

Inspections, Compliance, Enforcement, and Criminal Investigations

National Genetics Institute 17-Jan-06



Department of Health and Human Services

Public Health Service
Food and Drug
Administration

Los Angeles District
19701 Fairchild
Irvine, CA 92612-2506
Telephone (949) 608-290

WARNING LETTER

W/L 14-06

CERTIFIED MAIL RETURN RECEIPT REDUESTED

January 17, 2006

Michael A. Aicher
Chief Executive Officer
National Genetics Institute
2440 S. Sepulveda Blvd., #235
Los Angeles, CA 90064-1744

National Genetics Institute
2112 Cotner Avenue
Los Angeles, CA 90025-5714

Dear Mr. Aicher:

During inspections of National Genetics Institute (NGI), located at 2440 Sepulveda Blvd, Los Angeles, California and 2112 Cotner Avenue, Los Angeles, California from August 22, 2005 to September 1, 2005, our investigators determined that your firm manufactures Human Immunodeficiency Virus Type 1 (HIV-1) nucleic acid tests (NAT) and Hepatitis C Virus (HCV) NAT, performs donor testing using those tests on donor samples received from source plasma collection establishments and provides test results to those establishments. Accordingly, NGI is subject to regulation as both the

manufacturer of the HIV-1 NAT and HCV NAT manufactured at these locations, and as a testing facility for source plasma. Donor testing is an important step in source plasma manufacture.

During the above stated inspections, violations applicable to your device manufacturing (Section 501(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and deviations from the applicable standards and requirements of Subchapter H, Part 820, Title 21, Code of Federal Regulations (CFR)) and source plasma manufacturing (deviations from the applicable standards and requirements of Subchapter F, Title 21, CFR) activities were documented. Significant deviations observed during the inspections included, but are not limited to, the following:

1) You failed to validate computer software used as part of production or the quality system for its intended use according to an established protocol and/or failure to document the validation activities and results, and failed to make adequate provisions for monitoring the reliability, accuracy, precision and performance of laboratory test procedures and instruments [21 CFR 606.140(b), 606.140(c), 820.70(i)].

a) There are no data to demonstrate that databases created in **[redacted]** computer software program, have been properly validated (installation qualification, operational qualification, and performance qualification) as acceptable for their intended uses. **[Redacted]** functions as the information management tool used to collect, organize, process, analyze, secure and maintain testing data. Specifically,

i) Twenty-one. (21) of the thirty-three (33) databases created in **[redacted]** are identified as "pending" and have not been validated. These databases include: **[redacted]**

ii) In addition, validation of one (1) of the thirty-three (33) **[redacted]** databases is identified as being in-progress **[redacted]** and validation of two (2) of the thirty-three (33) databases have been executed but not completed **[redacted]**

b) There are no data to demonstrate that the quality control/quality assurance spreadsheets used for tracking and trending various quality metrics have been properly validated (installation qualification, operational qualification, and performance qualification) and are performing as intended. Examples of these spreadsheets include: **[redacted]**

2) You failed to establish and maintain written standard operating procedures (SOPs) for steps in the testing of blood and blood components including acceptance activities such as: inspections, tests, or other verification activities [21 CFR 606.100(b), 820.80(a)]. Your SOP K 11.7 entitled "Procedure for Determining and Releasing Qualitative PCR Results from Multiplex Runs" does not reference all steps required to assure the criteria are met for release of PCR testing results and any deviations associated with the testing have been resolved. For example, instructions for verifying the information in the five fields in the **[redacted]** such as Internal Control, Lab Comments, Comments,

Instructions and Temp Marker are not included in the SOP.

3) You failed to establish and maintain adequate procedures for steps in the testing of blood and blood components, including implementing corrective and preventive action, investigating the cause of non-conformances relating to product, processes and the quality system, and implementing adequate laboratory control procedures [21 CFR 606.140, 820.100(a)(2)]. Specifically:

a) "Failed Run and Aberrant Control Monthly Summary" "Pre-PCR" reports for January and February 2005 revealed reporting discrepancies for the total number of failed runs, and total number of runs with aberrant controls. The numbers reported on the February 2005 summary for the previous month (January 2005) did not agree with the numbers originally listed on the January 2005 summary and there was no explanation for the discrepancy.

b) "Failed Run and Aberrant Control Monthly Summary" "Pre-PCR" reports for total numbers of aberrant controls for HIV and HCV testing in January, and April 2005 and total numbers of failed runs for HIV testing in February and April 2005 revealed reporting discrepancies. The numbers in the "Failed Runs and Aberrant Controls" database do not match the numbers that appear on the monthly summary reports for calculations performed on the percent Averages, percent Standard Deviations, and the **[redacted]**.

c) "Failed Run and Aberrant Control Monthly Summary" "Pre-PCR" reports from September 2004 through April 2005 revealed reporting discrepancies in that the percent Average and percent Standard Deviation results did not change from month to month on the Aberrant Controls, Failed Run or Failed Runs/Aberrant Controls spreadsheets. The error was due to failure to use the current rolling 12- month formula in the spreadsheet calculations.

d) In the February 2005 "Failed Run and Aberrant Control Monthly Summary" "Pre-PCR" report "Response Form" an error in the calculation of the averages and standard deviations was identified because a rolling 12 month period was not utilized for the calculation. A recalculation was performed and an alert level for HIV was identified. The "Response Form" states that the primary cause of the alert level is the introduction of a **[redacted]** control in the National Genetic Institute (NGI) multiplex standard in which not all **[redacted]**. A thorough investigation was not documented and an investigation did not extend to previous failed runs using the **[redacted]**

