DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

M410SN

Chicago District
300 S. Riverside Plaza, Suite 550 South
Chicago, Illinois 60606
Telephone: 312-353-5863

August 11, 2000

WARNING LETTER
CHI-29-00

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Harry M.J. Kraemer, Jr.,
Chairman and Chief Executive Officer
Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, IL 60015

Dear Mr. Kraemer:

During an inspection of Baxter's aseptic parenteral manufacturing operations located at Route 120 & Wilson Road, Round Lake, Illinois, conducted from September 7 through November 18, 1999, FDA Investigators Bruce McCullough and David Perkins 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 of the Quality Control Unit to investigate sodium acid pyrophosphate (SAPP) residues in the peroxide bath, follow-up with appropriate corrective actions, and implement necessary procedures to both control SAPP residues in the peroxide bath and to prevent SAPP adherence to the plastic film (which becomes the drug product container). Situations in which SAPP build-up was noted were documented as "isolated incidence" or "no corrective action needed." [21 CFR 211.22, 21 CFR 211.192, and 21 CFR 211.100]
- Failure to validate the addition of SAPP to the hydrogen peroxide bath used to sterilize the containers in the firm's aseptic processing operations. [21 CFR 211.100]
- Failure to test drug product lots for the presence of SAPP and failure to establish a procedure/specification/limit for SAPP carry-over into either in-process materials or finished drug products. [21 CFR 211.160, 21 CFR 211.165, 21 CFR 211.100 and 21CFR 211.110]
- Failure to validate the use of NaOCl fog used to remove SAPP residue from the [redacted] machine. [21 CFR 211.100]
- Failure to collect a sufficient number of samples to evaluate for particulate matter based on a validated statistical plan. [21 CFR 211.110]

- Failure to design and maintain the Water For Injection/Distilled Water System in the Drug Delivery and Penicillin Buildings. [21 CFR 211.42 and 21 CFR 211.58]
- Failure to establish sufficiently detailed and validated instructions for batch adjustment (reprocessing). [21 CFR 211.100, 21 CFR 211.110 and 21 CFR 211.115]
- Failure to validate the environment in which the [redacted] aseptic filling machines are located. The levels of viable and non-viable particulates observed during production cannot be related to media fills or any other qualification study. [21 CFR 211.113 and 21 CFR 211.100]
- Failure to conduct and/or document input/output checks of the [redacted] computer system. [21CFR 211.68]
- Failure to maintain separate master production and control records for each batch size. The firm's material specification document includes a "range" of allowable batch sizes. [21 CFR 211.186(a)]
- Failure to provide sufficient detail describing the methods used to clean the firm's mix tanks. The volume of cleaning solution, time to spend in manual scrubbing, and parameters for rinse water are not fully described. [21 CFR 211.67(b)(3)]

We have reviewed Baxter's response dated November 30, 1999, which was written in response to the FDA-483 issued on November 18, 1999, and Baxter's letter dated December 8, 1999, which was written in response to a December 7, 1999 meeting with the Chicago District FDA. Although your responses indicate certain corrective actions have occurred and other studies have been done to address the SAPP issue, the written responses lack sufficient detail for a substantive evaluation.

We also acknowledge Baxter's response to a December 2, 1999, District "Withhold Notification." That letter was not an all-inclusive list of the GMP issues of concern. Therefore, your response, which was limited to those specific items mentioned in the letter, does not enable FDA to make a complete assessment of your current GMP status.

In addition, we further request details regarding steps your firm is taking to bring your electronic cGMP records into conformance with the requirements of 21 CFR Part 11; Electronic Records; Electronic Signatures. Part 11 establishes requirements to ensure that electronic records and electronic signatures are trustworthy, reliable and generally equivalent substitutes for paper records and traditional handwritten signatures. Electronic records and electronic signatures may be used to meet record and signature requirements of 21 CFR Parts 210 and 211 when Part 11 requirements are met.

This inspection disclosed deficient controls in the laboratory electronic record keeping system, which is used for maintaining chromatographs and audit trails. In addition to a response to the deficiencies noted earlier in this letter, please outline your firm's global corrective action plan, including timeframes for correction, to address this Part 11 issue.

The cGMP deviations identified above are not to be considered an all-inclusive list of the deficiencies at your facility. Please submit an additional written response in which you provide additional details of your corrective actions within 30 days of receipt of this letter. Your response should be addressed to Richard Harrison, Compliance Director, at the address in the letterhead. At that time, we also recommend that you arrange a regulatory meeting with the Chicago District office. Please contact me at 312-353-5863, x189 or my secretary at x190 to arrange the meeting.

Sincerely,

\s\
Raymond V. Mlecko
District Director

cc: Bill Young, Vice President
Quality and Sterility Assurance
I.V. Systems Division
Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, IL 60073-0490

cc: John L. Quick, Corporate Vice President
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