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CELLTEX
THERAPEUTICS

Joel Martinez
Consumer Safety Officer
Bioresearch Monitoring Specialist
US Food and Drug Administration
10100 Reunion Place
Suite 100
San Antonio TX 78216-4153

Linda M. Hoover
Investigator
US Food and Drug Administration
200 Chestnut Street
US Custom House
Room 900
Philadelphia PA 19106

– CONFIDENTIAL –
NOT SUBJECT TO PUBLIC DISCLOSURE
FOIA EXEMPT, 5 USC 552(b)(4)

Dear Mr. Martinez and Ms. Hoover:

This letter is a response to your request that Celltex Therapeutics Corporation ("Celltex") provide a written explanation of why the adult adipose-derived mesenchymal stem cells ("AdMSCs") banked and/or expanded at Celltex are not drugs under the federal Food, Drug and Cosmetic Act ("FDCA"). Below we explain in detail. We welcome the opportunity to discuss this further with FDA, including meeting with CBER officials in Washington if that would aid in this evaluation. We can also provide additional information upon request.[1]

Confidentiality Statement

This letter contains confidential business data and strategy information throughout its content and also contains trade secrets. All of that information is closely held by

[1] We have cited to (and have attached) the most recent review articles that provide summaries of the original research in this area. This does not represent all of the scientific literature on the topics discussed in this letter. There are many more peer-reviewed articles on these topics available that we can provide at your request.

Celltex and could potentially give competitors and Celltex's business relationships a competitive advantage. Celltex limits access to that information to its staff and agents who must have access in order to perform their duties. This letter is thus exempt from the public disclosure requirements of the Freedom of Information Act (FOIA) for confidential business records and trade secrets under 5 USC 552(b)(4). Please keep this letter secure and limit access to those FDA employees who must have access in order to perform their duties. If any other disclosure is contemplated please contact Celltex or its counsel in advance so that Celltex may determine the nature and significance of the disclosure.

Celltex's Services

Celltex currently provides two services, both only for adult AdMSCs: (1) banking and (2) multiplication. For the purposes of this letter, "banking" refers to placing the AdMSCs in appropriate long-term cryopreservation conditions (b) (4) at Celltex's laboratory, the registered establishment. The specific steps for banking relevant to this letter are explained below. For the purposes of this letter, "multiplication" refers to using tissue culture techniques in Celltex's laboratory under sterile conditions, as discussed below, to allow the AdMSCs to naturally multiply in number, then placing the cells in sterile saline, and, finally, providing a specified quantity of stem cells to a physician for use in his/her clinical care of the person from whom the cells were recovered.

Celltex does not perform recovery services nor does it provide the HCT/Ps (the AdMSCs) back to the individual. Instead, it only provides the AdMSCs to the individual's treating physician. Upon a physician's determination that an individual is an appropriate candidate to receive a therapeutic quantity of AdMSCs, a physician's office or other qualified healthcare office performs the AdMSC recovery service by extracting between (b) (4) and (b) (4) ccs (depending on the age of the individual) of adipose tissue from the person's (b) (4) or (b) (4) region. The extraction procedure is relatively simple, requiring only local anesthetic (generally referred to as a "(b) (4) " and performed (b) (4) using a (b) (4) Recovery is performed only by healthcare providers (currently (b) (4)) who Celltex has evaluated and trained in advance. The adipose tissue is labeled by the medical staff of the office in accordance with Celltex's training then shipped to Celltex's laboratory by (b) (4) again in accordance with Celltex's training, in shipping material provided by Celltex. The laboratory services for banking and multiplication are discussed further below, showing that the cells in each service are not drugs.

Banked cells are cryopreserved and stored in Celltex's laboratory (b) (4) storage facility. Upon the treating physician's request, Celltex sends the AdMSCs by (b) (4) ((b) (4)) to the physician with appropriate shipping and packaging conditions to keep the cells secure and safe. Celltex's services are for autologous use only (whether for banking or multiplication).