4) You failed to establish and maintain process control procedures, including documented instructions and written SOPs for steps in the testing of blood and blood components [21 CFR 606.100(b), 820.70(a)(1)]. Specifically:

a) There are no written procedures describing computer software **[redacted]** functional requirements or descriptions of functions and there is no computer manual. The database functions as the information management tool used to collect, organize, process, analyze, secure and maintain testing data.

b) There is no written procedure defining the deviation types currently existing in the deviation report database in **[redacted]**. Specifically, some of

the field selections for deviation types defined in SOP B 4 "Procedure for Reporting Deviations" (Revision 8) (e.g. Procedural Non-Compliance, Technician Error/Laboratory Accident, Other) and those appearing in the deviation report database drop-down list fields (e.g. General, Process, Documentation Omission, Non-Deviation, Error-Technician) do not correlate. Furthermore, you have not documented the changes made to the drop down list tables for the deviation report database.

c) There are no established written standard operating procedures for entering "Lab Comments" into **[redacted]**. Deviation Report (DR) 2005-0303 was generated for specimen # **[redacted]** and **[redacted]** and matrix **[redacted]** due to possible sample position mix up on a **[redacted]** sample matrix at positions **[redacted]** and **[redacted]**. There are no "Lab Comments" entered in **[redacted]** to notify the review analysts of this deviation.

d) SOP B 17.4 "Procedure For Investigating Failed Runs And Runs With Aberrant Controls", approved on February 17, 2003, was not followed in that you did not document the results for six of the seven investigation criteria listed in this procedure for Accessioning number (AC) #05-34249, 05-34238, 04-28115, 04- 29101, 04-28346, 05-37738, 05-38477, 05-38476, and 05-38393. This procedure states "If a run fails to meet the acceptance criteria for any reason other than the failure of a single control, further investigation . . . takes place."

e) SOP B 6.5, which outlines the NGI auditing program, does not include directives for reviewing failed runs and aberrant control. However, reports to assure these investigations are being performed and documented are required in SOP B 17.4 "Procedure for Investigating Failed Runs and Runs with Aberrant Controls."

We also note that you have failed to establish an adequate system for authorizing, granting, and rescinding computer access to functions in the **[redacted]** and adequate computer security provisions to assure data integrity. Current users do not use appropriate access such as passwords and user-id and personnel who have changed jobs still have access to the system.

The deviations identified above are not intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility as management to assure compliance with all requirements of the federal regulations and the standards in your license.

Federal agencies are advised of the issuance of all Warning Letters pertaining to medical devices so that they may take this information into account when considering the award of contracts.

We acknowledge receipt of your written response dated October 14, 2005, which addresses the inspectional observations on the Form FDA 483, issued at the end of the inspection to management at the Sepulveda Boulevard facility. We have completed our review and although some corrective actions have been implemented, your responses are inadequate in a number of respects and for the following reasons, do not adequately

address our concerns. The items numbered below correspond to the observations listed on the Form FDA 483:

1) Responses to Observations 1, 2, 4, 5 and 6 are considered inadequate in that:

a) In your response, you propose delaying validation of some systems until May 2006. We recommend that you re-evaluate your timeframe and implement the corrective action as soon as possible.

b) Several pertinent documents which were referenced in your response were not submitted to the FDA including:

- i) NGI SOP L22 "Procedure for Using **[redacted]** Applications"
- ii) Plan for completion of "retrospective" validation of **[redacted]**
- iii) Change control documents that address the issues associated with the database.

2) Responses to Observations 3, 13 and 14 are considered inadequate because several pertinent documents which were referenced in your response were not submitted to the FDA including:

- i) Spreadsheets used for Quality Control and Quality Assurance including tracking and trending which were included in a list of items for validation.
- ii) Documentation of your investigation of the failed run and aberrant control report for February 2005.
- iii) NGI SOP K11 "Procedure for the Data Entry of Qualitative Samples and Worklist Generation".
- iv) NGI SOP K30 "Procedure for Using pool Results to Determine the Status of Component Samples".

3) Responses to Observations 9, 10, 11 are considered inadequate because documented investigations were not initiated to address the violations and there is no proposal for corrective actions.

4) Responses to Observations 7, 12, 16, 17 and 20A are considered inadequate because certain aspects of the violations were not addressed in your response including:

- i) The status of final test results of nine samples which were included in testing that either had a failed run or aberrant controls, since SOP B 17.4 "Procedure for investigating Failed Runs and Runs with Aberrant Controls" was not being followed.
- ii) A plan to address the review of investigations of failed run and aberrant controls in your newly expanded audit program.
- iii) A plan to include review of fields in the **[redacted]** including Internal controls, Lab comments, Comments, Instructions and Temp Marker prior to release of test results, in your revised SOP K11 "Procedure for the Data Entry of Qualitative Samples and Worklist Generation".

5) Responses to Observations 18 and 19 appear to be adequate, but will require a review of SOP B6 "Quality Audit Program", SOP B7 "Procedure for Generating Trend and Summary Reports for Management Review" and SOP K27 "Procedure for Reviewing and Releasing Raw Data Images and Run Sheets from the Post-PCR Laboratory" during your next inspection.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, license suspension, and/or revocation.

Please notify this office within fifteen (15) working days of receipt of this letter of the specific steps you have taken to correct the noted violations including an explanation of each step being taken to identify and prevent the recurrence of similar violations. If corrective action cannot be completed within (15) working days, state the reason for the delay and the time within which the corrections will be completed.

If you have any questions regarding this letter, please contact Ms. Maiiza M. Jafary, Compliance Officer at 949-608-2977.

Your written reply should be addressed to:

Pamela B. Schweikert
Director, Compliance Branch
Food and Drug Administration
19701 Fairchild
Irvine, CA 92612-2446

Sincerely,

/S/

Alonza E. Cruse
District Director