DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214) 253-5200 Fax:(214) 253-5314 Industry Information: www.fda.gov/oc/industry	04/16/2012 - 04/27/2012
	FEI NUMBER 3009499974

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: David G. Eller,, CEO and President

FIRM NAME	STREET ADDRESS
Celltex Therapeutics Corporation	12621 W. Airport Blvd, Suite 800
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Sugarland, TX 77478	Biological Drug Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically,

You have manufactured (mesenchymal stem cells) MSC's which you have released for distribution at least (b) (4) times between 7/1/11 and to the present, however:

A. You have not performed a process validation for manufacturing MSC's to assure batch uniformity and integrity as related to each of the following finished product characteristics: viability of cells, the specified cell count, cell type, and appearance of cells.

B. You have not performed (b) (4) analyses on the final product to assure (b) (4) of the (b) (4) (b) (4) the final MSC's.

C. You have not verified the final product with a (b) (4) to assure the identity of the cell type in the final MSC's.

D. You have not performed (b) (4) assay to verify the (b) (4) the MSC's.

E. You have not performed installation qualification, operational qualification, and performance qualification on the biological safety cabinets, the incubators, and the centrifuges.

F. You have not performed a validation of your banking and thawing process to assure viability of MSC's.

G. You have no requirement for pressure differential between the clean rooms and the exterior rooms to assure that non-controlled air does not flow in the cleanrooms.

H. You have not monitored the temperature or humidity of the processing rooms where you manufactured

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mesenchymal stem cells (MSC's). The manufacturer's manual for your (b) (4) biological safety cabinets states that they should be operated in environmental conditions of a (b) (4)

OBSERVATION 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, and followed.

Specifically,

You have manufactured MSC's which you released for distribution at leas(b) (4) times between 7/1/11 to the present. The MSC's are intended to be administered to patients either intravenously or injected intra-articularly and must be sterile. This inspection revealed:

A. You have failed to validate your aseptic (mesenchymal stem cells) MSC's manufacturing process in order to prevent microbiological contamination. Sterility test failures have occurred of the following MSC's:(b) (4) (b) (4) and(b) (4)

B. You have not validated your aseptic gowning process in order to prevent microbiological contamination. In addition there is no data to support the validation/qualification of the autoclave cycle. The autoclave is used to sterilize gowning wardrobe (lab coat) and parts of the incubators.

C. You have not performed environmental swabbing of your (b) (4) biological safety cabinets as part of your environmental monitoring program. In addition a(b) (4) study has not been performed to assure an adequate air flow pattern underneath the biological safety cabinet. The biological safety cabinets are used to aseptically manufacture the MSC's.

D. Environmental test results of the clean room, biosafety cabinets, and gowning area show the isolation of microorganisms as the result of the use of settling plates. Some of the microbiological counts documented are beyond the established specifications. There is no data to show that the microorganisms isolated have been identified or investigated.

OBSERVATION 3

Written records are not made of investigations into the failure of a batch or any of its components to meet specifications.

Specifically,

A failure investigation was not performed for the following out of specification results and/or failures to determine the underlying reason or source of the failure:

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A. Sterility Testing: Sterility test results show the following MSC's failed initial and repeat testing for sterility: (b) (4) and (b) (4). The following MSC's failed initial sterility testing: (b) (4) and (b) (4)

B. Endotoxin Testing: Endotoxin test records show the following MSC's units failed initial endotoxin testing: (b) (4) on 12-20-11, (b) (4) on 12-7-11, (b) (4) and (b) (4) on 11-10-11.

C. Environmental Testing: Bacteria and Fungi test results have been exceeded for the BSC-(b) (4) (Biosafety Cabinet-CleanRoom(b) (4) Gowning Area, (b) (4) (CleanRoom(b) (4), (b) (4) (CleanRoom(b) (4) and BSC(b) (4) (BioSafety Cabinet-Clean Room(b) (4) BSC-M (Biosafety Cabinet-Manufacturing), BSC-Q (Biosafety Cabinet-Quality Control), CleanRoom(b) (4)

In addition there is no written procedure for conducting failure investigations.

OBSERVATION 4

Drug product production and control records, are not reviewed by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.

Specifically,

You manufactured MSC's which you released for distribution at least (b) (4) times between 7/1/11 to the present. However, you have not reviewed all manufacturing records, (b) (4) test records, endotoxin test records, or sterility test records prior to the release for distribution of the mesenchymal stem cells (MSC's) that you manufactured as evidenced by the following:

A. (b) (4) - The inspector signature line on the manufacturing record dated 10-20-11 is blank, however, according to the outgoing log the MSC's were released for intravenous infusion on 10-21-11.

