



Dallas District
3310 Live Oak Street
Dallas, Texas 75204-6191

February 7, 2000

WARNING LETTER

Ref: 2000-DAL-WL-04

VIA FEDERAL EXPRESS

Mr. Miles D. White
Chief Executive Officer;
Chairman of the Board of Directors
Abbott Laboratories, Inc.
100 Abbott Park Road
Abbott Park, IL 60064-6092

Dear Mr. White:

During an inspection of your medical device manufacturing facility located in Irving, Texas, from 10/26/99 to 12/22/99, our investigators determined your establishment manufactures clinical chemistry analyzers. Clinical chemistry analyzers are devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The above-stated inspection revealed these devices are adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation are not in conformance with the Quality System/Good Manufacturing Practice (QS/GMP) Regulation as specified in Title 21, Code of Federal Regulations (CFR), Part 820, as follows:

1. Failure to appropriately document and or investigate incidents of nonconformance to the depth necessary to correct and prevent problems from recurring [21 CFR 820.90 (a)]. Specifically,

Failure to enter nonconformances into the NCR database which is used to record and monitor nonconformances. For example during the period from 3/17/99 to 8/25/99, [REDACTED] nonconformances were not entered into the NCR database e.g. NCR # [REDACTED]

2. Failure to establish and maintain procedures needed to correct and prevent the recurrence of nonconforming product and other quality problems [21 CFR 820.100(a)(3)]. For example,

The Corrective and Preventive Action Procedure (DA-01 ADD Dallas Quality System Manual) fails to identify the procedures to be used for identifying and tracking software related complaints.

The practice of "closing" uncorrected software and/or instrument problem reports against one version of software and renumbering them for possible correction in a subsequent version of the software is not described in the CAPA procedures.

Failure investigation for Alcyon S/N [REDACTED] was not performed for customer complaint involving unresolved DIV errors, sample and ion specific electrode (ISE) arm crashes, and burning smell. The risk assessment concluded there was no risk to the operator or patient because the instrument was not longer in the possession of the customer. A thorough investigation was not done to identify other problems that could be inherent in all similar products.

Failure investigation for Alcyon S/N [REDACTED] noted the device locked-up in the middle of a run. There is no investigative information regarding the actual use conditions of the device at the time of the lock-up.

Failure investigation for Alcyon S/N [REDACTED] showed repetitive attempts at correcting the problem in the field by replacing the ISE module and tubing, only to have additional complaints for the same problem. The in-house failure investigation repeated the same field action of replacing the ISE module and tubing and concluded the problem was solved. No further investigation was made to determine why previous corrective actions with the replacement of the ISE module and tubing were not effective.

3. The Corrective and Preventative Action (CAPA) Procedures failed to analyze all sources of quality data to identify existing and potential causes of nonconforming product or other quality problems [21 CFR 820.100(a)(1)]. For example,

Nonconformance data from printed circuit boards returned from field service, non-conforming components and processing defects such as solder joint failures are not compiled and analyzed for trends.

Failure to investigate the cause for [REDACTED] Alcyon devices failing the accuracy and precision tests during finished device testing during the period from March 10, 1999 to November 11, 1999.

4. Failure to establish and maintain procedures that will verify the effectiveness of corrective and preventive action(s) taken [21 CFR 820.100(a)(4)]. For example,

There are numerous unresolved hardware and software reliability problems associated with the Alcyon Analyzer. Problems including known system lock-up and system reliability issues were identified prior to the release of software version 1.0 in April 1998. Some of these problems still exist and additional

reliability problems have since been identified and remain uncorrected in the current software version 1.5. There are no plans to address these problems with the corrective actions to be implemented with software version 1.8, proposed for release in July 2000.

Test Process Change Notice #4170 dated 10/8/99 directed a change involving component (U29) was incorrectly identified as U9. The change was reviewed, approved and implemented without the error being detected.

System Problem Reports identified under DAL- [REDACTED] covered several lock-up problems and failed to provide sufficient information to determine if a software revision introduced a new lock-up problem or if the specific lock-up problem was in a pre-existing version of the software.

