DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Our STN: BLA 103795/5391
BLA 103795/5397
BLA 103795/5400

SUPPLEMENTAL APPROVAL
June 3, 2010

Immunex Corporation
A wholly-owned subsidiary of Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Attention: Carol Waldo, MPH, RAC
Director, Regulatory Affairs

Dear Ms. Waldo:

Please refer to your supplemental biologics license applications (BLA) dated October 31, 2008 (5391), December 22, 2008 (5397), and February 6, 2009 (5400), received November 3, 2008, December 22, 2008, and February 9, 2009, submitted under section 351 of the Public Health Service Act for Enbrel (etanercept).

We acknowledge receipt of your amendments dated January 21, June 12 and 26, September 4, 16 and 25, and December 1, 2009, and February 10, April 6 and 8, 2010, and May 20, 2010 for BLA 103795/5391, your amendments dated March 20, April 29, September 15, October 15, and December, 9, 2009, and January 26, February 5, March 11, and April 8, 2010 for BLA 103795/5397, your amendments dated April 27, June 17, and December 4, 2009 for BLA 103795/5400.

We also acknowledge receipt of your submission dated February 10, 2010 which contained the proposed survey methodology for conducting an assessment of patients' understanding of the serious risks presented in the Enbrel Medication Guide. We have reviewed your proposed methodology and find it acceptable.

We also refer to our September 4, 2008, letter notifying you that, under Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA), modifications to your approved REMS were necessary to ensure the benefits of Enbrel (etanercept) outweighed the risks of histoplasmosis and other serious invasive fungal infections. In addition, we refer to the email correspondence between FDA and Amgen dated June 2, 2010, in which agreement was reached on the content of the REMS document.

Your supplemental biologics license application (103795/5391) provides for a proposed modification to the approved REMS for Enbrel (etanercept).

Your supplemental biologics license application (103795/5397) provides for the conversion of your package insert to the Physicians Labeling Rule (PLR) format and the addition of hypoglycemia in the Use in Specific Populations section of the label.

Your supplemental biologics license application (103795/5400) provides for the addition of uveitis and macrophage activation syndrome to the ADVERSE REACTIONS section of the package insert.

We have completed our review of these applications, as amended, and they are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] 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 and Medication Guide.). 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/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from 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 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Enbrel (etanercept) was originally approved on June 23, 2008 (103795/5359). The REMS consisted of a Medication Guide and a timetable for submission of assessments of the REMS. Your proposed modified REMS contains a revised Medication Guide and a new communication plan to inform patients and healthcare providers, respectively, of the risks of histoplasmosis and other serious invasive fungal infections with use of Enbrel (etanercept), and a timetable for submission of assessments of the REMS.

Your proposed modified REMS, submitted on May 20, 2010, amended as agreed upon in the June 2, 2010 email correspondence, and appended to this letter, is approved. The REMS consists

of a Medication Guide, a communication plan, and a timetable for submission of assessments. The timetable for submission of assessments of the REMS is revised to include one additional REMS assessment at 28 months.

In addition to the items described in our letter dated June 23, 2008, the REMS assessment plan should also include, but is not limited to, the following:

a. An evaluation of patients' and providers' understanding (i.e., surveys) of the serious risks of Enbrel (etanercept).
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)(B) and (C) include requirements for 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 the submission containing the 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 103795 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 103795
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 103795
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information 21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the following address or by facsimile at 301-847-8444:

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

In addition, as required under 21 CFR 601.12(f)(4), you must submit your updated final promotional materials, and the package insert(s), 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/ucm090142.htm.

LETTER TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this BLA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

If you have any questions, please contact Ladan Jafari, Safety Regulatory Health Project Manager at (301) 796-1231 and Jessica Benjamin, Regulatory Project Manager at (301) 796-3924 in the Division of Pulmonary, Allergy and Rheumatology Products.

Sincerely,

//Larissa Latpeva, M.D., M.H.S.//

Larissa Lapteva, M.D., M.H.S.
Deputy Director for Safety
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Content of Labeling
Medication Guide
REMS
REMS materials