



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

472-35 M3187M

WARNING LETTER

19900 MacArthur Blvd., Ste 300
Irvine, California 92612-2445
Telephone (714) 798-7600

NOV 10 1999

CERTIFIED MAIL – RETURN RECEIPT REQUESTED

Tae W. Kang, Ph.D.
Director
Bio-Science Research Institute, Inc.
4813 Cheyenne Way
Chino, CA 91710

W/L 08-00

Dear Dr. Kang:

During an inspection of your manufacturing facility located at 4813 Cheyenne Way, Chino, CA conducted August 30th through August 31st, 1999, FDA investigators documented deviations from the Current Good Manufacturing Practices (cGMPs) for Finished Pharmaceuticals (Title 21, Code of Federal Regulations (CFR), Part 211). Those deviations cause all drug products tested at your facility to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act). The violations from 21 CFR 211 include:

1. Failure to establish and document the accuracy, sensitivity, specificity and reproducibility of test methods employed [211.165]. For example:
 - a. Bacteriostasis/Fungistasis testing is not performed to validate product sterility tests.
 - b. Inhibition/Enhancement tests are not performed to validate product Limulus Amebocyte Lysate (LAL) testing.
 - c. Preparatory tests using USP specified microorganisms are not performed to validate product Microbial Limits testing.
 - d. Validation of Chemistry Test Method HPLC assay for [REDACTED] does not include linearity, precision or accuracy determinations.
 - e. No method validation was performed for the procedure Determination of [REDACTED]

2. Failure to establish and follow laboratory controls, which are based on sound scientific specifications, standards, and test procedures [211.160]. For example:
 - a. The autoclave used for sterilization of materials used for product testing is not validated.
 - b. There are no written procedures for any microbiological tests performed.
 - c. Growth promotion tests are not performed on each autoclaved lot of medium used for Sterility and Microbial Limits testing.
 - d. There is no procedure for the maintenance and storage of ATTC strains used for growth promotion studies.
 - e. There is no written procedure nor is testing performed to monitor the test environment or personnel during sterility testing.
 - f. There are no written procedures for conducting investigations of test failures or to delineate sterility retest policies.
 - g. Lysate sensitivity tests and positive product control containing 2 Lambda endotoxin are not performed for each test as required
 - h. Thermo-probes used to monitor rabbit temperatures during pyrogen testing are not calibrated to the required sensitivity.
 - i. Weights used to calibrate balances are not standardized against ASTM conforming weights.
 - j. There are no chromatographic system suitability tests performed nor is there any data to demonstrate the chromatographic system is calibrated.
 - k. There is no established calibration specifications for the Infrared Spectrophotometer when the spectrum of polystyrene is recorded.
 - l. There is no data to justify the expiration dates and storage conditions established for reference standards such as [REDACTED] and [REDACTED] in [REDACTED]

3. Failure to maintain complete data from all tests necessary to assure compliance with established specifications and standards [211.194]. For example:
 - a. Sterility test records do not record the amount of product tested or the media batches used for the test.
 - b. LAL test records do not record sensitivity or product tests documenting dilutions used, endotoxin and lysate lot numbers or their sensitivities, incubation times or temperatures and calculation of results.
 - c. Results for Particulate Matter in Injectable Products do not show actual counts observed.
 - d. Results for aerobic plate count determinations do not show the amount of product tested, actual counts observed or product dilutions used.
 - e. There are no records describing media batch preparation.
 - f. Standard weights, sample weights and calculations are not recorded nor referenced in laboratory notebooks.
 - g. "Unofficial" composition notebooks in which raw data is recorded but not reviewed are maintained. These notebooks had entries obliterated so that the original entries could not be read.
 - h. Informative statements of method used are not always recorded in laboratory notebooks.
 - i. Chromatograms of product tests are not always retained.
 - j. UV and IR spectra of product tests are not always retained.
 - k. Data for the preparation and use of reference standards is not always recorded and/or retained.
 - l. The review and approval of laboratory data does not include all data recorded for a test in "unofficial" notebooks.
 - m. Test results are released to clients before appropriate review and approval of laboratory data occurs.

- n. Chromatographic laboratory data for ██████████ (lot #1558) that had run #13 removed and run #14 substituted in its place was approved for release on 8-25-99.
4. Failure to ensure that equipment has the appropriate design, adequate size and is suitably located to facilitate operations for its intended use and for its cleaning and maintenance. [211.63]. For example:
 - a. Sterility testing is performed in a hood located in the general laboratory area.
 - b. Media required to be incubated at 20 – 25°C are incubated at room temperature without monitoring.
 - c. The room housing the rabbit colony (used for pyrogen testing) is not temperature monitored or controlled to the required sensitivity.
 - d. The Particulate Matter test is not performed in a laminar flow hood.
 - e. The microscope used in the performance of the Particle Matter test has no external light source or an objective eyepiece with a graticule field of view and control sizing circles of 10 and 25 um size.
 - f. The filtering apparatus used in the performance of the Particulate Matter test does not have a vacuum system capable of maintaining the required vacuum range.
 5. Failure to establish and follow procedures designed to adequately maintain equipment [211.67]. For example:
 - a. The HEPA filters of the laminar flow hood used for sterility testing are not aerosol tested to demonstrate filter integrity.
 - b. There is no written procedure for HEPA filter testing or the routine periodic re-certification of the laminar flow hood used for sterility testing.
 6. Failure to ensure that employees wear clean clothing appropriate for the duties they perform [211.28]. Sterility test analysts do not wear appropriate sterile garments and perform tests with exposed face and hand skin surfaces.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. A list of observations (Form FDA-483) was issued and discussed with you at the conclusion of the inspection. It is your responsibility to assure adherence with each

requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts. Additionally, pending Antibiotic Form 6, New Drug Applications, Abbreviated New Drug Applications or export approval requests may not be approved until the above violations are corrected.

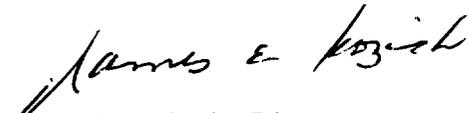
We realize your firm is a contract testing laboratory and as such does not have ultimate responsibility for the drug products being tested. However, 21 CFR 210.3(b)(12) defines testing as part of the drug product manufacturing, processing, packaging and holding process. Therefore, your firm is subject to cGMP requirements pertaining to product testing.

You should notify this office in writing 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 prevent the recurrence of similar violations. If corrective action cannot be completed within fifteen days, state the reason for the delay and the time within which corrections will be completed. In addition, we request that you contact this office to arrange a meeting with us to discuss the serious nature of these violations. You may schedule this meeting by calling the District Director's office at 949-798-7774.

Your written response should be directed to the Food and Drug Administration, Attention:

Thomas L. Sawyer
Director, Compliance Branch
Food and Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Sincerely,


Acting District Director