Summary of Legal Status of Celltex's AdMSCs

Below are the relevant legal authorities that apply to Celltex's services. Celltex's "products" (the AdMSCs cells for which it provides services) are HCT/Ps regulated solely as "361 products" under section 361 of the Public Health Services Act (PHS). They are not drugs under the FDCA. To summarize, the AdMSCs are not more than minimally manipulated at Celltex so that there is no alteration of their relevant biological characteristics. Celltex separates the AdMSCs and then stores the cells, either for long-term cryopreservation or under conditions that allow them to expand in number without differentiation, a natural characteristic of these cells. 21 CFR 1271.10(a)(1). The AdMSCs are for homologous use only. Celltex intends them to remain, from the beginning to end of its services, multipotent AdMSCs. Celltex intends the AdMSCs – that are returned to the physician treating the individual from whom they were recovered to perform the same basic functions – to be multipotent AdMSCs. That intention is reflected in Celltex's current protocols and its seminar training materials for physicians. 21 CFR 1271.10(a)(2). Celltex's "manufacture" of AdMSCs combines[2] the cells only with storage agents: a cell culture media (that is well-tested and described in peer-reviewed scientific literature) that allows the cells to expand under their natural capabilities without differentiation, then sterile saline. The cells undergo (b) (4) (for banking) or (b) (4) (for multiplication) and then are collected and suspended in sterile saline for use. As discussed below, those storage conditions do not raise new clinical safety concerns. 21 CFR 1271.10(a)(3). Finally, the AdMSCs have a systemic effect and are for autologous use only. 21 CFR 1271.10(a)(4)(i). Thus these are 361 products only, not drugs. Each point is discussed further below for each Celltex service.

Relevant Legal Authorities

21 CFR §1271.3 states in pertinent part:

> (a) Autologous use means the implantation, transplantation, infusion or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered.
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> (c) Homologous use means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.
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> (d) Human cells, tissues or cellular or tissue-based products (HCT/Ps) means articles containing or consisting of human cells or tissues that are

[2] There is an initial step where the cells are separated from the adipose tissue by the addition of the (b) (4) to (b) (4) in the connective tissue and (b) (4) which then (b) (4) of stem cells. Both of those techniques are well-described and understood in scientific literature to keep cells intact and unaltered.

intended for implantation, transplantation, infusion, or transfer into a human recipient.

(e) Manufacture means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor.

(f) Minimal manipulation means: … (2) for cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

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(ff) Processing means any activity performed on an HCT/P other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage. 21 CFR 1271.10 is the controlling regulation.

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(jj) Storage means holding HCT/Ps for future processing and/or distribution.

21 CFR §1271.10 states the following:

(a) An HCT/P is regulated solely under section 361 of the PHS Act and the regulations in this part if it meets all of the following criteria:
   (1) the HCT/P is minimally manipulated;
   (2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indicia of the manufacturer's objective intent;
   (3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids or the sterilizing, preserving or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
   (4) Either
      a. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

b. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function and:
   i. Is for autologous use;
   ii. Is for allogenic use in a first-degree or second-degree blood relative; or
   iii. Is for reproductive use

Below we apply these regulatory criteria to our banking and multiplication services.

Celltex's AdMSCs Are Only 361 Products Under 21 CFR 1271.10

The AdMSCs in Celltex's banking and multiplication procedures are not more than minimally manipulated.

Mesenchymal stem cells have a well-documented inherent ability for self-renewal and proliferation. *E.g.* Deak E, Seifried, E, Henschler, R. "Homing Pathways of Mesenchymal Stromal Cells (MSCs) and Their Role in Clinical Applications." Int'l Rev of Immunology, 29:514-529 at 515, 2010.

Celltex licenses the technology of RNL Bio Co. Ltd., Korea (RNL) for AdMSCs. In 2011, RNL published its methodology for these services in the peer-reviewed journal Stem Cells and Development. Ra, JC, Shin IS, Kim SH et al. "Safety of Intravenous Infusion of Human Adipose Tissue-Derived Mesenchymal Stem Cells in Animals and Humans," Stem Cells and Development, 20(8):1297-1308 (2011)(hereinafter "Ra, Shin *et al*"). That methodology was reviewed by other independent researchers in the editorial Gimble JM, Bunnell BA, Chiu ES, and Guilak F. "Taking Stem Cells Beyond Discovery: A Milestone in the Reporting of Regulatory Requirements for Cell Therapy." Stem Cells and Development 20(8):1295-1296 (2011).

