DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125276/64

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT
NEW POSTMARKETING REQUIREMENT

Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080

Attention: Stuart Heminway
Program Director, Regulatory Affairs

Dear Mr. Heminway:

Please refer to your Supplemental Biologics License Application (sBLA), dated June 28, 2012, received June 29, 2012, submitted under section 351(a) of the Public Health Service Act for Actemra (tocilizumab).

We acknowledge receipt of your amendments dated August 27, September 12 and 27, and October 24 (2), 2012, and January 18, April 3, 15, 19, and 23, 2013. The April 23, 2013 submission comprised an assessment of your risk evaluation and mitigation strategy (REMS), required with submission of your sBLA for a new indication for use.

This Prior Approval supplemental biologics application provides for the use of Actemra (tocilizumab) for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older and a proposed modification to the approved REMS.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry

titled “SPL Standard for Content of Labeling Technical Qs and As” at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your June 28, 2012, submission containing final printed carton and container labels.

Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. Approval of this submission by FDA is not required before the labeling is used.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

This supplement also addresses the required pediatric assessment for the following postmarketing requirement listed in the January 8, 2010, approval letter for BLA 125276/0.

1 Assessment of pharmacokinetic (PK/PD) parameters and dosing, efficacy, safety, tolerance and immunogeniticty in the pediatric population ages ≥ 2 years to < 17 years with polyarticular JIA.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements listed in the January 8, 2010, and April 15, 2011 approval letters that are still open.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes 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.

Actemra (tocilizumab) was approved on January 8, 2010, for adults with rheumatoid arthritis (RA). Data from the adult RA clinical trials showed an association between Actemra (tocilizumab) treatment and the risks of serious infection, gastrointestinal perforation, and the potential for malignancy. Since Actemra (tocilizumab) was approved, we have become aware of events of serious infections in clinical trials of pediatric patients with polyarticular JIA (pJIA). The pediatric clinical trials in patients with pJIA comprise a relatively limited safety database, therefore the risks of serious infection, gastrointestinal perforation, and malignancy need to be defined in this pediatric population. In addition, since the long-term risks of Actemra (tocilizumab) in pediatric patients with pJIA are unknown and these patients will require chronic treatment, further investigation of the long-term safety of Actemra (tocilizumab) is essential. We are also aware of literature suggesting that IL6 has important functions on the developing musculoskeletal system, raising concern regarding effects on growth in pJIA patients with Actemra (tocilizumab). We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known risk of serious infections and gastrointestinal perforations and the unexpected serious risk of malignancy and effects on growth with Actemra (tocilizumab).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1 A long-term safety study in 400 pediatric patients 2-17 years of age with polyarticular JIA (pJIA) treated with tocilizumab to evaluate for the risk of malignancies, serious infections, gastrointestinal perforation, and effects on growth. The study should include a control group of 400 pediatric pJIA patients treated with other biologics as standard of care. Patients should be followed for 5 years.

The timetable you submitted on April 15, 2013 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	February 2014
Study Completion:	September 2022
Final Report Submission:	April 2023

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocol to your IND 11972, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify submissions with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Actemra (tocilizumab) was originally approved on January 8, 2010, with the most recent REMS modification approved on October 11, 2012. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of the addition of information in the appended REMS materials, specifically the Dear Healthcare Professional letter and the journal information pieces, to describe the new indication for the use of Actemra (tocilizumab) in polyarticular JIA patients.

Your proposed modified REMS, submitted on June 28, 2012, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on January 8, 2010.

There are no changes to the REMS assessment plan described in our June 20, 2012, letter.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125276 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

BLA 125276 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125276
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125276
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the

proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Philantha Bowen, Senior Regulatory Project Management Officer, at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY M SEYMOUR
04/29/2013
for Badrul Chowdhury