DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125261/0

BLA APPROVAL
September 25, 2009

Centocor Ortho Biotech, Inc.
Attention: Kim Shields-Tuttle
Senior Director, Global Regulatory Affairs, Immunology
200 Great Valley Parkway
Malvern, PA 19355

Dear Ms. Shields-Tuttle:

Please refer to your biologics license application, dated November 28, 2007, received November 29, 2007, submitted under section 351 of the Public Health Service Act for Stelara™ (ustekinumab).

We acknowledge receipt of your submissions dated November 7 and 21 and December 8, 12, 16, and 18, 2008; January 9, March 5, 23, and 27, April 1, 10, and 27, May 1 and 13, June 25 and 26, July 24, August 5, 11, 12, 14, 17, 21 and 27, and September 11 and 23, 2009.

The January 9, 2009 submission constituted a complete response to our December 18, 2008 action letter.

We have approved your biologics license application for Stelara™ (ustekinumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Stelara™ (ustekinumab) under your existing Department of Health and Human Services U.S. License No. 1821. Stelara™ (ustekinumab) is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Under this license, you are approved to manufacture Stelara™ (ustekinumab) drug substance at Centocor Biologics, LLC in St. Louis, Missouri. The final formulated product will be manufactured, filled, labeled, and packaged at Cilag AG, Schaffhausen, Switzerland. You may label your product with the proprietary name Stelara™ and will market it in 45 mg/0.5 mL and 90 mg/1 mL vials.

Stelara™ (ustekinumab) Pre-Filled Syringe, 45 mg/0.5 mL and 90 mg/1 mL is not approved and review will continue under STN BL 125261/1.

The dating period for Stelara™ (ustekinumab) drug product shall be 12 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 your drug product and drug substance under 21 CFR 601.12.

You currently are not required to submit samples of future lots of Stelara™ (ustekinumab) 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.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of ustekinumab, or in the manufacturing facilities.

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 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 (discussed in items 2, 3, 8, and 9) and b) safety data in pediatric subjects exposed to Stelara™ (ustekinumab) *in utero* or postnatally (described in Items 4, 5, and 6). 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

Submit final study reports to this BLA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessment**."

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) 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 (section 505(o)(3)(A)).

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 infection; or to identify unexpected serious risks of malignancy, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic events, adverse pregnancy and fetal outcomes, adverse effects on immune system development, or altered metabolism of co-administered drugs.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following studies:

2. Enroll 4,000 Stelara™ (ustekinumab)-treated subjects into the Psoriasis Longitudinal Assessment and Registry, (PSOLAR) and follow for 8 years from the time of enrollment. Subjects will be followed for the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events,

   Submit this information according to the following timetable:

Final Protocol Submission:	January 15, 2010
Annual Reports:	2011, 2012, 2013, 2014
Interim Summary Report:	2015
Annual Reports:	2016, 2017, 2018, 2019
Study Completion Date:	December 1, 2019
Final Report Submission:	December 1, 2020

3. Provide data analyses from the Nordic Database Initiative regarding the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events with exposure to ustekinumab.

   Submit this information according to the following timetable:

Final Protocol Submission:	January 15, 2010
Annual Reports:	2011, 2012, 2013, 2014
Interim Summary Report:	2015
Annual Reports:	2016, 2017, 2018, 2019
Study Completion Date:	December 15, 2019
Final Report Submission:	December 15, 2020

4. Establish a U.S.-based prospective, observational pregnancy exposure registry that compares the pregnancy and fetal outcomes of women exposed to Stelara™ (ustekinumab) during pregnancy to an unexposed control population. Outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life.

