DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125288/0

BLA APPROVAL
June 15, 2011

Bristol-Myers Squibb Company
Attention: Mary Christian, PharmD
Group Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Christian:

Please refer to your Biologics License Application (BLA) dated June 30, 2009, received July 1, 2009, submitted under section 351 of the Public Health Service Act for Nulojix (belatacept) for injection.

We acknowledge receipt of your amendments dated:

May 18, 2010	December 8, 2010	March 18. 2011
June 30, 2010	December 13, 2010	March 21, 2011
July 12, 2010 (2)	December 15, 2010	March 25, 2011
August 13, 2010	December 20, 2010	March 30, 2011
August 16, 2010	January 20, 2011	April 4, 2011
September 9, 2010	January 28, 2011	April 6, 2011
September 24, 2010	February 2, 2011	April 8, 2011
September 27, 2010	February 15, 2011	April 13, 2011
October 21, 2010	February 25, 2011	June 1, 2011
November 3, 2010	March 7, 2011	June 3, 2011
November 24, 2010	March 9, 2011	June 15, 2011
November 30, 2010	March 14, 2011	
December 3, 2010	March 15, 2011	

The December 15, 2010, submission constituted a complete response to our May 1, 2010, action letter.

We have approved your BLA for Nulojix (belatacept) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, belatacept under your existing Department of Health and Human Services U.S. License No. 1713. Belatacept is indicated for the prophylaxis of organ rejection in adult patients receiving kidney transplants.

Under this license, you are approved to manufacture belatacept drug substance at Bristol-Myers Squibb Company in East Syracuse, New York. The final formulated product will be

manufactured, [redacted] in Manati, Puerto Rico. You may label your product with the proprietary name Nulojix and will market it in 250 mg per vial.

The dating period for Nulojix (belatacept) shall be 30 months from the date of manufacture when store at 2-8°C and protected from light. The date of manufacture shall be defined as [redacted] the formulated drug product. The dating period for drug substance shall be [redacted]. The stability protocol in your license application are considered approved for the purpose of extending the expiration dating periods of your drug substance and drug product as specified in 21 CFR 601.12.

You currently are not required to submit samples of future lots of belatacept 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.

Any changes in the manufacturing, testing, packaging, or labeling of belatacept, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

We are approving this application 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 [21 601.14(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). 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 125288**."

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container 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 (June 2008)". 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 BLA STN 125288**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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.

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.

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 a known serious risk of post-transplant lymphoproliferative disorder (PTLD), predominantly in the central nervous system (CNS), and progressive multifocal leukoencephalopathy (PML) associated with Nulojix (belatacept) and identify any unexpected serious risk during the manufacturing process of Nulojix (belatacept) associated (b) (4)

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:

CLINICAL

1. Conduct a prospective, observational study utilizing data from the United Network for Organ Sharing (UNOS) on the pattern of belatacept use in US adult kidney-only transplant recipients at transplant and one year post-transplant. Specifically, the study will assess the prevalence of belatacept use and the characteristics of belatacept users, as related to the risk of PTLD, including Epstein-BarrVirus (EBV) and cytomegalovirus (CMV) serostatus. In

addition, the study will collect information on adult kidney-only transplant recipients who switch to or from belatacept within one year post-transplant. (Protocol Number IM103074)

The timetable you submitted on June 3, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2012
Study Completion:	04/2019
Final Report Submission:	04/2020

2. Conduct a prospective observational study utilizing data from the United Network for Organ Sharing (UNOS) on the incidence rates of post-transplant lymphoproliferative disorder (PTLD) in US adult kidney-only transplant recipients who are treated with belatacept compared to recipients treated with calcineurin inhibitor (CNI)-based regimens. Recipient characteristics will be collected, including EBV and CMV serostatus, location of the PTLD, and outcome (survival or mortality). Incidence rates of PTLD in belatacept-exposed patients will be quantified beginning when 500 belatacept-exposed patients have at least 1 year of follow-up. Relative risks of PTLD for belatacept compared to CNI-based regimens will be estimated after 1,000 person years have been accumulated in transplant recipients initiated on belatacept at transplantation. (Protocol Number IM103075)

The timetable you submitted on June 3, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2012
Interim Analysis Report:	06/2014
Study Completion:	04/2019
Final Report Submission:	04/2020

3. Conduct a prospective registry of belatacept use in US adult kidney-only transplant recipients to determine the incidence rates of post-transplant lymphoproliferative disorder PTLD, PTLD in the central nervous system (CNS PTLD), and progressive multifocal leukoencephalopathy (PML) in US adult EBV seropositive kidney transplant recipients treated with belatacept in clinical practice. All US adult kidney transplant centers dispensing belatacept will be asked to participate in the study (i.e., if a center does not respond or declines to participate, the reason(s) for nonparticipation will be identified and documented). Recipient characteristics will be collected, including EBV and CMV serostatus, timing of initiation of belatacept in relation to the transplant, location of the PTLD, and outcome (survival or mortality). (Protocol Number IM103076)

The timetable you submitted on June 3, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2012

Study Completion: 04/2019
Final Report Submission: 04/2020

MANUFACTURING

4. Conduct a study to quantify at the end of the proposed [redacted] (b) (4) Provide a worst case risk assessment for those [redacted] (b) (4), including potential toxicity to humans, in your final report.

