HFD-205
FOI

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Manufacturing and Product Quality, HFD-320
7520 Standish Place
Rockville, Maryland 20855-2737

TELEPHONE: (301) 594-0095
FAX: (301) 594-2202

MAY 23 1997

WARNING LETTER

Mr. Tsunekazu Sakano, Chairman
Nippon Kayaku Co., Ltd.
Tokyo Fujimi Building
11-2, Fujimi 1-chome
Chiyoda-ku, Tokyo 102, Japan

Dear Mr. Sakano:

This is regarding an inspection of your sterile pharmaceutical finished dosage form manufacturing facility in Takasaki, Japan, by Investigator Dr. David C. Pulham and Microbiologist Raymond T. Oji during the period of February 3 - 7, 1997. The inspection revealed significant deviations from U.S. current good manufacturing practice (CGMP) regulations in the aseptic manufacture of sterile pharmaceutical finished products. The deviations were presented to Mr. Hajime Yoshitake, Plant Manager of the Takasaki Plant, on an Inspectional Observations form FDA-483 at the close of the inspection. These CGMP deviations cause your sterile pharmaceutical products to be unacceptable for use in the United States, since under United States law, those CGMP deviations make your products adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

We have reviewed your March 7, 1997 response to the FDA-483 observations submitted to Mr. John M. Dietrick, Foreign Inspection Team (HFD-322), by Mr. Hajime Yoshitake, Plant Manager of the Takasaki Plant. We have also evaluated the information provided to us in a May 13, 1997 letter by Mr. Ike Shimohigashi, Director of Nippon Kayaku America, Inc., White Plains, N.Y. We note that many corrections were implemented at the conclusion of the inspection or will soon be implemented. However, there are some responses that lack sufficient detail, explanation, or documentation to adequately address the deviations noted during the February 1997 inspection. Our comments regarding the most significant observations are shown below:

Monitoring the environmental conditions of an aseptic operation is considered essential. It should be performed during each day's production, and should include active samples taken from qualified critical locations through the aseptic area under dynamic conditions.

The response to items a - c above lacked documentation to substantiate your claims, such as revised procedures, protocols, or data from the newly implemented daily monitoring areas. Furthermore, it did not address the type of equipment, locations to be monitored, frequency and evidence that the selection of the monitoring locations were based on airflow studies.

The CGMP deviations identified above are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits which are not intended to determine all deviations from CGMPs that exist at a firm.

We recommend that you evaluate your facility on an overall basis for CGMP compliance. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to assure compliance with U.S. standards for current good manufacturing practices for pharmaceutical manufacturers.

Until FDA has confirmed that your firm is in CGMP compliance, we will not recommend approval of any applications listing your firm as a supplier of sterile finished dosage drug products.

Within 30 days of the date of this letter, please inform us of any plans for further shipments of sterile pharmaceuticals to the United States, including any references in pending drug applications. Unless an adequate response is received any sterile pharmaceuticals produced by your firm may be denied entry into the United States.

Please contact Edwin Melendez, Compliance Officer, at the address and telephone numbers shown above if you have any questions. Within your written response to this letter, please describe corrective actions you plan to take or have taken to bring your operations into compliance. Please include a timetable of when each of the corrections will be completed and attach English translations of supporting documents. Please reference CFN # 9610291 within your written response.

To schedule a reinspection of your facility, after corrections have been completed and your firm is in compliance with CGMP requirements, send your request to: Deborah Browning, Consumer Safety Officer, Drug Group, of FDA's Division of Emergency and Investigational Operations (HFD-133), 5600 Fishers Lane, Rockville, Maryland, 20857. You can also contact the office at (301) 827-5648 or by FAX at (301) 443-6919.

Sincerely,

Douglas I. Ellsworth,
Director
Division of Manufacturing and
Product Quality, HFD-320