   Submit this information according to the following timetable:

Final Protocol Submission:	January 15, 2010
Annual Reports:	2011, 2012, 2013
Study Completion Date:	July 15, 2013
Final Report Submission:	July 15, 2014

5. Provide data analyses from the Pregnancy Research Initiative (study C0168T71).

   Submit this information according to the following timetable:

Final Protocol Submission:	January 15, 2010
Annual Reports:	2011, 2012, 2013, 2014
Interim Summary Report:	2015
Annual Reports:	2016, 2017, 2018, 2019, 2020
Study Completion Date:	December 15, 2020
Final Report Submission:	December 15, 2021

6. Conduct a lactation study in women who are breastfeeding while exposed to Stelara™ (ustekinumab). This study may be conducted in a subset of women enrolled in the U.S.-based pregnancy registry (discussed in PMR # 4) who choose to breastfeed their infants, and should assess for the presence of Stelara™ (ustekinumab) in breast milk and potential adverse effects in nursing infants.

   Submit this information according to the following timetable:

Final Protocol Submission:	January 15, 2010
Annual Reports:	2011, 2012, 2013
Study Completion Date:	July 15, 2013
Final Report Submission:	July 15, 2014

7. Conduct an *in vitro* study to assess whether IL-12 and/or IL-23 modulate expression of major CYP enzymes (i.e., CYP 3A4, CYP 1A2, CYP 2C9, CYP 2C19, and CYP 2D6). If, upon review, there is no marked modulation of any of the major CYP enzyme(s) observed, further exploration would not be necessary.

   The timetable you submitted on August 17, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	February 2010
Study Completion Date:	July 2010
Final Report Submission:	December 2010

Finally, we have determined that only clinical trials (rather than an observational study) will be sufficient to assess the known risk of serious infection; or to identify unexpected serious risks of malignancy, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic events, or altered metabolism from co-administered drugs.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trials:

8. Complete the treatment and evaluation of subjects enrolled in the ongoing PHOENIX 1 (C0743T08) trial for a total of 5 years from initial enrollment unless a safety signal is identified that indicates the potential risks of such continued long-term treatment outweigh the benefits. Evaluation of subjects should continue through 5 years (even if treatment is not continued for this duration). Subjects will be followed for the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events.

   The timetable you submitted on August 5, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	September 2005
Trial Completion Date:	May 2011
Final Report Submission:	January 2012

9. Complete the treatment and evaluation of subjects enrolled in the ongoing PHOENIX 2 (C0743T09) trial for a total of 5 years from initial enrollment unless a safety signal is identified that indicates the potential risks of such continued long-term treatment outweigh the benefits. Evaluation of subjects should continue through 5 years (even if treatment is not continued for this duration). Subjects will be followed for the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity

reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events.

The timetable you submitted on August 5, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	December 2005
Trial Completion Date:	October 2011
Final Report Submission:	June 2012

10. If the results of the *in vitro* study (discussed under PMR #7) are positive (i.e., if there is marked modulation of any of the major CYP enzyme(s)) conduct a clinical trial to determine the potential of ustekinumab to alter CYP substrate metabolism in psoriasis patients (e.g., using a cocktail of relevant CYP probe drugs).

    The timetable you submitted on August 17, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	September 2011
Trial Completion Date:	December 2012
Final Report Submission:	September 2013

Submit the protocols to your IND, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Using the following designators to prominently label all submissions, including supplements, relating to these postmarketing study requirements 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR 601.70

We also acknowledge your written commitments as described in your letter dated August 5, 14, and 17, 2009 as outlined below:

11. Provide information on maintenance of response with dosing intervals longer than every 12 weeks among relevant populations (e.g., subjects whose psoriasis is cleared as measured by PGA and PASI or who have minimal psoriasis). This information will be obtained from a study of at least 300 subjects treated with Stelara™ (ustekinumab) for a minimum of one year.

    The study should not be undertaken until there is agreement with the Agency on the design of your study.

