



Food and Drug Administration
Detroit District
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Detroit, MI 48207-3179
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CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER
2001-DT-07

January 16, 2001

John W. Wireman, Ph.D.
President
Biological Research Solutions, Inc.
2727 Second Avenue
Detroit, MI 48201

Dear Dr. Wireman:

Investigators Renee L. Rice and Miah I. Schneider conducted an inspection of your firm on September 13 through October 10, 2000. At the conclusion of the inspection the investigators issued to you a FORM FDA-483, list of Inspectional Observations. The numerous, significant deviations from the Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Part 211), as listed on the FDA-483, cause the drug products tested by your firm to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act).

1. 211.22 Responsibility of the quality control unit Failure to have a quality control unit adequate to perform its functions and responsibilities, as required by 21 CFR 211.22. Your failure to have an adequate quality control unit is demonstrated by the number and types of inspectional observations made during this inspection. Some examples from the FDA-483 are:
 - a. Item 2. There are no written procedures to ensure that all data reported are periodically reviewed by management. 211.22(c) and (d)
 - b. Item 14. USP Mold and Yeast results were reported in ~~1~~ days, whereas the USP procedure requires incubation for 5-7 days. This discrepancy was not noted during any quality assurance review. 211.22(a)
 - c. Item 15. The laminar flow hood failed a sterility test, but was used for subsequent testing after an unvalidated cleaning procedure was performed, until acceptable sterility test results were obtained ~~1~~ days later. 211.22(b)
 - d. Item 19. Cross outs and written-overs were observed throughout the laboratory records with out explanation, date and initial. 211.22(a)
 - e. Item 27. There is no documentation that your firm investigated temperature failures that occurred for the incubators and refrigerators. 211.22(a)

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2. 211.25 Personnel qualifications

The training program fails to assure your employees and supervisory employees are trained in the specific tasks and in their assigned responsible functions. Examples from FDA-483 Item number 5 are:

- a. There are no written procedures for conducting training for specific tasks or for good laboratory practice training. 211.25(a)
- b. The training records do not sufficiently document that analysts have been trained for the specific tasks that they perform. 211.25(a)
- c. There is no documentation that management reviewed the adequacy of the training. 211.25(b).

3. 211.160 Laboratory Controls-General Requirements

Your firm failed to have in place written procedures for many of the operations performed by your laboratory, that were drafted by an appropriate organizational unit and reviewed and approved by a quality control unit. These procedures should include scientifically sound specifications and test procedures. Some examples from the FDA-483 are:

- a. Item 1. There are no written procedures describing the preparation and maintenance of ATCC stock and working cultures (standards). 211.160(b)(1)
- b. Item 4. There are no written procedures in place to evaluate samples that are out-of-specifications and are subsequently re-tested and pass. 211.160(b)(2)
- c. Item 6. There are no written procedures in place for the [REDACTED] negative and positive staining used for identifying bacteria morphology. 211.160(b)(1)
- d. Item 7. There are no written procedures in place for, nor is there any testing performed, for environmental monitoring for airborne contaminants or surfaces of laboratory equipment and benches. 211.160(b)(1)
- e. Item 20. Laboratory procedures for calibration of various instruments lacked some or all of the following information: persons responsible for the calibration; specifications or limits; action to be taken if a test fails; and a periodic review by management. 211.160(b)(4)
- f. Item 25. There is no documentation to support that the procedures for cleaning the laboratory benches and laminar flow hood are effective from microbiological contamination. 211.160(b)(1)
- g. Item 29. There is no written procedure for performing the QC testing for each lot of [REDACTED] reagent against [REDACTED] cultures as required by the manufacturer's ([REDACTED]) instructions. 211.160(a)

4. 211.194 Laboratory Controls-Laboratory Records

The laboratory records fail to consistently and accurately include complete data derived from all tests necessary to assure compliance with specifications and standards.