5. Failure to document all activities and results required for the corrective and preventive action system [21 CFR 820.100 (b)]. For example,

There is no assurance all complaints involving software defects are recorded in a software problem report. A System Problem Report was not generated for [REDACTED] ticket # [REDACTED] dated 5/15/99 involving an AxSYM software error.

There is no assurance software problem reports are accurately associated with the correct version of software. For example, in AxSYM SPR DAL- [REDACTED] the field for affected version references version 3.04; however, the narrative in the detailed problem description references version 3.60.

System Problem Reports for the Alcyon devices do not always show an instrument serial number or complaint ticket number so that the SPR can be traced to the original field complaint. On occasion, this information is recorded in the memo text field of the report, which is not easily extracted.

6. Failure to establish and maintain procedures to ensure the design requirements relating to the Alcyon software are appropriate and address the intended use including user needs [21 CFR 820.30(c)]. Specifically, neither the ADD Software Development Requirements nor the Product Version Description Document (PVDD) for the Alcyon software version 1.5 make reference to any boundary condition(s) such as minimum, maximum or normal number of tests the Alcyon device is designed to perform within a given time period. Additionally, the PVDD for software version 1.7 contains no documentation showing that user needs have been addressed in the current software revision 1.5 or the next software version (1.8) as evidenced by over [REDACTED] open enhancement system problem reports.
7. Failure to establish and maintain procedures that verify and document that the design output conforms to design input requirements and that the design outputs were documented, reviewed and approved prior to release [21 CFR 820.30 (f)]. Specifically,

The Verification and Validation Test Protocol (# [REDACTED]), used in the testing of software versions 1.6 and 1.7, did not define the number of repetitions to be used in the performance of the stress test, the boundary conditions for volume and load, and the criteria used to accept the test results.

The PVDD Version 1, Alcyon rev 1.5 showed over [REDACTED] open System Problem Reports (SPRs) at the time of its release in November 1998.

The PVDD, Version 2, Alcyon rev.1.0 for software version 1.7 showed open SPRs which had been identified as software problems during the testing of versions 1.0 through 1.5, e.g. DAL [REDACTED] and DAL [REDACTED].

8. Failure to establish and maintain procedures for the documentation, verification, review and approval of design changes before their implementation [21 CFR 820.30(i)]. For example,

Engineering Change Process procedure No. DA-04, Rev. K, dated 6/28/99, used for post-production changes did not have provisions for addressing pre-production change control and risk analysis.

ECN [REDACTED] dated 10/12/99, Software version 1.5, which was under development, was used in design verification and validation when the protocol specified that version 1.02 was to be used. There was no documented protocol approval of this design change prior to its implementation.

9. Failure to fully validate the Surface Mount Technology process used in the production of printed circuit boards (PCBs) in that the data from only [REDACTED] boards from [REDACTED] run were used. Evaluation of temperature profile effects on temperature sensitive components, solder paste application and other production variables were not included or were not equivalent to a full production run [21 CFR 820.75(a)].
10. Failure to establish and maintain acceptance procedures to ensure that PCBs processed on the Surface Mount Technology line meet specified requirements [21 CFR 820.80 (c)].
11. Failure to establish and maintain finished device acceptance procedures that ensure that finished devices meet acceptance criteria [21 CFR 820.80(d)]. Specifically, Alcyon S/Ns [REDACTED] and [REDACTED] were released with incorrect values for the A-PNA Extinction Factor, which resulted in the failure of each unit to meet the Gamma-Glutamyl Transferase assay specification.

This letter is not intended to be an all-inclusive list of the deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA-483 (copy enclosed) issued at the conclusion of the inspection to Mr. Jorge F. Artilles, Quality Assurance and Regulatory

Affairs Manager, Abbott Laboratories, Diagnostic Division, Irving, Texas, may be symptomatic of serious underlying problems in your establishment's manufacturing, quality assurance and/or quality management systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be system problems, you must initiate actions that will permanently correct the root causes of the problems.