Concept Paper Submission:	March 2010
Draft Protocol Submission:	September 2010
Final Protocol Submission:	December 2010
Final Report Submission:	6 months after completion of study

12. Evaluate approaches to improve drug tolerance in the assay method for anti-drug antibodies (ADA). If a suitable method is developed, it will be applied to assess ADA in patient samples banked from the pivotal trials, if available, and on-going clinical trials. Alternatively, documentation will be submitted to the FDA demonstrating, with due diligence, that such an assay could not be feasibly developed.

Final Report Submission:	December 31, 2012

13. Establish quantitative drug product release and stability specifications for the non-reduced cSDS assay when sufficient commercial experience with the assay has been gained. A proposed specification including justification based on supporting data will be submitted as a prior approval supplement.

Final Report Submission:	September 2011

14. Collect drug product release and stability data to reassess and lower the allowable number of sub-visible particles. A proposed specification including justification based on supporting data will be submitted as a CBE-0 supplement.

Final Report Submission:	September 2010

15. Reassess release and shelf-life specifications for the ustekinumab drug substance and drug product within 2 years from the date of this letter and submit in an annual report.

Final Report Submission: Annual Report 2011

16. Conduct end-of-life concurrent validation of (b) (4) (b) (4) resins at the manufacturing scale. The studies will include an assessment of yield, chromatographic profile, and impurities where appropriate. Data will be submitted as a CBE-0 supplement.

    Final Report Submission: September 2011

17. Perform reduced scale end-of-life viral removal studies for the (b) (4) resin. Study conditions will adequately reflect the manufacturing scale process.

    Final Report Submission: September 2010

18. Revise the (b) (4) SDS-PAGE and IEF stability specifications upon review of available stability data. The proposed specifications, including justification based on supporting data, will be submitted as a CBE-0 supplement.

    Final Report Submission: September 2010

19. Develop and validate the Microflow Digital Imaging assay and incorporate this assay into the annual stability testing program with appropriately justified specifications. Alternately, documentation can be submitted to FDA demonstrating with due diligence that this assay could not be feasibly developed.

    Final Report Submission: September 2011

20. Perform both IEF and cIEF in parallel for future batches as part of the commercial stability program until sufficient data demonstrate that the cIEF is as stability indicating as the IEF. Data will be submitted as a CBE-30 supplement.

    Final Report Submission: September 2011

21. Perform an extensive qualification study for multi-use of the glass syringes which are used for (b) (4) of vials for the visible particle assay to ensure continued effectiveness of the cleaning procedure. Data will be provided within one year of the date of this letter in an annual report.

    Final Report Submission: Annual Report 2010

22. Continue the root cause investigation to identify the causative factor(s) that led to increased visible particle counts on stability for the clinical and validation drug product batches. The final report will be provided within one year of the date of this letter in an annual report.

Final Report Submission: Annual Report 2010

23. Develop and implement a bioburden test method that uses an increased sample volume for the determination of bioburden in the pre-harvest ((b) (4) (b) (4) and harvest samples. The acceptance criteria for bioburden in-process controls should be consistent with historical data and reported as CFU/volume tested.

    The revised test method and acceptance criteria including justification based on supporting data will be submitted as a prior approval supplement.

    Final Report Submission: September 2011

We request that you submit clinical protocols to your IND, with a cross-reference letter to this BLA. 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.accessdata.fda.gov/scripts/cder/pmc/index.cfm). 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/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077374.pdf**)** for further information.

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)).

Your proposed REMS, submitted on September 23, 2009, and amended 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:

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 314.81(b)(2)(vii) [or 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 the submission containing the REMS assessments or proposed modifications 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.

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/oc/datacouncil/spl.html, 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 125261/0**." 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 BLA.

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 125261/0**." 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 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
Division of Drug Marketing, Advertising, and Communications

5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), 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 Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

If you have any questions, call the Regulatory Project Manager, Sue Kang, at 301-796-4216.

Sincerely,

/John Jenkins, M.D./ September 25, 2009
John Jenkins, M.D. on behalf of Julie Beitz, M.D.
Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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