



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
a 3626d

October 15, 2002

Dallas District
4040 North Central Expressway
Dallas, Texas 75204-3145

Ref: 2003-DAL-WL-01

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Miles White
Chairman and Chief Executive Officer
Abbott Laboratories, Inc.
100 Abbott Park Road
Abbott Park, IL 60064-3500

Dear Mr. White:

During an inspection of your drug manufacturing facility located in Austin, Texas, conducted August 19-28, 2002, our investigators documented deviations from the Current Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Parts 210 & 211). These deviations cause your drug product(s) to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

At the conclusion of the inspection, a FDA-483 (List of Inspectional Observations) was issued to and discussed with Mr. Ronald Kirkpatrick, Site Director. A copy of the FDA-483 is attached and it identifies many production and operational deficiencies causing the drug products manufactured by your firm to be adulterated. The deviations include the following:

1. Failure of the Quality Assurance Unit to follow written procedures, which require oversight and review responsibilities [21 CFR 211.22(d)]. For example, the following procedures are not being followed.
 - A1-00, Corporate Regulatory and Quality Science Policy
 - BQA0035, Global Quality System Overview
 - GN.10-05, HPD Quality Policy, QA Functions and Responsibilities
2. Failure to assure that automated equipment will perform a function satisfactorily during the manufacturing process for your drug products [21 CFR 211.68]. For example,

- The [REDACTED] process control computer monitoring system that is used to monitor various production and processing operations (e.g., operation conditions, equipment and component status, historical trending of collected data) is not validated to the current corporate standards. The following equipment and support utilities are not validated:
 - Continuous Sterilizer
 - Solution Preparation Equipment/Process
 - HVAC
 - Lifecare Rotary Fillers [REDACTED]
 - Part Fill Autofillers [REDACTED]
 - Irrigation Filler [REDACTED]
 - ADD-Vantage Autofillers [REDACTED]
 - PVC Compounding
 - Bag Fabrication Seal Thickness Measurement System
 - Reverse Osmosis Water Purification System and Water for Injection System
3. Failure to avert contamination in separate or defined areas designed to prevent contamination from occurring during manufacturing and processing operations [21 CFR 211.42(c)(5)]. For example,
- The controlling and monitoring of the movement and ingress of personnel, including maintenance personnel, components, and ancillary materials, such as tools necessary for equipment repairs/adjustments into the [REDACTED] filling areas is not being performed.
 - BMFG1413, "General Good Employee Practices", states: do not "bring in or use rusty racks, tools, furniture, etc. in the clean areas". However,
 - Rust was observed on the metal support backing of at least four stools in the [REDACTED] critical filling zones.
 - Rust was observed covering the overall surface of a stainless steel rack used to transport equipment parts into and out of the critical [REDACTED] filling zones.
 - Rust and corrosion was observed on the base and impeller blades on active air sampler, equipment no. [REDACTED] which was observed in use in the critical manufacturing areas.
 - Stools used by operators in the [REDACTED] filling zones were observed with worn conditions, e.g. cover worn to the point the interior foam padding was no longer confined by the plastic/vinyl cover.
 - The following is a summary list of the areas in [REDACTED] rooms with rust build up:
 - Rotary Station #'s [REDACTED]
 - Irrigation Filling Station #'s [REDACTED]
 - Part Fill Station #'s [REDACTED]
 - Manual Fill Station [REDACTED] and recirculating air unit
 - Auto Filler #'s [REDACTED]

4. Failure to restrict access by unauthorized personnel from entering areas designated as limited access areas [21 CFR 211.28(c)]. For example,
 - The ingress and egress of maintenance personnel into the [REDACTED] filling areas was not restricted to non-processing times of operation.
5. Failure to have adequate systems to control contaminants in areas where air contamination occurs during production [21 CFR 211.46(c)]. For example,
 - There are numerous HEPA filter metal grills that have a build up of rust-like material and discoloration (e.g. Rotary [REDACTED], Irrigation Filling, Part Fill Filling, and Manual Filling). Two HEPA filter grills are bent and reveal a buildup of mold-like and other unknown material and these grills are located immediately above the [REDACTED] filling zone.
6. Failure to follow written production and process control procedures [21 CFR 211.100(b)]. For example,
 - BMFG1413, "General Good Employee Practices", states: do not "bring in or use rusty racks, tools, furniture etc. in the clean areas";... "helps control particulate counts". However,
 - Rust was observed on the metal support backing of at least four stools in the [REDACTED] critical filling zones.
 - Rust was observed covering the overall surface of a stainless steel rack used to transport equipment parts into and out of the critical [REDACTED] filling zones.
 - Rust and corrosion was observed on the base and impeller blades on active air sampler, equipment no. [REDACTED] which was observed in use in the critical manufacturing areas.
 - Stools used by operators in the [REDACTED] filling zones were observed with worn conditions, e.g., cover worn to the point the interior foam padding was no longer confined by the plastic/vinyl cover.
7. Failure to establish and follow written procedures for the cleaning and maintenance of equipment used in the manufacture, processing, packing or holding of a drug product [21 CFR 211.67(b)]. For example,
 - There are no established written procedures currently in place indicating/detailing specific requirements with regards to controlling and monitoring the movement and ingress of personnel, including maintenance personnel, components, and ancillary materials, such as tools necessary for equipment repairs and/or adjustments, into the [REDACTED] filling areas.
8. Failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications [21 CFR 211.192]. For example,
 - BQA0014, "Handling of Product Complaints and WIP Shipment Complaints", does not describe the level of investigation to be performed

