**DEPARTMENT OF HEALTH & HUMAN SERVICES**
Food and Drug Administration
New England District

One Montvale Avenue
Stoneham, Massachusetts 02180
(781) 596-7700
FAX: (781) 596-7896

February 22, 2007

Mr. Michael Settles
President
TGA Sciences, Inc.
47 Hall Street
Medford, Massachusetts 02155-4927

Dear Mr. Settles:

We are enclosing a copy of the establishment inspection report (EIR) for the inspection conducted at your premises at 47 Hall Street, Medford, Massachusetts on July 11, 2006, July 13, 2006, July 17, 2006 and July 18, 2006 by the U.S. Food and Drug Administration (FDA).

When the Agency concludes that an inspection is "closed," under 21 C.F.R 20.64 (d) (3), it will release a copy of the EIR to the inspected establishment. This new procedure is applicable to EIRs for inspections completed on or after April 1, 1997. For those inspections completed prior to the above date, a copy of the EIR may still be made available through the Freedom of Information Act (FOIA).

The Agency is working to make its regulatory process and activities more transparent to the regulated industry. Releasing this EIR to you is part of this effort. The copy being provided to you comprises the narrative portion of the report; it reflects redactions made by the Agency in accordance with the FOIA and 21 CFR Part 20. This, however, does not preclude you from requesting and possibly, obtaining any additional information under FOIA.

If there is any question about the released information, feel free to contact William S. Boivin, Supervisory Consumer Safety Officer at (781) 596-7783 or write to: U.S. Food and Drug Administration, One Montvale Avenue, Fourth Floor, Stoneham, Massachusetts 02180.

Sincerely,

Gail T. Costello
District Director
New England District Office

Enclosure
FMD06-749

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## SUMMARY

This inspection was requested as an FY 2006 PDUFA GLP Surveillance Inspection, Bioresearch Monitoring, Human Drugs. (FACTS assignment 701362) This is the initial GLP inspection of the firm. TGA Sciences currently only analyzes samples via contract for GLP studies. The firm specialized in ELISA testing. Three studies were audited and all data was found to be accurate. Minor discrepancies were noted and discussed with management at the close out meeting. A two item FDA 483 was issued for deficiencies in QAU procedures which include immediately notifying management and the study director of problems found which may affect study integrity and the lack of a procedure for auditing of computer operations. The second 483 item concerned the lack of a validation master plan for the validation of the plate readers and associated software. The firm promised to respond in writing. I provided the firm with an address for C.T. Viswanathan Ph.D. to send their response to.

## ADMINISTRATIVE DATA

| | |
|---|---|
| Inspected firm: | TGA Sciences, Inc. |
| Location: | 47 Hall Street<br>Medford, MA 02155-4927 |
| Phone: | 781393-6910 |
| FAX: | |
| Mailing address: | 47 Hall Street<br>Medford, MA 02155-4927 |
| Dates of inspection: | 7/11/2006, 7/13/2006, 7/17/2006, 7/18/2006 |
| Days in the facility: | 4 |
| Participants: | Amber G. Wardwell, Investigator |

## HISTORY

The previous inspection was conducted in March of 2005. The inspection was conducted in accordance with CP 7356.002 Drug Process Inspection. The following systems were covered during the inspection: Quality, Laboratory Controls, Facilities & Equipment, and Materials. The inspection was classified NAI. Prior to that the firm was inspected 9/17/02 to gather information as the firm was not fully operational at the time. The inspection was classified NAI.

## GENERAL

The TGA Sciences organization chart [**Exhibit 1**] identifies Mr. Michael Settles as President of TGA Sciences. Mr. Settles was present to receive the FDA 482 notice of Inspection and for the close out meeting to receive the FDA 483 List of Objectionable Conditions. Ms. Jill Settles is identified as the Quality Assurance Unit. Ms. Settles does not participate in the conduct of studies. Ms. Settles was present for the entire inspection and provided me with all documentation and information requested. A facility floor-plan was collected [**Exhibit 2**]. GLP areas are limited to the immunochemistry lab. The firm specializes in ELISA testing particularly the development and validation of ELISA tests specific to client request. The master schedule [**Exhibit 3**] contains 36 studies which include GLP, GCP, and R&D studies. GLP studies make up approximately 11% of the master schedule.

