DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration
Baltimore District Office
6000 Metro Drive, Suite 101
Baltimore, MD 21215-3215
Telephone: (410) 779-5454

WARNING LETTER
VLN# 06200780

January 5, 2007

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. I. Andrew Passmore II, President
Bell-More Laboratories, Inc.
4030 Gill Avenue
Hampstead, Maryland 21074-2213

Dear Mr. Passmore:

During an August 7 through August 17, 2006, inspection of your pharmaceutical facility, located at 4030 Gill Avenue, Hampstead, Maryland, investigators from this office and the Center for Drug Evaluation and Research (CDER) documented deviations from the Current Good Manufacturing Practice (CGMP) regulations in 21 Code of Federal Regulations (CFR), Parts 210 and 211, that cause your finished drugs to be adulterated within the meaning of 21 U.S.C. § 351(a)(2)(B) (Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act)). The following are examples of some of the significant CGMP deviations that were found during our inspection of your firm:

1. **Failure to establish defined areas or such other control systems to prevent contamination or mix-ups for handling and/or manufacturing potent compounds. [21 CFR § 211.42(c)]**

   For example, your firm lacked an adequate assessment of the cross-contamination risks posed by the manufacture of several potent compounds (e.g. cytotoxic and hormone products, as well as other products of high pharmacologic activity) at your facility. Controls necessary to prevent cross-contamination of products were not adequately defined. Your firm lacked documentation to determine sources of potential airborne transfer, mechanical transfer, and/or mix-up in the manufacturing and handling of these potent compounds. Specifically, potent active pharmaceutical ingredients (APIs) were introduced into the manufacturing environment during sampling of APIs, formulation of batches in open equipment, aseptic filling of solutions into open vials, and lyophilization of solutions into partially stoppered vials. Furthermore, your firm's potent compound formulation room (Class 10,000) exhausted directly into the entry room (Class 100,000) where operators move throughout the parenteral manufacturing areas, including the aseptic filling room. Your firm utilized a single air pathway for manufacturing different potent compounds. Finally, operators de-gowned after handling potent compounds in an unclassified corridor between the manufacturing area and the packaging area. Due to the above factors, possible migration of levels of potent compounds may have occurred at your manufacturing facility.

2. **Failure to have adequate building design and construction used in manufacture, processing, packing, or holding of drug products to facilitate cleaning, maintenance, and proper operations. [21 CFR § 211.42(a)]**

   For example,

   a. Your firm uses drop ceiling panels of porous, drywall-like material that is not easily cleaned in the formulation room (Class 10,000), entry room (Class 100,000), and processing room (Class 100,000). Numerous ceiling tiles were not seated flush with the metal frame revealing gaps between the ceiling tiles and the metal frame.

   b. A hole (approximately 2" X 1") was observed at the junction of the ceiling and the wall of the entry room (Class 100,000), where a sprinkler head was mounted.

3. **Failure to maintain any building used in manufacture, processing, packing, or holding of a drug product in a good state of repair. [21 CFR § 211.58]**

   For example,

   a. Gaps were observed between the ceiling tiles and the metal frame in the formulation room (Class 10,000) and in the entry room (Class 100,000). The caulk-like substance, which is used to fill in the gaps, had separated from the metal frame. For example, there is a gap measuring approximately 23 inches long in the formulation room (Class 10,000) directly in front of the doorway at the wall-to-ceiling junction where the metal frame abuts the tile. Also the tile was observed to be elevated from the metal frame.

   b. Rust-like substance was observed in two locations on the metal frame above the door from the entry room (Class 100,000) into the processing room (Class 100,000), the first measuring approximately five inches long and the second measuring approximately 23 inches long. Additionally, this rust-like substance was observed running along the entire length of the bottom of this door.

   c. Rust-like substance was observed on the metal frame surrounding the ceiling tiles and HEPA filters in the processing room (Class 100,000).

   d. Rust-like substance was observed on two free-standing cabinets in the processing room (Class 100,000). One of these cabinets was used to store mixing rods.