Celltex's isolation and culture methodology is stated in step by step detail in Ra, Shin *et al* on page 1298. Celltex uses that method including the use of the same reagents and media with only one minor change, using a media from a company located in a country that is BSE (bovine spongiform encephalitis) free. That change in media was made because after the Ra, Shin *et al* study was performed, the country from which the original media was purchased had a BSE finding. Celltex, from the beginning of its operations, has used only media from BSE-free countries. RNL validated that the current media is a valid substitute for the media used in the study. A copy of that documentation is available on request.

Cells for banking are cultured for (b) (4) and then (b) (4), and (b) (4) in sterile (b) (4) saline as specified in Ra, Shin *et al*. They are then frozen and placed in the facility's (b) (4) freezer for long-term cryopreservation. Cells for multiplication are cultured through (b) (4) passages and then washed,

collected, and suspended in sterile (b) (4) saline[3], again as specified in Ra, Shin *et al*. No stimulant or other chemical is added to stimulate proliferation of the cells. Cell proliferation occurs at its natural rate, a characteristic of AdMSCs. Tolar, JT, Le Blanc K, Keating, A, Blazar BR. "Concise Review: Hitting the Right Spot with Mesenchymal Stromal Cells." Stem Cells, 28 1446-1455 (2010).

Ra, Shin *et al* examined the relevant biological characteristics of the AdMSCs after culturing multiple passages: morphology, immunophenotype, differentiation capability, and genetic stability. Those include the biological characteristics recognized as the definition of MSCs by the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy ("ISCT"). The ISCT characteristics are plastic adherence, lack of hematopoietic markers (CD45, CD34, CD14, CD11b, CD79α, CD19, or HLA-DR expression); and trilineage (adipogenic, chondrogenic, and osteogenic differentiation) potential. Deak *et al*; *See also* Parekkadan B, Milwid JM. "Mesenchymal Stem Cells as Therapeutics," Annu. Rev. Biomed. Eng. 12:87-117 at 93 (2010). Ra, Shin *et al* added to that other characteristics of morphology (in addition to plastic adhesion) and genetic stability. Each is discussed below.

Morphology (Ra, Shin *et al* at 1300). AdMSCs were spindle-shaped with a fibroblast-like morphology. They adhered to the plastic plate during cell culture. Those characteristics were well-preserved during repeated subculture. *Id.* Thus the morphology of the AdMSCs remained intact and also met the ISCT standard.

Immunophenotype (Ra, Shin *et al* at 1300). The immunophenotypic characterization of the cells, the surface protein expression, was assessed by (b) (4) *Id.* Every population showed a (b) (4) of cells. Negative markers (b) (4) and (b) (4) remained low through all passages and positive markers ((b) (4)) remained high through multiple passages, most particularly the (b) (4) passages which Celltex uses in banking and multiplication services. Thus the immunophenotype of the AdMSCs remained intact and also met the ISCT standard.

Differentiation capability (Ra, Shin *et al* at 1301). The cells were cultured in each passage up to (b) (4) . Multiplication was designed specifically to keep the cells from differentiating in culture, so that they remain MSCs. However, the differentiation capability of MSCs is a key biological characteristic. The ability of these cells to differentiate after multiplication was examined. Ra, Shin *et al* confirmed that after proliferation these cells remain capable of differentiation into adipocytes, osteoblasts, chondroblasts, myoblasts, and neuronal cells. The confirmation was determined by (b) (4) . Thus the AdMSCs continued to have trilineage differentiation potential, meeting the ISCT standard.

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[3] Ra, Shin *et al* 2011 verified the stability of the AdMSCs in saline solution for the storage time and conditions. There was no significant decrease in survival rate or total cell number. Positive and negative surface markers for MSCs were verified at each time point for each sample, confirming the cells were MSCs.

