Inspections, Compliance, Enforcement, and Criminal Investigations

TCA Cellular Therapy, LLC 8/15/11

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

August 15, 2011

By Facsimile Transmission and Overnight Delivery CBER – 11-03

Charles Naparalla, Chief Executive Officer
TCA Cellular Therapy, LLC
101 Judge Tanner Boulevard, Suite 502
Covington, Louisiana 70433

Warning Letter

Dear Mr. Naparalla:

This letter describes the results of a Food and Drug Administration (FDA, the Agency) inspection conducted between February 22, 2011, and March 31, 2011. The FDA investigators met with you and the staff of TCA Cellular Therapy, LLC (TCA) to review TCA's conduct as a sponsor and as a biological drug product manufacturer. This inspection was conducted as part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational drugs.

At the end of the inspection, the FDA investigators met with you and TCA staff to discuss the items listed on the Form FDA 483, Inspectional Observations. Dr. Gabriel Perez Lasala, TCA Medical Director, responded to the Form FDA 483 in a letter dated April 19, 2011 ("TCA letter") sent to the New Orleans District Office. Based on our review of the inspection report, the supporting documents submitted with that report, other information available to the Agency, and the TCA letter, we have determined that TCA violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, **Code of Federal Regulations** (CFR) Part 312, and violated the regulations governing human cells, tissue, and cellular and tissue based products (HCT/Ps) in 21 CFR Part 1271, which were designed to prevent the introduction, transmission and spread of communicable disease (available at http://www.gpoaccess.gov/cfr/index.html). The applicable provisions of the CFR are cited for each violation listed below.

TCA is the sponsor of the following Investigational New Drug Applications (INDs):

IND 11643: Autologous Mesenchymal Stem Cells Expanded Ex Vivo, Mixed with Bone Marrow-Derived Mononuclear Cells, Administered via Balloon Catheter or Intraoperatively
Indication: Treatment of Myocardial Infarction
Clinical Investigator: Gabriel P. Lasala, M.D.

IND 13139 Autologous Bone Marrow-Derived Mononuclear Cells and Autologous Bone Marrow-Derived Mesenchymal

Stem Cells, Administered by Intramuscular Injection
Indication: Treatment of Critical Limb Ischemia
Clinical Investigator: Gabriel P. Lasala, M.D.

IND 13562 Autologous Bone Marrow-Derived Mononuclear Cells and Autologous Bone Marrow-Derived Mesenchymal Stem Cells, Administered Intracoronary by Voyager (Guidant)
Indication: Treatment of Severe Coronary Ischemia
Clinical Investigator: Gabriel P. Lasala, M.D.

IND 13729 Autologous Bone Marrow-Derived Mesenchymal Cells; Administered via Lumbar Puncture
Indication: Treatment of Amyotrophic Lateral Sclerosis (ALS)
Clinical Investigator: Gabriel P. Lasala, M.D.

IND 13981 Autologous Bone Marrow-Derived Mesenchymal Cells; Administered Intrathecally
Indication: Treatment of Spinal Cord Injury
Clinical Investigator: Gabriel P. Lasala, M.D.

1. You failed to fulfill the general responsibilities of sponsors to ensure that investigations were conducted according to the investigational plan and you failed to monitor the progress of ongoing investigations. [21 CFR §§ 312.50 and 312.56(a)].

A sponsor is responsible for ensuring proper monitoring of investigations and ensuring that the investigations are conducted in accordance with the general investigational plan and protocols contained in the sponsor's IND.

A. The FDA inspection revealed that autologous investigational products were repeatedly administered to individuals who were not enrolled in TCA's IND studies.

Autologous investigational products were repeatedly administered to individuals not enrolled in IND studies, even though these individuals were treated for the same indications covered by TCA's INDs. Moreover, in at least five cases, these autologous products were administered while the relevant INDs, (IND 13729 and IND 13981) were on clinical hold as ordered by FDA.

