U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Biochem Laboratories Inc. 2/17/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 331-4904

WARNING LETTER

12-NWJ-12

February 17, 2012

VIA UPS

Thain Yang Wey, Director
Biochem Laboratories Inc.
56 Park A venue
Lyndhurst, New Jersey 07071

Dear Mr. Wey:

During our May 18, 2011 through June 15, 2011 inspection of your pharmaceutical contract testing laboratory, Biochem Laboratories Inc., located at 56 Park Avenue, Lyndhurst, New Jersey, investigators from the Food and Drug Administration (FDA) identified significant violations of the Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. These violations cause your clients' drug products 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 June 20, 2011, 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 not established scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)].

For example:

a. FDA investigators identified significant deficiencies in the spectroscopic assay procedures that your firm used to analyze finished drug products and stability samples. For example, your firm used Infrared (IR) spectroscopy to **(b)(4)**. The IR sample spectra collected do not appear to contain the active peak. Furthermore, the sample spectra resemble the diluent blank that contains no active ingredient. Therefore, the test results reported are not considered valid.

b. FDA investigators identified significant deficiencies in the chromatographic assay procedures that your firm used to analyze finished drug products and stability samples. For example, your firm used high-performance liquid chromatography (HPLC) to **(b)(4)**. All HPLC chromatograms collected by our investigator appear to indicate the presence of multiple coeluting peaks which may represent interfering analytes, potential instrument problems, or degradation products. The standard chromatograms differ from analysis to analysis, and HPLC test results were not consistently calculated. Therefore, the test results reported using this HPLC procedure is not considered valid and reliable.

In your response, you state that you will correct their IR spectra inconsistency, that you have implemented a new method for Benzophenone assay, and that you are in the process of "troubleshooting" all the HPLC and gas chromatography (GC) methods. Your response, however, is inadequate because you do not provide a timeline for accomplishing the intended corrective actions, nor do you provide adequate assurance that the newly implemented Benzophenone method is accurate and reliable. Further, you failed to address the impact of the observed method deficiencies on the test results provided to your customers and to indicate whether you will inform your customers of the result of such evaluation.

2. Your firm has failed to establish and document the accuracy, sensitivity, specificity, and reproducibility of test methods [21 CFR 211.165 (e)].

For example:

a. Your firm cites eleven USP drug substance monographs that you use to analyze finished drug products. However, these USP monographs have not been shown to be effective for the finished dosage forms being tested. For example, your firm referenced USP 'Octisalate' drug substance monograph to quantitate octyl salicylate in cream samples. The USP method does not include any extraction procedure to isolate the active from the formulation matrix, and your firm has failed to establish the accuracy of the method for the samples. Therefore, there is no assurance that the assay values reported for these samples are accurate and reliable.

b. Your firm failed to validate the specificity of the test procedures used to analyze finished product stability samples to ensure that the methods are stability-indicating. For example, your firm determined the content of salicylic acid in **(b)(4)** stability samples by titration. Your firm has not demonstrated the specificity of the method for degradation products. The method may not allow you to detect the presence of degradation products that may indicate deterioration of the drug product.

In your response, you state that you have informed your clients on the importance of validating the methods, but they have chosen not to validate the methods. In addition, you state that you will inform them again in writing. Your response, however, is inadequate because you do not provide your firm's planned corrective actions for this CGMP violation. You are responsible for ensuring that the test methods used by your firm are validated. Circumstances in which an unvalidated method might be appropriately used should be strictly limited to non-CGMP purposes. In such a case, any written report of results (including a certificate of analysis) to your customer should include a statement that the data was generated by an unvalidated method(s) and should not be used for establishment of expiration dates, commercial batch

release, or other CGMP decisions.

3. Your firm has not cleaned and maintained equipment at appropriate intervals to prevent contamination that would alter the safety, identity, strength, or quality of the drug product [21 CFR 211.67(a)].

