



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
Denver District Office
Building 20 – Denver Federal Center
P.O. Box 25087
Denver, Colorado 80225-0087
TELEPHONE: 303-236-3000

July 1, 1999

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Clateo Castellini
Chairman of the Board
President and Chief Executive Officer
Becton Dickinson and Company
1 Becton Drive
Franklin Lakes, NJ 07417-1880

Ref # - DEN-99-12

PURGED

Dear Mr. Castellini:

An inspection of your facility located at 9450 South State St., Sandy, Utah, was conducted between the dates of April 12 and 27, 1999. The inspection served as both a Current Good Manufacturing Practices (CGMP) inspection covering commercially marketed products; and a Pre-Approval inspection covering NDA [redacted], and ANDA [redacted]

Our investigators documented serious deviations from the Current Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Part 210 and 211) in conjunction with your firm's manufacture of finished pharmaceuticals.

These deviations were presented to Mr. Calvin C. Alexander, VP Worldwide Operations, on an FD-483 List of Observations at the close of the inspection on April 27, 1999 (copy enclosed). The CGMP deficiencies cause your products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

The deficiencies described in this Warning Letter apply to your commercially marketed drug products. Due to the deficiencies listed on the FDA-483 related to the pre-approval portion of the inspection, we are recommending to the Center for Drug Evaluation and Research that approval of pending NDA [redacted] and ANDA [redacted] be withheld.

The CGMP deviations observed during our inspection include but are not limited to the following:

1. Qualification and control of the ambient temperature and accelerated temperature stability rooms is inadequate to effectively assess the stability characteristics of drug products as required by 21 CFR 211.166. For example:
 - There is no approved protocol, test results, or summary for the qualification of the ambient temperature stability room.
 - There is no documentation of the installation or operational qualification of the accelerated stability room.
 - There is no documented procedure (SOP) for temperature and humidity monitoring including changing and reviewing charts, control of alarms and handling out-of-specification temperature and humidity readings.
 - There is no QA or departmental review of temperature/humidity recording charts.
2. Validation of the ~~xxx~~ packaging lines is not adequate to assure batch uniformity and integrity of drug products as required by 21 CFR 211.110. For example:
 - Worst case situations such as challenging viscosity, fill volumes and length of run were not included.
 - No heightened level of sampling was used.
 - Installation, operation and/or limitations of the equipment was not addressed.
3. Batch production and control records are inadequate to assure conformity with the Master Record as required by 21 CFR 211.188. For example:
 - During the inspection several instances were observed of manufacturing personnel recording raw data, such as in-process ~~xxx~~ weights, leak test results and packaging rejects, on pieces of paper which were later discarded after recording the data elsewhere.
 - Equipment numbers of ~~xxxxxx~~ systems used to ~~xxxx~~ solution during the manufacturing process are not recorded.
 - There is no accountability for the soap solution used during the manufacturing process.
4. Testing of components is inadequate to verify conformity with all appropriate written specifications for purity, strength, and quality as required by 21 CFR 211.84(d)(2). For example:
 - There is no assurance that a representative sample is taken for incoming chemical raw material lots as only one four-ounce sample is collected from the top of one drum regardless of the size of the lot.

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The container from which the [redacted] sample is collected is not marked or identified as such.

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 practices regulation. We recommend that you conduct a complete evaluation of your facility for CGMP compliance.

We acknowledge receipt of your company's May 14, 1999, response to the FDA-483, and note that corrections to most of the deficiencies pointed out during the inspection are promised. These corrections will be verified during a future inspection of your facility.

There is a discrepancy in the May 14, 1999 response regarding temperature and relative humidity specifications for the accelerated stability room ([redacted]) that should be clarified. In your firm's response to FDA-483 item 9c the specification for [redacted] is stated as [redacted] and [redacted] RH. In the response to FDA-483 item 12a the specification is stated as [redacted] and [redacted] RH. In the draft SOP [redacted], submitted as a corrective action to FDA-483 item 9, the specification is stated as [redacted] and [redacted] RH. It is unclear which is the true specification. SOP [redacted] also states under section [redacted] [redacted] that major discrepancies in temperature or humidity will be reported to the R&D laboratory supervisor. Major discrepancies are not defined thus it is unclear when an event would be reported. During the inspection, our Investigators documented numerous occasions when the stability rooms were out of specification for temperature and/or humidity for periods as long as one month, yet they were never reported to a supervisor or other management personnel.

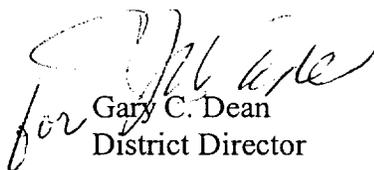
Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

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

Your reply should be sent to the Food and Drug Administration, Denver District Office, P.O. Box 25087, Denver, Colorado, 80225-0087, attention H. Tom Warwick, Compliance Officer. He may be reached at (303) 236-3054 if you have any questions about this matter.

Sincerely,

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for Gary C. Dean
District Director

Enclosure:
As Stated