Genetic stability (Ra, Shin *et al* at 1301). (b) (4) and (b) (4) were used to examine genetic stability during proliferation. (b) (4) identifies the (b) (4) if a large DNA area is affected while (b) (4) shows changes in a small DNA area. (b) (4) analysis showed no abnormalities in any sample up to (b) (4) (b) (4) results did not show any substantial genotypic differences regardless of passage number with in the same origin. While not specified for MSCs, the International Stem Cell Initiative considers Karyotyping and SNP genotyping a necessary control for genetic integrity of embryonic stem cells. *Id.* Applying that standard to MSCs, the tests show that the genetic integrity of AdMSCs remains intact.

Thus, all relevant biological characteristics of AdMSCs remain the same and are not altered by the cell banking and multiplication services. The AdMSCs are not more than minimally modified under 21 CFR 1271.10(a)(1).

The AdMSCs in Celltex's banking and multiplication procedures are homologous.

The human body is designed to heal itself through a number of mechanisms. One of its healing tools is mesenchymal stem cells (MSCs).[4] Parekkadan and Milwid at 97. MSCs have several characteristics that contribute to this function. First, MSCs are multipotent, meaning they can differentiate into cells of multiple types including adipocytes, osteocytes, chondrocytes, hepatocyes, neurons, muscle cells and epithelial cells depending on the surrounding microenvironment. Ra JC, Kang SK, Shin IS, Park HG, *et al.* "Stem cell treatment for patients with autoimmune disease by systemic infusion of culture-expanded autologous adipose tissue derived mesenchymal stem cells, J Translational Medicine," 9:181 1-11 (2011). (hereinafter "Ra, Kang *et al*"); *see also* Parekkadan and Milwid at 96-97; 104. Thus, MSCs have a potential for engraftment into a number of different tissues.

Second, MSCs have been demonstrated to home to sites of inflammation following a density gradient of chemokines that leads the MSCs to inflammation sites in the body. Salem HK and Thiemerman C, "Mesenchymal Stromal Cells: Current Understanding and Clinical Status." Stem Cells,28:585-596 at 587 (2010). Chemokines are released after tissue damage and during inflammation. MSCs express multiple receptors for chemokines. Salem at 587. This homing mechanism makes systemic intravenous delivery both effective and safe. *Id*; Tolar at 1451. MSC's injected systemically are inherenly capable of homing to the site(s) where their natural functions are needed.

Finally, MSCs also have immunomodulatory properties and paracrine effects. Ra, Kang *et al* at 2; Parekkadan and Milwid at 97-99; Tolar at 1448; Djouad F, Bouffi C, Ghannam S, Noel D, Jorgensen C. "Mesenchymal stem cells: innovative therapeutic

[4] As stated above, MSCs are distributed throughout the body. *Eg*, Ra, Kang *et al.* Adipose tissues contain approximately 100,000 MSCs in each gram of fat. Ra, Shin *et al.* As stated above, the term "AdMSCs" refers to MSC's recovered from adipose tissue, in Celltex's methodology that recovery is from the (b) (4) region. *Id.*

tools for rheumatic diseases." Nat. Rev. Rheumatol. 5, 392-399 at 394-395 (2009). MSCs have been shown to secrete large quantities of immunomodulatory molecules including cytokines, antioxidants, proangiogenic substances, and trophic factors that function to limit the body's stress response, block apoptosis and recruit other immune and reparative cells in the environment. Tolar at 1448. They also stimulate resident cells and attract cells to the environment for tissue regeneration functions. Djouad at 393-394. They have been shown to stimulate angiogenesis and to have anti-fibrotic properties. Djouad at 394.

Celltex's objective intent is reflected in its IRB-approved protocols and in its seminar for physicians. At this time it has no other promotional materials. Its website is in development and will be consistent with the protocols and seminar. A copy of the seminar slideshow was provided during the inspection. The slideshow goes over each of the above characteristics and excerpts from the published peer-reviewed literature where those characteristics have been documented in disease or injury treatment studies. Celltex's seminar discusses the above-described characteristics of MSCs (including AdMSCs). Those materials demonstrate that it is Celltex's objective intent to provide cells to supplement the body with the person's own AdMSCs. Those supplemental AdMSCs perform the same basic function as the AdMSCs that were extracted from the person. Thus, under 21 CFR 1271.3(c) the cells are for homologous use under 21 CFR 1271.10(a)(2).

The AdMSCs in Celltex's banking and multiplication services are combined only with storage and preservation agents that do not raise new clinical safety concerns with respect to the HCT/P.