Individuals administered autologous cellular product for the same indications covered by an IND, but not enrolled in the IND studies, are represented in the table below.

IND	IND Indication	Individuals Identification #	Date of Autologous Infusion
13139	Limb Ischemia	**(b)(6)**	**(b)(6)**
		(b)(6)	**(b)(6)**
13981	Spinal Cord Injury	**(b)(6)**	**(b)(6)**
13562	Coronary Ischemia	**(b)(6)**	**(b)(6)**
		(b)(6)	**(b)(6)**
		(b)(6)	**(b)(6)**
		(b)(6)	**(b)(6)**
11643	Myocardial Infarction	**(b)(6)**	**(b)(6)**
		(b)(6)	**(b)(6)**

The TCA letter attempts to justify these actions by stating that these individuals were terminally ill and severely debilitated with no other options for treatment and, as a result, Dr. Lasala treated these patients with intent to expand access for compassionate use.

B. Although TCA's INDs were limited to autologous use of bone marrow-derived cells, study records show that allogeneic cells were administered to patients who were not enrolled as study subjects in any of TCA's INDs. Indeed, during FDA's inspection, Dr. Lasala also admitted to the FDA investigators that he administered allogeneic cells to patients outside of clinical protocols, conduct he described as a "compassionate illegal act," "completely wrong," and "completely illegal." The following individuals received allogeneic cells rather than autologous cells, as required by the IND protocols.

Indication	Individual	Date of Infusion
Coronary Ischemia	**(b)(6)**	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**

	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
Limb Ischemia	**(b)(6)**	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**

Indication	**Individual**	**Date of Infusion**
ALS	**(b)(6)**	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
Spinal Injury	**(b)(6)**	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**
	(b)(6)	**(b)(6)**

The TCA letter attempts to justify these actions in the same way as was described in paragraph 1.A. above.

C. You failed to monitor the progress of all clinical investigations being conducted under IND.

i. There was no evidence that the following studies were monitored by TCA: Study **(b)(6)** under IND 13563, Study **(b)(6)** under IND 13729, and Study **(b)(6)** under IND 13981.

The TCA letter attempts to justify a lack of monitoring by explaining that the contracted monitor could no longer perform monitoring as of January 2011 and negotiations were ongoing with another company to begin monitoring in March 2011. The TCA letter further explains that after the inspection, Dr. Lasala, TCA Managing Member, discovered that the last monitoring visit was August 26, 2008.

ii. During our inspection, we discovered that a serious protocol violation had occurred regarding the infusion of an incorrect investigational product into subject **(b)(6)**. The protocol for Study **(b)(6)** (IND 13981) requires that "a Bone Marrow (BM) aspiration be scheduled within 10 days of the signed consent" and that these are the cells that will be processed and reinfused. Subject **(b)(6)** signed the informed consent for the study on August 4, 2010. The Case Report Forms for Visit 2 – Primary Bone Marrow Aspiration - show that a **(b)(6)** was infused into this subject on **(b)(6)** and that these cells were collected from this subject during a bone marrow aspiration performed over ten months earlier, on **(b)(6)**.

The TCA letter acknowledges that the protocol for IND 13981 does not include a provision for the infusion of **(b)(6)**.

iii. Subject **(b)(6)** was administered allogeneic donor cells from TCA Donor Stock instead of autologous stem cells as required by section 3.1 of the study protocol. During the inspection, Dr. Lasala and Dr. Minguell told the FDA investigators that they could not identify the source of the cells administered to this subject. In the TCA letter, Dr. Lasala identified the donor cell source as "**(b)(6)**" and explained that donor "**(b)(6)**" was intended for Crohn's disease patient **(b)(6)**, whose procedure was cancelled. The TCA letter further explains that Dr. Lasala had administered donor "**(b)(6)**" cellular product to

subject **(b)(6)**, rather than discard the cellular product, resulting in subject **(b)(6)** receiving allogeneic cells.