For example:

a. FDA investigators observed glassware frosted from chemicals, white residue throughout the hood area and on the oven, unlabeled glass containers filled with clear liquid in the fume hood, white powder-like crystals and flakes on the bench, and glassware that was not clean.

b. You did not appropriately maintain the deionized (DI) water system used for chemistry testing of OTC drug products in your main laboratory. The red light (indicating a filter change is needed) was on, the inside of the dispensing hose was discolored, there was a bronze-like color coating on the outside of the dispensing hose and connections to the hose. Given the lack of maintenance records, it was unclear how long the filter light had been on or if the filters had been replaced since installation in October 2010.

In your response, you state that the DI water filters have been changed and your staff has been instructed to keep the oven and the DI water system clean. Your response, however, is inadequate because it does not provide adequate assurance that you will clean and maintain the equipment at appropriate intervals to prevent the recurrence of these violations. Your response does not indicate whether your firm will implement new standard operating procedures (SOPs) or will make necessary changes to the existing SOPs outlining equipment cleaning and maintenance instructions, employee training, and documentation of cleaning and maintenance.

4. Your firm has failed to exercise appropriate controls over computer or related systems to assure that changes in master production and control records, or other records, are instituted only by authorized personnel [21 CFR 211.68(b)].

For example:

a. Your firm did not put in place requirements for appropriate usemames and passwords to allow appropriate control over data collected by your firm's computerized systems including UV, IR, HPLC, and GC instruments. All employees in your firm used the same usemame and password. In addition, you did not document the changes made to the software or data stored by the instrument systems. Without proper documentation, you have no assurance of the integrity of the data or the functionality of the software used to determine test results.

b. Your firm had no system in place to ensure appropriate backup of electronic raw data and no standard procedure for naming and saving data for retrieval at a later date.

In your response, you state that you will maintain backup of electronic raw data and all technicians will have their own user identification (ID) and password. Your response, however, is inadequate because you do not describe how your firm intends to save and back-up the electronic raw data, nor whether your firm will implement audit trails on your computerized systems. Further, you do not provide a timeframe for accomplishing the intended corrective actions or describe the changes you have made to relevant SOP(s).

5. Your firm has failed to maintain complete records of all testing and standardization of laboratory reference standards and standard solutions [21 CFR 211.194(c)].

For example:

a. Your firm used unqualified secondary standards for the assay analysis of over-the-counter (OTC) drug products, including but not limited to **(b)(4)**. Therefore, you have no assurance that the assay results determined with these reference standards are accurate and reliable.

b. Your firm failed to standardize the titrant solutions prior to using them for the titration assay analysis of titanium dioxide and salicylic acid. In addition, your firm failed to establish a schedule for required restandardization of commercially purchased standard solutions. Therefore, you lack assurance that the assay results determined with these titrants are accurate and reliable.

In your response, you state that "we are already using the USP standards" or that you have implemented the use of USP standards since the inspection. In addition, you state that you are implementing a new SOP to restandardize titrants. Your response, however, is inadequate because it does not include an evaluation of the data already provided to your clients, which were generated using the unqualified reference standards and unstandardized titrant solutions. Furthermore, your response does not indicate whether you will inform your customers of the result of such evaluation as it relates to their drug product(s).

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, 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 reinspect to verify corrective actions have been completed.

We are concerned that your firm has failed to comply with other basic GMP requirements. Regardless of the therapeutic category of the drug products your firm tests and your firm's size, you are responsible for prompt correction of these violations of CGMP requirements. We emphasize that failure to do so may result in regulatory action. We also recommend that you engage a third party consultant having appropriate CGMP expertise to assess your firm's facility.

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 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 products under contract to drug manufacturers, and provide the date(s) and reason(s) you ceased testing.

Send your reply to the following address: U.S. Food & Drug Administration, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey 07054, Attn: Andrew Ciaccia, Compliance Officer.

Sincerely,

/s/

Diana Amador-Toro
Director, New Jersey District

Links on this page:

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
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