DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125261/1

December 30, 2009

Centocor Ortho Biotech, Inc.
Attention: Sue Popma, O.D.
Associate Director, Global Regulatory, Immunology
200 Great Valley Parkway
Malvern, PA 19355

Dear Ms. Popma:

Please refer to your supplemental biologics license application (BLA) dated March 3, 2009, received March 3, 2009, submitted under section 351 of the Public Health Service Act for Stelara™ (ustekinumab) pre-filled syringe indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

We acknowledge receipt of your amendments dated June 9, July 10 and 15, August 7 and 24, September 15, 21, 22, 25 and 30, and October 12, 16, and 28, 2009. We also acknowledge your submission dated November 20, 2009, containing your proposed REMS modification, your submission dated December 23, 2009, containing your proposed REMS modification amendment, and your submission dated December 28, 2009, containing your REMS Assessment.

Your request to supplement your biologics license application for Stelara™ (ustekinumab) to include a pre-filled syringe, 45 mg/0.5 mL and 90 mg/1mL formulation is approved.

Under this license, you are approved to manufacture Stelara™ (ustekinumab) drug substance at Centocor Biologics, LLC in St. Louis, Missouri. The final formulated pre-filled syringe product will be manufactured and filled at Baxter Pharmaceutical Solutions, Bloomington, Indiana. Assembly of the pre-filled syringe with the (b) (4) Delivery System, and labeling and packaging will be performed at Cilag AG, Schaffhausen, Switzerland.

The dating period for Stelara™ (ustekinumab) pre-filled syringe drug product presentation shall be 18 months from the date of manufacture when stored at 2 – 8 °C. The date of manufacture shall be defined as the date of (b) (4) of the formulated drug product. The dating period for bulk drug substance shall be 36 months when stored at -40 °C. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of the drug substance under 21 CFR 601.12. Due to failures in the pre-filled syringe drug product stability observed at 24 months, extension of the drug product expiration dating period will require submission of a Prior Approval Supplement per 21 CFR 601.12 (b).

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The risk evaluation and mitigation strategy (REMS) for Stelara™ (ustekinumab) was originally approved on September 25, 2009, and consists of a Medication Guide, a communication plan, and a timetable for submission of assessments. A modification to the approved REMS was required because of revisions to the Medication Guide. On December 28, 2009 you submitted an amendment to your modified REMS that included a statement that the revised Medication Guide with the proposed modifications would be adequate to achieve its purpose.

The modifications to the Medication Guide include the addition of your contact information to report adverse events, the addition of an inactive ingredient, removal of the website www.STELARAinfo.com, modification of the manufacturing information, and modification of the revision date of the Medication Guide. The timetable for submission of assessments remains unchanged from the timetable in the approval letter of September 25, 2009.

The proposed modified REMS contains the same Medication Guide, communication plan, and timetable for submission of assessments as the original REMS, with the exception of the modifications to the Medication Guide.

Your proposed modified REMS amendment, submitted on December 23, 2009, and appended to this letter, is approved.

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

1. Evaluations of dermatologists/healthcare providers' understanding and patients' understanding of the risks of Stelara™ (ustekinumab), including evaluations of the following:

    a. Prescribers' understanding of the risks of Stelara™ (ustekinumab), including the risks of serious infection, RPLS, and malignancy and how to select patients who are appropriate for treatment.

    b. Patients' understanding of the risks of Stelara™ (ustekinumab), including the risks of serious infection, RPLS, and malignancy.

2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

3. A report on failures to adhere to Medication Guide distribution and dispensing requirements, and corrective actions taken to address noncompliance.

4. A summary of all reported serious infections, RPLS, and malignancies with analysis of adverse event reporting by prescriber type (e.g., dermatologist, nurse, internist, oncologist), when available.

5. Based on the information submitted, an assessment 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), information on the status of any postapproval 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 to the REMS with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125261 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125261
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR BLA 125261
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

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.

We are deferring submission of your pediatric protocol until December 1, 2022, because pediatric studies should be delayed until additional adult safety and efficacy data have been collected. Pediatric studies are deferred pending analyses of a) safety data from adults in PHOENIX 1 (C0743T08), PHOENIX 2 (C0743T09), the PSOLAR registry, and the Nordic Database Initiative and b) safety data in pediatric subjects exposed to Stelara™ (ustekinumab) *in utero* or postnatally. These safety analyses must establish that there are no safety issues that

would preclude study of pediatric subjects. Pediatric studies should not be undertaken until there is agreement with the Agency on the design of such studies.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below:

1. Conduct studies to evaluate the safety and efficacy of ustekinumab in pediatric subjects with plaque psoriasis.

   Pediatric Protocol Submission Date: December 1, 2022

We request that you submit clinical protocols to your IND, with a cross-reference letter to this BLA, STN BL 125261. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessment**."

