CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

STN 103795/5102

Administrative

2. Failure to prepare and maintain complete and accurate case histories. [21 CFR § 312.62(b)].

   A. Subject diaries and/or Case Report Forms recording study drug administration were incomplete for the following: ——— ———, for Subject 0046, Weeks 25-29 for Subject 0048, Weeks 1-12 for Subject 0054, Weeks 1-24 for Subject 0056, and Weeks 25-26 for Subject 0606. (Dr. Cohen)

   B. Week 4 Physician Global Assessment was missing for Subject 0584 at the time of inspection. (Dr. Cohen)

   C. Transcription errors from source documents to case report forms were noted for Subjects 605, 611, 7051, and 7557. (Dr. Gottlieb)

3. Failure to assure Institutional Review Board (IRB) review. [21 CFR § 312.66]

   The first annual IRB continuing review for Dr. Gottlieb's study was performed on 9/13/01, five months past the annual approval date. The IRB initially approved the study on 4/11/00. In addition, subject educational materials were not submitted for IRB review. (Dr. Gottlieb)

ADDITIONAL COMMENTS:

We note that Dr. Cohen performed the Week 4 joint assessment for Subject 0076 with the sponsor's permission.

Section 6.2 of the protocol requires that injections of study drug be "administered twice weekly at approximately the same time each day" and states that study subjects "will be supplied with a diary in which to record the date and time of each study dose." A letter to the investigational sites from the sponsor dated 4/11/00 states "the diary asks for the time – but the case report forms do not. Thus, we are deleting the "time" from the Diaries." The sponsor did not amend the protocol to reflect this change. The FDA investigators noted that compliance with the protocol requirement that the study drug be administered "at approximately the same time each day" could not be verified without the diary "time" entries.

BIMO ADMINISTRATIVE FOLLOW-UP

Correspondence addressing concerns raised by the inspections has been issued to Dr. Alice Gottlieb and Dr. Stanley Cohen.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

Memorandum

Date: August 21, 2003

From: Karen D. Jones
Regulatory Project Manager
Division of Application Review and Policy, HFM-588
Office of Therapeutics Research and Review

To: STN BL 103795/5102 File

Subject: Biologic Therapeutic SBA equivalent for:

- **Product: Etanercept, [Enbrel® is proprietary name]**
- **Manufacturer: Immunex Corporation**
- **License Number 1132**

Indications and Usage

The **expanded indication** approved for this BLA supplement is as follows: Enbrel® is indicated for reducing signs and symptoms and **inhibiting the progression** of structural damage of active arthritis in patients with psoriatic arthritis.

Dosage Form, Route of Administration, and Recommended Dosage

- Enbrel® is supplied as a sterile, white, preservative-free lyophilized powder for parenteral administration after reconstitution with 1 mL of the supplied Bacteriostatic Water for Injection (BWFI), USP (containing 0.9% benzyl alcohol)
- Enbrel® is available in a multiple use vial containing 25 mg Etanercept, 40 mg mannitol, 10 mg sucrose and 1.2 mg tromethamine and is packaged in a carton containing four dose trays that each include one vial of Enbrel, one diluent syringe (1 mL Sterile Bacteriostatic water for Injection, USP, containing 0.9% benzyl alcohol, one 27 guage ½ inch needle, one vial adapter, one plunger, and two alcohol swabs.
- Dosing: for adult patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis, 25 mg is given twice weekly as a subcutaneous injection 72-96 hours apart.

Basis for Approval

The following reviews, filed in the CDER/OTRR correspondence section of the license file for STN 103795/5102, comprise the SBA equivalent for this application:

Discipline	Reviewer Name	Date
Clinical (Safety and Efficacy)/Statistical	Elektra Papadopoulos, MD Satish Misra, PhD	8/21/03
	George Mills, MD	8/21/03
Bioresearch Monitoring	Christine Drabick	5/23/03

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Trade secret and/or confidential commercial information

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