The only GLP testing conducted to date by TGA sciences is toxicokinetic and immunogenicity testing of samples by ELISA. The facility is capable of housing and handling mice, rats, guinea pigs and hamsters. Currently only mice are being housed for transgenic breeding purposes not related to GLP studies. Samples for GLP testing are submitted by the sponsor and or contract testing facility. The firm has a new tissue culture lab not yet in use for GLP studies. Outsourced functions relevant to GLP studies include equipment calibration conducted by Biometrix.

## ORGANIZATION AND PERSONEL

Standard Operating Procedures were reviewed. Procedures are in place for all responsibilities in 21 CFR 58.31 which apply to this facility (example: test and control articles are not handled at this facility). Job summaries and training records were reviewed for all employees (8 employees total). Personnel appear to have been adequately trained to carry out testing and have been trained in GLP regulations. Ms. Jill Settles is responsible for computer operations at TGA Sciences and is the computer system administrator. Ms. Settles conducted and documented the IQ/OQ/PQ of equipment and associated software.

The study director is not located on site for the studies reviewed. Studies were conducted at WIL Research Laboratories LLC in Ashland OH. TGA Sciences was responsible for sample analysis and the test method development and validation. TGA Sciences appoints a coordinator who oversees study conduct as applicable for 21 CFR 58.33 study director responsibilities. These responsibilities are established in a written procedure (GP-06-01) It was noted during review of the internal auditing procedure that provisions were not included to immediately notify the study director and management of any problems likely to affect study integrity (see **Objectionable Condition #1**).

## QUALITY ASSURANCE UNIT

Ms. Jill Settles is the quality assurance unit (QAU). Ms. Settles does not participate in the conduct of studies (sample analysis). Procedures for responsibilities of the QAU (21 CFR 58.35) were reviewed. The following deficiencies were noted (See **Objectionable Condition #1**): The internal auditing procedure QA-03-02 [**Exhibit 4**] lacks provisions to immediately notify the study director and management of any problems noted which may affect study integrity. Secondly, there is no procedure for quality assurance inspection of computer operations. Excel is used as a data calculation program for test results and equipment calibration. Results generated from Excel are audited as part of the internal audit procedure however Excel templates used for data calculations and equipment calibration are not inspected.

## FACILITIES

The only facility used in GLP testing is the immunochemistry laboratory. The laboratory appeared to be of adequate size and design for conduct of the testing. Samples are stored in freezers until tested. The monitoring and calibration was reviewed for the freezers used for sample storage for studies audited without comment

## EQUIPMENT

The facility specializes in ELISA testing. Equipment used in testing includes plate washers, plate readers and a computer for data analysis. Data is transmitted from the plate readers (EMax & VMax) by Softmax Pro Enterprise software version 4.8. The system is run by Molecular Devices Enterprise Administrator Software version 1.1.

Procedures for the use, maintenance, and calibration of plate readers were reviewed in addition to the maintenance and use logs. The EMax and VMax plate readers are calibrated per internal procedure EQ-27-01 [**Exhibit 5**] Calibration of Molecular Devices EMax and VMax Plate Readers. The procedure was developed by Ms. Settles. Per the recommendation of the manufacturer Molecular Devices the equipment is calibrated with the Universal Absorbance Test Plate manufactured by BioTek. (No documentation of this recommendation was available.) The calibration procedure requires that calibration be conducted for wavelengths 405nm, 450nm, 570nm, and 650nm. Alignment, accuracy, repeatability, and linearity have been established using the calibration plate instructions and equipment specifications. Instructions, plate certification, and reader specifications were reviewed [**Exhibit 5 p 7-9**].