4. **Failure to keep records for the maintenance, cleaning, and sanitizing of equipment. [21 CFR § 211.67(c)]**

   There were no equipment cleaning records for several of the product contact, multi-use formulation mixing rods. The investigators observed that there was no evidence to demonstrate that the mixing rods were dedicated to specific products.

5. **Failure to adequately validate cleaning procedures for equipment used in**

manufacturing and packaging operations of drug products. [21 CFR § 211.67(a)]

For example, your firm lacked adequate evaluation of possible migration of potent compounds throughout the facility. Specifically, the cleaning validation study, "Validation of Cleaning and Decontamination of Controlled Areas, Non-Dedicated Equipment, and Work Surfaces Used in the Manufacturing of Cytotoxic Products," Protocol #VP033.001, was inadequately performed in that recovery studies have not been performed on material coupons (samples of materials used for wall coverings, countertops, ceiling, and stainless steel) to demonstrate the ability to recover cytotoxic products from surfaces and equipment used in production as required by the protocol. Also, the above validation study addressed only Mitomycin and failed to include testing (recovery studies) of other cytotoxic ([redacted]), and hormone ([redacted]) products manufactured by your firm. In addition, records did not indicate that pre-cleaning samples were collected prior to cleaning of sampled surface areas. Also, the sampling records failed to show time of sampling, and the area cleaning records failed to show the time of cleaning. Finally, the sampling locations were not defined and evaluated as possible worst case locations.

6. **Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, and followed. [21 CFR § 211.113(b)]**

For example,

a) your firm failed to adequately document air flow (smoke) studies to demonstrate unidirectional airflow under dynamic conditions. Your firm's air flow patterns procedure lacked specific acceptance criteria. Your airflow study documentation included hand drawings that provided insufficient information to determine whether HEPA-filtered air used in the manufacturing area (and sterility test laboratory) robustly sweeps away particles and maintains unidirectional airflow protection under dynamic production conditions.

b) air pressure differentials are not continuously monitored nor frequently recorded during aseptic filling operations. No system is in place to adequately monitor or record pressure differentials to assure that the rooms are maintained at the correct air pressure differential at all times.

c) there was no documentation to demonstrate that the process used to sterilize the evacuated vials was validated.

d) investigators observed the following inadequate aseptic techniques during the filling operations of Mitomycin Injection, 20 mg, lot [redacted] on August 9, 2006:

i. operators dragged their sleeves across trays of stoppers and partially stoppered vials.
ii. operators held vials by the neck with their palms directly over the open top of the unstoppered vials.
iii. operators used a rake to adjust and position lyophilizer trays in the open lyophilizer. The handle of the rake was observed propped on the floor when not in use.
iv. operators were observed with their arms and heads inside the lyophilizer during the

loading of trays of partially-stoppered vials.

v. operators moved rapidly in the filling and stoppering hood as well as near the opened lyophilizer door.

vi. operator was observed using his hands to move a chair, he failed to sanitize his hands, and then performed adjustments to the filling apparatus and the filling syringe.

7. **Failure to have written procedures for production and process control designed to assure your drug products have the identity, strength, quality, and purity they purport or are represented to possess. [21 CFR § 211.100(a)]**

For example, no standard operating procedures were available that establish defined areas or controls necessary to reduce risk of product cross-contamination with potent compounds. Your firm also failed to have an SOP for sterility testing of sterile evacuated vials. Finally, your firm lacked SOPs that address evaluation of possible migration of potent compound contaminates during manufacturing in your contract multi-product parenteral manufacturing areas. The firm has failed to evaluate the following factors:

a. The cytotoxic and hormone active pharmaceutical ingredients (APIs) are in powder form.

b. Product introduction to the manufacturing environment occurs during sampling of APIs, formulation of batches in open equipment, aseptic filling of solutions into open vials, and lyophilization of solutions.

c. The formulation room (Class 10,000) exhausts into the entry room (Class 100,000) where operators move throughout the multiple parenteral manufacturing areas.

d. The multi-use lyophilizer # 5 has not been revalidated to demonstrate that the cleaning procedures are effective at removing chamber residues of other compounds that are lyophilized.

