DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125057/232

SUPPLEMENT APPROVAL

Abbott Laboratories
Attention: Bonnie Kain
Associate Director, Regulatory Affairs – PPG
200 Abbott Park Road
Abbott Park, IL 60064

Dear Ms. Kain:

Please refer to your Supplemental Biologics License Application (sBLA), dated January 25, 2011, and received March 30, 2012, submitted under section 351 of the Public Health Service Act for Humira (adalimumab).

We acknowledge receipt of your amendments dated March 25, 2011, April 28, 2011, May 24, 2011, May 27, 2011, June 06, 2011, July 25, 2011, July 27, 2011, September 21, 2011, September 29, 2011, October 07, 2011, October 12, 2011, March 30, 2012, July 23, 2012, July 27, 2012, August 01, 2012, August 15, 2012, August 22, 2012, September 17, 2012, September 18, 2012, and September 26, 2012.

The March 30, 2012, submission constituted a complete response to our November 21, 2011, action letter.

This Prior Approval supplemental biologics application proposes the addition of a new indication for Humira (adalimumab) for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine.

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, text for the patient 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. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125057/232.**"

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications 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.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your March 25, 2011, submission containing final printed carton and container labels.

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.

Because an orphan designation was granted for your pediatric indication, you are exempt from this requirement.

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.

Since Humira (adalimumab) was approved on December 31, 2002, we have become aware of additional cases of Hepatosplenic T-cell Lymphoma (HSTCL), a rare form of malignancy, in patients with inflammatory bowel disease (IBD) receiving Humira (adalimumab). In addition, there are literature reports of an increased risk of serious adverse events in patients receiving

higher doses of Humira (adalimumab), including opportunistic infections and malignancies.[1] 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 serious risks of HSTCL and other serious adverse events in patients receiving higher doses of adalimumab, including opportunistic infections and malignancies.

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 these serious risks.

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

PMR #1 A study in inflammatory bowel disease (IBD) patients treated with Humira (adalimumab) in which you will bank tissue or blood samples (as appropriate) and then analyze them to identify genetic mutations and other biomarkers that predispose these patients to developing Hepatosplenic T-Cell Lymphoma (HSTCL).

The timetable you submitted on September 26, 2012 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Study Completion:	09/2019
Final Report Submission:	09/2020

PMR #2: A multi-center observational study of Humira (adalimumab) in adults with moderately to severely active ulcerative colitis treated in a routine clinical setting, to assess the long-term safety as measured by the incidence of opportunistic infections and malignancies. Long-term effectiveness should be assessed as a secondary goal. The proposed study should follow patients for a period of at least 10 years from time of enrollment in order to ascertain adverse events with longer latency periods such as malignancies. The primary analysis is to summarize safety data for patients on adalimumab and patients on non-biologic immunomodulator therapy. The study should be adequately sized to sufficiently detect a doubling of the risk of lymphoma events in each treatment group. A secondary analysis is to summarize safety data for patients on adalimumab and patients on the combination of adalimumab and non-biologic immunomodulator therapy. In addition, the study is to document and evaluate effects of withdrawal and re-

[1] Bongartz T, et.al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006 May 17;295(19):2275-85.

treatment with adalimumab and "switching" with other tumor necrosis factor (TNF)-blockers or biologics.

The timetable you submitted on September 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2013
Study Completion:	12/2027
Final Report Submission:	12/2029

PMR #3 Develop, qualify, and implement improved validated anti-adalimumab antibody (AAA) assays with reduced sensitivity to product interference. Until assays have been developed and validated, patient blood samples collected from clinical studies and trials should be banked under appropriate storage conditions. You will provide assay SOPs, validation protocols, and validation final reports that include data demonstrating that the assay is specific, sensitive and reproducible, and capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling.

The timetable you submitted on September 26, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission:	12/2013

PMR #4 Utilizing a validated AAA assay as described in PMR #3 above, you should measure and analyze the immunogenicity profile based on post-dose patient samples from completed study M10-223, the trial conducted under PMR #5, the trial conducted under PMR #6, and the trial conducted under PMC #7.

The timetable you submitted on September 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Study Completion:	03/2018
Final Report Submission:	03/2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known risk of serious adverse events, including opportunistic infections and malignancies, in patients receiving higher doses of adalimumab.

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

PMR #5 Conduct a trial in moderately to severely active ulcerative colitis patients to evaluate the safety of induction regimens of adalimumab at doses higher than 160/80 mg. In this trial, the efficacy of Humira (adalimumab) should also be assessed, both during induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. In this trial, collecting samples for immunogenicity testing (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) and conducting analyses of the impact of immunogenicity on safety, pharmacokinetics, and efficacy is important. The protocol should be agreed upon by the agency prior to the initiation of the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	03/2018
Final Report Submission:	03/2019

PMR #6 A safety and pharmacokinetic trial as a sub-study of the trial described in PMR #5 above to evaluate trough concentrations of adalimumab and antibody levels (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) at the time of loss of clinical remission in patients whose physicians plan to escalate the dose (e.g., decrease the dosing interval to weekly or increase the dosage) in response to loss of remission. Trough concentrations will be evaluated to determine whether patients who have low adalimumab exposures benefit from dose escalation without increasing risk of serious adverse events. The protocol should be agreed upon by the agency prior to initiation of the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	03/2018
Final Report Submission:	03/2019

Submit the protocols to your IND 100103 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission 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 314.81(b)(2)(vii) 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 314.81(b)(2)(vii) 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 314.81(b)(2)(vii). 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 UNDER SECTION 506B

We remind you of your postmarketing commitment:

PMC #7 Conduct a one-year, multi-center, randomized, double-blind placebo-controlled trial to evaluate the efficacy, safety and pharmacokinetics of adalimumab in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis. In this trial, the efficacy of adalimumab should be assessed during induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. Also, collect samples for immunogenicity testing (utilizing a validated AAA assay as described in PMR #3 above) and conduct analyses of the impact of immunogenicity on pharmacokinetics, efficacy and safety. The protocol should be agreed upon by the agency prior to the initiation of the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	06/2013
Trial Completion:	06/2018
Final Report Submission:	12/2019

Submit clinical protocols to your IND 100103 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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 Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., F.A.A.P., C.P.I.
Deputy Division Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

ANDREW E MULBERG

09/28/2012

Division Deputy Director
DGIEP
Signatory Authority