Calibration is conducted using protocol files in Excel. It was also noted the protocol file extensions (.ppr) are incorrect in the calibration procedure. File extension (.ppr) were used for Softmax Pro Enterprise software version 3.0. Currently used protocol files have an extension of (.epr) for version 4.8. Calibration records were reviewed for both plate readers. Calibration records for the VMax plate reader (EQ3026) were collected [**Exhibit 6**]. This plate was calibrated at 560nm rather than 570nm per the calibration procedure. According to Ms. Settles this reader is not calibrated at 570nm because it doesn't have a 570nm filter. Ms. Settles promised to revise the procedure to reflect the correct file extensions and wavelengths applicable for equipment. Calibration records were reviewed for the EMax plate reader (EQ3019) as well [**Exhibit 7**]. Currently the firm only runs ELISA testing at 450nm a wavelength both readers are calibrated at.

Protocol or template files used for calibration at 405nm, 450nm, 490nm, 570nm, and 650nm were reviewed on screen with Ms. Settles. These are Excel worksheets with preset locked formulas for calculation of Alignment, Accuracy, Repeatability, and Linearity. It was noted that the cells for Alignment contain "pass" as a result when no values are entered. Printouts of blank templates were collected for each wavelength [**Exhibit 8**]. I discussed with Ms. Settles that this was unacceptable, while the occurrence may be unlikely, test would pass even if it wasn't conducted or values were not entered. I explained that these templates should be reviewed by quality as part of a review of computer operations.

Computer operations are not inspected by the Quality Assurance Unit see **Objectionable Condition #1**.

IQ/OQ/PQ of the plate reader equipment, Administrator software, and Softmax Pro software were reviewed as the validation of the system. As previously described two plate readers are used (EMax & VMax). ELISA testing is conducted at 450nm. The Softmax Pro Enterprise software version 4.8 communicates data from the plate readers to the computer run by the Enterprise Administrator Software version 1.1. Data is entered by hand into excel spreadsheets for calculation.

The firm's procedures indicate that manufacturer's validation packages will be used when available in lieu of creating IQ/OQ/PQ protocols. The firm has an established procedure for validation. Validation Policy GP-17-01 [**Exhibit 9**] defines validation as assurance that equipment, systems, methods, or processes do what is required. A master validation plan is defined as "A prospective and approved plan written to detail the necessary steps and requirements to validate a facility, or a group of equipment, methods or processes." This procedure requires a master validation plan be documented and put in place specifying validation requirements and procedures for validation activities and that the plan will detail necessary steps and requirements to ensure validation activities are thoroughly and accurately completed.

A master validation plan was not established for validation of the plate reader system see **Objectionable Condition #2**. During review of IQ/OQ/PQ several discrepancies were noted which should have been addressed in a master validation plan. The calibration procedure for plate readers was used for functional testing during OQ of both plate readers. Plate readers were not tested at 570nm as required by the calibration procedure and no justification is included in OQ documentation. The VMax plate reader was tested at 560nm [**Exhibit 12 p. 4**]. The EMax plate reader was not tested at 570nm, this wavelength is lined out on documentation [**Exhibit 13 p. 4**]. Additional discrepancies were noted in the Performance qualification of the system [select pages collected **Exhibit 14**]. Not all tests included in Molecular Devices Software Validation Package were conducted. According to Ms. Settles the test not conducted are for features of the plate readers not required for the testing TGA Sciences conducts and therefore were not purchased. I discussed with Ms. Settles that TGA Sciences procedure requires a master validation plan and that the plan would define what equipment is included in the system and which tests are required to assure that validation activities are complete and accurate.

Permissions and user roles for each user were reviewed for the Molecular Device Enterprise Administrator Software [**Exhibit 10**]. No user has permission to clear an audit trail. Ms. Settles is the administrator for this system and is responsible for setting permissions. Out dated software versions are maintained on disk and archived (Softmax Pro Enterprise software version 3.0). All files on the firm's server are continuously backed up by Secure Socket Layer by Live Vault Corp. a contract firm located at 201 Boston Post Road, Marlborough, MA 01752.