The TCA letter attempts to justify the Clinical Investigator's decision to treat the subject with allogeneic cells based on the severity of the subject's condition.

When the FDA investigators inquired about TCA Donor Stock, Dr. Minguell originally explained that TCA Donor Stock was a term used to refer to "surplus cells" that were retained for calibrations and testing new lots of fetal bovine serum. Dr. Minguell subsequently admitted that TCA Donor Stock is comprised of allogeneic donor aspirates that are not intended for any specific recipient. He then apologized to the FDA investigators during the inspection for having intentionally misled them in regard to the donor cells.

2. You initiated clinical investigations without an IND in effect. [21 CFR §§ 312.20 and 312.40].

At the End-of-Phase 2 meeting with FDA for IND 13139 held on November 22, 2010, TCA proposed the use of autologous bone marrow-derived mononuclear cells (BM-MNC) combined with **allogeneic** bone marrow derived mesenchymal cells (BM-MSC) as the investigational product for a Phase 3 study. The BM-MNC and BM-MSC used to conduct the existing Phase 1 and Phase 2 studies were **autologous**. You were advised by FDA during the meeting that a new IND would be required for the use of allogeneic bone marrow derived mesenchymal cells. As documented in the meeting minutes dated December 8, 2010, you have no safety or preliminary efficacy data, and FDA advised you that the Agency considered this to be a first-in-human Phase 1 study, which would require submission of a new IND, and which should focus on assessment of safety for this new allogeneic product.

Despite FDA's conclusions that a new IND would be required for the use of allogeneic BM-MSC, TCA subsequently administered allogeneic cell products to the following individuals:

Identification	Infusion Date	Indication
(b)(6)	**(b)(6)**	Spinal cord injury
(b)(6)	**(b)(6)**	Spinal muscular atrophy
(b)(6)	**(b)(6)**	Spinal muscular atrophy
(b)(6)	**(b)(6)**	Muscular dystrophy
(b)(6)	**(b)(6)**	ALS
(b)(6)	**(b)(6)**	Progressed muscular atrophy
(b)(6)	**(b)(6)**	Spinal cord injury
(b)(6)	**(b)(6)**	Severe limb ischemia
(b)(6)	**(b)(6)**	Severe limb ischemia
(b)(6)	**(b)(6)**	Spinocerebellar ataxia
(b)(6)	**(b)(6)**	Spinal cord injury
(b)(6)	**(b)(6)**	Spinal cord injury
(b)(6)	**(b)(6)**	ALS
(b)(6)	**(b)(6)**	Spinal cord injury
(b)(6)	**(b)(6)**	Traumatic musculoskeletal injury

Furthermore, FDA's inspection revealed that you had initiated this treatment with allogeneic BM-MSC even before the November 22, 2010 meeting. In fact, you treated at least -b(4)- individuals with allogeneic cells before November 22, 2010 for a variety of indications, including but not limited to severe coronary ischemia, musculoskeletal disorder, muscular dystrophy, primary lateral sclerosis, spinocerebellar ataxia, spinal muscular atrophy, and spinal injury.

Indication	Number of Individuals Treated
Severe coronary ischemia	**(b)(6) (b)(4)**
ALS	**(b)(6) (b)(4)**
Limb ischemia	**(b)(6) (b)(4)**
Musculoskeletal disorder	**(b)(6) (b)(4)**
Muscular dystrophy	**(b)(6) (b)(4)**
Primary lateral sclerosis	**(b)(6) (b)(4)**
Spinocerebellar ataxia	**(b)(6) (b)(4)**
Spinal muscular atrophy	**(b)(6) (b)(4)**
Spinal injury	**(b)(6) (b)(4)**
Epilepsy	**(b)(6) (b)(4)**
Thalamic abscess	**(b)(6) (b)(4)**
Renal Disease	**(b)(6) (b)(4)**
Alzheimer's	**(b)(6) (b)(4)**
Progressed muscular atrophy	**(b)(6) (b)(4)**

Multiple sclerosis	**(b)(6) (b)(4)**
Spinal (stroke)	**(b)(6) (b)(4)**
Neuropathy	**(b)(6) (b)(4)**

The TCA letter attempts to justify these actions in the same way as was described in paragraph 1.A. above.

