DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

SEP 27 2004

Our STN: BL 103795/5184

Immunex Corporation
Attention: Kenneth B. Seamon, Ph.D.
1201 Amgen Court West
Seattle, WA 98101

Dear Dr. Seamon:

Your request to supplement your biologics license application for Etanercept to provide a new formulation and presentation of drug product (DP) 50 mg/mL liquid supplied in a single dose pre-filled syringe (PFS) has been approved.

We have approved the stability protocol in your application for the purpose of extending the expiration dating period of your single use pre-filled syringe under 21 CFR 601.12.

We acknowledge your written commitments of September 17, 24, and 27, 2004 to conduct postmarketing studies as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. To assess the rate of antibody formation in a minimum of 400 subjects receiving Enbrel liquid for the first time in an ongoing or planned clinical study. Subgroup analyses will be performed to assess the relative rate of antibody formation in subjects with and without concomitant methotrexate (MTX) therapy. Approximately half of the patients will not be on concomitant MTX. Serum samples will be taken prior to administration of Enbrel liquid, at the time of initiation of Enbrel liquid, and two times post-treatment; one of which will be at least six months after baseline. A detailed analysis plan will be submitted by January 30, 2005, a final study protocol will be submitted by June 30, 2005, patient enrollment will be completed by June 30, 2006, the study completed by December 31, 2006, and a final report submitted by July 31, 2007.

Postmarketing Studies not ubject to reporting requirements of 21 CFR 601.70.

2. To submit a list of corrective and preventative actions taken to ensure that future lots of Enbrel prefilled syringes will be shipped at the appropriate temperature. Amgen will submit this information no later than October 15, 2004.

3. To submit a summary of the temperature tracking data (hours below, above, and at the proposed shipping temperature) for the next five shipments from Amgen Manufacturing Ltd. (AML) to the product distribution center in Kentucky. A summary report will be submitted by January 30, 2005.

4. To incorporate a gray band on the syringe label that will indicate the fill volume that is acceptable for use by the patient. The label placement will be validated to ensure that the lower and upper limits of the gray band coincide with the lower and upper limits of the validated fill volume. Amgen will also modify the Patient Instruction Leaflet to advise patients to visually assess the fill volume prior to use.

   Amgen commits to submit a prior approval supplement with the revised labeling, summary of the associated printing and label placement validation, and revised Patient Instruction Leaflet by January 30, 2005.

5. To perform a risk assessment for the likelihood that drug product will come in contact with the natural rubber needle shield either for short term or long term exposures. If there is any likelihood that drug product may come in contact with the natural rubber, the sponsor should propose solutions to address any product quality or safety concerns arising from exposure to, or potential leachables derived from, the rubber needle shield.

   Amgen will submit this information no later than March 30, 2005.

6. To set appropriate endotoxin specifications for acceptance or rejection of each lot of syringe plunger stoppers and syringe assembly (barrel and needle) by December 2004. Amgen will provide the revised component endotoxin specifications in the BLA annual report targeted for submission in December 31, 2004.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 103795. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA STN BL 103795. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- Postmarketing Study Protocol
- Postmarketing Study Final Report
- Postmarketing Study Correspondence
- Annual Report on Postmarketing Studies

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment), and

- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

Please submit final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective Oct. 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

This information will be included in your biologics license application file.

Sincerely,

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Marc K. Walton, M.D., Ph. D.
Director
Division of Biological Internal Medicine Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Encl. Package Insert (PI) and
Patient Package Insert (PPI)

CONCURRENCE PAGE

Letter Type: LETTER: Approval (AP)

Summary Text: Manuf. Supplmt. Other
REVIEW COMPLETION REQUIRED BY: RIS

SS Data Check:
- **Place copy of Approval Ltr. with original signature concurrence page in Archival package behind the "Approval Materials" Tab after LAR (Licensing Action Recommendation).**

RIS Data Check:
- **Verify short summary Ltr. & Submission screen should match.**
- **Check Letter for PMCs (if PMCs add "PMCs Approved With" special characteristic code.)**
- **Perform Review Completion Process**
- **Milestone: Confirm Approved Status**

cc: HFM 555/K. Clouse
HFM 599/A. deMarco
HFM 588/E. Dye
HFM 555/J. Kutza
HFM 585/C. Michaloski
HFM-576/R. Neuner
HFM 576/K. Schneider
HFM 599/M. Smedley
HFM 576/H. Zhao
HFM 555/K.Kozlowski
HFM 576/M. Walton
HFM-500/G. Jones
HFD-240/OTCOM/ B. Poole (if labeling changes)
HFD-322/IPCB E. Rivera-Martinez
HFM-110/RIMS R. Eastep
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History: Michaloski\letters\103795_5184ap.doc.rev.9.24.04rev9.25.04rev9.27.04

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