## TESTING FACILITY OPERATIONS

Procedures are in place for those areas TGA Sciences are responsible; Laboratory testing, data handling, and equipment maintenance and calibration. During review it was noted that all procedures were appropriately authorized, signed and dated and only current SOPs were available to employees. Employee training records were reviewed in addition to the training SOP which familiarizes employees with procedures. The firm's internal auditing procedure provides for data checking and verification. Review of the computer system verified audit trails are kept for all data changes and no employees have privileges to clear and audit trail. Procedures are in place for periodic review of SOPs and the current SOP index reflects the effective date, review date, and date the next revision is due.

## REAGENTS AND SOLUTIONS

Procedures for the purchase, receipt, and labeling of reagents was reviewed. During a walk-through of the facility it was noted that all reagents and solutions were labeled and stored appropriately. Reagent logs were reviewed. Several instances were noted where expiration dates were not recorded in the log as required per procedure. Records for reagents involved were reviewed and none were expired when used. It was also noted in one instance that a solution was prepared for testing and given an expiration date later than the expiration date of one of the reagent ingredients. This solution was used in testing however it was consumed prior to the earliest expiration date. This practice was discussed with the firm and the procedure for expiration dating was promised to be revised to assure the earliest expiration date is assigned.

## ANIMAL CARE, TEST AND CONTROL ARTICLES, PROTOCOL AND CONDUCT OF NONCLINICAL LABORATORY STUDIES

Animals are not housed or handled in the facility for GLP studies nor are test or control articles mixed or handled. This facility does not generate nonclinical laboratory study protocols. They analyze samples collected during non clinical studies and their responsibilities are included in the protocol issued by the testing facility. [**Exhibits 16, 19 & 21**]. Test methods for analysis are developed and validated by TGA Sciences and this was covered during the data audit.

## RECORDS AND REPORTS

TGA Sciences is not responsible for the final study report. A final report of results is prepared and submitted to the testing facility as a contributing report. The report is signed by the study coordinator and contains the required GLP compliance statement issued by Ms. Settles the Quality Assurance Unit. All study data and reports are maintained in the firm's locked archive room. The only employees with access to this room are the President Michael Settles (also a study coordinator), QAU Jill Settles, and Study Coordinator Lisa

Greenleaf. A log of all documents and data in the archive is kept. A sign out sheet is completed for anything removed from the archive. It was noted that studies removed for review during this inspection were not signed out when removed as required per procedure. When this was brought to Ms. Settles attention the log was completed and dated with annotation of the date materials were removed and the date the log was actually filled in.

## DATA AUDIT

The master schedule [**Exhibit 3**] is separated in to GLP, cGMP, and GCLP (clinical) studies. Currently the firm has been involved in 4 GLP studies. All of the GLP studies were ELISA tests, 2 are ongoing and 2 have been completed. The firm initiated GLP testing in September of 2004. Clients notify the laboratory if a study is a GLP study.

Studies were selected for auditing by Headquarters contact Mark Seaton. For each study audited data was found to be attributable, legible, contemporaneous, original, and accurate. Protocols for overall studies are not the responsibility of this facility. Test methods for each study were validated. Completed final reports included the QAU statement. Each study was sponsored by: Dyax Corp. (300 Technology Square, Cambridge, MA 02139). Studies were conducted by WIL Research Laboratories, LLC (1407 George Road, Ashland, OH 44805). TGA Sciences received and tested specimen samples.

The master schedule [**Exhibit 3**] identified Study Protocol WIL-446010 as an active study. This is an immunogenicity study evaluating blood samples from Cynomolgus Monkeys after administration of DX-88. TGA Sciences was contracted by Dyax Corp. to develop and validate a test method and to test the blood samples [Service proposal **Exhibit 15**]. The study was conducted at and the samples were shipped from WIL Research Laboratories to TGA Sciences [Protocol pages WIL6010 **Exhibit 16**].

Test method validation of ELISA to Detect IgG to DX-88 in Monkey Sodium Citrate Plasma [Validation Final Report **Exhibit 17**] was completed May 11th, 2005. The study of samples was initiated on June 7th, 2005. All phases of the study are complete except the review and sign off of the final report. Validation of the test method was reviewed during this inspection and found to be adequate.