3. You initiated clinical investigations without either submitting a protocol amendment or a new IND to FDA. [21 CFR §§ 312.20, 312.30 and 312.40].

You failed to either submit a protocol amendment or new IND to FDA for treatment of new indications with autologous BM-MSC, as shown in each of the instances described in the table below.

Identification	Indication	Comments
(b)(6)	Musculoskeletal disorder	
(b)(6)	Musculoskeletal disorder	
(b)(6)	Stomach cancer	
(b)(6)	Musculoskeletal disorder	
(b)(6)	Epilepsy	This individual was 10 years old; all protocols in TCA's five INDs excluded subjects under the age of 18.
(b)(6)	Optic nerve atrophy, and arteriovenous malformation of the brain	This individual was 24 months old; all protocols in TCA's five INDs excluded subjects under the age of 18. Furthermore, the intraocular injection of the investigational product is a new route of administration.
(b)(6)	Neuropathy	
(b)(6)	Traumatic brain injury	This individual was 14 years old; all protocols in TCA's five INDs excluded subjects under the age of 18.
(b)(6)	Glioblastoma	

The TCA letter attempts to justify these actions in the same way as was described in paragraph 1.A. above.

4. You administered an investigational product in violation of a clinical hold. [21 CFR § 312.42(a) and (e)].

A. IND 13729 was on clinical hold from July 11, 2008 through January 8, 2010. During that time period, the following individuals were treated with the investigational product for IND 13729 for the same indication as referenced in the IND, namely, ALS. These individuals were not enrolled in the study and were treated while the study was on hold.

Individual	Date of Aspirate	Date of Infusion
(b)(6)	**(b)(6)**	**(b)(6)**
(b)(6)	**(b)(6)**	**(b)(6)**
(b)(6)	**(b)(6)**	**(b)(6)**

B. IND 13981 was on clinical hold from April 10, 2009 until April 14, 2010. The following individuals were treated with the investigational product for IND 13981 for the same indication as referenced in the IND, namely, treatment of spinal cord injury. These individuals were not enrolled in the study and were treated while the study was on hold.

Individual	Date of Aspirate	Date of Infusion
(b)(6)	**(b)(6)**	**(b)(6)**
(b)(6)	**(b)(6)**	**(b)(6)**

In addition to these violations of FDA regulations addressing the conduct of clinical studies, you also violated FDA regulations that set forth requirements for determining eligibility of HCT/P donors. You repeatedly administered allogeneic cells to patients, as described in detail above. FDA regulations require you to determine the eligibility of donors of such products based on donor screening and testing for relevant communicable disease agents and diseases.

5. You failed to determine whether an HCT/P donor is eligible based on the results of donor screening in accordance with 21 CFR § 1271.75 and donor testing in accordance with 21 CFR §§ 1271.80 and 1271.85 [21 CFR § 1271.50(a)].

For example:

Donor **(b)(6)** underwent a primary bone marrow aspiration to collect stem cells on **(b)(6)**. These cells were subsequently transfused into individual **(b)(6)** for treatment of Coronary Ischemia (CI). There is no evidence that **(b)(6)** was screened, through a review of relevant medical records, for risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases. There are also no records documenting that a specimen from **(b)(6)** was tested for evidence of infection due to relevant communicable disease agents.

The TCA letter fails to provide any evidence of subsequent testing or medical follow-up in regard to communicable diseases for donor **(b)(6)** or the recipient of donor **(b)(6)** cells. Please include any evidence of further testing or medical follow-up in regard to communicable diseases in your response to this letter.

