CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

BLA 125118/000

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125118/0

Bristol-Myers Squibb
PO Box 4000
Princeton, NJ 08543-4000

Attention: Anthony J. Calandra, Ph.D.
Director, Global Regulatory Strategy

Dear Dr. Calandra:

We are issuing Department of Health and Human Services U.S. License No. 1713 to Bristol-Myers Squibb, Princeton, NJ, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Abatacept. Abatacept is indicated for reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease Modifying Anti-Rheumatoid Drugs (DMARDs), such as methotrexate or TNF antagonists. Abatacept may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

Under this license, you are approved to manufacture Abatacept drug substance at Bristol-Myers Squibb in East Syracuse, NY. The final formulated product will be manufactured, filled, labeled, and packaged at Bristol-Myers Squibb Holdings Pharma, Ltd., Manati, Puerto Rico. You may label your product with the proprietary name ORENCIA and will market it in single-use vials containing 250 mg Abatacept.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, and the text for the patient package insert) and the submitted labeling (immediate container and carton labels submitted August 25, 2005). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

The dating period for Abatacept shall 24 months from the date of manufacture when stored at 2°C to 8°C. The date of manufacture shall be defined as [the date of [(b) (4)] of the formulated drug product. The dating period for your drug substance shall be for 9 months when stored at 40°C. Drug substance may also be stored for 60 days at 2°C to 8°C prior to freezing at 40°C. Results of ongoing stability studies should be submitted throughout the dating period, as

they become available, including results of stability studies from the first three production lots. The stability protocols in your license application are considered approved for the purpose of extending the expiration dating period of your drug substance and drug product as specified in 21 CFR 601.12.]

You currently are not required to submit samples of future lots of Abatacept to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Abatacept or in the manufacturing facilities.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages up to 2 years and deferring pediatric studies for ages 2 to 16 years for this application

We acknowledge your written commitments as described in your letter of December 21, 2005, as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 601.70. This commitment is the deferred pediatric study under PREA for the treatment of polyarticular course juvenile rheumatoid arthritis in pediatric patients ages 2 to 16. We note that a study responsive to this commitment is underway.

   Final report submission date: November 30, 2006

   Submit the final study report to this BLA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "Required Pediatric Study Commitment".

2. Protocol IM101045A, a pharmacoepidemiology study to assess the short term (2 years) and potential long-term (4 years) risk of hospitalization due to infection (all hospitalized infections, hospitalized pneumonia, and all opportunistic infections) among patients with RA treated with Abatacept in comparison to other DMARDs within a large cohort of individuals with commercial health insurance. This study will also characterize patients receiving Abatacept and monitor any off-label use. The study will be completed per the following timetable:

Protocol submission date:	January 31, 2006
Enrollment completion date:	December 31, 2011
Observation period completion date:	December 31, 2015
Final report submission date:	December 31, 2016

3. Protocol IM101045B, proposed as an observational prospective pharmacoepidemiology cohort study to assess the short and long-term risk of malignancies and infection in patients with RA treated with Abatacept in comparison to other DMARDs within an existing registry containing patients with rheumatoid arthritis. Follow-up will be for at least 5 years after the last patient is enrolled. The study will be completed per the following timetable:

Protocol submission date:	January, 312006
Enrollment completion date:	June 1, 2009
Observation period completion date:	June 31, 2014
Final report submission date:	December 31, 2016

4. To continue the open label extensions of 5 studies (IM101-100, IM101-101, IM101-102, IM101-029, IM101-031) to obtain data and perform appropriate safety analyses for 5-years' exposure to Abatacept for 1000-1500 patients according to the following timetable.

Open label extension completion date:	September 30, 2009
Integrated Safety Analysis submission date:	June 30, 2010

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

Regarding raw materials and in-process controls:

5. To conduct additional validation studies to evaluate the specificity of the (b) (4) ELISA for assessment of host cell proteins. A summary report and data will be provided by March 31, 2006.

6. To submit the results and conclusions of the bioburden mapping study together with proposed revisions to your bioburden control program by August 31, 2006.

7. To establish raw materials specifications and in-process controls for impurities in (b) (4) A report, proposed controls and data will be provided by October 31, 2006.