B. (b) (4) The inspector signature line on the manufacturing record dated 7-26-11 is blank, however, according to the outgoing log the MSC's were released for intravenous (IV) infusion on 10-11-11.

C. (b) (4) - The inspector signature line on the manufacturing record dated 10-6-11 is blank, however, according to the outgoing log the MSC's were released for intravenous (IV) infusion on 10-7-11.

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OBSERVATION 5

Batch production and control records do not include complete information relating to the production and control of each batch.

Specifically:

A. You do not document the addition of (b) (4) to your (b) (4) and (b) (4) media used in the manufacture of the MSC's.

B. You do not document the addition of (b) (4) to the (b) (4) media used for the banking of the MSC's.

C. You do not document the (b) (4) checks of your culture-expansion flasks of MSC's for evidence of contamination.

D. Manufacturing records lack required signatures. For example:

1. (b) (4) - Lacks a biopsy date, signature of tissue acceptance, inspector signature, performer signature.
2. (b) (4) - Lacks a signature of tissue acceptance, inspector signature, release signature for banking.
3. (b) (4) - Lacks a signature of tissue acceptance, inspector signature, release signature for banking

E. You do not document the identity of personnel involved in the packaging of the finished product (MSC's) for release and delivery to the consignee/physician for use.

F. You do not document in the Manufacturing Record the lot numbers used, or the expiration dates, of the following supplies and reagents used during the manufacture of the mesenchymal stem cells (MSC's):

1. The (b) (4) used to (b) (4) the (b) (4)
2. The (b) (4) used to (b) (4) the (b) (4)
3. The (b) (4) culture media.
4. The (b) (4) culture media.
5. The (b) (4) used to prevent bacterial and fungi growth
6. The (b) (4) and (b) (4) flasks used for cell culture expansion
7. The (b) (4) used to rinse the MSC's.
8. The (b) (4) used to harvest the MSC's
9. The (b) (4) and (b) (4) centrifuge tubes
10. The lot number of the (b) (4) serological pipettes is not recorded
11. The sterile saline for injection used to suspend the MSC's in the finished product

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12. The (b) (4) added to the culture media as cryopreservative

OBSERVATION 6

Equipment used in the manufacture, processing, packing or holding of drug products is not suitably located to facilitate operations for its intended use.

Specifically,

Table-top type centrifuges and (b) (4) incubator that you used for the manufacture of mesenchymal stem cells (MSC's) during this inspection were observed to have been operated while on the floor. You have (b) (4) model (b) (4) centrifuges, (b) (4) incubator model (b) (4) and (b) (4) incubator model (b) (4) on the Stem Cell Laboratory floor. This has been your standard of practice since your operations began on/about July 2011. All steps in the manufacture of mesenchymal stem cells (MSC's) requiring the use of these centrifuges or (b) (4) incubators was performed with these pieces of equipment on the floor.

OBSERVATION 7

HCT/Ps made available for distribution were not labeled accurately.

Specifically,

You distributed mesenchymal stem cells (MSC's) which were not labeled accurately in that the labels did not include the following:

A. The identity of the product (type of tissue), including whether or not it is sterile

B. The strength of the product (such at the number of MSC's per milliliter or syringe)

C. The statements "AUTOLOGOUS USE ONLY" or "NOT EVALUATED FOR INFECTIOUS SUBSTANCES"

D. The Biohazard legend

E. Instructions for use related to the prevention, transmission, or spread of communicable diseases

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OBSERVATION 8

The distinctive code for each lot of components is not used in recording the disposition of each lot.

Specifically,

A. You did not maintain a record of the receipt of supplies and reagents that you used to manufacture mesenchymal stem cells (MSC's), including:

1. Reagent or supply type
2. Quantity
3. Manufacturer
4. Lot number
5. Date of receipt
6. Expiration

B. Supplies and reagents that you regularly use during the manufacture of mesenchymal stem cells (MSC's) include:

1. The (b) (4) used to (b) (4) the (b) (4)
2. The (b) (4) used to (b) (4) the (b) (4)
3. The (b) (4) culture media.
4. The (b) (4) culture media.
5. The (b) (4) to prevent bacterial and fungi growth
6. The (b) (4) and (b) (4) flasks used for cell culture expansion
7. The (b) (4) used to rinse the MSC's.
8. The (b) (4) used to harvest the MSC's
9. The (b) (4) and (b) (4) centrifuge tubes
10. The (b) (4) serological pipettes
11. The sterile saline for injection
12. The (b) (4) added to the culture media as cryopreservative

OBSERVATION 9

Each lot of components was not appropriately identified as to its status in terms of being quarantined, approved or rejected.

