



CBER 00- 005

NOV 8 1999

WARNING LETTER

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

John Geigert, Ph. D.  
Vice President, Quality  
IDEC Pharmaceutical Corporation  
11011 Torreyana Road  
San Diego, CA 92121

Dear Dr. Geigert:

The Food and Drug Administration has completed its review of the inspection of your pharmaceutical manufacturing facility located at 11011 Torreyana Road, San Diego, California, between May 17 – 27, 1999. The inspection revealed significant deviations from current good manufacturing practice regulations (CGMP) in the manufacture of an active pharmaceutical ingredient. These violations of the CGMPs render your products adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

Significant deviations observed during the inspection include but are not limited to:

INVESTIGATION OF FAILURES

1. There is no indication that failures are fully investigated or that investigations are extended to other batches as appropriate. For example:
  - a. Variance Report #0910 reported an out of limit result for a Limulus Amebocyte Lysate (LAL) test at process stage \_\_\_\_\_ for Rituximab Formulated Bulk (IDEC- \_\_\_\_\_, lot 102-079. Although the report states that endotoxin was removed downstream of this step, a thorough investigation has not been conducted to demonstrate that the remaining downstream processing steps including the \_\_\_\_\_ Column

Chromatography process and \_\_\_\_\_ Column Chromatography process will remove or reduce levels of endotoxin.

- b. There was no investigation for the split peaks found on the \_\_\_\_\_ Column Chromatography IDEC- \_\_\_\_\_ chromatograms for lots 102-118, 102-137, 102-145, 102-146, 102-149, 102-151, and 102-153. In addition, there was no investigation regarding the variability of peak cutting. Peak cutting is conducted to accommodate the capacity of vessel \_\_\_\_\_

#### CLEANING AND MAINTENANCE OF EQUIPMENT

2. Appropriate validation has not been conducted on critical equipment. For example:
  - a. There is no data to support a \_\_\_\_\_ storage expiration for non-glass equipment and utensils such as tubing, hoses, and filters. This equipment is stored in a Class \_\_\_\_\_ area.
  - b. The procedure entitled "Cleaning Validation Study of \_\_\_\_\_ and \_\_\_\_\_ Resins at the End of their Lifetime Use" did not demonstrate the removal of endotoxins after the sanitization and cleaning of \_\_\_\_\_ and \_\_\_\_\_ columns.
  - c. The performance qualification study entitled "Cleaning Validation \_\_\_\_\_" has not been performed. The filters, which are tested using the unit, are utilized in the \_\_\_\_\_ system.

#### ACCEPTANCE CRITERIA

3. There is no assurance that results obtained during validation testing are meaningful. Acceptance criteria for results were not established in the validation protocol entitled "Identification of Aerobic Bacteria Using the \_\_\_\_\_"

We acknowledge receipt of your response dated June 25, 1999, which addresses the inspectional observations on the Form FDA-483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate; however, your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our evaluation of your response follows, and is numbered to correspond to the items listed on the Form FDA-483:

4. The response failed to address the split peaks present in the \_\_\_\_\_ column chromatography and the impact on the product. Please provide the following: (1) the cause of the sudden change in output volume for the lots in

question, (2) a description of the lots used in support of the validation including a determination of whether the lots were manufactured under the planned variance, and (3) comparative data and summaries of the \_\_\_\_\_ column chromatograms used for the latest validation and those originally submitted in your product license application.

5. Please provide additional information that demonstrates that the implicated lots of product do not contain elevated levels of endotoxin. Please note that we are aware that endotoxin removal has not been evaluated in your purification process.

We note that IDEC Pharmaceutical Corporation performs an LAL test at process stage \_\_\_\_\_ Cell Free Receiving Tank, and reports the result as a "Report Value." Please explain the purpose of a "Report Value" including how Quality Assurance and Production managers use this information to assess product quality and purity. In addition, please explain the benefit of collecting this information if atypical results (when compared to historical data) are not investigated i.e., an assessment of impact to product and other associated batches, identification of the cause of the problem, and implementation of corrective actions.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deviations. It is your responsibility to ensure that your facility is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act and all applicable regulations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes license suspension and/or revocation, seizure and/or injunction.

You should notify this Office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Compliance and Biologics Quality, HFM-600, Suite 200N, 1401 Rockville Pike, Rockville, Maryland 20852-1448.

Sincerely yours,



Deborah D. Ralston  
Acting Director  
Office of Regional Operations