DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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JUL 8 1998

WARNING LETTER

Mr.

Holopack Verpackungstechnik GmbH
Bahnhofstrabe
Abtsgmund/Untergroning,
Germany
D-73453

Dear Mr.

The Food & Drug Administration has completed its review of the inspection of your sterile pharmaceutical manufacturing facilities in Sulzbach-Laufen and Abtsgmund, Germany by Investigator Manuel Garza, during the period of March 16-19, 1998. The inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of sterile pharmaceuticals. The deviations were presented to your attention on an FDA 483 List of Observations at the close of the inspection. The CGMP deviations cause these sterile pharmaceuticals to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

The following are among the most significant CGMP deviations noted in the inspection:

PRODUCTION DESIGN AND OPERATIONS

1. The monitoring program was inadequate to meaningfully monitor processing batch operations. Monitoring during each batch operation was not required. Instead, infrequent sampling was scheduled by your firm. Assessment of the quality of the processing should be included in each shift. In addition, samples were only taken while operations were not in progress (static conditions) rather than under dynamic conditions.

While your firm states general plans to correct this deviation, the written FDA 483 response failed to specifically address the nature, number, and timing of samples which will be required by the planned revised

program.

2. The testing area was not adequately designed (e.g., to allow for adequate inspection for product contamination or container-closure defects.

Please include the method's capability (sensitivity) in detecting and any formal specifications for within your written response.

3. Exposed sterile product was not adequately protected from the potential introduction of contaminants prior to sealing.

Our inspection noted that no barrier existed which would prevent overhead matter from falling into formed containers prior to filling and sealing steps. Within your response, please address this issue and provide the Standard Operating Procedures (SOPs) which describe the sanitization or sterilization methods used (e.g., for the enclosure, including surfaces which are not in direct contact with the product.

LABORATORY CONTROL

4. had not been with to determine its capability. Moreover, no supplier qualification studies had been performed.

Your firm's evaluation of included samples of manufacturing plant which would be expected to with a subsequent confirmation of on the

5. In some instances, batches were stored in a warehouse at temperatures ranging from

UNIT

6. An adequate program for conducting and preparing annual product reviews was not in place. Trending issues which should be addressed by annual reviews include but are not limited to: in-process testing (e.g., tests); manufacturing deviations; failures; complaints; and finished product batch testing data.

We acknowledge receipt of your firm's April 20, 1998 letter. In general, this response lacked sufficent detail regarding what steps are planned to correct the FDA 483 deficiencies

and timeframes for implementation of corrective actions.

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 reinspected your facility and confirmed that your facility is in CGMP compliance, we will not recommend approval of any applications listing the site as a manufacturer of sterile finished dosage forms. If these deficiencies are not corrected, any sterile finished dosage forms produced by your firm may be denied entry into the United States.

Please contact Compliance Officer Richard L. Friedman [telephone: (301) 594-0095; fax: (301) 827-0145] of this division at the above address if you have any questions. Within your written response to this letter, detail 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# 9614976 and 9614991** within your written response.

To schedule a reinspection of your facility, after corrections have been completed and your firm has thoroughly evaluated overall compliance with CGMP requirements, send your request to: Director, International Drug Section, HFC-134, Division of Emergency and Investigational Operations, 5600 Fishers Lane, Rockville, MD 20857. You can also contact that office by telephone at (301) 827-5655 or by fax at (301) 443-6919.

Sincerely,

Joseph C. Famulare
Director
Division of Manufacturing and
Product Quality, HFD-320