Until these violations are corrected, and FDA has documentation to establish that such corrections have been made, federal agencies will be advised of the issuance of this Warning Letter so that they may consider this information when considering the award of contracts.

We have received and reviewed your letter, dated January 14, 2000, in response to our inspectional findings. In general, we find it inadequate. Your response lacks supporting evidence and in some instances, fails to address underlying issues that may have contributed to or resulted in the deficiencies. We are also concerned over the proposed time frame for implementing some of the corrections. Some of our concerns are:

Observations 1, 6: We are not convinced that the use of a simulator to run worst case scenarios will identify all the conditions contributing or leading to the system lock-ups. Use of a simulator requires the input of known conditions or variables and may not consider conditions that may exist in real time use. The use of a simulator alone is not a substitute for full and complete validation of the software. Please explain how you plan to handle unresolved hardware and software problems.

Observation 2: Although the SOP (Q04.02, ADD Software Development Process) may correct the problem, we remind you that it should incorporate the consideration of user needs which may or may not be completely identified through a review of the SPRs. Please explain if this procedure is to be implemented division-wide. If not, why? Please provide an explanation as to why it will require nearly 3 months to implement the SPR Review Procedure.

Observation 7: Although you reference several existing procedures which address the soldering process of printed circuit boards, your response contains no evidence that the procedures employ an effective quality control program over the process. Solder joints are not something that can be tested with automated circuit testers since a number of bad solder joints such as insufficient solder, lack of or insufficient heat, cracked joints, and contaminated joints will pass electrical tests. We wish to point out that your own trending data identified solder joint failures as a problem. This problem arose under the current quality program. Therefore, we find your response unacceptable. We note in the response a reference to an Attachment #5 that was not provided.

Observation #8: In your response to item 8.a., you state you will develop a new SOP to address the tracking of software failure investigations and will implement this procedure by May 31, 2000. Please provide an explanation as to why it will require nearly 3 months more to implement the procedure.

In your response to item 8.b., you state that all open SPRs will be reviewed for inclusion in the Alcyon version 1.8. We remind you that the larger issue is the handling of all SPRs. The underlying problem(s) are not limited to the Alcyon device.

Observation 12: We find your response unacceptable. Your response fails to provide any documentation showing the soldering processes, particularly the paste application and component placement, have been properly validated. Possible underlying issues that need to be addressed include how your firm approved the validation protocol and data when the testing wasn't representative of the process over time. We also note in your response a reference to Attachment #6, a 1996 validation package for the [REDACTED] Oven. This document was not included in attachments provided.

Observation 13: You identify several steps you plan to take to identify the root cause of the lock-up problems. We believe you are negating the most vital source of information, that obtained directly from the user. Although you indicate you will review the SPRs, we remind you that during our inspection, our investigators noted that many of the SPRs lacked basic information concerning the conditions leading or contributing to the problem. Failure to obtain this data raises questions on the reliability of the action(s) you might take to correct the lock-up problem(s).

Observation 14: Your response to item 14.a. does not address the underlying issue of what led to the issuance and approval of an SOP that would permit non-conformances to go uninvestigated or partially investigated. Additionally, issuing a new procedure is only part of the solution. Please provide an explanation as to how you plan to monitor and evaluate adherence to the new SOP i.e., Q14.03.

In your response to item 14.b., you state you will issue a Quality Directive that will detail the information customer service representatives need to obtain for a thorough evaluation of the system lock-ups. Please provide an explanation as to how this directive will fit into the CAPA system.

We find your response to item 14.e. inadequate. You state the service manual addresses the failure mode of the ISE module and consequently no further action is necessary. We disagree. Please provide an explanation as to why the field service technician(s) and the in-house investigator(s) tried to resolve the problem by replacing the ISE module and related tubing on several occasions instead of recognizing the problem as specified in the service manual. Please explain why the investigation was closed when the only apparent solution was to replace the ISE module without having determined the root cause of the problem. Identify the steps you plan to take to prevent the recurrence of this kind of performance and your plans to monitor and evaluate adherence to the corrective action plan.

