DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103772/5301

SUPPLEMENT BLA APPROVAL
September 23, 2011

Janssen Biotech Inc.
Attention: Barbara Rake
Director, Global Regulatory Affairs, Immunology
200 Great Valley Parkway
Malvern, PA 19355

Dear Ms. Rake:

Please refer to your Supplemental Biologics License Application (sBLA) submitted on December 23, 2010, under Section 351 of the Public Health Service Act, for Remicade (infliximab).

We acknowledge receipt of your amendments dated February 15, 2011, March 18, 2011, April 01, 2011, April 06, 2011, April 15, 2011, April 29, 2011, May 04, 2011, May 24, 2011, May 26, 2011, June 30, 2011, July 18, 2011, July 26, 2011, August 04, 2011, August 15, 2011, August 26, 2011, September 08, 2011, September 15, 2011, September 21, September 22, 2011 and September 23, 2011.

This "Prior Approval" efficacy supplement to your biologics license application proposes to add pediatric ulcerative colitis to the current indications.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

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 103772/5301.**

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.

The SPL will be accessible via publicly available labeling repositories.

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 this drug product for this indication has an orphan drug designation, 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 Remicade (infliximab) was approved on August 24, 1998, we have become aware of additional cases of Hepatosplenic T-cell Lymphoma (HSTCL) in inflammatory bowel disease (IBD) patients receiving infliximab. In addition, there are literature reports of an increased risk of serious adverse events in patients receiving higher doses of infliximab.[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 risk of HSTCL and the increased risk of serious adverse events in patients receiving higher doses of infliximab, such as opportunistic infections and congestive heart failure.

[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.

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 to bank samples for future evaluation to identify genetic mutations and other biomarkers that predispose inflammatory bowel disease (IBD) patients to developing Hepatosplenic T-Cell Lymphoma (HSTCL).

The timetable you submitted on September 21, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2012
Study Completion:	06/2018
Final Report Submission:	06/2019

PMR 2: Expand the Pediatric IBD Registry (DEVELOP) to include pediatric patients with ulcerative colitis (UC) and indeterminate colitis (IC).

The timetable you submitted on September 21, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2012
Study Completion:	12/2044
Final Report Submission:	12/2045

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 in patients receiving higher doses of infliximab.

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

PMR 3: A safety and pharmacokinetic trial as a substudy of the DEVELOP registry to evaluate whether trough concentrations at the time of loss of clinical response can be used to identify pediatric UC and Crohn's disease patients who have low infliximab exposures and would benefit from a dose increase above that approved without increasing risk of serious adverse events.

The timetable you submitted on September 21, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2012
Trial Completion:	06/2017
Final Report Submission:	06/2018

Submit the protocols to your IND 005389 with a cross-reference letter to this BLA. Submit all final reports to your BLA. 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 601.70, require 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 UNDER SECTION 506B

We remind you of your postmarketing commitment:

PMC 4: A survey of providers and patients during initial use of Remicade for UC that will evaluate whether the risks of Hepatosplenic T-cell Lymphoma are being adequately communicated to and understood by the patients and/or their caregivers.

The timetable you submitted on September 22, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2012
Study Completion:	09/2012
Final Report Submission:	12/2012

PMC 5: A study to develop, qualify, and implement an improved ADA assay format with reduced sensitivity to product interference.

The timetable you submitted on September 21, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2013

PMC 6: A study to reanalyze available samples from trial C0168T72 that have been banked frozen at -70°C to determine the presence of ADA using the new assay developed in PMC 5.

The timetable you submitted on September 21, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2013

PMC 7: A study to analyze samples from the Pediatric IBD registry (DEVELOP) and PMR 3 to determine the presence of ADA using the new assay developed in PMC 5.

The timetable you submitted on September 21, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2045

Submit clinical protocols to your IND 005389 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
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(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 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,

/Donna Griebel/
Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling