U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Advanced Testing Laboratory Inc 10/12/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Cincinnati District Office
Central Region
6751 Steger Drive
Cincinnati, OH 45237-3097
Telephone: (513) 679-2700
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October 12, 2010

WARNING LETTER

CIN-11-108087-01

Via United Parcel Service

Gregory A. Neal
President and Owner
Advanced Testing Laboratory, Inc.
6954 Cornell Road, Suite 200
Cincinnati, Ohio 45242

Dear Mr. Neal:

During our February 18, 2010 to April 9, 2010 inspection of your pharmaceutical contract testing laboratory, Advanced Testing Laboratory, Inc., located at 6954 Cornell Road, Cincinnati, Ohio, an investigator from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your client's drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have reviewed your firm's response of April 29, 2010, and note that it lacks sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm has failed to establish scientifically sound and appropriate test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 C.F.R. §211.160(b)]. For example:

> a. Your firm's microbiology laboratory processed 97 of 611 Agar plates on March 22, 2010, and 39 of 260 Agar plates on April 2, 2010, that were desiccated to a point where the medium was cracking or pulling away from the side of the plate. These Agar plates are used to test for objectionable microorganisms in your drug products and as such, it is unknown whether these defective plates can support microbial growth.

In your response, your firm states that you would assess the technique used to prepare the plates, incubator temperature, the incubation times, and the failure of management to document and address the issue. In addition, you state that you would conduct additional training and conduct process reviews to address procedures requiring five-day incubation times at temperatures that may cause desiccation.

Your response, however, is inadequate because you have not addressed the impact of the desiccated plates on the test

results provided to your customers, nor have you performed any additional testing concerning test samples in desiccate plates observed during our inspection. Moreover, during the inspection your laboratory manager suggested that the problem with desiccated plates could be resolved by pouring additional media into the plates. Adding new media to a previously processed Agar plate may compromise both medium sterility and stability.

b. Your firm's microbiology laboratory did not record the presence of colonies in five plates because the colonies were considered contamination from laboratory personnel. According to Standard Operating Procedure (SOP) 300-M-0030, "Aerobic Plate Count and Enrichment Option," and SOP 300-M-0020, "Yeast and Mold Count," your analysts must record the number of colonies or each type of organism, respectively, as Colony Forming Units (CFU) in each countable plate. Your firm does not, however, define or have criteria to determine whether colonies present are due to personnel contamination.

In your response, your firm states that you will develop a new SOP to document the current peer review process regarding the counting and recording of microbial counts, including the identification of contamination and required documentation. However, your response does not include criteria to differentiate a false positive CFU without performing analytical identification of a colony observed on a plate.

In addition, please include your investigation methodology for false positive CFUs and the rationale for your approach in your response.

2. Your firm has failed to calibrate instruments and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions fo remedial action in the event accuracy and/or precision limits are not met [21 C.F.R. § 211.160(b)(4)]. For example:

a. Several laboratory instruments (i.e., incubator #277, incubator #612, FT-IR spectrophotometer #597, ICP spectrometer #532, atomic absorption spectrophotometer #481, oven #112, and vacuum oven #113) used to analyze various drug components and drug products were either out of calibration, had not received proper maintenance according to your schedule, or a combination of both. Five of the seven instruments had no calibration records prior to the start of the inspection. Your SOP 600-G-0050, "General Calibration and Maintenance Procedure for Laboratory Equipment," states that laboratory equipment must be maintained and calibrated properly according to the calibration and maintenance schedule.

In your response, your firm states that all annual calibrations and scheduled maintenance will be current and documented, and that your analysts will be trained to comply with SOP 600-G-0050. However, your response only refers to those instruments listed above and does not include a review of all analytical instrumentation to ensure calibration an scheduled maintenance was performed. In addition, your response does not assess the validity of prior analytical test results using instruments that were not calibrated or lacked proper maintenance.

b. Incubators #277 and #9210-590 were not qualified properly for their intended use. Specifically, heat distribution studies were not conducted for these incubators prior to their use in performing stability studies for Over-the-Counter (OTC) drug products (e.g., **(b)(4)** and **(b)(4)**).

In your response, your firm states that you will perform internal heat distribution studies for the incubators. However, your response is inadequate because you do not address extending these same studies to other incubators.

3. Your firm has failed to establish and document the accuracy, sensitivity, specificity, and reproducibility of test method [21 C.F.R. § 211. 165(e)].

For example, your firm performed analytical method transfers for 236 protocols without determining whether those methods had been properly validated by your clients.

In your response, your firm states that you will develop a new procedure to ascertain the validation status of your client's methods and to assure that all methods used for product release testing are properly validated. You also state that your firm will conduct and document employee training. However, your response does not include a plan for conducting a retrospective review of your client's methods to ensure that they are adequately validated and that the method transfer was sufficient to ensure accurate results.

4. Your firm has failed to follow written responsibilities and procedures applicable to the quality control unit [21 C.F.R. § 211.22(d)].

