DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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JAN 27 1997

WARNING LETTER

Mr. Herman C. Scheffer
Executive Chairman
Gist-Brocades B.V.
A. Fleminglaan 1
AX2613 Delft
The Netherlands

Dear Mr. Scheffer:

FDA has completed its review of the inspection of your non-sterile and sterile bulk pharmaceutical chemical manufacturing facility in Delft, The Netherlands by Investigator Dr. David Pulham and Analyst Raymond T. Oji during the period of May 6-13, 1996. The inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of sterile pharmaceutical chemicals. The deviations were presented to your attention on an FDA-483 List of Observations at the close of the inspection. These CGMP deviations cause your bulk pharmaceutical chemicals (BPCs) to be unacceptable for use by pharmaceutical dosage form manufacturers in the United States, since, under United States law, those CGMP deviations render your products adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

We note that your firm manufactures approximately sixteen products for the U.S. market, including several sterile bulk drugs. A previous Warning Letter of July 14, 1995 was issued to your firm, following June 1993, May 1994, and February 1995 inspections which disclosed numerous CGMP deficiencies. Your firm met with our office in November 1995, to present a corrective action plan, including plans for extensive facility renovations many of which are being completed at this time.

In a recent December 20, 1996 meeting, your firm again met with representatives of our office and presented an action plan relative to deficiencies cited during the May 1996 inspection. This plan is intended to correct several significant CGMP deviations cited during the inspection.

In our previous November 1995 meeting and within the July 14, 1995 Warning Letter, we noted that inspections of your manufacturing site over the preceding few years had revealed numerous deficiencies. We acknowledge the considerable effort and expense your firm has expended in order to improve the physical facility. However, our review of FDA's past inspections of your firm indicates that individual CGMP deficiencies are often corrected without a more global approach to achieving comprehensive CGMP compliance.

The 1993 inspection revealed Quality Control Unit and sterile facility suitability deficiencies (the latter was also identified as a problem during the previous 1988 inspection). The May 1994 inspection found deficiencies relating to WFI sampling, failure investigations, environmental monitoring, and nonsterility complaint investigations. The February 1995 inspection found sterile processing and sanitization documentation, calibration, QC testing, and training documentation deficiencies.

Among the significant deviations found in the most recent May 1996 inspection are:

FACILITY DESIGN AND MONITORING

1. Sterile processing areas were not adequately monitored.

   - Areas in which aseptic additions of sterile raw materials and aseptic assembly of sterilized equipment are performed were not classified or monitored under actual conditions of use.

   - No microbiological monitoring was conducted during operations in the bulk aseptic filling area and the sterile buffer preparation area, both class clean zones.

   - Gowning rooms for the aseptic filling and aseptic buffer preparation rooms were not classified.

   Initial facility design should include studies under dynamic conditions which establish cleanroom classifications for areas in which activities related to sterile manufacturing are performed. For instance, zones in which aseptic additions and gowning take place should be adequately qualified or classified, then monitored routinely.

Moreover, the inspection found deficiencies in the design of the sterility testing area.

INVESTIGATIONS

2. There was no investigation or follow-up of out-of-specification differential pressure results.

   The CGMP regulations regarding the manufacture and control of a batch require review and approval of all records associated with the lot by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. In addition, discrepancies or failure (e.g., of any systems associated with processing) to meet specifications must be thoroughly investigated. Other batches, including other drug products that may have been associated with the specific failure or discrepancy must be considered. A written record of the investigation including conclusions and provisions for timely follow up measures are an integral part of the investigation. Additionally, procedures must be established to assure that responsible officials not involved in daily operations are notified of any investigations conducted.

VALIDATION

3. Sterile filter validation had not been conducted for four sterile drug substances.

   We acknowledge and agree with the course of action outlined in your firm's written response. The response states that the contract laboratory performing the filter validation studies will be repeating these studies at your request.

4. Sterility test methods were not validated.

   An appropriate laboratory determination of each batch's satisfactory conformance to final specifications can only be realized with test methods for which adequate accuracy, sensitivity, specificity, and reproducibility has been established and documented.

   Our inspection team also noted that analytical methods validation had not yet been completed for approximately methods.

5. Media fills did not simulate worst-case conditions.

   Our inspection found that the longest interval between sterilizations during a was not considered in the process simulation study design. Please detail in your written response if your firm has reviewed written SOPs to assure that any expected and unexpected worst-case conditions are now adequately simulated during media fills.

PRODUCTION CONTROLS

6. Production time limitations had not been established.

The chemical stability and microbial quality of in-process materials and products at successive processing stages should be assessed and appropriate, justifiable storage times formalized.

As discussed during our December 20, 1996 meeting, the 6-month storage period for tanks which hold sterilized product, was not justified by the study provided in your November 1996 response. The acceptance criteria permitted *contamination* of these pre-sterilized tanks after six months of storage. The study showed 2 CFU contamination in the second of the three runs. Sterilized tanks should be shown to remain sterile for the storage period established by your firm.

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.

Finally, please recall our request, during the December 1996 meeting, to submit to our office the following information:

1) An update of which methods have been validated as well as those which still require validation;

2) Media fill study frequency (written SOP), specifications, and results since December 1994;

3) The list of and schedule for studies for which your firm has decided that Retrospective Validation is appropriate.

Upon receipt of methods validation and retrospective validation study updates, we will reassess the status of your firm's non-sterile BPC profile classes. Any sterile drug substances will remain unacceptable until FDA has reinspected your facility and confirmed that your firm is in CGMP compliance. We will not recommend approval of any applications listing your firm as a supplier of sterile drug

substances. Any sterile BPCs 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# 9610341** in 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) 443-1855 or by fax at (301) 443-6919.

Sincerely,

Douglas I. Ellsworth
Director
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