DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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WARNING LETTER

FEB 19 1997

Thomas McKilliop, CEO
Zeneca Pharmaceuticals
Macclesfield Works
Hurdsfield Industrial Estate
Macclesfield, Cheshire, England SK10 2NA

Dear Mr. McKilliop:

We have completed our review of the inspection of your pharmaceutical manufacturing site at Hurdsfield in Macclesfield, Cheshire, England by FDA investigator Richard Friedman on November 28, 1996 through December 4, 1996. This inspection revealed significant deviations from Current Good Manufacturing Practices (CGMPs) in the manufacturing of sterile pharmaceutical products. These CGMP deviations cause your 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.

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

1 Failure of your Quality Control Unit to:

a. Properly monitor glove sampling procedures.

b. Control production personnel

c. Fully document all investigative work performed and corrective actions implemented.

d. Establish investigative conclusions, explore trends, or investigate the need for additional testing.

e. Approve all product specifications and monitor unapproved changes to QA approved procedures.

2 Failure to conduct critical post-sterilization operations under adequately controlled conditions.

3 Failure of Master and/or Batch Control Records to contain documentation that each significant step in the manufacturing process is accomplished and contain complete manufacturing specifications.

4 Non-viable counts exceeding conditions during production.

We have also reviewed the written response submitted by your company dated December 20, 1996, signed by J.D. Gartside, Site Manager, and the additional information provided during the meeting with FDA on February 11, 1996. We note that many corrections have been made, or will be soon implemented. However, we still have the following concerns:

ENVIRONMENTAL MONITORING

The response to FD-483 observation 1c regarding identification of critical sites for routine monitoring, fails to explain why this function had not been performed by your firm's Quality Control Unit. Newly identified critical sites have not yet been submitted. It also does not indicate any corrective action regarding the QC unit's failure to meet this responsibility.

The response indicates that a "feasibility of adopting alternative arrangements" review will be conducted in response to FD-483 observation eight (8). Please submit a summary report of this review. We are concerned that the tighter controlled system (glove box), cited as being used in your other plants, is not already being used at the plant distributing product to the United States.

PERSONNEL SAMPLING

The responses submitted for FD-483 observations 1d and 2 are unacceptable in regard to aseptic room production personnel performing their own glove sampling and critical surface/air monitoring. The U.S. CGMP assigns the responsibility for critical functions such as : setting performance specifications, monitoring and assessing the performance of production equipment, personnel, systems, and processes, as well as ensuring that established controls are implemented, to the QC Unit. Critical sampling; therefore, should be performed by, or continually monitored by the QC Unit. The collection of this data by those same individuals whose actions are being assessed, (production employees)without routine monitoring may not provide a true picture of your firm's state of control.

Your commitment to have the QC Unit perform random audits does not meet the responsibility to ensure that established controls are correctly implemented on a batch by batch basis.

The response also indicates that other enviornmental monitoring samples are also collected in this same manner. This should be addressed in your response to this issue.

NON-VIABLE PARTICULATE MONITORING

The commitment to review a specific process and identify stages of transient high particle counts cited in FD-483 observation number 7 and establish subsequent operating limits, fails to address the problem of counts outside of established limits. Your description of the high counts as "transient" (i.e., lasting only a short time) does not correct the deficiency, nor will the commitment to establish new operating limits. The approach should be to identify the cause and modify or correct the situation causing the high counts so that the already established action limit can be met. We are also concerned that this was not corrected by your QC unit before FDA arrival.

As discussed during the meeting with FDA, if additional monitoring is needed to correlate these "transient" excursions with identifiable manufacturing conditions this should be documented upon each occurrence.

The response states that this process will be reviewed by March 31, 1997. Please provide a written summary of the investigation and subsequent corrections.

Our comments regarding your firm's QC units and submitting documentation of corrections to FDA are also applicable to the response regarding extrusion operations as cited in Observation 8 on the FD-483. From the response, it appears your firm may be employing tighter control of the process step at other 'Zoladex' plants which are not distributing product to the United States.

MASTER/BATCH PRODUCTION RECORDS

Your firm's response (FD-483 item #15) failed to contain any documentation of the reported corrections. If these changes require filing amendments to Drug Master Files and/or New Drug Applications, please advise us when amendments are submitted.

BUILDING DESIGN

Although not cited on the FDA-483, List of Inspectional Observations Form issued at the conclusion of the inspection, our investigator was, due to the plant design, unable to view many critical portions of your sterile operation without entering the aseptic area. As in the previous inspection, this appears to be due to inadequate inspection windows and/or poor camera coverage/resolution. This was discussed with plant management during the inspection by our investigator, and previously brought to your attention in a July 26, 1995 Warning Letter. This situation may impede or minimize the ability of your QC Unit to meet its responsibility for monitoring aseptic conditions and procedures.

The CGMP deviations identified above or on the FD-483 are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections of firms are audits which are not intended to determine all deviations from CGMPs that exist at a firm. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to assure compliance with all U.S. Standards for Current Good Manufacturing Practices.

During the meeting with FDA in February 11, 1997, your firm indicated that additional corrective actions have been, and are being implemented and that documentation of the corrections would be submitted. Until that documentation is submitted or corrections are confirmed by a reinspection, this office will not recommend approval of any new applications listing your firm as the manufacturer of sterile drug products.

Failure to correct these deficiencies may result in FDA denying entry of articles 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 510 (a)(2)(B) of the Act.

In any response to this agency, you should include copies of SOPs generated/records amended, as well as data collected in your correction of deficiencies brought forward during the inspection. Specific time frames for correction and commitments with follow up documentation should also be supplied or reported as forthcoming.

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.

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

CC:

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