the example given in Point 10 that considers processing of adipose tissue as more than minimal manipulation. This implies that the stromal vascular fraction (SVF) commonly isolated from dissociation of subcutaneous adipose tissue would be regulated as a drug and we concur with this view (see additional comments for the Adipose Tissue-related guidance below). We also agree with Point 12 that any processing -including, but not limited to, ex vivo expansion- “that alters any relevant biological characteristics of cells or nonstructural tissues generally would be considered more than minimal manipulation”.

Nevertheless, there are other passages in the draft guidance that are unclear and may re-introduce ambiguity in the interpretation of the guidance. For example, there is not a clear definition of tissues that have a dual role, i.e. perform both structural and non-structural (metabolic) functions such as fat tissue (Point 2 of the guidance). This may cause confusion as some manipulations may alter the structural but not the metabolic function and vice versa. Furthermore, the sentence “...separation of structural tissue into components in which the relevant characteristics relating to reconstruction, repair, or replacement are not altered generally would be considered minimal manipulation...” from Point 7 needs clarification. Does the sentence refer to all components of the tissue? Would, for instance, the fat fraction and the SVF originating from enzymatic treatment of fat tissue be considered minimally manipulated?

2) “Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products”

We welcome this guidance that is supposed to further clarify the concept of “homologous use” for HCT/Ps. Although the guidance provides several examples of homologous and non-homologous use for various cell/tissue products, it does not directly address the two major unregulated cell therapies currently advertised and administered to patients with respiratory diseases, namely SVF and unexpanded mesenchymal stromal cells (MSCs). We presume that the sentence “Generally, if an HCT/P is intended for use as an unproven treatment for a myriad of diseases or conditions, the HCT/P is likely not intended for homologous use only” in Q&A 1 indirectly refers to such products but we think additional examples will be useful. Most of the providers of SVF and unexpanded MSCs claim generic anti-inflammatory effects of their products. Does the FDA consider reduction of inflammation as one of the main functions of native SVF or resident MSCs (from bone marrow, adipose tissue etc.)? If not, it should be clearly stated that use of purified SVF or unexpanded MSCs for most conditions, including lung diseases, is non-homologous use and their putative anti-inflammatory effects arise from more than minimal manipulation.



3) “Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations”

The fact that the FDA has developed a draft guidance specifically for HCT/Ps derived from adipose tissue indicates that the Agency is determined to take a more active stance against the unregulated use of SVF as cell/tissue therapy. We welcome this development since we have witnessed the proliferation of outfits offering SVF as treatment for several respiratory diseases with no proof of long term safety or of efficacy. Therefore, we agree with the FDA that separation of SVF from adipose tissue is more than minimal manipulation and that a “surgical exemption” does not apply, even if the extracted SVF is destined for autologous use in the same surgical procedure. This is a critical regulatory issue, as SVF separation is a commonly utilized method employed by a large number of outfits authorizing unproven and unregulated use of cell administrations. Nevertheless, as the guidance is non-binding, it is not clear to us whether it will inform future FDA actions regarding outfits treating patient with SVF. It is critical to make this binding and/or have clear methods of enforcement.

4) “Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception”

The purpose of this guidance is to further clarify the so-called “surgical exemption” (found in 21 CFR 1271.15(b)) that refers to autologous use of HCT/Ps in the same procedure and it states: “You are not required to comply with the requirements of this part if you are an establishment that removes HCT/P’s from an individual and implants such HCT/P’s into the same individual during the same surgical procedure (ATS note: *not necessarily on the same day*)”. The ATS considers this guidance a useful extension of previous rules regarding this exemption. Although this guidance is non-binding, we hope it will lead to better monitoring of “clinics” that offer unproven tissue and cell-based therapies claiming the “surgical exemption” for their procedures. This is important since such establishments do not have to register and list with the FDA, essentially operating under the Agency’s radar.

Thank you for your consideration of our comments. Please contact Nuala S. Moore, Assoc. Director of Government Relations at (202) 296.9770 or Nmoore@thoracic.org with any questions.

Sincerely,



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President
American Thoracic Society

