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

WARNING LETTER

FEB 19 1997

Mr. Takashi Nakajima, President
Nippon Rikagakuyakuhin Co. Ltd.
610 Yanada-Cho
Ashikaga-shi, Tochigi-ken
Japan

Dear Mr. Nakajima;

We have completed our review of the inspection of your Bulk Pharmaceutical Chemical (BPC) manufacturing facility conducted by the United States Food and Drug Administration (FDA) on November 11-13, 1996, performed by FDA investigator, Jose R. Hernandez. This inspection revealed significant deviations from Current Good Manufacturing Practices (CGMPs) for bulk pharmaceutical chemicals. The deviations were presented to you on a five (5) item, FDA-483, List of Inspectional Observations, at the close of the inspection. These CGMP deviations cause Bulk Pharmaceutical Chemicals manufactured by your facility to be unacceptable for use in the United States, since under United States law, the CGMP deviations make these products adulterated within the meaning of Section 501 (a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act).

Specific areas of concern include, but are not limited to the following:

1. Failure to have validated the water system used in plant two (2) production;

2. Failure to have validated the additional piping used to transport water from Plant NNC to Plant D-IT and discharge hoses used in production;

3. Failure to properly monitor the performance of the water system in plant NNC.

The written response submitted by your company dated December 20 1996, signed by Yukio Takizawa, Manager, Pharmaceutical Control Section, was also reviewed and is considered inadequate for the following reasons:

WATER SYSTEM PLANT TWO

The response fails to provide any information about what water will be substituted for that of the system which you cannot validate, or what additional controls will be put into place such as a batching system, in the year (twelve months) pending your construction of a new validated system. Further, the recirculating loop description provided via diagram fails to document any temperature considerations or flow rates for the loop.

WATER SYSTEM PLANT NNC/D-IT

The response fails to provide any time frame for the reconstruction of the system operating between both buildings, the action or actions to be performed while construction is on-going to transport water from the point of generation to point of use, and no written plan (protocol) to validate this extensive water system upgrade.

The sampling plan for points of use described in the response involving the basic system appears to remain insufficient in that all points of use may not be sampled until a month or more of time has passed.

The attached Figure three (3) diagram for the heat exchanger appears to indicate a temperature of
which may be insufficient to deter microbial growth in the recirculating loop and the extensive amount of piping.

The response concerning the hoses used to supply water from the points of use fails to state if any validation of their storage practices has been performed and if the rinse procedure used as a sterilization step is truly effective.

We are also concerned that your firm has failed to make corrections in a global manner in light of the fact that our last inspection (December 1994) also found deficiencies in the validation of water systems. Your firm should not limit corrections to only those deviations listed on the FDA-483 issued at the conclusion of our inspections. You should establish a quality control unit that embraces the concept of process change control, i.e., determine if revalidation is necessary when changes are made in any system.

Again, the CGMP deviations identified above or on the FD-483 issued to your firm 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 continually evaluate your facility on an overall basis for CGMP compliance.

Until FDA has reinspected your facility and confirms compliance with CGMPs and correction to the deficiencies noted during the most recent inspection, this office will recommend disapproval of any applications listing your firm as the supplier of any Bulk Pharmaceutical Chemical.

Failure to promptly correct these deficiencies may result in FDA denying entry of drug products manufactured by your firm into the United States. The articles could be subject to refusal of admission pursuant to Section 801 (a)(3) of the Act in that the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practices within the meaning of Section 501 (a)(2)(B) of the Act.

You may contact Michael J. Verdi, Consumer Safety Officer, at the address and telephone numbers shown above if you have any questions, written response or concerns regarding these decisions.

Please include your Central File Number "9611676" in any correspondence to this office.

To schedule a reinspection of your facility after corrections have been completed, contact Deborah S. Browning, Consumer Safety Officer, Drug Group, of FDA's Division of Emergency and Investigational Operations (HFC-133), Division of Field Investigations, 5600 Fishers Lane, Rockville, Maryland 20857. You may wish to contact her office at (301) 443-1855 or by FAX at (301) 443-6919.

Sincerely,

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