

[Home](#) [Inspections, Compliance, Enforcement, and Criminal Investigations](#) [Enforcement Actions](#) [Warning Letters](#)
Inspections, Compliance, Enforcement, and Criminal Investigations

Celltex Therapeutics Corporation 9/24/12



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville, MD 20852-1448

WARNING LETTER

September 24, 2012

CBER-12-10

VIA FACSIMILE AND UPS

David G. Eller
Chief Executive Officer and President
CellTex Therapeutics Corporation
12621 W. Airport Blvd., Suite 800
Sugarland, TX 77478

Dear Mr. Eller:

During an inspection of your firm, CellTex Therapeutics Corporation, located at 12621 W. Airport Blvd., Suite 800, Sugarland, Texas 77478, conducted between April 16 and April 27, 2012, the Food and Drug Administration (FDA) determined that your firm receives adipose tissue (aka lipoaspirate) that has been recovered from autologous donors. Using **(b)(4)**, your firm isolates cells from the lipoaspirate, and selects and expands through cell culture, adipose derived mesenchymal stem cells (AdMSC). The autologous product is administered to patients by **(b)(4)** for a wide variety of indications.

Our investigation of your firm further determined that your firm promotes your process and the use of AdMSC to physicians by encouraging physicians to enroll patients in one of your clinical trials. Your protocols entitled, **(b)(4)** both explain that patients have an opportunity to be enrolled in these clinical trials if they are presently diagnosed with an **(b)(4)** for which there is hypothesized or demonstrated clinical benefit for the **(b)(4)** of the AdMSC product.

CellTex's product is a human cell, tissue, or cellular and tissue-based product (HCT/P) as defined in 21 CFR 1271.3(d). However, this product does not meet all of the criteria in 21 CFR 1271.10(a) and therefore is not regulated solely under section 361 of the Public Health Service Act (PHS Act) [42 U.S.C. 264] and the regulations in 21 CFR Part 1271. Specifically, your processing with **(b)(4)** alters the original relevant characteristics of the adipose tissue relating to the tissue's utility for reconstruction, repair, or replacement. Therefore, your processing does not meet the definition of minimal manipulation for structural tissue such as adipose tissue as

described in 21 CFR 1271.3(f)(1). Furthermore, your firm's process of tissue culture, expansion and passaging also fails to meet the definition of minimal manipulation for structural tissue in 21 CFR 1271.3(f)(1). As a result, the CellTex product does not meet the criterion in 21 CFR 1271.10(a).

Additionally, the clinical uses detailed in your protocols do not meet the definition of homologous use in 21 CFR 1271.3(c). Also records collected during inspection indicate clinical uses of the AdMSC product involving **(b)(4)**. These uses would likely not be considered homologous use and as a result, the CellTex product does not meet the criterion in 21 CFR 1271.10(a) for regulation solely under section 361 of the PHS Act and 21 CFR Part 1271.

You are promoting the CellTex product in a manner that causes the product to be a drug under section 201(g) of the FDC Act [21 U.S.C. 321(g)] and a biological product as defined in section 351(i) of the PHS Act [42 U.S.C. 262(i)]. Please be advised that in order to lawfully market such a biological drug product, a valid biologics license must be in effect [21 U.S.C. 355(a); 42 U.S.C. 262(a)]. Such licenses are issued only after a showing of safety and efficacy for the product's intended use. While in the development stage, for example, while being studied in a clinical investigation, such products may be used in humans only if the sponsor has an investigational new drug (IND) application in effect as specified by FDA regulations [21 U.S.C. 355(i); 21 CFR Part 312]. The CellTex AdMSC product is not the subject of an approved biologics license application (BLA) nor is there an IND in effect. Based on this information, your product violates the FDC Act and the PHS Act.