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR 601.70

We acknowledge your written commitments as described in your letter dated December 7, 2009 as outlined below:

2. Collect trend and review data from release and stability testing annually. Appropriate modifications will be made and reported in an annual trending report provided in the annual report. In addition, data will be evaluated statistically after 3 years or after 30 commercial batches. Appropriate modifications will be made and provided in a 3 year/30 batch review.

   Final Report Submission: Annual Report 2012

3. Establish quantitative drug product release and stability specifications for the non-reduced SDS-PAGE assay when sufficient commercial experience with the assay has been gained. Data and specification assessments will be provided as a Changes Being Effected-30 (CBE-30) supplement.

   Final Report Submission: December 31, 2011

4. Place the first commercial 45 mg and 90 mg (b) (4) pre-filled syringe drug product lots produced into the non-annual commercial drug product stability program. Real time stability data and results from accelerated stability studies will be submitted in annual reports.

   Final Report Submission
   for accelerated stability studies: Annual Report 2011

   Final Report Submission
   for real time stability studies: Annual Report 2013

5. Conduct a study to identify the composition of the peak with a (b) (4)-HPLC relative retention time of (b) (4) observed in placebo syringes stored at 25°C in the pre-filled syringe container/closure leachable studies, and provide a risk assessment on the impact this leachate may have on product quality.

   Final Report Submission: Annual Report 2010

6. Conduct a study to characterize the (b) (4) that appears by IEF under accelerated storage conditions and in photostability studies. Until this (b) (4) has been characterized in regard to product quality, and the cIEF assay has been demonstrated to be as sensitive a stability indicating assay as the IEF assay, the IEF will be included in the annual and non-annual stability program as a stability specification.

   Final Report Submission: Annual Report 2010

7. Conduct an investigation to understand the increased rate of formation of translucent visible particles in the pre-filled syringe validation batches stored under recommended storage conditions compared to clinical pre-filled syringe batches 903393, 903394, and 905162.

   Final Report Submission: Annual Report 2010

8. Provide the sensitivity of the dye ingress study for the Stelara syringe in (b) (4) at Cilag. Information and data should be provided in a Prior Approval Supplement.

   Final Report Submission: 1st Quarter 2011

9. Validate the in-process hold time by one additional batch at scale. Bioburden and endotoxin validation data should be provided in a CBE-0 supplement at the end of the study.

   Final Report Submission: June 2010

We request that you submit clinical protocols to your IND, with a cross-reference letter to this BLA, STN BL 125261. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this BLA. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing commitments as appropriate:

- **POSTMARKETING COMMITMENT PROTOCOL**
- **POSTMARKETING COMMITMENT – FINAL STUDY REPORT**
- **POSTMARKETING COMMITMENT CORRESPONDENCE**
- **ANNUAL STATUS REPORT OF POSTMARKETING STUDY COMMITMENTS**

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 February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cder/guidances/5569fnl.htm**)** for further information.

ADVERSE EVENT REPORTING

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). In addition, submit any adverse event reports related to malignancy, serious infections (including opportunistic infections and tuberculosis) and serious neurologic events as 15-day reports. 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 http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.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 Food and Drug Administration, Center for Drug Evaluation and Research, Division of Compliance Risk Management and Surveillance, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Biological product deviations sent by courier or overnight mail should be addressed to Food and

Drug Administration, Center for Drug Evaluation and Research, Office of Compliance, Division of Compliance Risk Management and Surveillance, 10903 New Hampshire Avenue, Bldg. 51, Room 4206, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the enclosed labeling (text for the package insert and Medication Guide). For administrative purposes, please designate this submission **"Product Correspondence – Final SPL for approved STN BL 125261/1**." In addition, within 21 days of the date of this letter, amend your pending supplements for the Pre-Filled Syringe (STN BL 125261/1) with content of labeling in SPL format to include the changes approved in this supplement.

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 BL 125261/1**." 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 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 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
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, at the time of initial dissemination or publication, accompanied by a Form FDA 2253 directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division

of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm09142.htm.

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.

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

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

/Susan J. Walker, M.D., F.A.A.D./December 30, 2009
Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures: Package Insert, Medication Guide, Carton and Container Labels, REMS (including Communication Plan)