



July 9, 1999

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Chicago, Illinois 60606  
Telephone: 312-353-5863

**WARNING LETTER**  
**CHI-27-99**

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

Mr. Miles D. White  
Chairman & Chief Executive Officer  
Abbott Laboratories  
One Abbott Park Road  
Abbott Park, IL 60064

Dear Mr. White:

During an inspection of Abbott's Hospital Products Division large and small volume parenteral drug manufacturing operations located at 14<sup>th</sup> & Sheridan Rd, North Chicago, Illinois, conducted from February 24, 1999, through May 26, 1999, FDA investigators Bruce McCullough and Susan Bruederle found serious deviations from the current Good Manufacturing Practice Regulations (cGMP) as specified in Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. These deviations 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 Act) as follows:

- Failure to follow established procedures as required by 21 CFR 211.100(b) during the validation of the SVP ambient loop conducted from 2/22/99 – 3/22/99. Extended steaming was performed once a week for each of the four weeks during the validation study. The established written sanitization procedure does not require the weekly extended steaming. Therefore, the validation study does not reflect actual processing conditions.
- Failure to collect sufficient data to successfully validate the LVP WFI systems as required by 21 CFR 211.100, 211.110(b), and 211.113(b).
- Failure to have sufficient production and process controls or to establish procedures to assure that drug products have the identity, strength, quality, and purity they purport or are represented to possess as required by 21 CFR 211.100 and/or failure to establish procedures designed to prevent microbiological contamination as required by 21 CFR 211.113. For example:

- a. Failure to establish procedures which recognize each LVP WFI distribution system separately. There are currently ten (10) separate WFI distribution systems; however, the procedure which addresses the WFI trending does not distinguish among them.
- b. The performance qualification or validation of the Distilled Water Central System has not evaluated the WFI after it passes through the single pass, ambient distribution system.
- c. Written procedures do not describe what to do with sterile product, vials and stoppers, when equipment adjustments or maintenance are performed during aseptic filling operations.
- d. There is no documented justification for the acceptance criteria used to evaluate the ability of [REDACTED] processors to reduce or remove endotoxins from stoppers.
- e. Media fills, which incorporate the same storage conditions used in the routine aseptic processing of sterile products stoppered after lyophilization, did not incorporate the 24 hour hold time in the purge cart.
- f. The WFI used by the bag rinsers is not sampled from the points of use for microbial and endotoxin testing in the part-fill east and west rooms.
- g. Procedures have not been established for sanitizing the components of the pre-treatment system, change-out of the ultraviolet lights in the pre-treatment system or replacement of the media in the carbon beds.
- h. No tests are done to assure the integrity of the [REDACTED]-micron filters, which are located in the pre-treatment water system after the reverse osmosis units.
- i. During aseptic filling of vancomycin on 5/12/99 in fill room 76, the operator committed several breaches of aseptic techniques in the Class 100 work area.
- j. No microbial monitoring of air is done in the Class 100 area in the Smeja unloading rooms.
- k. Maintenance performed on aseptic fill lines is not always checked or verified in a timely manner as evidenced by entries in the maintenance logs.
- l. The preventive maintenance schedule for replacement of the [REDACTED]-micron filters does not assure that the filters will be replaced as specified in written procedures.

