DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

JUN 30 2000

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS
AND OPPORTUNITY TO EXPLAIN

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Peter K. Law, Ph.D., Chairman
Cell Therapy Research Foundation
1770 Moriah Woods Boulevard, Suite 18
Memphis, TN 38117

Dear Dr. Law:

Between July 12 and September 15, 1999, Food and Drug Administration (FDA) investigators, conducted an inspection of the following six clinical studies under IND for which you are the sponsor and principal investigator on record:

Protocol 93-5 (revision 12/14/93): Myoblast Transfer Therapy as an Experimental Treatment for Duchenne Muscular Dystrophy;

Protocol 95-1 (rev. 12/11/98): Whole Body Myoblast Transfer Therapy (MTT) as an Experimental Treatment for Duchenne Muscular Dystrophy (DMD) – Pivotal Trial;

Protocol 95-2 (rev. 11/10/95): Whole Body Myoblast Transfer Therapy as an Experimental Treatment for Becker Muscular Dystrophy;

Protocol 99-1 (rev. 1/18/99): Whole Body Myoblast Transfer Therapy (MTT) as an Experimental Treatment for Duchenne Muscular Dystrophy (DMD) – Expanded Access;

Protocol 99-2 (rev. 3/3/99): Single Patient Treatment using Whole Body Myoblast Transfer Therapy (MTT) as an Experimental Treatment for Duchenne Muscular Dystrophy (DMD);

Protocol 99-4 (rev. 4/22/99): Single Patient Treatment using Whole Body Myoblast Transfer Therapy (MTT) as an Experimental Treatment for Duchenne Muscular Dystrophy (DMD).

This inspection was conducted as part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research involving

investigational articles and the protection of the rights and welfare of human subjects participating in research.

At the conclusion of the inspection, our investigators discussed the inspectional findings with you, and, on September 15, 1999, issued to you a Form FDA-483. We received and reviewed your October 6, 1999, written response to the items listed on the Form FDA-483, which you sent to the FDA Nashville Branch Office.

Based on our evaluation of information obtained by FDA, we believe that you have repeatedly or deliberately violated the regulations governing the proper conduct of clinical studies involving investigational articles as published under Title 21, Code of Federal Regulations (CFR), Part 312 (copy enclosed).

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding to determine whether you should be disqualified from receiving investigational articles as set forth under 21 CFR 312.70.

A listing of the violations follows. These findings relate to your responsibilities as sponsor-investigator. The applicable provisions of the CFR are cited for each violation. In summary:

General violations pertaining to all clinical studies:

I. Failure to fulfill the general responsibilities of a sponsor-investigator: [21 CFR 312.50, 312.53 and 312.60]

A. As the sponsor and principal investigator on record, you provided inaccurate and misleading information to FDA regarding the conduct of your clinical studies. You failed to conduct your studies according to the signed investigator statement, the investigational plan, the protocol(s), and the applicable regulations for protecting the rights, safety and welfare of subjects. Although you listed at least two physicians (C J) as responsible for the medical evaluation and safety of subjects in your studies, the inspection revealed that there is no licensed physician responsible for the overall medical evaluation and oversight of the subjects participating in any of your clinical studies from study enrollment to study completion.

In the documentation (Form FDA-1571's and clinical study protocols) submitted to your IND, you listed C J M.D., as Co-Investigator and sub-investigator, responsible for ensuring and monitoring the safety of subjects enrolled in the clinical studies. However, the inspection revealed that in actual practice, Dr. C J role was limited to the administration of the study drug. He was not providing the medical oversight and safety evaluation of subjects participating in your clinical studies from study initiation through completion. C J M.D., your Clinical Study Monitor from 1993 to 1997, who conducted medical evaluations of study subjects and study records, was not a physician licensed to practice medicine in the State of Tennessee at that time. C J , your current Clinical Study Monitor, lacks medical

training and is therefore unqualified to perform responsibilities requiring medical expertise in this position.

B. As the principal investigator, although you have no formal training in medicine, you rendered medical judgment on the safety and welfare of study subjects and donors without appropriate medical expertise. In the studies conducted under this IND, donors and subjects were routinely screened, evaluated, and enrolled without the oversight of a licensed physician. Moreover, you accepted and signed off on laboratory test results on donors and subjects even though you have no medical training. Additionally, you performed medical procedures, such as "muscle stimulations" involving multiple 22 gauge spinal needle insertions into the rectus femoris muscle of donors, without a licensed physician present, according to your documentation.

