



DEPARTMENT OF HEALTH & HUMAN SERVICES

415886
Public Health Service
Mid-Atlantic Region

Telephone (201) 331-2906

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

December 3, 1996

WARNING LETTER

RELEASE
REVIEWED BY DCE
C.J.
12/3/96
DATE

Jorge Engel, President
Berlex Laboratories, Inc.
300 Fairfield Road
Wayne, NJ 07470-7358

Dear Mr. Engel:

File No: 97-NWJ-07

This is regarding an inspection of your facility located at 300 Fairfield Road, Wayne, New Jersey between the dates of August 19 and October 1, 1996. During the inspection our investigators documented serious deviations from the Current Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Parts 210 & 211) in conjunction with your firm's manufacture, processing, packing, and holding of various drug products.

These deviations were noted on the FDA-483 presented to your firm at the close of the inspection on October 1, 1996. These CGMP deficiencies cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act

The significant observations are as follows:

Regarding Fludara for Injection, stability studies in support of the labeled hold time for reconstituted product do not mimic actual manufacturing and storage conditions.

We do not agree that the studies discussed in your response adequately support the stability of the reconstituted product for eight hours. We are concerned about the lack of data regarding the reconstituted product, held at room temperature, since your label does not specifically state that reconstituted product should be refrigerated. Your response indicates room temperature testing of the reconstituted product will be added to the annual stability commitment. What data do you currently have to support the 8 hour, room temperature hold time? The drug product should meet established specifications upon initial evaluation and after holding of the reconstituted product, as allowed by the product label. Please explain why the addendum to PNO64 indicates the specifications are tentative for the reconstituted product.

Appropriate storage conditions were not established for fludarabine phosphate drug substance which is known to degrade at elevated temperatures and humidity. The drug substance was

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Merlex Laboratories, Inc.
Bayne, NJ 07470-7358

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stored in a warehouse without humidity control. Samples used to release the bulk drug substance were not representative. Samples are stored in a desiccator, sometimes for 9-12 months, before analysis, while product was stored in the warehouse.

Appropriate storage conditions should be determined to assure that the drug substance will not be adversely effected. Please clarify what data shows degradation at 30°C for fludarabine phosphate. Your response indicates the product is now stored under refrigerated conditions. What data do you have to support these storage conditions as appropriate for this product?

The fludarabine phosphate drug substance assay method was changed when it was determined, through investigations, that the method was not rugged. The effect of this change on lots released using the old method was not evaluated.

Your response indicates that the old method was fully validated and only lacked desired robustness. How are you assured that this method was reliable during normal use for product that has been released?

Stability testing is not performed according to established protocol schedules. Initial time stations on stability are performed approximately one year into product expiry for Agnevist Injection and Fludara Injection. Some time stations are not performed at all. Supervisory review of stability data is not performed in a timely manner. Supervisors do not review all chromatograms in the Technical Service Laboratory where stability testing and method validation are performed.

We acknowledge your commitments to address the timely review and approval of data. Please provide your rationale for using C1 values of $\geq -1.4\%$ in monitoring drug substance lots on stability. DP No. [REDACTED], Stability Program states under Section 7.4 that test stations will be canceled if the product expiry is within two months. Please explain your rationale.

Appropriate controls are not exercised over the [REDACTED] Software, used by Quality Control and Technical Services, to assure that changes in laboratory control records are instituted only by authorized personnel.

**Jorge Engel, President
Berlex Laboratories, Inc.
Wayne, NJ 07470-7358**

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There are no written procedures defining the appropriate use for the abort, terminate, suspend, restart, and stop functions which are accessible to all analysts. Also, the terminate and suspend functions were not evaluated during validation.

There are no requirements for analysts to document or notify the supervisor when these functions are used. There is no documentation indicating that analysts were trained in the appropriate use of these commands.

This system does not have the ability to maintain an audit trail.

A backup file of data entered into the computer should be maintained except where data, such as calculations are eliminated by the computer. Hard copy or alternative systems designed to assure that data is exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained. Instruction that analysts not use the terminate and suspend commands does eliminate the need to evaluate the effect these commands have on data acquisition. In addition, without an audit trail to check the use of these functions how is your firm assured that appropriate control has been exercised? Your SOP [REDACTED] does not define the level of authority needed to execute these commands.

Security measures have not been instituted to prevent unauthorized access to the [REDACTED] system used in the Quality Control and Technical Services Laboratory for Fludara raw material and finished product testing. Your firm did not perform software validation prior to initiation of product testing in 5/92. This system was not evaluated for installation, operation, or performance qualification prior to use at the Wayne facility.

Please clarify how your password protection program. What analysts have security access? How is this determined? Please provide an update on the status of the Instrument Performance Verification.

There is no formal change control system which designates who has the authority to approve changes or how such changes should be handled.

Please provide an update on implementation of your change control procedure. The protocol for validating the change in Fludara

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drug product assay does not contain specifications. A validation protocol needs to specify predetermined specifications. Your response to observation 12 indicates a Method Validation SOP is under review. Please provide a copy of this SOP.

Drug product complaints are not handled in a timely manner. Many complaints dating back to 1/95 are still open. The SOP for Drug Product Complaints, No. [REDACTED], does not define timeframes to assure a timely review.

We acknowledge the revision of your Drug Product Complaint SOP to include time frames. How does your firm intend to assess the current backlog of complaints?

The autoclave used for sterilizing media and clean room equipment has not been validated.

Without a formal evaluation of the autoclave how are you assured that the calibration program is efficient for maintaining proper performance? How is placement of the bioindicators determined? How are you assured that the bioindicator accurately reflects all areas of the autoclave? How do you know the temperature throughout the autoclave is consistent? The investigators noted that growth promotion testing was not consistently documented. What assurance do you have that this media was suitable for growth?

Impurity profiles for quinidine gluconate active drug substance, which is used to manufacture Quinaglute Tablets, have not been established for the two bulk manufacturers, [REDACTED] and [REDACTED].

What information was used to qualify these suppliers? What comparison information do you have regarding these two suppliers?

We have reviewed your letter of October 18, 1996 in response to the list of Inspectional Observations (FDA-483) issued to your firm at the close of the inspection on October 1, 1996.

Except where we have listed comments within this letter, we view your response as adequate. We will confirm your intended corrective actions and their adequacy during our next FDA inspection.

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Berlex Laboratories, Inc.
Wayne, NJ 07470-7358

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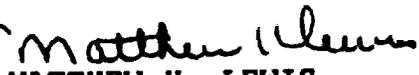
The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Possible actions include seizure and/or injunction.

Please notify this office in writing within 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 15 working days, state the reason for the delay and the time needed to complete the corrections.

Please submit your response to Attention: Diane Edson,
Compliance Officer, Food and Drug Administration, 10 Waterview
Blvd., 3rd Floor, Parsippany, New Jersey 07054.

Sincerely,


MATTHEW H. LEWIS
District Director
New Jersey District

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

DCE:np