Additionally, during the inspection, FDA investigators documented evidence of significant deviations from current good manufacturing practice (CGMP) and current good tissue practice (CGTP) in the manufacture of **(b)(4)** batches of your AdMSC product from July 2011 through April 2012. These deviations from CGMP and CGTP include the applicable requirements of Section 501(a)(2)(B) of the FDC Act, Sections 351(a) and 361 of the PHS Act, and Title 21, Code of Federal Regulations, (21 CFR) Parts 210, 211, and 1271.

At the close of the inspection, our investigators issued a Form FDA 483, Inspectional Observations, which described a number of significant objectionable conditions relating to your facility's compliance with CGMP and CGTP. These include, but are not limited to the following:

1. Failure to establish and follow written procedures designed to prevent microbiological contamination of drug products purporting to be sterile. Such procedures shall include validation of all aseptic and sterilization processes [21 CFR 211.113(b)]. For example:
 - a. The aseptic manufacturing process at your Sugarland, Texas facility has not been validated.
 - b. You have not validated your aseptic gowning process and routine personnel monitoring is not performed.
 - c. You have not validated your autoclave sterilization cycle. The autoclave is used to sterilize equipment used in aseptic processing.
2. Failure to establish and follow written production and process control procedures designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess and to assure such procedures are drafted, reviewed and approved by the appropriate organizational units [21 CFR 211.100(a)]. For example, you have failed to validate your manufacturing process at your Sugarland, Texas facility.
3. Failure to maintain laboratory controls that include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)]. Specifically, you do not perform testing of the final AdMSC product, including tests for identity, safety, purity and potency.

4. Failure to test the AdMSC product, a **(b)(4)** drug product, for the presence of **(b)(4)** although a reasonable possibility exists that the **(b)(4)** drug product has been exposed to cross contamination with **(b)(4)**. Your firm used **(b)(4)** during culturing of your AdMSC product. Specifically, **(b)(4)** was used during manufacturing of the **(b)(4)** batches of your AdMSC product reviewed. The **(b)(4)** drug product must not be marketed if detectable levels of **(b)(4)** are found.

5. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed [21 CFR 211.192]. For example, there were no investigations performed for the following:

- a. There were numerous in-process sterility failures for AdMSC batches.
- b. Bacterial and fungal limits have been exceeded for the Biological Safety Cabinets (BSCs) used in manufacturing, and in the gowning and general areas.

6. Failure to assure all drug product production and control records, including those for packaging and labeling, are reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before the batch is released or distributed [21 CFR 211.192]. There was no evidence of review and approval by the quality control unit prior to release of any of the **(b)(4)** batches of your AdMSC product.

7. You failed to assure batch production and control records are prepared for each batch of drug product produced and that you document that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished [21 CFR 211.188(b)]. For example:

- a. There is no documentation of the addition of **(b)(4)** to your final AdMSC product.
- b. There is no documentation of the personnel involved in packaging of the final AdMSC product.

8. Failure to assure that distribution records contain the name and strength of the product and the description of the dosage form, and the name and address of the consignee [21 CFR 211.196]. Specifically, of the **(b)(4)** batches reviewed, all were lacking a product name, dosage form, and the name and address of the consignee.

9. Failure to establish and follow written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures [21 CFR 211.80(a)]. Specifically, there are no written procedures in place for the supplies and reagents you use to manufacture your AdMSC product at your Sugarland, Texas facility.

10. Failure to assure that each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit [21 CFR 211.84(a)]. For example, the following components and containers are not tested or examined before release:

- a. The **(b)(4)** used to rinse the cells and formulate the final drug product. More importantly, the Certificate of Analysis for the **(b)(4)** states: "For in vitro diagnostic use. CAUTION: Not for human or animal therapeutic use. Uses other than the labeled intended use may be a violation of local law."
- b. The **(b)(4)** that contain the final product.

11. Failure to establish a written record of major equipment cleaning, maintenance and use to include in that record the date, time, product and lot number of each batch processed [21 CFR 211.182]. For example, there are no written records of cleaning, maintenance and use for the **(b)(4)** and BSCs used for aseptic processing or the refrigerators and freezers used to store **(b)(4)** and reagents used to manufacture the AdMSC product.