Examples from the FDA-483 are:

- a. Item 8. Procedure (LP 1) was not followed in that samples from [REDACTED] were incorrectly logged in under a different firm's name during 3/22-4/16/00 and 8/2-9/11/00. 211.194(1)
- b. Item 9. There is no documentation of the receipt and use (e.g. USP requires no more than five passages removed) for the [REDACTED] cultures. 211.194(c)
- c. Item 10. The system is inadequate for identifying if inhibitory testing was performed for each of the different types of pharmaceutical products tested. 211.194(a)(2)
- d. Item 11. Procedure (CM 1) for the quality control of media was not always followed in that expired media was used, different test organisms than specified were used as positive controls, and negative and positive control testing was not performed. 211.194(a)(8)
- e. Item 12. Procedure (CM 9) for the quality control of broth media was not followed in that, media having a pH value outside of specification was used, and there was a lack of performing negative and positive control testing. 211.194(a)(8)
- f. Item 16. Analysts notebooks failed to always document the following pertinent information:
 1. person performing the analysis 211.194(a)(7)
 2. analytical method used 211.194(a)(2)
 3. media and inhibitory agents used including lot numbers and dates made 211.194(c)
 4. sample amount used for analysis 211.194(a)(3)
 5. incubator used and its temperature 211.194(d)
 6. the incubation start and end date 211.194(d)
- g. Item 17. Analysts notebooks fail to document individual plate results when an average of the two was reported as the test result. 211.194(4)&(5)
- h. Item 18. The analytical report generated on 9/7/2000 for samples [REDACTED] incorrectly stated the sample numbers to be [REDACTED]. The report was signed and dated by management. 211.194(a)(6) and 211.22(a)
- i. Item 21. There is no documentation that equipment calibration was performed when scheduled as stated in your firm's procedures (e.g. incubator, LFH, balances, thermometers). 211.194(d)
- j. Item 23. There is no documentation that laboratory equipment cleaning was conducted when scheduled in your firm's procedures. 211.194(a)(8)
- k. Item 24. Cleaning of the laminar flow hood the day after samples are processed in the hood, as required by your firm's procedure (EM 5), is not always documented. 211.194(a)(8)

- l. Item 26. Daily temperature readings for incubators and refrigerators are not always documented as required by your firm's procedures (EM 1) & EM 2). 211.194(d)
- m. Item 28. Your firm's procedure (EM 8) for maintaining the [REDACTED] deionized water unit is not always followed in that daily resistance readings are not always documented, lot number and expiration dates of replaced cartridges are not recorded, and monthly maintenance testing is not documented. 211.194(d)

The above list of deviations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence to each requirement of the Good Manufacturing Practice Regulations. Other 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 NDA, ANDA, or export approval requests may not be approved until the above violations are corrected.

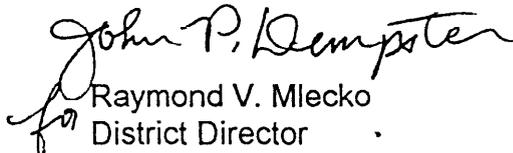
We request that you take prompt action to correct these violations. Failure to promptly correct these violations may result in enforcement action being initiated by the Food and Drug Administration without further notice, such as seizure and/or injunction.

We acknowledge receipt of your November 10, 2000 written response to the list of inspectional observations and your commitments to take specific steps to correct the noted violations. We request that you thoroughly evaluate the adequacy of your procedures and controls, and that you take whatever actions are necessary to make systemic corrections and to assure that similar violations will not recur.

Please notify this office in writing, within fifteen (15) working days of receipt of this letter, as to any additional steps you have taken to correct these violations, including an explanation of each step being taken to identify and make corrections to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time frame within which the corrections will be implemented.

Your reply should be directed to Melvin O. Robinson, Compliance Officer, at the above address.

Sincerely,


for Raymond V. Mlecko
District Director
Detroit District