CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125289

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Our STN: BLA 125289

BLA APPROVED

Centocor Ortho Biotech Inc.
200 Great Valley Parkway
Malvern, PA 19355

APR 24 2009

Attention: Bethany K. Paxson
Senior Director, Global Regulatory Liaison

Dear Ms. Paxson:

Please refer to your biologics license application (BLA) dated and received June 24, 2008, submitted under section 351 of the Public Health Service Act for Simponi (golimumab).

We acknowledge receipt of your submissions dated August 18, September 8, October 3, 9, 20(2), 21, 22, and 31, November 10, 11, and 12, and December 4, 9, 19, and 30, 2008, and January 26, February 6, 12, 13, 18, and 23, March 19 and 20, and April 3, 16, 17, and 20, 2009.

We have approved your biologics license application for Simponi (golimumab) effective this date April 24, 2009. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Simponi (golimumab) under your existing Department of Health and Human Services U.S. License No. 1821. Simponi (golimumab) is indicated for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

Your application for Simponi (golimumab) was not referred to an FDA advisory committee because your product is a member of the class of tumor necrosis factor (TNF)-blockers, and the safety and efficacy data did not pose unique concerns beyond those applicable to other biologic products in the TNF-blocker class approved for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.

Under this license, you are approved to manufacture golimumab drug substance at Centocor B.V. manufacturing facility in Leiden, the Netherlands. b(4)

The final drug product will be assembled at the Cilag, AG, facility in Schaffhausen, Switzerland, and labeled and packaged at the Ortho-McNeil Pharmaceuticals, Inc., facility in Raritan, New Jersey. You may label your product with the proprietary name Simponi and market it in 50 mg/0.5 mL single-dose prefilled syringes or prefilled SmartJect autoinjectors.

The dating period for Simponi (golimumab) shall be 24 months from the date of manufacture when stored at 2° to 8°. b(4)

[redacted] The dating period for your drug substance shall be 36 months when stored at -40°C. b(4)

You currently are not required to submit samples of future lots of Simponi (golimumab) 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.

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

We are waiving the pediatric study requirement for juvenile psoriatic arthritis and juvenile ankylosing spondylitis for 0 to 16 years of age and juvenile idiopathic arthritis for 0 to less than 2 years of age because the necessary studies are impossible or highly impracticable. This is because there are too few children with the diseases to study.

We are deferring submission of your juvenile idiopathic arthritis pediatric study for 2 to 16 years of age for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.70 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

1. Assess the pharmacokinetics, safety, immunogenicity, and efficacy of golimumab in pediatric patients 2 to 16 years of age with active polyarticular juvenile idiopathic arthritis (pJIA).

We acknowledge the timetable you submitted on March 31, 2009, which states that you will conduct this trial according to the following schedule:

Protocol Submission:	October 2009
Trial Completion Date:	June 2013
Final Report Submission:	October 2013

Submit final reports to this BLA. Use the following designator to prominently label all submissions:

Required Pediatric Assessment

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS OF 21 CFR 601.70

We remind you of your postmarketing commitment described in your email dated April 22, 2009, and outlined below:

2. To optimize the existing adventitious virus assay or develop an improved assay for use at all locations performing adventitious virus contamination testing of unprocessed bulk harvest.

   Study Completion Date: by April 2010
   Final Report Submission: by April 2010

Submit clinical protocols to your IND, with a cross-reference letter to this BLA. Submit nonclinical and product quality protocols and all final reports to this BLA. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing commitments, as appropriate:

Postmarketing Commitment Protocol
Postmarketing Commitment - Final Report
Postmarketing Correspondence
Annual Status Report of Postmarketing Commitments

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **PMC Submission –Status Update**. The status report for each commitment should include:

- The original schedule for the commitment, and
- The status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted).

When you have fulfilled your commitment, submit your final report as **PMC Submission – Final Report** or **Supplement Contains Postmarketing Commitment – Final Report**.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Simponi (golimumab) to ensure the benefits of the drug outweigh the risks of serious infections, including tuberculosis, invasive fungal infections and other opportunistic infections, as well as malignancies, congestive heart failure and peripheral demyelinating disorders.

As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Simponi (golimumab) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Simponi (golimumab). FDA has determined that Simponi (golimumab) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Simponi (golimumab). FDA has determined that Simponi (golimumab) is a product for which patient labeling could help prevent serious adverse events. Under 21 CFR Part 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Simponi (golimumab).

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on April 17, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. Patients' and providers' understanding (i.e., surveys) of the serious risks of Simponi (golimumab).
b. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that provider awareness is not adequate.
c. Periodic summaries of adverse reporting of histoplasmosis and other invasive fungal infections including an analysis of deaths and whether appropriate antifungal therapy was instituted promptly.
d. Based on the information reported, an assessment of and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that 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 FDCA.

Prominently identify submissions containing 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:

BLA 125289 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125289
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125289
NEW INDICATION FOR USE
REMS ASSESSMENT
If appropriate: **PROPOSED REMS MODIFICATION**

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

ADVERSE EVENT REPORTING

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). We ask that you submit any adverse event reports related to malignancy, serious infections (including opportunistic infections and tuberculosis), serious hemorrhage, and serious skin reactions (e.g., Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme) as 15-day reports, per reporting regulation 21 CFR 600.80. Serious events are defined as events leading to death, hospitalization, disability, or reported as life threatening. 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, 10903 New Hampshire Avenue, Bldg. 51, Room 4203, Silver Spring, MD 20993-0002.

CONTENT OF LABELING

Within 14 days of the date of this letter, submit 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 in content to the enclosed labeling text. 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 BLA 125289/0."

We remind you that pursuant to 21 CFR 201.57(x)(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.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed draft labels as soon as they are available but no more than 30 days after they are printed. 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 (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved STN BLA 125289/0.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

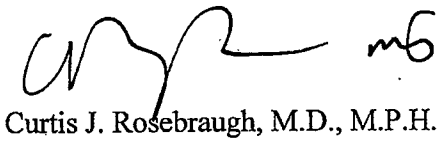
You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, 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 information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, contact Sharon Turner-Rinehardt, Regulatory Project Manager, at 301-796-2254.

Sincerely,



Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Package Insert
Medication Guide
Patient Instructions for Use
Carton and immediate container labels
REMS