Observation 15: You state that a new CAPA procedure will issue to add consistency to the problem tracking and resolution processes. Underlying issues that need to be investigated include variables contributing to the lack of consistency e.g., employee understanding of the SOP, clarity of the SOP, outside influences (such as time, resources), etc. Please specify how the SOP will accomplish this goal and how it will address the practice of closing SPRs and renumbering them against future software revisions. Include in your explanation the measures you plan to take to monitor and evaluate adherence to the new SOP.

Observation 18: Provide an explanation as to how the ADD division instrument system problem reporting process procedure will achieve consistency in the tracking and resolution of problem reports and how it will change the practice of employees ignoring or circumventing valid SOP's without documentation. Also explain if the procedure will be implemented division-wide and what measures you plan to take to monitor and evaluate employee adherence to this new SOP and others e.g. OP-DA-04, Engineering Change Process.

Your response to observations 18.b.i and ii. is unacceptable. You state that the process change (ECN) was written, reviewed and approved with the incorrect information on the ECN. You do not address how the ECN cleared the approval process with the incorrect information or without documented justification of the error or the manner in which the ECN was ultimately handled. Please provide an explanation of the measures you plan to take to prevent the recurrence of the procedural failures.

Similarly, in your discussion of the actions you plan to take to correct the problems identified in observation 18.c., you indicate you will implement a new procedure or change existing procedure(s). Although the SOP(s) may need changing, your response does not address the underlying issue of why the original procedure was not followed and how you plan to monitor and evaluate adherence to the new procedure(s).

Observation #19: Please explain if the new procedure for the technical design review (OP-DA-27) will be a division-wide procedure. If not, explain why the procedure needs to be different from the Lake County procedure and how it relates to OP.J207.

Observation 20: Your response is not acceptable. Although you provided data showing the error posed no clinical significance, you failed to address the cause of the problem(s) and what steps you will take to prevent its recurrence. Furthermore, your response only mentions the fact that several finished devices (by your count) were released for distribution that failed to meet a finished product test specification. We wish an explanation as to how this situation could be undetected for nearly a year.

Observation 24: We note in your response that your investigation into the cause of the failures of the ratio dispense tests for accuracy and precision will be completed by March 31, 2000. Yet you state the instruments that failed this test specification during the period from 3/10/99 to 11/11/99 were corrected prior to release. If the investigation is still ongoing (not complete), please provide a detailed explanation as to what assurances you have that the units were properly fixed prior to release and the step(s) you plan to take to prevent the recurrence of this situation.

You also state that a Dallas site standard for root cause analysis will be implemented. Explain if this standard will be effective division-wide and if not, why.

Observation 25: Although you state you will clarify the instructions to improve the coding process to be used to categorize non-conformances by part number, we question whether this action alone will achieve the desired improvement. Please explain how the new instructions will ensure consistency in the coding process and your plan to monitor and evaluate adherence to the procedure. If the Dallas site standard for trending is applicable

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only to the Dallas site, please explain why it shouldn't apply division-wide. Additionally, we note in your response that a [REDACTED] by part number is included among the assessments tools used to trend non-conformances. We question the reliability of this information given the inconsistencies in the categorization process that was cited as a deficiency.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to seizure, injunction, and/or civil penalties.

Please notify this office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct and prevent the noted violations and to address our concerns. 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 response should be sent to John W. Thorsky, Acting Compliance Officer, Food and Drug Administration, 1445 North Loop West, Suite 420, Houston, TX 77008.

Finally, we acknowledge receipt of and concurrence with your company's decision to recall the Alcyon 300/300i from the United States market place. However, we remain deeply concerned that these deviations may impact other devices made at the Irving, Texas facility and those Alcyon devices that will be marketed in foreign countries. We remind you of your commitment given to this agency on 12/22/99 not to distribute any of the Alcyon 300/300i devices until the software problems have been corrected and FDA approval of software version 1.8 has been obtained.

Sincerely,



Michael A. Chappell
District Director
Dallas District

Enclosure-FDA-483

cc: Mr. Thomas D. Brown, President
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