DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

DEC 21 2000

Steven L. Basta
President
Gliatech, Inc.
23420 Commerce Park Road
Beachwood, Ohio 44122

Regarding: [redacted]

Dear Mr. Basta:

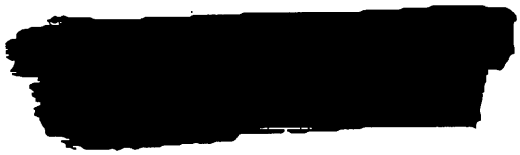
The Food and Drug Administration (FDA) has reviewed the September 14, 2000 letter and supporting documents sent to Henry L. Fielden, District Director, FDA, from Thomas O. Oesterling, Ph.D., former President and Chief Executive Officer, Gliatech, Inc. (Gliatech), responding to the Form FDA 483 - Inspectional Observations, issued to Dr. Oesterling on August 23, 2000 (copy of Form FDA 483 enclosed). We have determined that the provisions of the Application Integrity Policy (AIP) (also known as the Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities Policy) should be applied to Gliatech based on the FDA inspectional findings from the inspection of your facility during the period of June 22, 2000 through August 23, 2000, and the information that we have reviewed. The FDA inspectional findings revealed, among other findings:

- Substitution of reread data for original data without notification to FDA;
- Failure to provide multiple study data analyses to FDA in a timely manner;
- Firm-wide and system-wide practices and procedures at Gliatech that do not provide adequate assurances of producing reliable data.

The findings are more fully described in the enclosed copy of the Form FDA 483.

In accordance with FDA policy, the FDA will assess the validity of the data and information in all of Gliatech's affected applications. This assessment will take priority over substantive scientific data review until questions regarding data integrity are resolved. This means that the FDA will defer substantive scientific review (including review of data and labeling) of any pending application, or any new application or

supplemental application filed after this notice. Accordingly, the FDA has suspended its substantive review of all premarketing applications that have been submitted by or on behalf of Gliatech. There are currently three (3) applications pending approval by the Center for Devices and Radiological Health (CDRH) that are affected by this policy:



The FDA may continue or resume substantive review of an application prior to the completion of the validity assessment in special circumstances where such action is clearly in the interest of public health.

The FDA policies regarding validity assessments and corrective actions that companies may take are described more fully in FDA's policy entitled, "Fraud, Untrue Statements of Material Facts, Bribery and Illegal Gratuities; Final Policy," which was published in the Federal Register dated Tuesday, September 10, 1991. Guidance for firms and the FDA in conducting validity assessments is also contained in a document entitled, "Points to Consider for Internal Reviews and Corrective Action Operating Plans," the availability of which was announced in the same issue of the Federal Register. Enclosed are copies of both documents. Copies of these documents can also be accessed at the following Internet addresses:

http://www.fda.gov/ora/fr/fraud_ill_grat.html
http://www.fda.gov/ora/compliance_ref/aip_points.html

You may request withdrawal of any pending application and any approved application that contains unreliable data. A listing is enclosed that identifies all of Gliatech's currently approved and pending applications filed with the FDA. This list includes the application that was withdrawn by your firm, [redacted] following the FDA inspection for which the Agency invoked the AIP.

The FDA Cincinnati District Office is available to meet with you to discuss resolution of the data integrity and reliability questions raised in the above-referenced applications. To arrange a meeting with the Cincinnati District Office, you may write or call Henry Fielden, District Director, Cincinnati District Office, U.S. Food and Drug Administration, 6751 Steger Drive, Cincinnati, Ohio 45237, telephone (513) 679-2700, extension 115.