Specifically,

Your process for verifying that your supplies and reagents used in the manufacture of MSC's met specifications before use did not include:

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A. The (b) (4) used to prevent bacterial and fungi growth in culture media

The Certificate of Analysis that you obtained for the Investigators during this inspection for the (b) (4) states, "FOR RESEARCH USE ONLY. CAUTION: Not intended for human or animal diagnostic or therapeutic uses."

B. The (b) (4) and (b) (4) flasks used for cell culture expansion

C. The (b) (4) used to rinse the MSC's.

The Certificate of Analysis for the (b) (4) that you obtained for the Investigators during this inspection states, "CAUTION: Not for human or animal therapeutic use. Uses other than the labeled intended use may be a violation of local law."

D. The (b) (4) used to harvest the MSC's

The Certificate of Analysis for the (b) (4) Express states, "FOR RESEARCH USE ONLY. CAUTION: Not intended for human or animal diagnostic or therapeutic uses.

E. The (b) (4) centrifuge tubes

F. (b) (4) used to (b) (4)

G. The (b) (4) serological pipettes

H. The (b) (4) added to the culture media as cryopreservative

You did not maintain certificates of analysis related to each lot of supplies and reagents that you used.

According to your General Manager in charge of Processing, this has been your standard of practice since your operations began on/about July 2011.

OBSERVATION 10

Routine calibration and checking of equipment is not performed according to a written program designed to assure proper performance.

Specifically,

A. You do not document the temperature and (b) (4) in your incubators used for storage/culture-expansion of mesenchymal stem cells (MSC's). Your manufacturing record specifies that culture is to be performed at (b) (4)

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degrees Celsius and (b) (4)

B. You did not calibrate your incubators for temperature and (b) (4) to assure that their displays are accurate.

C. You do not document checks of incubators for contamination, or the routine of changing the (b) (4) in the (b) (4)

D. You do not document the temperature of the (b) (4) incubator used during the (b) (4) step for isolating MSC's. Your manufacturing record specifies that the temperature of the (b) (4) incubator is to be (b) (4) degrees Celsius for the (b) (4) step.

E. You do not document the temperature of the (b) (4) used to thaw banked MSC's. Your manufacturing record specifies that the temperature of the (b) (4) is to be (b) (4) degrees Celsius for the thawing procedure.

F. You do not document the temperature of the refrigerators and freezers used to store culture media, saline, and reagents used to manufaoture MSC's.

OBSERVATION 11

The batch records do not record the distinctive identification number and code to identify major equipment to show the specific equipment used in the manufacture of a batch of a drug product.

Specifically, the distinctive identification number is not always recorded in the manufacturing record for the biosafety cabinets and incubators used in the manufacture of the mesenchymal stem cells.

OBSERVATION 12

Written procedures are lacking which describe in sufficient detail the identification and handling of components.

Specifically,

During this inspection, I (LH) observed misidentification/mislabeling of components in your mesenchymal stem cell (MSC) manufacturing area, as follows.

A. A bottle labeled (b) (4) Medium) on one side was labeled (b) (4) (for (b) (4) (b) (4) on the other side.

B. A bottle of containing the MSC culture medium (b) (4) was labeled (b) (4) (the base for manufacturing (b) (4) and (b) (4) on the lid.

C. A bottle labeled (b) (4) was used to hold used pipette tips (waste).

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Further, a bottle of (b) (4) in English was also labeled as a cleaning/sanitizing chemical in Korean (translated for me (LH) by your Vice President)

OBSERVATION 13

Distribution records do not contain the name and strength of the drug product, description of dosage form, name and address of consignee, date and quantity shipped, and lot or control number of drug product.

Specifically,

There are no destruction records for the following MSC's that failed sterility testing:

A. 2012: (b) (4)

B. 2011: (b) (4)

OBSERVATION 14

Washing and toilet facilities are not easily accessible to working areas.

Specifically,

Specifically, you have no hand washing facility in the Stem Cell Laboratory where you manufacture mesenchymal stem cells (MSC's)

Going to the nearest employee restroom entails going through strip curtains in the (b) (4) clean room within the Stem Cell Laboratory followed by at least 3 doors. It involves un-gowning. The worker must re-gown prior to re-entering the Stem Cell Laboratory.

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