8. **Failure to establish sampling plans, test procedures, or laboratory control mechanisms for testing your finished product sterile evacuated vials. [21 CFR § 211.160(a)]**

For example, investigators observed black colored particles in at least one evacuated sterile vial. The microbiologist performing sterility testing on the vials was observed removing the vial with the black colored particles and replacing the vial. No sampling plan or test procedures were available to justify replacement of the finished product evacuated vial.

We acknowledge receipt of your September 8th and October 20th 2006, letters in response to the Form FDA-483, Inspectional Observations. We have reviewed your responses and have the following comments:

Observation 1
As stated above, the agency believes your current assessment of control systems is inadequate for manufacturing potent compounds [cytotoxic and hormone products, and other products of high pharmacologic activity]. Therefore, the cleaning validation protocols submitted as part of your responses are considered incomplete in that you have not provided an assessment as to whether defined or such other controls are necessary to prevent cross-contamination of products. Furthermore, you have not provided a procedure that identifies products that pose significant cross-contamination risk. Regardless of how often any product (e.g., Mytomcycin) is manufactured, due to the potential risk of cross-contamination, a risk assessment is necessary to determine whether you need separate and defined areas for manufacturing potent and non-potent products.

Observation 1b
We note in your October 20, 2006, response that additional cleaning evaluations of work areas for potent compounds will be performed before they are manufactured. Your response is inadequate in that you do not provide an evaluation of cleaning of controlled areas for non-dedicated equipment and work areas.

Observation 1aa
We note in your October 20, 2006, response that "Mitomycin, [redacted] are all in a granulated form which does not become air borne when weighed and formulated." Regardless of whether the form of these materials is considered powder or granulated, the concern for possible migration of trace levels of potent compounds is considerable due to spread of potential aerosols formed from these materials during formulation and handling operations.

Observation 1cc
We note in your October 20, 2006, response that "an air return with filtration will be installed to eliminate the air exhausting into entry room." Your response is inadequate because you have not made a commitment to determine the adequacy of possible contamination of return make-up air in your air filtration system. As stated above, your firm provides no risk assessment to determine the hazard classification of your products. Your firm's use of multiple potent compounds, even those manufactured on a short term basis, with no assessment of risk posed by the manufacturing operation of these products, is not acceptable due to the potential for cross-contamination.

Observation 4
We note in your October 20, 2006, response that your firm performed additional smoke studies including simulations of loading of the lyophilizer. Your hand drawings are insufficient documentation to determine if airflow is maintained under dynamic conditions. Therefore, regardless of additional simulations performed under your current protocol, unless substantial changes are made, your smoke study documentation is still considered inadequate.

Observation 5
Your October 20, 2006, response states your firm now has a visual and audible alarm in the aseptic fill room to signal aberrant air pressure differentials. We agree an alarm is helpful; however, no validation of your alarm system or approach to data recording was noted in your response.

The issues and 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 or the occurrence of other violations.

It is your responsibility to assure that your firm complies 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 new drug applications listing your facility as a supplier or manufacturer until the above violations are corrected. A reinspection may be necessary.

Due to the severity of the violations and the inadequate FDA-483 responses, we are requesting that you and/or your representatives come into the Baltimore District Office for a meeting and present your corrective action plan to the agency. We have tentatively scheduled a time of 12:00 -2:00 pm on January 22, 2007 or 12:30 – 2:30 pm on January 25, 2007.

During this meeting please be prepared to provide the following: 1) the additional specific steps that you will take to correct these violations, including an explanation of each step being taken to prevent the recurrence of the violations; 2) a detailed risk assessment of all your potent compound drug products; and 3) the estimated completion date for all proposed corrective actions. If your corrective actions cannot be completed timely, please specify your reasons. Further, if you are going to discontinue drug manufacturing operations until an adequate corrective action plan is in place to assure your firm is in an overall state of control or if you permanently cease manufacturing and marketing potent compounds, please provide the reasons for and the date on which you cease production.

Please contact Randy F. Pack, Compliance Officer, U.S. Food and Drug Administration, 6000 Metro Drive, Suite 101 Baltimore, MD 21217, to schedule a date for the meeting. If you have any questions, please contact Mr. Pack at (410) 779-5417.

Sincerely yours,

Evelyn Bonnin,
District Director
Baltimore District Office