The master schedule [**Exhibit 3**] identified Study Protocol WIL-446005 as completed. This is a toxicokinetic study evaluating sodium citrate plasma samples from Hanford Mini Pigs after administration of DX-88. TGA Sciences was contracted by Dyax Corp. to develop and validate a test method and conduct testing of samples. [Service proposal **Exhibit 18**]. The study was conducted at and the samples were shipped from WIL Research Laboratories to TGA Sciences [Protocol pages WIL-446005 **Exhibit 19**]. The final report [**Exhibit 20**] dated February 28, 2005 was audited along with the test method and raw data. Reported information appears accurate.

The master schedule [**Exhibit 3**] identified Study Protocol WIL-446012 as completed. This is another toxicokinetic study evaluating sodium citrate plasma samples from Hanford Mini Pigs after administration of DX-88. TGA Sciences was contracted by Dyax Corp. to develop and validate a test method and conduct testing of samples. [Service agreement **Exhibit 18**]. The study was conducted at and the samples were shipped from

WIL Research Laboratories to TGA Sciences [Protocol pages WIL-446005 **Exhibit 21**]. The final report [**Exhibit 22**] dated December 21, 2005 was audited along with the test method and raw data. Reported information appears accurate.

## OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

### Observations listed on form FDA 483

### OBSERVATION 1

The quality assurance unit failed to maintain and make available for inspection required records regarding its responsibilities and procedures and the method of indexing such records.

Specifically,

A. There is not a written and established procedure for QA inspection of computer operations. Excel is used for data manipulation and calculations. Templates are created for calibration of equipment or for interpretation of study data by entering equations into cells. While the data entered is reviewed as part of the established internal auditing procedure there is no procedure for inspection of the templates and equations.

B. It was noted that document GP-01-01 Internal Auditing indicates management is to be notified of audit findings by audit report within 10 working days. This established procedure does not provide for immediate notification of the study director and management of any problems likely to affect study integrity.

Reference: 21 CFR 58.35(c)

Supporting Evidence and Relevance:

Exhibit 4 is the quality assurance unit procedure for internal auditing of studies. This procedure does not state that management and the study director will be immediately notified of any problems found that may affect study integrity.

Exhibits 6-8 are calibration records for the plate readers. Calibration is dependent on the use of Excel templates (Exhibit 8) for the calculation of data. The templates currently used for calibration have a value of "pass" automatically put into the results field for Alignment testing. The results would be "pass" if data weren't entered and/or the test wasn't

conducted. Excel templates containing calculations are used to determined data to be reported. The equations and templates need to be audited by the Quality Assurance Unit.

Discussion with Management:

Management promised corrections would be made for this observation. Ms. Settles did point out that she is the quality assurance unit and she is also responsible for generating templates so she does review them although there is no established procedure for QAU review. She also stated that the study director and management are immediately notified of any problems found during QAU auditing which may affect study integrity. She promised this provision would be added to the internal auditing procedure.

**OBSERVATION 2**

Not all equipment used in the generation, measurement, or assessment of data is of appropriate design and adequate capacity to function according to the protocol and is suitably located for operation, inspection, cleaning, and maintenance.

Specifically, the validation of plate readers with operating software lacks a master validation plan. Document GP-17-01 Validation Policy indicates that a master validation plan is to be in place detailing necessary steps and requirements for validation a group of equipment to ensure all necessary validation activities are thoroughly and accurately completed. Your firm elected to follow document EQ-27-01 Calibration of Molecular Devices EMax & VMax Plate Readers to satirist functional testing as part of the operation qualification of plate readers. Testing did not include reading at 570nm as prescribe in the procedure for the VMax (EQ3026). No justification is given. Also, testing of the EMax (EQ3019) included reading at 560nm rather than the 570nm as required by the test procedure. No justification is given. Performance Qualification was conducted by following testing provided by the manufacturer. Multiple tests provided as part of the manufacturers validation test instructions were omitted without justification. A master validation plan was not created to assure validation activities were accurate for specific equipment and that such activities were complete.