C. Cyclosporine was prescribed and administered to each study subject without a licensed physician responsible for determining the proper dosage and for monitoring the toxicity of this drug in treated subjects. Study records reveal that subjects were instructed to initiate dosing with Cyclosporine before the patient consent form was signed. Inspection of subject study records revealed that Cyclosporine serum level testing was often performed less frequently than the protocol-stated intervals and Cyclosporine blood levels were frequently outside the protocol's blood level maintenance requirements of [redacted].

D. You placed the safety and welfare of subjects enrolled in your studies at risk by the administration of myoblast cells manufactured from batches of product with evidence of microbial contamination and questionable sterility and/or viability test results. At least 18 batches of myoblast cells made in your manufacturing facility had evidence of microbial contamination. Sterility test failures in cell cultures and several cases of media components contaminated with yeast, mycoplasma, and bacteria including Pseudomonas species were found. Products from these contaminated batches were used in MTT treatment of study subjects. You did not perform required endotoxin testing of the cells.

II. Export of investigational new drug without FDA authorization [21 CFR 312.110(b)] and failure to maintain control of the investigational drug [21 CFR 312.61]

A. Under your direction and supervision, you allowed the exportation of your investigational drug by having Cell Therapy Research Foundation (CTRF) personnel transport investigational product to countries such as Brazil and South Korea without applying for or receiving FDA authorization.

B. You failed to exercise control of your investigational drug by supplying it to and allowing unauthorized personnel to administer it to subjects overseas without your direct personal oversight. Furthermore, you commercialized your investigational drug by charging or receiving payment (compensation) from your overseas contacts in return for the use of your investigational drug without seeking FDA approval or authorization to charge and export.

use of your investigational drug without seeking FDA approval or authorization to charge and export.

Violations specific to each study protocol:

III. You failed to conduct the studies in accordance with the approved protocols [21 CFR 312.53(c)(1) (vi) (a) and 21 CFR 312.60]

A. Protocol 93-5:

1. There were no records to show that pulmonary function test results from study subjects were reviewed and evaluated by a board-certified pulmonologist as required by the clinical protocol.

2. For subjects who received the [redacted] there were no records to document the performance of the required [redacted] pulmonary function tests that were to be conducted for [redacted] months by each subject's local physician for safety monitoring.

3. According to protocol requirements, subjects were to have been diagnosed by their local physicians with DMD as documented by the absence of dystrophin determined by immunocytochemistry or Western Blot. At least 8 subjects (Subjects # [redacted]) were entered in the study without a confirmed diagnosis of DMD.

B. Study 95-1:

1. The original medical diagnosis of subject # [redacted] was changed from Becker MD to DMD by your former Clinical Study Monitor, [redacted], M.D., who was not licensed to practice medicine in Tennessee. This subject was then enrolled in the study in violation of the study protocol.

2. You failed to comply with the protocol's exclusion criteria for donors. At least 3 donors with creatine kinase levels outside the protocol required limits were allowed to donate muscle cells for MTT.

C. Study 95-2:

1. One subject with a diagnosis of Limb-Girdle and three subjects with unconfirmed diagnoses of Becker MD were entered in the study in violation of the study protocol.

2. Donors greater than [redacted] years old were to be excluded according to the Donor Inclusion/Exclusion Criteria. The case report form for Subject #[redacted] indicates that the donor was [redacted] years old.

IV. You failed to notify FDA and your Institutional Review Boards (IRBs) of adverse effects that may reasonably be regarded as caused by, or probably caused by, the drug. [21 CFR 312.64, 312.66 and 312.50]

A. Study 93-5:

Inspection of medical study records revealed that 18 out of —enrolled subjects experienced adverse events (e.g., nausea, vomiting, edema, bruising, pain, elevated temperature, hypotension, swelling at temples, swollen parotid glands, stomach pain, eyelid puffiness and sore throat) that were not reported.

B. Study 95-1:

1. Nine out of — enrolled subjects experienced adverse events (e.g., hot flashes, swollen legs, pain in knee joints, vomiting, nausea, elevated blood pressure, elevated heart rate, pain in knee joints, vomiting, bruising at injection sites, increased respiration) that were not reported.

2. At least two donors experienced adverse events (e.g., infection at biopsy site, sharp shooting pain at the biopsy site) that were not reported.

C. Study 95-2:

Five of the —enrolled subjects (subjects # ( ) experienced adverse events that were not reported in the case report forms.

V. Failure to maintain adequate and accurate case histories designed to record all data observations pertinent to the investigation. [21 CFR 312.62(b)]

A. Study 93-5:

1. At least two subjects (i.e., subject with initials ————) who received a second MTT treatment did not have documentation that biopsies were conducted as required by the study protocol.