- when product complaints describing particulate matter in injectable products are received.
- A number of complaints for particulates were received, but no attempt to determine the source was made.
 - Environmental monitoring results are not routinely evaluated when complaints for metallic particles or other particulates are confirmed by analysis.
 - Retention samples are not routinely analyzed or evaluated as part of the complaint investigation.
9. Failure to establish and follow adequate procedures describing the handling of complaints related to drug products [21 CFR 211.198]. For example,
- BQA0014 "Handling of Product Complaints and WIP Shipment Complaints" does not describe the level of investigation to perform when product complaints describing particulate matter in injectable products are received.
 - The investigation of PER #100361029, lot #74087-JT determined and/or confirmed metallic particles and synthetic fibers near the port. However, there was no attempt to determine the source of the particulates at the manufacturing site, there was no review of environmental monitoring data that was obtained during manufacturing and filling operations for the referenced lot, nor was any batch record review conducted.
 - The investigation of PER #100449835, lot #78125-JT documented the presence of "brown floater in solution". Lab analysis identified this as fragments of brown paper, possibly from corrugated paper. No attempt was made to ascertain the source of these fragments at the manufacturing site. A review of retain samples was requested, but was not performed nor was the batch record reviewed.
 - Elemental analysis of metallic particulate referenced in PER #100484617, lot #74129-JT showed copper, tin and chlorine, possibly indicative of an alloy coating. However, there was no attempt to ascertain the source of the particle at the manufacturing site.
 - This appears to be a persistent problem. In a previous inspection, after a complaint was received regarding mold in the product, the presence of mold was confirmed by analysis. The investigation did not indicate any review or evaluation of environmental monitoring data as a result of the confirmation that there was mold growth on the caps or any attempt to ascertain the source of the mold.
10. Failure to establish scientifically sound and appropriate sampling plans designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality and purity [21 CFR 211.160(b)]. For example,

- BBQA0009, "Particulate Counting via the [REDACTED]", and P-0452, "[REDACTED] Test Method for LVI and Irrigating Solutions using [REDACTED]", are unclear regarding the number of finished product units required to be tested for visible and sub-visible particulates. P-0452 indicates that no less than [REDACTED] units per lot are to be tested. Management indicated that lot sizes vary between [REDACTED] and [REDACTED] finished product units and that the routine is to test [REDACTED] units per lot, regardless of lot size. This sampling plan does not conform to statistically valid or scientifically sound sampling principles.

11. Failure to maintain records so that data therein could be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications, manufacturing, or control procedures [21 CFR 211.180(e)]. For example,

- Monitoring for non-viable particulates performed 10/26/01 in room 2217 (Part Fill filling area) recorded counts over the action limit in the [REDACTED] area. There was no deviation report, investigation, or corrective measure undertaken in response to this event.

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.

We are aware of your firm's agreement to correct various deficiencies documented during the inspection and on the FDA-483. We have also received your firm's written responses dated September 11, 12, and 30, 2002 and have considered the information provided during your meeting with us on October 11, 2002. However, the response and information do not adequately address the deviations listed above. For example, the failure to validate the [REDACTED] monitoring systems has an impact on whether the production and process control system is validated. We believe that because the [REDACTED] monitoring systems have not been validated to current standards, the validation of the production and process control system is in question. For this reason, we continue to find the proposed timeline to complete validation of the [REDACTED] monitoring systems to be unacceptable. The [REDACTED] monitoring systems should not be in use unless they have been completely validated to current standards. The proposed correction to your sampling plans is not acceptable in that it does not conform to statistically valid and scientifically sound sampling principles. We find the investigational approach for handling product complaints to be incomplete in that it fails to include steps necessary to determine the root cause or prevent future occurrences of similar product defects. In light of the seriousness of the above-listed deviations and the inadequacies of your responses to date, we have determined that the issuance of this letter should not be delayed.

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Abbott Laboratories, Inc.
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You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further informal 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 and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Your reply should be sent to the Food and Drug Administration, Dallas District Office, Attention: Brenda C. Baumert, Compliance Officer, at the above letterhead address.

Sincerely,



SoL

Michael A. Chappell
District Director

MAC: bcb

Cc:

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Enclosure