12. Failure to assure that automatic, mechanical and electronic equipment used in the manufacture, processing, packing and holding of a drug product is routinely calibrated, inspected or checked according to a written program designed to assure proper performance, and that written records of those calibration checks and inspections are maintained [21 CFR 211.68(a)]. Specifically, there is no evidence that operational or performance qualification has been performed for your BSCs to assure their proper function.

13. Failure to assure an adequate control system for temperature and humidity is in place to prevent contamination during aseptic processing [21 CFR 211.42(c)(10)(ii)]. Specifically, there is no system for the monitoring of temperature or humidity of the processing rooms at your Sugarland, Texas facility, where you manufacture the AdMSC product. The manufacturer's manual for your **(b)(4)** BSCs states that they should be operated in environmental conditions of a maximum relative humidity of **(b)(4)**

14. Failure to assure an air supply filtered through high-efficiency particulate air filters under positive pressure for aseptic processing operations is in place to prevent contamination during aseptic processing [21 CFR 211.42(c)(10)(iii)]. Specifically, your Sugarland, Texas facility does not filter the air supply through high-efficiency particulate air filters under positive pressure between the clean rooms and the exterior rooms to assure that non-controlled air does not flow into the clean rooms.

15. Failure to assure a system for monitoring environmental conditions is in place to prevent contamination during aseptic processing [21 CFR 211.42(c)(10)(iv)]. Specifically, your Sugarland, Texas facility does not have an established environmental monitoring program.

16. Failure to establish and follow written procedures describing the handling of all written and oral complaints regarding a drug product [21 CFR 211.198(a)]. Specifically, during the inspection you could not provide evidence of the existence of written procedures describing the handling of written and oral complaints related to your AdMSC product.

17. Failure to establish a quality control unit that shall have:

- a. The responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated [21 CFR 211.22(a)];
- b. The responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the product [21 CFR 211.22(c)];
- c. The responsibilities and procedures applicable to the quality control unit in writing [21 CFR 211.22(d)].

18. Failure to label each HCT/P in accordance with the requirements in 21 CFR 1271.370. For example:

- a. The following information does not appear on the AdMSC product label: a distinct identification number affixed to the HCT/P container, and assigned in accordance with 21 CFR 1271.290(c); a description of the type of HCT/P; an expiration date, if any.

- b. The AdMSC product, which is for autologous use, was not prominently labeled as being "For autologous use only." This warning is required under 21 CFR 1271.90(b).

Additionally, significant deviations in the manufacture of your AdMSC intermediates were observed during the inspection. These deviations violate Section 501(a)(2)(B) of the FDC Act and Section 351(a) of the PHS Act. Specific areas of concern include, but are not limited to:

EQUIPMENT

19. You have not qualified any of the equipment used in manufacture, processing, packaging and holding of your AdMSC intermediates at your Sugarland, Texas facility.
20. There are no procedures designed to assure proper performance of equipment used in the culture/expansion of your AdMSC intermediates. For example:
- a. You did not calibrate your **(b)(4)** for temperature and **(b)(4)** to assure that their displays are accurate. Your manufacturing record specifies that culture is to be performed at **(b)(4)** degrees Celsius and **(b)(4)**
 - b. There is no indication that the temperature of the refrigerators and freezers used to store culture media, **(b)(4)**, and reagents used to manufacture the AdMSC product is consistently monitored.
21. The **(b)(4)** and **(b)(4)** used in production are placed directly on the floor rather than elevated on tables. Discarded **(b)(4)** and media bottles were observed next to this equipment during use.

