



November 17, 2000

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

Ref: 2001-DAL-WL-04

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. T.R.G. Sear, President and CEO
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Mr. Sear:

During an inspection of your drug and device manufacturing facility located in Fort Worth, Texas, conducted October 12–27, 2000, our investigators documented serious deviations from the Current Good Manufacturing Practices for Finished Pharmaceuticals and the Quality System Regulations (Title 21, Code of Federal Regulations [CFR], Parts 210 and 211; and 21 CFR Part 820, respectively). These deviations cause your drug products and medical devices to be adulterated within the meaning of Sections 501(a)(2)(B) and 501(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

At the conclusion of the inspection, a FDA-483 (List of Inspectional Observations) was issued to and discussed with Ed McGough, General Manager, Fort Worth Manufacturing. A copy of the FDA-483 is attached for your information. The inspection noted the following CGMP deviations:

- 1) Failure to establish appropriate written procedures designed to prevent microbial contamination in drug products purporting to be sterile [21 CFR Part 211.113(b)] and failure to maintain complete data from all tests necessary to assure compliance with established specifications and standards [21 CFR Part 211.194(a)]. For example, the lack of testing of media filled units produced during the manual intervention steps of your Aseptic Filling Process fails to demonstrate that your Aseptic Filling Process is adequate.
- 2) Failure to adequately validate the Aseptic Filling Process with a high degree of assurance that devices meet approved specifications [21 CFR Part 820.75]. For example, data from media fill runs, that may demonstrate your worst case scenario,

is not captured and documented. The absence of this data does not allow you to fully evaluate the adequacy of the Aseptic Filling Process. Therefore, your conclusion of a competent Aseptic Filling Process is unacceptable and possibly false.

- 3) Failure to assure and document that automated equipment used in manufacturing, processing, packaging, and holding of drug products will perform its intended function satisfactorily [21 CFR Part 211.68]. Similarly, failure to establish and document procedures to assure that drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR Part 211.100], as well as failure to verify and document that equipment used for monitoring processing equipment and environmental conditions is adequate and functioning properly [21 CFR Part 820.70]. As examples,
 - a) Necessary actions have not been predetermined and documented when responding to alarms from the [REDACTED]. Also, this alarm system is unable to store more than [REDACTED] transgressions, and these transgressions are not recorded. There is also no secondary review of such alarm events, and any corrective actions taken are not documented.
 - b) The alarm system and its backup system for the stability chambers are not challenged to demonstrate that they would function as intended.
- 4) Failure to clean, maintain, and sanitize equipment to prevent malfunctions or contamination that would alter the safety, strength, identity, quality, or purity of your drug products; and failure to establish and follow such written procedures. Additionally, failure to maintain records of such operations [21 CFR Part 211.67]. As examples,
 - a) No procedures or documentation exist to show that all materials in aseptic filling areas and associated utensils are cleaned and sanitized. This includes paper records, metal clips, writing pens, a plastic scoop, and plastic bags used in the aseptic filling areas.
 - b) Procedures relating to cleaning and sanitizing the Product Transfer Line and Line [REDACTED] Filler are not followed. Records relating to this operation are not checked, as is required in the SOP.
- 5) Failure to establish and follow specifications, standards, and sampling plans; and failure to document and justify deviations from existing procedures. Also, failure to establish procedures designed to assure drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR Part 211.160]. As examples,
 - a) The smoke study done to evaluate unidirectional flow of air within the aseptic fill zone and the surrounding Class [REDACTED] Clean Room did not include an evaluation of personnel simulating routine manual operations and interventions.

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- b) [REDACTED] panels sitting or located below the HEPA filter system have rips and tears however, there is no record documenting these tears or their repairs. In addition, procedures do not address tear size limitations or the number of repairs that are allowed before functionality of the panels is adversely affected.
 - c) No justification is given for the rationale used to determine worst case locations for challenge positioning of Chemical Indicators used in the [REDACTED] [REDACTED] distribution testing within the [REDACTED]. Adherence to the manufacturer's specifications regarding relative humidity limits for Chemical Indicator storage is not monitored or documented.
 - d) The [REDACTED] has been modified from the original "as-build" drawings. The Computer Aided Drafting drawing prepared to reflect the modification does not identify the preparer or the approving official.
- 6) Failure to determine appropriate storage conditions for stability characteristics of drug products [21 CFR Part 211.166(a)]. For example, samples used for determining stability characteristics of [REDACTED] drug products were shipped via common carrier from Texas to New Jersey during the month of July 2000 without monitoring their temperature during shipment. There is no documentation regarding how these samples were subsequently handled.

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 compliance with the Act, and adherence with each requirement of the Good Manufacturing Practice Regulations for drugs and devices at all Alcon facilities. 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. Additionally, pending Antibiotic Form 6, NDA, ANDA, PMA, or export approval requests may not be approved until the above violations are corrected.

We are aware of Alcon's agreement to correct various deficiencies documented during the inspection and annotated on the FDA-483. We have also received Alcon's written responses dated November 3 and November 10, 2000. As was discussed during our meeting with your representatives at this office on November 8, we are in disagreement regarding Alcon's destruction of the media filled units from manual interventions and the absence of those units from complete testing. We continue to find the response for this issue to be insufficient for determining an accurate contamination rate.

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.

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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,



Michael A. Chappell
District Director

MAC: bcb

Enclosure