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San Francisco District
1431 Harbor Bay Parkway
Alameda, CA 94502-7070
Telephone: 510/337-6700

AMENDED WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Our ref: 2937793

July 16, 1998

Dennert O. Ware
President and CEO
Boehringer Mannheim Corp.
9115 Hague Rd.
P. O. Box 50457
Indianapolis, IN 46250-0457

Dear Mr. Ware:

This letter is being issued as an amendment to a warning letter dated June 16, 1998. The previous letter had incorrectly named the device manufactured by your firm in Fremont, CA as the CoaguChek Monitor. The correct name for the product which had been the subject of the inspection is the CoaguChek Plus Monitor. Below you will find the full text of the June warning letter with the corrections to the product name made. In addition, you will find in the text of this letter San Francisco District's response to your July 6, 1998 correspondence which resulted from the receipt of our June warning letter.

Amended text of warning letter:

An inspection was conducted between May 26 and June 11, 1998 of Boehringer Mannheim Corporation, 48431 Milmont Dr., Fremont, CA by Investigator Debra L. Frost of this office. She determined that the facility manufactures the CoaguChek Plus Monitor, Prothrombin Time Cartridges, and Prothrombin Time control reagents for determination of blood coagulation times. These products are devices as defined by Section 201(h) of the Federal Food, Drug and Cosmetic Act.

The inspection revealed that 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, packaging, storage, or installation are not in conformance with either the Good Manufacturing Practice Regulation (GMPs) or the Quality Systems Requirements (QSRs) for medical devices as set forth in Title 21, Code of Federal Regulations (CFR) Part 820 as follows:

1. You have not validated the manufacturing process for the prothrombin time bulk reagent. The investigator noted that for 1998 to date, you have received 26 complaints regarding a matching problem between the prothrombin (PT) test cartridge and the control used to check the accuracy of the CoaguChek Plus Monitor. Those test cartridges had been produced with reagent lot number [REDACTED]. The reagent test results were not within your established specification of [REDACTED] absorbance at [REDACTED] for that reagent lot, yet there was no documentation which justified the use of this lot. Similar complaints have been received for at least one other reagent lot which might be attributed to a matching problem between the test cartridge and the control. [21 CFR 820.75, 820.90]

2. Records of functional test results for the CoaguChek Plus monitor were found with one of five data points frequently removed without justification. The number of data points that can be removed from finished product testing is not addressed in your statistical technique document entitled "Statistical Determination of Outliers" which was approved on November 2, 1994.

Additionally, you have not established and maintained procedures which justify the use of coefficients of variation which fall outside your accepted tolerances. [21 CFR 820.250]

3. The inspection has also revealed that you have not corrected an objectionable condition which was observed during a previous inspection of your firm, namely the conducting of boundary testing of your wave soldering operation for printed circuit boards. [21 CFR 820.75]

This letter is not intended to be an all-inclusive list of 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 FDA483 issued at the conclusion of the inspection to Ms. Maria C. Navarro, Director of Operations may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, requests for Certificates of Exportability and to Foreign Governments will not be cleared until the violations related to the subject devices have been corrected.

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 the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the date on which the corrections will be completed.

Your response should be sent to the following:

Andrea P. Scott
Compliance Officer
U. S. Food and Drug Administration
96 North Third St.
San Jose, CA 95112

Adequacy of response to warning letter:

San Francisco District has received and reviewed your response of July 6, 1998 to the warning letter. We acknowledge that the facility which was inspected in Fremont, CA is in the process of closing, and that future manufacturing of products will occur at either a contract manufacturing site or at another Roche/Boehringer Mannheim facility offshore. The corrective measures which you have described in your correspondence are acceptable as long as they are applied to operations at these other sites. A copy of this letter will be forwarded to our Detroit District office, which services your main office, so that FDA it may continue to track the follow-up to these corrective measures at the corporate level.

Thank you for your timely response to our inspectional findings.

Sincerely yours,

Charles D. Moss
Acting District Director

for

Patricia C. Ziobro
Director
San Francisco District

cc: Maria C. Navarro
Director of Operations
Boehringer Mannheim Corp.
48431 Milmont Dr.
Fremont, CA 94538-7388

Debara R. Reek
Director, Quality and FDA Compliance
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