PRODUCTION AND PROCESS CONTROLS

22. You have not validated your cell culture process and the aseptic processing involved in culturing of the cells. There were numerous in-process sterility failures for AdMSC batches indicating a lack of control of your aseptic process.
23. You do not document the daily checks of your culture **(b)(4)** for evidence of contamination.
24. You do not document checks of **(b)(4)** for contamination, or the routine changing of the **(b)(4)** in the **(b)(4)**
25. You do not document the temperature of your **(b)(4)** used during the adipose tissue **(b)(4)** step for isolating stem cells. Your Batch Production Record specifies that the temperature of the **(b)(4)** be **(b)(4)** degrees Celsius for the **(b)(4)** step.
26. The components used in production were not always labeled correctly, which could result in mix-ups. For example:
- a. A bottle labeled **(b)(4)** on one side was labeled **(b)(4)** on the other.
 - b. A bottle containing the culture medium **(b)(4)** (mesenchymal stem cell attachment culture medium supplemented with **(b)(4)**) was labeled **(b)(4)** on the lid, but **(b)(4)** on the side.

RECORDS AND REPORTS

27. On numerous occasions you failed to conduct investigations on sterility, **(b)(4)** and **(b)(4)** failures or "Indeterminate" results. Additionally, you did not investigate environmental excursions of "Too Numerous to Count" (TNTC) in the **(b)(4)** used for manufacture of your AdMSC intermediates.

CONTROL OF COMPONENTS

28. There are no procedures for receipt, identification, storage, handling, sampling, testing, and approval or rejection of the following supplies and components used to culture and expand the AdMSC intermediates.

- a. The (b)(4) used to prevent bacterial and fungal growth in the culture media.
- b. The (b)(4) and (b)(4) used for cell expansion.
- c. The (b)(4) used to harvest the AdMSC intermediates.
- d. The (b)(4) and (b)(4) conical (b)(4) tubes.
- e. The (b)(4), and (b)(4) serological pipettes.
- f. The (b)(4) added to the cells as a (b)(4).

29. (b)(4) frozen vials of isolated AdMSCs, which had not been expanded in culture, were received from the RNL locations in Germantown, MD, and Seoul, Korea for use in manufacturing. You had no records associated with these components.

REVIEW OF INSPECTIONAL RESPONSES

We acknowledge receipt of your written responses dated April 27, May 18, May 31, July 31, and August 31, 2012, which seek to address the inspectional observations on the Form FDA 483 issued at the close of the inspection, and we have reviewed their contents. We have concluded that your responses did not provide sufficient detail to fully assess the adequacy of your corrective actions.

Overall Response

Please provide details as to how you plan to deal with the biological drugs that have already been manufactured at your Sugarland, Texas facility in violation of the FDC Act and PHS Act. Additionally, we note that SOP's and records collected during the inspection as well as translated copies provided in your correspondence appear to relate to your RNL Bio facility in Korea and not your Sugarland, Texas facility. In your response, please address the concerns that your AdMSC product is a drug as defined in section 321(g) of the FDC Act and biological product as defined in section 351(i) of the PHS Act.

Neither this letter nor the observations noted on the form FDA 483, which were discussed with you at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility as management to assure that your establishment is in compliance with the provisions of the FDC Act, PHS Act, and all applicable Federal laws and regulations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include seizure and/or injunction.

For further information about IND requirements, contact Dr. Patrick Riggins, Director of Regulatory Management Staff, Office of Cellular, Tissue, and Gene Therapies, at (301) 827-5366. Please include a copy of this letter with your initial submission to CBER.

Please notify this office in writing, within 15 working days of receipt of this letter, of any additional steps you have taken or will take to correct the noted violations and to prevent their recurrence. Include any documentation necessary to show that correction has been achieved. Corrective actions addressed in your prior responses may be referenced in your subsequent response. If you do not believe your product is in violation of the FDC Act and PHS Act, include your reasoning and any supporting information for our consideration. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to the U.S. Food and Drug Administration, Center for Biologics

Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, Maryland 20852-1448. If you have any questions regarding this letter, please contact the Division of Case Management, CBER at 301-827-6201.

Sincerely,
/S/
Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Warning Letter Company Response

- [Celltex Therapeutics Corporation Response Letter 10/16/12](#)¹

Page Last Updated: 11/29/2012

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Links on this page:

1. [/ICECI/EnforcementActions/WarningLetters/2012/ucm329736.htm](#)