Please inform the FDA of the action that you intend to take with regard to each of these applications within ten (10) working days of the date of issuance of this letter. Your response should be directed to:

Charma A. Konnor, R.Ph., RAC, Director
Division of Bioresearch Monitoring, HFZ-310
Office of Compliance
Center for Devices and Radiological Health, FDA
2098 Gaither Road
Rockville, Maryland 20850

If you have any questions or wish to discuss the FDA's finding that a validity assessment is warranted, please contact Ms. Kathleen Swisher at (301) 594-4723, extension 142, or Mr. Carl DeMarco at (301) 594-2022, extension 134.

Sincerely yours,

David W. Feigal, Jr., M.D., M.P.H.
Director
Center for Devices and
Radiological Health

Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 6751 Steger Dr Cincinnati, OH 45237
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED Thomas O. Oesterling	PERIOD OF INSPECTION 6/22-8/23/00 · C.F. NUMBER
TITLE OF INDIVIDUAL Chairman of the Board & CEO	TYPE ESTABLISHMENT INSPECTED Sponsor
FIRM NAME Gliatech, Inc.	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same
STREET ADDRESS 23420 Commerce Park Rd.	STREET ADDRESS OF PREMISES INSPECTED Same
CITY AND STATE (Zip Code) Cleveland, OH 44122	CITY AND STATE (Zip Code) Same

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1. The scar score data in the final report for the U.S. Adcon-L Study are not the original scores for 115 of 324 subjects. Instead, scar scores from an Intraobserver Reliability Study were substituted for the original data.

   a. The worst scar score for 32 of these 115 subjects changed from the original scores. Eighteen of the twenty whose new score resulted in a lesser score were Adcon-L patients. Eleven of the twelve subjects whose new score resulted in a more severe score were Control patients.

   b. Only subjects whose scar scores had not previously been submitted to FDA in an Interim Report for the U.S. Adcon-L Study were chosen for this reliability study. The MRI's for the other study subjects were not re-read.

   c. The substitution of the re-read scores for the original scores was not discussed in the final U.S. Adcon-L Study report submitted to FDA.

2. The Intraobserver Reliability Study was performed to assess the reliability of the scar scores given by [redacted] He was to re-read some of the MRI's that he had originally read and scored during the U.S. Adcon-L study. His re-read scores were to be compared to his original scores.

   a. There was no protocol detailing such things as how the subjects would be selected or what results would be acceptable.

   b. The scar score results obtained during the re-reading of the MRI's were recorded in pencil and had erasures and write-overs. Three of the erasures caused Adcon-L patients to have the worst scar score improve from a 4 to a 3. Three write-overs (from a 1 to a 4) caused the worst scar score for control patients to worsen to a 4.

3. The 'original' scar score sheet [redacted] at center 6 was a photocopy. Quadrants 3b, 3d, 4b, and 4d showed heavy shading but were scored 1, 0, 1, and 1, respectively. This sheet, like all the other score sheets for the original reads, was not signed by [redacted]. When the MRI was re-scored on 8/4/00 the shadings were very similar to the first sheet but the scores were 3, 3, 4, and 3, respectively. This was an Adcon-L patient.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	[illegible]	Frederick M Luchner Investigator; Stephen J. [illegible]	8/23/00

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 6751 Steger Dr Cincinnati, OH 45237	
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4. Many scar score sheets (originals and re-reads) had scores in quadrants that were not shaded and had no scores in quadrants that were shaded.

5. Six of the 280 subjects determined to be evaluable for scar scoring did not meet all of the criteria to be included in the evaluable group. The MRI's for 30 subjects showed herniations at the surgery site (15 marked as recurrent, 3 as residual, and 12 not specified) but these subjects were not excluded from the evaluable group.

6. One control subject was excluded by [redacted] because herniation at L1-L2 might interfere with the MRI findings but the surgery was at L5-S1 and [redacted] who read the MRI's, felt the MRI was satisfactory and gave scores of 1.

7. The MRI's for 38 of the 280 evaluable subjects were taken more than one month late.

all items - under consideration

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Frederick M. Lochner (signature)	Frederick M. Lochner Investigators Stephanie Kilby	8/23/00