DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103705/5211

FEB 28 2006

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Attention: Robert L. Garnick, Ph.D.
Senior Vice President, Regulatory Affairs, Quality and Compliance

Dear Dr. Garnick:

Your request to supplement your biologics license application for RITUXAN to include a new indication for use of RITUXAN (rituximab) in combination with methotrexate to reduce the signs and symptoms in adult patients with moderately- to severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies has been approved.

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 deferring submission of your pediatric studies for ages 0 to 17 years until April 30, 2013.

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 601.70. This commitment is listed below.

    a. Deferred pediatric study under PREA for the treatment of polyarticular juvenile idiopathic arthritis in pediatric patients ages 0 to 17.

    b. Final Report Submission: April 30, 2013

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

2. Study of the rituximab 0.5 g × 2 dose in combination with MTX to assess its safety and efficacy in relation to the 1 g x 2 + MTX dose in single and repeat dosing

   Protocol submission date: Submitted July 14, 2005

   Final report submission date: January 30, 2011

3. Study of the safety and efficacy of rituximab re-treatment

   Protocol submission date: Submitted October 15, 2005

   Final report submission date: November 15, 2009

4. Study of the efficacy and safety of rituximab retreatment in patients who are HACA positive

   Final report submission date: July 31, 2011

5. Study of the ability of patients to mount a humoral response to vaccination following treatment with rituximab and B cell recovery

   Protocol submission date: Submitted August 19, 2005

   Final report submission date: June 30, 2009

6. Study of combination use of rituximab with TNF blockers (If you are planning to begin with an exploratory study in combination with etanercept it would be important to state your plans for subsequent study of combination therapy with other TNF blockers.)

   Protocol submission date: Submitted December 19, 2005

   Final report submission date: May 30, 2008

7. Study of combination use of rituximab with DMARDs other than MTX, i.e. leflunomide, sulfasalazine, hydroxychloroquine and combinations of these (A study of this type may enroll patients receiving a variety of DMARD regimens in proportion to their use in usual clinical practice.)

   Protocol submission date: August 30, 2006

   Final report submission date: September 16, 2011

8. Long-term safety of rituximab in an open label chronic treatment study of approximately 1000-1500 patients followed for 5 years, with yearly reports focused on deaths and serious adverse events, particularly serious infections, cardiovascular thrombotic events and seizures

   Protocol submission date: August 30, 2006

   Final report submission date: July 30, 2014

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 103705/5211. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA STN BL 103705/5211. 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.

We acknowledge your agreement to provide additional information and to conduct postmarketing studies as described in your commitment letter of February 24, 2006, and as outlined below:

Pharmacovigilance as outlined in your Risk Management Plan for serious adverse events, focusing particularly on infections SAE's

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

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

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

Sincerely,

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

RITUXAN can cause chest pain and irregular heart beats which may require treatment.

- **Infections.** RITUXAN can increase your chances for getting infections. Call your doctor right away if you have a persistent cough, fever, chills, congestion, or any flu-like symptoms while receiving RITUXAN. These symptoms may be signs of a serious infection.
- **Stomach and bowel problems.** Serious stomach and bowel problems have been seen when RITUXAN has been used with anti-cancer medicines in some patients with non-Hodgkin's lymphoma. Call your doctor right away if you have any stomach area pain during treatment with RITUXAN.

Common side effects with RITUXAN include:
Fever, chills, shakes, itching, hives, sneezing, swelling, throat irritation or tightness, and cough. These usually occur within 24 hours after the first infusion. Other common side effects include headache, nausea, upper respiratory tract infection, and aching joints. If you have any of these symptoms, tell your doctor or nurse.

What if I still have questions?
If you have any questions about RITUXAN or your health, talk with your doctor. You can also visit the RITUXAN internet sites at www.RITUXAN.com or the companies' internet sites at www.Gene.com or www.Biogenidec.com or call (800) XXX-XXXX.

Jointly Marketed by: Biogen Idec Inc. and Genentech, Inc.

Manufactured by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Patient Information Approval [Date]