- Failure to conduct investigations as required by 21 CFR 211.192. For example:
  - a. The discrepancy associated with the ambient WFI drop in Mix Room 2 was not thoroughly investigated. Sample site 389 was found over alert limits [REDACTED] in [REDACTED] [REDACTED] during February, 1999. The investigation that was conducted (resampling and trends) was found “acceptable.” No follow-up was done or corrective action taken in response to the above data.
  - b. Investigations of the cause and impact of [REDACTED] findings, associated with dry oil free compressed air used to purge carts containing filled open vials of sterile lyophilized powder, were not conducted in a timely manner.
  - c. The investigation into the failure of employees to follow established aseptic techniques and gowning procedures during the filling of Abbokinase on 4/16/99 did not extend to other lots associated with those same employees.
  - d. There is no record of an investigation or resolution of finding detectable endotoxin on stoppers on 4/14 & 15/98.
- Failure to retain records as required by 21 CFR 211.180. For example:
  - a. Daily room check sheets, which are used to document daily preventive maintenance of the LVP water system are discarded after 30 days.
  - b. Records of observations made during media fills are routinely discarded.
- Failure to review all production and control records as required by 21 CFR 211.192. For example:
  - a. LVP room check sheets were not always reviewed on a daily basis.
  - b. Steaming logs, which are used to document the sanitization of the WFI distribution system, were not always reviewed on a daily basis.
- Failure to maintain records as required by 21 CFR 211.180. For example:
  - a. The time that the weekly two-hour steaming cycle of the Water for Injection (WFI) storage and distribution system started and stopped is not documented.
  - b. The batch records for media fills do not describe all rejects.

- c. Batch production and control records do not include complete information as evidenced by: 1) No mention or reference to maintenance performed during filling of vancomycin lot 49-965-Z7 and lot 52-704-Z7; 2) Downtime log sheets which show the reason for downtime during aseptic processing are not filed with or referred to in the batch records; 3) Lot 51-913-Z7 batch record included no reference to the failure to follow established procedures during aseptic processing; 4) There are no data entries in the batch record for media fill 48-845-Z7 for the "excessive number of interventions."
- Failure to maintain records as required by 21 CFR 211.194. For example:
    - a. Tubes containing sample preparations and positive/negative controls for LAL testing are not identified with sample numbers or control types.
    - b. The calculation and check calculation of the geometric mean in the acceptance testing of Bacterial Endotoxin Gel Clot Test Reagents is not documented.
  - Failure to maintain equipment as required by 21 CFR 211.67. For example:
    - a. Not all WFI piping and associated equipment in the LVP area have been inspected to determine their current condition. According to your response, these are not scheduled to be completed until September 30, 1999.
    - b. A leaking valve was allowed to remain uncorrected for six days on two separate occasions in April 1999. The valve was located as part of the WFI system for rinsing the interior of parenteral bags prior to product filling.
    - c. LVP preventive maintenance room checks are not always carried out on a daily basis.
  - Failure to document equipment maintenance and adjustments as required by 21 CFR 211.67 and 21 CFR 211.180. For example, the excessive numbers of interventions that occurred during the filling operation on line 77 on 1/3/99 were not recorded.

We have reviewed your response dated June 7, 1999, which was written in response to the FDA-483 issued on May 26, 1999, and have the following comments.

Your response regarding updating the BOP to reflect the extended steaming procedures fails to address the issue of assuring that actual current practices are reflected in any subsequent validation studies. Although the issue of updating the BOP was corrected and verified, there is no mention of the associated validation issue.

Your response regarding investigations of OAL microbial occurrences relating to whether or not to issue a PACAR fails to address your process/procedure for assuring that all OAL data will be properly evaluated in the future.

Your response regarding LVP WFI validation is incomplete. It fails to provide assurance that the WFI currently in use can be successfully validated. The "new" WFI hot loop for LVP production will not be installed and validated until 7/31/2000.

Your response regarding media fill records states that the entries related to interventions are part of Abbott's internal audit procedures, and as such, are destroyed after completion of the audit (and associated corrections). Any records associated with media fills are control records and are subject to all applicable provisions of 21 CFR 211, Subpart J, Records and Reports, including record retention.

The above list of violations is not intended to be an all-inclusive list of deficiencies at your firm. It is your responsibility to ensure that all of your firm's products are in compliance with all requirements of the Act and its implementing regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices 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. These include seizure and/or injunctions.

You should 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 within which corrections will be completed. Your response should be addressed to Richard Harrison, Compliance Director, at the address provided in the letterhead.

Sincerely,

rs\

Raymond V. Mlecko  
District Director

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