There are no clinical safety concerns concerning the AdMSCs that undergo Celltex's services. Ra, Shin *et al* details the isolation and culture of these cells and the agents used. In summary, the adipose tissue is (b) (4) with (b) (4) then centrifuged to isolate a (b) (4) that is (b) (4) and then cultured. The culture media is (b) (4) (b) (4) containing (b) (4) and (b) (4) (b) (4) and then changed for subsequent passages to (b) (4) media with (b) (4) . After culturing is completed, the cells are completely washed repeatedly with sterile (b) (4) until all medium is removed. That is verified through (b) (4) using a (b) (4) kit to measure that (b) (4) The cells for use by physicians are (b) (4) in sterile saline. Ra, Shin *et al*. No stimulants or other modifying agents are added at any stage in the process. The process is specifically designed to provide a well-established laboratory environment for the cell's to proliferate, an innate characteristic. Use of these agents is well-understood in the scientific literature. In addition to the long history of use of these agents in cell proliferation for clinical applications, the articles Ra, Shin *et al* and Ra, Kahn *et al* also show that specifically this combination presents no new safety concerns. Thus under 21 CFR 1271.10(a)(3) there are no clinical safety concerns with using these storage and preservation agents.

The AdMSCs in Celltex's banking and multiplication services are intended for a systemic effect/metabolic processes and are only for autologous use.

As stated above, Celltex provides services for only autologous use of stem cells. It releases stem cells only to physicians for clinical use in the same person as the donor. It uses redundant checks in its laboratory in compliance with the Good Tissue Practices (GTP) of 21 CFR Part 1271 to ensure that the cells are labeled and tracked throughout all steps and ensured to be autologous at the time of release. Thus, the AdMSCs are for autologous use only under 21 CFR 1271.10(a)(4)(b)(i).

Conclusion

Celltex is in compliance with applicable federal law. Its AdMSCs are 361 products under Section 361 of the PHS as described in detail above. In accordance with 21 CFR 1271.10 Celltex's AdMSCs are only 361 products, not drugs under the FDCA. If FDA has any questions about the above analysis we welcome the opportunity to discuss the matter further.

Please do not hesitate to contact me with any questions.

Best regards,

David G. Eller
Chief Executive Officer
Celltex Therapeutics Corporation

Attachments

✓ Deak E, Seifried, E, Henschler, R. Homing Pathways of Mesenchymal Stromal Cells (MSCs) and Their Role in Clinical Applications. Int'l Rev of Immunology, 29:514-529 at 515, 2010.

✓ Djouad F, Bouffi C, Ghannam S, Noel D, Jorgensen C. Mesenchymal stem cells: innovative therapeutic tools for rheumatic diseases. Nat. Rev. Rheumatol. 5, 392-399 at 394-395 (2009).

✓ Gimble JM, Bunnell BA, Chiu ES, and Guilak F. Taking Stem Cells Beyond Discovery: A Milestone in the Reporting of Regulatory Requirements for Cell Therapy. Stem Cells and Development 20(8):1295-1296 (2011).

✓ Parekkadan B, Milwid JM. Mesenchymal Stem Cells as Therapeutics, Annu. Rev. Biomed. Eng. 12:87-117 at 93 (2010).

✓ Ra JC, Kang SK, Shin IS, Park HG, *et al.* Stem cell treatment for patients with autoimmune disease by systemic infusion of culture-expanded autologous adipose tissue derived mesenchymal stem cells, J Translational Medicine, 9:181 1-11 (2011).

✓ Ra, JC, Shin IS, Kim SH et al. Safety of Intravenous Infusion of Human Adipose Tissue-Derived Mesenchymal Stem Cells in Animals and Humans, Stem Cells and Development, 20(8):1297-1308 (2011)

✓ Salem HK and Thiemerman C, Mesenchymal Stromal Cells: Current Understanding and Clinical Status. Stem Cells,28:585-596 at 587 (2010).

✓ Tolar, JT, Le Blanc K, Keating, A, Blazar BR. Concise Review: Hitting the Right Spot with Mesenchymal Stromal Cells. Stem Cells, 28 1446-1455 (2010).