For example, your Quality Control Unit (QCU) does not fully document and evaluate internal defects. Between Decembe 28, 2008, and December 31, 2009, 946 internal defects were recorded without laboratory codes as required by your SOI 700-G-0160, "Internal Defect Reporting & Tracking Procedure." Further, your firm was unable to provide either a Defect Report Form (DRF) or a Defect Summary Report (DSR) for any internal defects recorded or documentation of any actions taken to address these defect trends.

In your response, your firm states that additional training will be provided concerning SOP 700-G-0160. However, your response is inadequate because you do not address: (1) the omission of required information for internal defects; (2) your failure to provide internal defect reports, and; (3) the need for a more complete trending analysis. Further, you have not provided a detailed explanation of your corrective actions or a timeframe of completion.

In addition, your firm is currently not initiating DRFs for internal defects as required by your SOP 700G-0160. Since the internal defects are not addressed, your firm may be releasing and distributing defective drug products. It is your responsibility to review all defects for products within expiry and to determine and implement adequate corrective actions. You should inform all affected clients of your findings and your proposed corrective actions.

5. Your firm has failed to follow and document, at the time of performance, established test procedures and laboratory

control mechanisms. Any deviation from the written test procedures and laboratory control mechanisms shall be recorded and justified [21 C.F.R. § 211.160(a)]. For example:

a. We observed 31 expired USP standards (i.e., **(b)(4)**) in a laboratory drawer next to a separate drawer containing unexpired standards. SOP 500-G-0330, "Qualification of Standards Used in the Analysis of a Drug Product," stated that expired material must be discarded.

In your response, your firm states that you have discarded the 31 expired standards and that you will conduct additiona enforcement and training of SOP 500-G-0330 to assure that all future expired standards are discarded immediately upor their expiration. Your response, however, is inadequate because you do not include a review or documentation of past analytical tests to assure that samples were tested with valid standards.

In addition, please describe any steps to prevent inadvertent use of expired standards, especially when your procedure states, "When a reference standard has expired, consult the laboratory manager prior to disposal as some standards are client specific and may be difficult to replace."

b. We observed 8 of 9 worksheets where one or more tabs with formula cells were not locked. These worksheets were used for analyzing raw data from drug component and product samples, including **(b)(4)**. Your firm's SOP 100-G-0110, "Creation and Use of Templates," stated that cells, in which data is entered, must be locked within their electronic template.

In your response, your firm states that you will enforce the existing procedure by reviewing the current inventory of electronic data files and disposing of non-compliant spreadsheets. In addition, you will retrain analysts on the current procedure. Your response, however, is inadequate because you do not assess whether the raw data results, generated using unlocked templates, are valid.

c. Between May 10,2009, and March 23,2010, your firm obtained daily plate counts from the Coliform Bath #542 exceeding the action level 70 times (28 as being "too numerous to count") and the alert level 106 times. There was no documentation showing that an investigation was initiated or corrective action(s) implemented. Your firm' SOP 600-M-0260, "Cleaning and Plating of Media Water Baths and Coliform Bath," describes alert levels as having 2-10 CFUs and action levels as having greater than 11 CFUs.

6. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed, nor have you extended investigations to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy [21 C.F.R. § 211.192].

For example, your firm was unable to provide documentation of any investigation associated with two Out-of-Specification (OOS) events listed in the OOS Tracking Log and one OOS event associated with a drug component sample **(b)(4)** (lab code #0905-0824). Your Quality Assurance Manager stated that OOS investigations are not normally conducted unless they are requested by the client. However, your firm's SOP 700-M-0070, "Out of Specification (OOS) Policy for the Microbiology Laboratory," and SOP 700-C-0010, "Out of Specification Policy for the Chemistry Laboratory,' both state that an OOS investigation must be performed whenever a client's sample results are outside of the stated specification.

In your response, your firm states that you will revise both OOS procedures to require that all OOS events will be completed regardless of client specific directives. However, your response does not address a review of current and recent OOS events to ensure that adequate investigations are performed. It is your responsibility to conduct adequate and complete investigations into OOS results to include the evaluation of all data associated with the lot.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. It is your responsibility to assure compliance with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

We are concerned that your extended autoclave sterilization cycle time may affect the liquid media to an extent whereb it is no longer viable and thus, possibly resulting in release of contaminated samples (i.e., false negative results). The manufacturer of the liquid media states that the media should not be overheated. We are concerned that the media may be denatured due to excessive sterilization time. Please provide your scientific rationale (and any supporting data) for the extended cycle time or a corrective action(s).

Your firm acts as a contract laboratory testing for various drug components and products including: Active Pharmaceutical Ingredients (APIs), excipients, and finished drug products (e.g., antimicrobial ointments and soaps, and hand sterilizers). It is essential that you understand your responsibility to operate in full compliance with CGMPs and to inform all of your customers of significant problems encountered during the testing of these products.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the

reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer test drug product(s) at this facility, and provide the date(s) and reason(s) you ceased testing.

Your reply should be sent to the following address:

U.S. Food and Drug Administration
c/o Mark E. Parmon, Compliance Officer
6751 Steger Drive
Cincinnati, Ohio 45237.

Sincerely,

/s/

Teresa C. Thompson
District Director
Cincinnati District

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