2. There was no record that pre-MTT viral testing was performed for Subject # — as required by the study protocol.

B. Study 95-1:

1. There was no record that "an outside statistician" generated the randomization code for this blinded study as required by the protocol. There was no documentation available to demonstrate that any randomization was carried out or that appropriate staff were blinded as to which muscle group received placebo or myoblasts and that study blinding was maintained during the

study. Additionally, no documentation was available to indicate when the blind was broken and who broke the study blind.

2. The study protocol requires that donors must have a negative rapid plasma reagin test (RPR) . Review of donor study records revealed that the donor for Subject #— did not have RPR results in his file.

3. Viral testing of subjects enrolled was required by the protocol. No viral testing documentation was available for subject # —

4. Six subjects (# ————————) of the — treated subjects did not have documentation to show that post MTT biopsies were conducted as required by the study protocol.

C. *Study 95-2:*

1. As mentioned above with other blinded studies, no documentation was available to demonstrate that the randomization code for this study was generated by an "outside statistician." Documentation providing assurance that MTT personnel involved in the evaluation were blinded was not available during the inspection.

VI. You failed to obtain Institutional Review Board (IRB) approval of some of your study protocols and the donor consent forms before initiating treatment in human subjects. You provided incomplete or inaccurate information to the IRB, which the IRB used as the basis for its initial and continuing review and approval decisions. [21 CFR 312.66]

A. *Study 95-2:*

1. Approval of this study protocol was granted by Essex IRB on 5/22/96. Records show that a donor was biopsied on 5/2/96, before the IRB approval. The consent form for this donor was signed on 4/26/96, prior to the date of IRB approval, and was not the version approved by the IRB.

2. The status report you submitted to Baptist Memorial Hospital Patient Participation Committee (BMH-PPC) on 4/27/99 did not provide accurate information on the reason why subjects withdrew or dropped out from the study. You reported that four subjects dropped out due to "difficulties in travel every 3 months." However, records obtained by FDA during the inspection revealed that one of these subjects dropped out because the parents did not see any significant improvements after 6 months post MTT.

B. *Study 99-2:*

Essex IRB and BMH-PPC were not informed that donors for the twin subjects for this study were biopsied on 1/20/99 and 1/21/99, before the study protocol and the donor consent form (Appendix II-Generic Muscle

Donor Informed Consent stamped "approved" with an expiration date of 3/5/2000) were submitted for IRB review and approval. The donor consent form submitted for review and subsequent approval by the Essex IRB was not the consent version provided to the donors to sign. The donor for the first twin subject signed a consent form dated 5/20/98. In addition, you did not inform both IRBs that each donor received compensation of $ —.

VII. You failed to ensure that the informed consent is obtained and documented in accordance with 21 CFR Part 50. [21 CFR 312.60]

A. Study 93-5:

1. At least 5 donors were biopsied in 1993, before the study received IRB approval in 1994.

2. The donor for Subject # — was biopsied on 11/9/94, but this donor did not sign the consent form until 2/14/95.

B. Study 95-1:

Four donors enrolled in this study were biopsied before you received IRB approval of the consent form.

C. Study 99-4:

1. The donor for this study was biopsied on 12/8/98, before the IRB approved the study protocol and the Appendix II, Generic Muscle Donor Informed Consent (revision date 3/12/99). This donor was given a consent form for a different study (Study 95-1), which he signed on 12/6/98.

2. The informed consent signed by the donor for this study was not the version approved by the IRB. In addition, the IRB was not made aware that donors were being paid $— compensation for biopsy/participation.

D. Study 99-1:

The Essex IRB requested that CTRF revise the donor informed consent containing language that signs away the donor's rights to the donated cells. Following revision and subsequent IRB approval of the revised consent form, the informed consent signed by the donor still contained the prohibited language which requires the donor "to give up and assign to CTRF all rights in and interest to the donated muscles and any products derived therefrom." The patient consent form used in this study was not the version approved by BMH-PPC.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of an investigational new drug. It is your responsibility as a sponsor-investigator to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above listed violations, FDA asserts that you have repeatedly or deliberately failed to comply with the cited regulations and it proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including any explanation of why you believe you should remain eligible to use investigational products and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 312.70.

Within fifteen (15) days of receipt of this letter, write or call me at (301) 827-6190 to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852-1448

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents, and you may be accompanied by a representative. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The Center will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered the opportunity to request a regulatory hearing before FDA, pursuant to 21 CFR Part 16 and 21 CFR 312.70. Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer free from bias or prejudice and who has not participated in this matter will conduct the hearing. Such a hearing will

determine whether or not you will remain entitled to receive investigational articles. You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely yours,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

Enclosures:
21 CFR Part 312
Form FDA-483, Inspectional Observations, dated 9/15/99
21 CFR Part 16

cc: Michael Carome, M.D., Chief
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