CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057/0

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 125057/0

DEC 3 1 2002

Abbott Laboratories
Attention: Ms. Jeanne Fox
Senior Director, PPD Regulatory Affairs
200 Abbott Park Road
D-491, AP30-1E
Abbott Park, IL 60064-6157

Dear Ms. Fox:

Your biologics license application for Adalimumab is approved effective this date. Abbott Laboratories, Abbott Park, Illinois is hereby authorized to introduce or deliver for introduction into interstate commerce, Adalimumab under Department of Health and Human Services U.S. License No. 0043.

Adalimumab is indicated for reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Adalimumab can be used alone or in combination with Methotrexate (MTX) or other DMARDs.

Under this authorization, you are approved to manufacture Adalimumab at your facility, [redacted] Final formulated drug product (vials) will be filled at [redacted] and unlabeled vials of drug product will be shipped to [redacted] or [redacted] for labeling, packaging and distribution. Final formulated drug product (syringes) will be filled at [redacted] and unlabeled syringes of drug product will be shipped to Abbott Laboratories at Abbott Park, Illinois or retained at [redacted] for labeling, packaging and distribution. In accordance with approved labeling, your product will bear the proprietary name HUMIRA™, and will be marketed in 40 mg/0.8 mL single use vials and 40 mg/0.8 mL single-use syringes.

The dating period for Adalimumab bulk drug substance shall be [redacted] months from the date of manufacture when stored at [redacted] C; this may include up to [redacted] days of temporary storage at [redacted] C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug substance. The dating period for drug product shall be 24 months for vials when stored at 2 to 8°C and 18 months for pre-filled syringes when stored at 2 to 8°C. Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

The stability protocols in your license application are considered approved for the purposes of extending the expiration dating period of your drug substance and drug product (vials and pre-filled syringes) as specified in 21 CFR 601.12.

The comparability protocol for the — manufacturing process in your license application is considered approved. As provided under 21 CFR 601.12(e), approval of a comparability protocol may justify a reduced reporting category for a particular change. Information validating that this change meets the requirements specified in your approved comparability protocol should be reported as a "Supplement - Changes Being Effected in 30 Days" (21 CFR 601.12(c)). This supplement should include the information described in 21 CFR 601.12(b)(3). Although product made using this change may be distributed 30 days after FDA receives that supplement, continued use of the change will be subject to final approval of the supplement.

You are not currently required to submit samples of future lots of Adalimumab to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specification.

Any changes in the manufacturing, testing, packaging or labeling of Adalimumab, or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

We acknowledge your written commitments to provide additional information on ongoing studies and to conduct postmarketing studies as described in your letters of December 18, 2002 and December 30, 2002 as outlined below:

1. To submit long term safety surveillance data by continuing three ongoing studies

, for a period of time such that each patient will have been exposed to Adalimumab for at least 5 years. Study — was filed to BB-IND — on December 16, 1999 and study — was filed to BB-IND — on June 26, 2000. Study — was not conducted under the IND but was submitted with BLA 125057/0 on March 28, 2002. Patient enrollment was completed on June 22, 2001 for — August 31, 2000 for — and April 5, 2001 for —

Study — completion will occur by June 22, 2006, — (extension study for — will complete by August 31, 2006, and Study — will complete by April 5, 2006. An interim integrated safety analysis will be submitted March 31, 2005. The final study reports for these three studies, and the integrated safety analyses and data sets will be submitted by March 31, 2007.

2. To submit final study with 5 year data for —

Study — was filed to BB-IND — on December 1999 and enrollment was completed on August 31, 2000. The study will be completed by August 31, 2005. A study report with x-ray data from the 2-year time point will be submitted by September 30, 2003. A final study report with data from the 3 and 5-year time points will be submitted by September 30, 2006.

3. To conduct a study on the impact of Adalimumab on pneumococcal vaccine immunization. The study will measure the humoral response in approximately 100 placebo and 100 Adalimumab-treated patients who will be given a polyvalent pneumococcal vaccine. The protocol for this study will be submitted by January 31, 2003. The study will be initiated by February 28, 2003 and the study will be enrolled by October 31, 2003. Study completion will occur by April 30, 2004. The final study report will be submitted by March 31, 2005.

4. To conduct a study on the impact of Adalimumab on the antibody response to a T cell dependent vaccine (such as influenza). The protocol for this study will be submitted by March 31, 2003. The study will be enrolled by February 28, 2005, the study will be completed by April 30, 2005 and the final study report will be submitted by July 31, 2005.

5. To continue study — , "A Multi-center, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Human Anti-TNF Monoclonal Antibody Adalimumab in Children With Polyarticular Juvenile Rheumatoid Arthritis" which is currently ongoing. The protocol was filed to BB-IND — June 28, 2002, and the study was initiated on September 13, 2002. Enrollment will be completed by June 30, 2003, and study completion will occur by June 30, 2004. The final study report will be submitted by June 30, 2005.

6. To establish a pregnancy registry of patients with RA who become pregnant while on anti-rheumatic therapy, including Adalimumab as well as other medications, which will run for 3 years. Abbott will submit a registry protocol with supportive documentation by March 31, 2003 and will start the registry by June 30, 2003. A final report will be submitted by March 30, 2007.

7. To further determine the immunogenicity of Polysorbate 80 (the marketed formulation) containing adalimumab, blood samples will be taken and analyzed from approximately 150 patients in study [redacted] who have taken the Polysorbate 80 containing formulation of Adalimumab for approximately 3 months, to determine the presence of anti-Adalimumab antibodies. Study [redacted] was filed to BB-IND [redacted] on June 26, 2000, and initiated on July 12, 2000. A report on the immunogenicity results will be submitted by December 31, 2003.

8. To perform the additional histopathological thymus evaluation as specified in study report [redacted], page 12 (BLA 125057/0). The examination will be initiated by January 10, 2003 and a final study report submitted by August 31, 2003.

9. To modify the label on the pre-filled syringe to contain volume graduations and submit this as a Changes Being Effected - 30 day Supplement by March 15, 2003. The supplement will contain the revised syringe label, the revised patient package insert (remove reference to the card and provide new instructions for the patient to check fill volume), and revised cartons (removing reference to the card).

Protocols should be submitted to your BB-IND with a cross-reference letter to the BLA.

It is required that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted in accordance with 21 CFR 600.81. Postmarketing adverse experience reports and distribution reports should be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. All adverse experience reports should be prominently identified according to 21 CFR 600.80.

You are required to submit reports of biological product deviations in accordance with 21 CFR 600.14. All manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution, should be promptly identified and investigated. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, a report must be submitted on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit all 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).

In addition, you may wish to submit three draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

/S/

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research