6. You failed to test a specimen from the donor for evidence of infection due to relevant communicable diseases agents, to adequately and appropriately reduce the risk of transmission of relevant communicable diseases. [21 CFR § 1271.85(a)(5)]. For example:

A. Donor **(b)(6)** underwent a primary bone marrow aspiration to collect stem cells on **(b)(6)**. These cells were processed and transfused into individual **(b)(6)** for treatment of Spinocerebellar Ataxia. There is no evidence that a specimen from **(b)(6)** was tested for Treponema pallidum (syphilis).

B. Donor **(b)(6)** underwent a primary bone marrow aspiration on **(b)(6)**. These cells were transfused into individual **(b)(6)** for the treatment of ALS. There is no evidence that a specimen from **(b)(6)** was tested for Treponema pallidum (syphilis).

The TCA letter includes a table that shows that donor **(b)(6)**and donor **(b)(6)** tested negative for syphilis. Please provide specific documentation of these test results with your response to this letter.

7. You failed to test a specimen from the donor of viable, leukocyte-rich cells to adequately and appropriately reduce the risk of transmission of relevant cell-associated communicable diseases including Human T-lymphotropic virus (HTLV) types I and II. [21 CFR § 1271.85(b)(1)]. For example:

A. Donor **(b)(6)** underwent a primary bone marrow aspiration to collect stem cells on **(b)(6)**. These cells were processed and transfused into individual **(b)(6)** for treatment of a musculoskeletal disorder. There is no evidence that a specimen from **(b)(6)** was tested for HTLV types I and II.

B. Donor **(b)(6)** underwent a primary bone marrow aspiration to collect stem cells on **(b)(6)**. These cells were processed and transfused into individual **(b)(6)** for treatment of Limb Ischemia (LI). There is no evidence that a specimen from **(b)(6)** was tested for HTLV types I and II.

The TCA letter includes a table that shows that donor **(b)(6)** and donor **(b)(6)** tested negative for HTLV. Please provide specific documentation of these test results with your response to this letter.

8. You failed to test a specimen from the donor of viable, leukocyte-rich cells for evidence of infection due to Cytomegalovirus (CMV) to adequately and appropriately reduce the risk of transmission [21 CFR § 1271.85(b)(2)].
For example:

A. Donor **(b)(6)** underwent a primary bone marrow aspiration to collect stem cells on **(b)(6)**. These cells were processed and transfused into individual **(b)(6)** for treatment of Muscular Dystrophy (MD). There is no evidence that a specimen from **(b)(6)** was tested for the presence of CMV.

B. Donor **(b)(6)** underwent a primary bone marrow aspiration to collect stem cells on **(b)(6)**. These cells were processed and transfused into individual **(b)(6)** for treatment of Limb Ischemia (LI). There is no evidence that a specimen from **(b)(6)** was tested for CMV.

The TCA letter includes a table that shows that donor **(b)(6)**and donor **(b)(6)** tested negative for CMV. Please provide specific documentation of these test results with your response to this letter.

This letter is not intended to be an all-inclusive list of deficiencies. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations.

We have reviewed your April 19, 2011 response to the Form FDA 483 and determined that your response is not adequate to

address the serious violations regarding human subject protection and prevention of transmission of communicable diseases that were discovered during our inspection.

Within fifteen (15) business days of receipt of this letter, please provide written documentation of the specific actions you will take to correct these violations and prevent the recurrence of similar violations in current and future studies for which you are the sponsor. Failure to respond to this letter and to take appropriate corrective action could result in FDA taking regulatory action without further notice to you.

Please send your written response to:

Christine Drabick
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, Maryland 20852-1488
Telephone: 301-827-6323

We also request that you send a copy of your response to the FDA District Office listed below.

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

cc:

District Director
Food and Drug Administration
Building 200, Suite 500
404 BNA Drive
Nashville, Tennessee 37217

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