Regarding specifications:

8. To re-evaluate all acceptance criteria for currently established release tests of Abatacept drug substance and drug product. Results will be provided by March 31, 2006.

9. To implement enhanced assay sensitivity controls and establish quantitative and semi-quantitative acceptance criteria for the (b) (4) methods, respectively. The proposed acceptance criteria and supporting data will be provided by March 31, 2006.

10. To establish new acceptance criteria for the reference material and for drug substance release for s (b) (4) eaks observed in the (b) (4) profile obtained by by December 31, 2006.

11. To modify acceptance criteria for the current peptide mapping procedure to include selected peak area and retention times. Report to be submitted by February 28, 2006.

12. To establish a drug substance release test specification for (b) (4) (b) (4) content by February 28, 2006.

13. To re-evaluate the appearance specification regarding number of vials tested and to summit revised specifications for this parameter by March 31, 2006.

14. To evaluate the revised capillary electrophoresis (CE) method for quantification and or characterization of minor peaks in Abatacept drug substance and drug product and submit results of this analysis together with any revised specifications by March 31, 2006.

15. To increase precision of the bioassay used for release and stability testing and revise the acceptance criteria accordingly. A summary report together with revised specifications will be provided by July 31, 2006.

Regarding assessment of additional product attributes:

16. To develop the (b) (4) (b) (4) test for quantification of (b) (4) (b) (4) for Abatacept drug substance and drug product. Results of this analysis together with how this assay will be implemented (i.e. use in specifications or characterization activities) will be submitted by March 31, 2006.

17. To further characterize the Fc portion of Abatacept for functional activity. Results of this analysis together with how this assay will be implemented (i.e. specifications or characterization activities) will be provided by June 30, 2006.

Regarding additional specification/characterization tests:

18. To develop a (b) (4) Abatacept species, possibly using (b) (4) A report together with proposed specifications will be submitted by December 31, 2006.

19. To validate the accuracy and specificity of the (b) (4) PLC for (b) (4) olecular weight species. A summary report and data will be provided by January 31, 2006.

Regarding Stability:

20. To perform a comprehensive analysis of the drug substance and drug product (b) (4) A plan for conducting this work will be provided by February 28, 2006 with a summary report together with any proposed modifications to the stability protocol will be provided by December 31, 2006.

21. To test for (b) (4) in drug substance stored at 2° - 8oC for (b) (4) in the final container a (b) (4) (b) (4) A report for both studies will be provided by December 31, 2006.

Regarding Immunogenicity Assays:

22. To provide updated information for the CTLA4-T reagent used in the immunogenicity assays. Information and data will be provided by July 31, 2006.

23. To evaluate the inclusion of an additional (b) (4) when testing patient samples so as to better (b) (4) A report will be submitted by April 28, 2006.

24. To provide information and data validating the specificity of the (b) (4) batacept (b) (4) assay by July 31, 2006.

In addition, we remind you of your agreements to do the following related to post-approval clinical information:

- To collect and analyze data (including spontaneous post-marketing reports) on the incidence rate of lung cancer in smokers and non-smokers of RA patients treated with Abatacept.

- To collect and analyze data (including spontaneous post-marketing reports) on the incidence of AEs and SAEs in patients receiving both leflunomide and Abatacept.

- To collect and analyze data (including spontaneous post-marketing reports) on the incidence of AEs and SAEs in patients with COPD who receive Abatacept.

- To conduct a pregnancy registry, with concurrent controls, for women who become pregnant while exposed to Abatacept to identify the pregnancy outcome and postnatal health status of the children.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125118. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL 125118. 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.

Under 21 CFR 201.57(f)(2), patient labeling must be reprinted at the end of the package insert.

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. 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, you must submit a report on Form FDA-3486 to the Division of Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Biological product deviations sent by courier or overnight mail should be addressed to Food and Drug Administration, CDER, Office of Compliance, Division of Compliance Risk Management and Surveillance, HFD-330, Montrose Metro 2, 11919 Rockville Pike, Rockville, MD 20852.

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 draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. 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. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Sincerely,

Robert J. Meyer, M.D. 12/23/05
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research