The timetable you submitted on June 3, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2012

Submit the protocols to your IND 9418, 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 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 NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

5. Conduct a trend analysis of [redacted] (b) (4) profiles based on the results from 30 consecutively released future drug substance batches. Re-evaluate the acceptance criteria for this product attribute and submit a PMC final report. The submission should include the proposed specifications and a justification that includes manufacturing data and data from lots used in the clinical trials.

The timetable you submitted on June 3, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2013

6. Conduct a trend analysis for (b) (4) content using an extended characterization (b) (4) to generate informational data and based on the results from 30 consecutively released future drug substance batches, evaluate the need for introducing a validated release method and setting acceptance criteria for this product attribute, or provide justification for not requiring a (b) (4) content release method.

The timetable you submitted on June 3, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2013

7. Provide a protocol describing the conditions and criteria which will be applied for assessing the stability of any drug substance lot held for the maximum hold time allowed at each (b) (4)

The timetable you submitted on June 3, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2011

8. Provide information and summary data on the product specific dye-ingress container closure, integrity test method and provide an updated post-marketing stability protocol replacing the sterility test with CCIT.

The timetable you submitted on June 3, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2012

9. Perform a study to support multiple freezing-thawing of drug substance (DS) that incorporates conditions reflective of the intended use (multiple freeze-thaws, including shipping). Also, provide DS stability data confirming a cumulative stability limit of greater than 12 months at 2-8°C before and after multiple freeze-thaw cycles. In addition, provide stability data for drug product produced from DS that has undergone multiple freeze-thaw cycles.

The timetable you submitted on June 3, 2011, states that you will conduct this study according to the following schedule:

Interim Report Submission: 12/2011
Final Report Submission: 12/2013

10. Develop characterization methodology for micron and submicron subvisible particulates using stressed and/or accelerated drug product samples to assess whether a correlation may exist between subvisible particulates in the micron and submicron ranges and propose an appropriate control strategy for drug product stored under the approved conditions.

The timetable you submitted on June 3, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2012

Submit clinical protocols to your IND 9418 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**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the 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)]. The details of the REMS requirements were outlined in our complete response letter dated May 1, 2010.

Your proposed REMS, submitted on June 3, 2011, and appended to this letter, is approved. The REMS consists of a Medication Guide, 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. The number of live webinars conducted and their dates.
2. The total number of unique participants at live webinars for the reporting period.
3. The date(s) of distribution of the Dear HCP Letter that occurred during the period
   a. The source(s) of the list of health care provider addresses
   b. The number of recipients at each distribution date

c. The number of returned items
d. A list of the documents included in each distribution

4. Journal information pieces published, including date and journal name, volume, and issue.
5. For each infusion center ordering Nulojix (belatacept) for the first time during the reporting period, the date of initial order, and the date of distribution of tear pads of pre-infusion checklists.
6. A survey of healthcare providers' and patients' understanding of the serious risks of Nulojix (belatacept).
7. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
8. A report on failures to adhere to distribution and dispensing of the Medication Guide, and corrective actions taken to address noncompliance.
9. A summary of all reported cases of PTLD and PML during the preceding reporting period.
10. An analysis of prescribers' compliance with the labeled contraindication regarding the use of Nulojix (belatacept) in EBV negative patients and patients in whom EBV-status is unknown.
11. A plan to monitor sales data to evaluate:
    a. A number of patients treated, reported by transplant organ received
    b. Number of units shipped, reported by year and type of healthcare setting (e.g., transplant center, infusion center, hospital)
12. Assessments of an approved REMS must also include, under 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. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. 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 material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the list above, the initial assessment should also include the following:

1. Launch date of Nulojix
2. The date the links to the full prescribing information, medication guide, and all approved REMS materials became available on the Nulojix REMS landing page.
3. Number of transplant centers visited within 90 days of launch and within 150 days of launch, and percentage of transplant volume covered by each transplant center visited.
4. The date(s) of distribution of the Dear Infusion Specialist Letter

a. The source(s) of the list of infusion specialists
b. The number of recipients
c. The number of returned items
d. A list of the documents included in the mailing

Assessments of the REMS are required annually from the date of the initial approval of the REMS for the first 5 years and again 7 years from the initial date of approval of the REMS. The first assessment should contain all of the above information with the exception of the evaluations of patients' and prescribers' understanding of the serious risks of Nulojix (belatacept). These evaluations should be included in each assessment for years 2 through 5 and in the 7 year assessment.

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 the 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 125288 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125288
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125288
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
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:

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
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

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

You must submit final promotional materials, and the package insert, 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.

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.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Ms. June Germain, Senior Regulatory Project Manager, at 301-796-1600.

Sincerely,

/_____/
Edward Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES: Content of Labeling (Package Insert, Medication Guide)
Carton and Container Labeling
REMS