DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125118/045

APR - 7 2008

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000

Attention: Anand S. Achanta, PhD
Associate Director, Global Regulatory Affairs

Dear Dr. Achanta:

Please refer to your supplemental biologics license application dated June 1, 2007, received June 8, 2007, submitted under section 351 of the Public Health Service Act for Orencia (abatacept).

We acknowledge receipt of your submissions dated October 12, November 9 and 16, 2007, and January 3, February 1, April 1, and April 7, 2008.

This supplemental biologics license application provides for a new indication for the treatment of moderate to severe polyarticular juvenile idiopathic arthritis (JIA).

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have fulfilled the pediatric assessment requirement under PREA for ages 6 to 16 years for Orencia (abatacept). As stated in commitment number #1 of the December 23, 2005 approval letter for Orencia (abatacept), reprinted here, the pediatric assessment requirement included ages 2 to 16 (pediatric assessments were waived for children under 2):

> " 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."

The clinical trial submitted in this supplement, and which enrolled patients ages 6-16, did not include pediatric patients ages 2 to 5. Under PREA, you are still required to study pediatric patients ages 2-5.

We are deferring submission of the pediatric assessment for ages 2 to 5 years until additional safety data have been collected from the animal safety studies as described below, and the final reports from these animal safety studies have been submitted:

1. Submission of the final study report for juvenile animal study DN07013.

Protocol Submission:	April 30, 2008
Study Start:	March 16, 2007
Final Report Submission:	June 30, 2008

2. Submission of the protocol and submission of the final study report for the follow up juvenile rat study assessing the effects of exposure at post-natal day 4 versus post-natal day 28 (DS07165).

Protocol Submission:	April 30, 2008
Study Start:	November 1, 2007
Final Report Submission:	January 30, 2009

3. Submission of the protocol and submission of the final study report for the follow up juvenile animal study assessing the mechanism of T-regulatory cell depletion (DS07166).

Protocol Submission:	April 30, 2008
Study Start:	September 27, 2007
Final Report Submission:	December 31, 2008

Pediatric Requirements #1-3 must be reviewed before the safety of initiating Pediatric Requirement #4 can be determined.

4. Deferred pediatric trial under PREA for the treatment of polyarticular juvenile idiopathic arthritis (JIA) in pediatric patients ages 2 to 5.

   Final Report Submission: December 31, 2011

The status of these deferred studies and pediatric trial, which are required under section 505B(a) of PREA, must be reported annually according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Food, Drug, and Cosmetic Act.

Submit final study and trial reports to this BLA 125118. For administrative purposes, all submissions related to these pediatric postmarketing requirements must be clearly designated **"Required Pediatric Assessment(s)."**

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) will not be sufficient to assess the signals of serious risks of the occurrence of malignancies, other autoimmune diseases, and serious infections. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established and is therefore not sufficient to assess signals of these serious risks. Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the Act, to conduct a postmarketing observational study of Orencia to assess the signal for the occurrence of malignancies, other autoimmune diseases, and serious infections.

You are required to conduct the following observational study:

5. A JIA patient safety registry comprised of at least 500 patients. The protocol for this study should include a plan for more intensive scrutiny for the first 3 years, with annual follow ups (which could be telephonic) assessing for occurrence of malignancies, other autoimmune diseases, and serious infections, for a total of 10 years. Patients turning 18 years of age or older should continue to be followed until they have completed the 10 year follow-up period. Information on these patients may be obtained via annual questionnaire/telephonic follow-up with attention to key adverse events rather than full clinic visit with examination. Occurrence of these serious events should be formally compared to the expected rate of these events in historical controls. The timetable you submitted states that you will conduct this study in accordance with the following timetable:

Protocol Submission:	December 31, 2008
Study Start:	June 30, 2009
Interim Report Submissions:	June 30, 2014
	June 30, 2019
	June 30, 2024
Final Report Submission:	June 30, 2029

Submit the protocol to your IND 9391, with a cross-reference letter to this biologics license application (BLA), STN BL 125118. Submit the final report to your BLA STN BL 125118. Please use the following designators to label prominently all submissions, including supplements, relating to this postmarketing study as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Study Report under 505(o)**

- **Required Postmarketing Correspondence under 505(o)**

You are required to report periodically to FDA on the status of any required study pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 601.70. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or trial otherwise undertaken to investigate a safety issue associated with Orencia.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "Product Correspondence – Final SPL for approved STN BL 125118/045" In addition, within 14 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

Pursuant to 21 CFR 201.57(c)(18) and 201.80(f)(2), patient labeling must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling.

We remind you of your agreement dated April 7, 2008, to submit a labeling supplement revising the adverse events to adverse reactions. You will need to readjudicate, and adjust numbers and events.

PROMOTIONAL MATERIALS

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the following address:

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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this BLA and the following address:

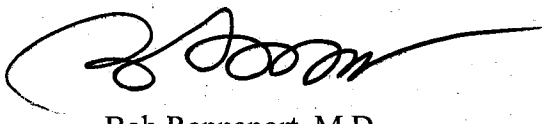
MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

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

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

If you have any questions, call Sara Stradley, Chief, Project Management Staff, at (301) 796-1298.

Sincerely,



Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
And Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Package insert
Patient Package Insert