Reference: 21 CFR 58.61

Supporting Evidence and Relevance:

Exhibits 9-14 relate to validation of the plate reader system and software. Exhibit 9 is the firm's validation policy which states on page 4 that a master validation plan will be established. Documentation of functional testing not conducted at 570nm is contained on page 4 of Exhibit 12 and page 4 of Exhibit 13. Testing not conducted during PQ is demonstrated on page 4 of Exhibit 14.

Discussion with Management:

Management promised corrections would be made for issues noted in this observation. Ms. Settles promised to create a master validation plan and evaluate the IQ/OQ/PQ conducted to assure that all aspects required in the master validation plan have been completed accurately and that any not done are completed.

## REFUSALS

There were not refusals encountered during this inspection. The firm was cooperative in response to all of my request and inquiries.

## GENERAL DISCUSSION WITH MANAGEMENT

Mr. Michael Settles, President and Ms. Jill Settles, QAU were present for the close out meeting. Also present were Ms. Anne Marie Woodland, Senior Director of Quality at Dyax Corp. and Mr. Eric Rosenberger, Senior Manager, Clinical QA at Dyax. The FDA 483 List of Objectionable Conditions was issued to Mr. Settles. In addition to items on the FDA 483 several discussion items were brought to management's attention.

1. File extensions for calibration protocols (templates) reflect those used for the previous version on Softmax Pro (v. 3.0). The current version 4.8 uses protocol files with (epr.) extensions. Ms. Settles promised to revise the procedure to reflect the correct file extensions.

2. The calibration procedure requires calibration at 570nm. The VMax plate reader (EQ3026) does not have a 570nm filter and is currently calibrated at 560nm instead. Ms. Settles promised the calibration procedure would be revised to reflect the appropriate wavelengths applicable for each piece of equipment.

3. During review of the reagent log several instances were noted where expiration dates were not recorded in the log as required per procedure. The firm promised to correct this issue.

4. On one instance a solution was given an expiration date later than the expiration date of one of the ingredients. This solution was consumed prior to the earliest expiration date. It was promised the procedure for expiration dating would be revised to assure the earliest expiration date is assigned.

5. The calibration procedure was created using a universal absorbance test plate made by Biotek. This was done per recommendation of the plate reader manufacturer Molecular Devices. It was suggested that documentation of the manufacturer's recommendation be retained.

## ASSIGNMENT MEMO INFORMATION

- GLP testing constitutes approximately 11% of the firm's total workload
- This is a contract facility to which testing is outsourced from a testing facility. All testing is conducted at TGA Sciences.
- This facility does not handle test articles
- This facility submits to the sponsor and testing facility a final report of results to attach to the studies final report as a contributing report.

## EXHIBITS COLLECTED

1. TGA Sciences Organizational Chart
2. Facility diagram
3. Master schedule
4. Internal auditing
5. Plate reader calibration procedure EQ-27-01
6. VMax EQ3026 calibration log and calibration record
7. EMax EQ3019 calibration log and calibration record
8. Calibration protocol template files all wavelengths in SOP
9. Validation Policy GP-17-01
10. IQ report Molecular Devices Enterprise Administrator Software v. 1.1
11. IQ report Molecular Devices Softmax Pro Enterprise Software v. 4.8
12. IQ/OQ report Molecular Devices VMax plate reader, EQ3026
13. IQ/OQ report Molecular Devices EMax plate reader, EQ3019

14. PQ report Molecular Devices Softmax Pro Software v. 4.8
15. Service proposal for WIL-446010
16. Protocol for WIL-446010
17. Test method validation for test used in WIL-446010
18. Service proposal for WIL-446005 & 446012
19. Protocol for WIL-446005
20. Final report for analysis of WIL-446005 samples
21. Protocol for WIL -446012
22. Final report for analysis of WIL-446012 samples

**ATTACHMENTS**
Assignment memo
FDA 482 Notice of Inspection
FDA 483 List of Objectionable Conditions

Amber G. Wardwell, Investigator