



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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RJP

Food and Drug Administration  
2098 Gaither Road  
Rockville MD 20860

MAY 30 1997

WARNING LETTER

VIA FEDERAL EXPRESS

Mr. Michihiro Watanabe  
Director and Mie Plant Manager  
Kawasumi Laboratories, Inc.  
Kawasumi Bld., 3-28-15, Minami-ohi  
Shinagawa-ku, Tokyo 140, Japan

Dear Mr. Watanabe:

During the Food and Drug Administration's (FDA) inspection of your firm located at Kawasumi Bld., 3-2815 Minami-ohi, Shinagawa-ku, Tokyo 140, Japan from February 17 through 18, 1997, our investigator determined that your firm manufactures tubing sets. Tubing sets are devices within the meaning of Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The above-stated inspection revealed that these devices are adulterated, in that the methods used in, or the facilities or controls used for the manufacture, packaging, storage, or installation are not in conformance with the Medical Device Good Manufacturing Practice regulations, as specified in Title 21, Code of Federal Regulations (21 CFR), Part 820, as follows:

1. Failure of the quality assurance program to assure that all quality assurance checks are appropriate and adequate for their purpose and are performed correctly, as required by 21 CFR 820.20(a)(4). For example, ethylene oxide residuals testing completed for release of each tubing lot does not conform to the PMA method as follows:
  - a. The sample is not maintained under chilled conditions prior to testing;
  - b. Analysis procedures are not performed at 5°C if possible;
  - c. Ethylene oxide standard solution is not prepared in a cold laboratory;
  - d. Concentration ratios of 0.2, 0.5, 0.8, 1.0, and 2.0 (ethylene oxide/propylene oxide) are not used to establish the calibration curve; and
  - e. The sample peak area is not measured using the "width-at-a-half-height" method.
2. Failure to assure that specification changes shall be subject to controls as stringent as those applied to the original device, as required by 21 CFR 820.100(a)(2). For example: review of the documentation relating the ethylene oxide residual testing conducted to verify the reduction from 10 to 6 days as the minimum degassing time found:

- a. Only two concentrations of ethylene oxide were used to establish the concentration curve; and
  - b. The concentration of ethylene oxide residuals obtained using the portion of the calibration curve was below the lower calibration standard.
3. Failure of the quality assurance program to identify, recommend, or provide solutions for quality assurance problems and verify the implementation of such solutions, as required by 21 CFR 820.20(a)(3). For example:
  - a. Complaints KW-101 and KW-102 received October 19, 1995, relate to reports of blood tubing return set plasma leakage at the bonding area of tubing and chamber cap. Failure investigation confirmed that the leakage was caused by incomplete bonding. No further action was taken.
  - b. Complaints KW-098, KW-113, KW-118, KW-123, KW-126, KW-141, and KW-145 were received from October 1995 to August 1996. These complaints relate to leakage of plasma (absorption line) or regeneration solution (regeneration line) at the female luer connector. Two of the above complaints (KW-118 and KW-1230) relate to leakage in the plasma absorption line for lot 5Z153. A design change was implemented on July 31, 1996 when it was determined that the luer connector was susceptible to stress-induced failure.
4. Failure to assure that the equipment used in the manufacturing process is appropriately designed, constructed, and installed, as required by 21 CFR 820.60. For example, the new sealing machine has greater seal strength variability across the seal. Test data shows several measurements recorded as low as 200 grams (minimum limit) and as high as 600 grams; in some cases this variation was documented for the same sample. No assessment has been made to determine the cause of this variability, whether the quality cause of this variability and the quality of the seal will remain within requirements throughout the product's shelf life.
5. Failure to establish, implement, and control reprocessing procedures to assure that the reprocessed device or component meets the original, or subsequently modified and approved, specifications, as required by 21 CFR 820.115(a). For example, there are no written procedures which identify what types of defects can be reworked and what additional testing may be necessary.
6. Failure of the device history record to include dates of manufacture, quantity manufactured, and quantity released for distribution, as required by 21 CFR 820.184. For example:
  - a. The device history record does not document rework of the LDL tubing due to leakage or other abnormalities; and
  - b. Not all in process defects such as leakage are documented in the device history record.

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 FDA 483 issued at the close of the inspection 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.

We acknowledge the receipt of the response of March 17, 1997. You may refer to this in future correspondence. Your response to the FDA-483 is not adequate. In order to determine the adequacy of your response, it will be necessary for you to submit copies of your revalidation of the change in the aeration cycle and all of your modified procedures.

Please notify this office in writing as to the specific steps you have taken, or intend to take, to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If the documentation is not in English, please provide a translation to facilitate our review. Please include any and all documentation to show that adequate correction has been achieved. In the case of future corrections, an estimated date of completion, and documentation showing plans for correction, should be included with your response to this letter. Please address your response and any questions to Mr. Timothy R. Wells, Chief, OB/GYN, Gastroenterology, and Urology Branch, at the letterhead address.

Should you require any assistance in understanding the contents of this letter, do not hesitate to contact Mr. Howard A. Press at the letterhead address or at (301) 594-4616 or FAX (301) 594-4638.

Sincerely yours,

  
Lillian J. Gill  
Director  
Office of Compliance  
Center for Devices and  
Radiological Health