DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125370/0

BLA APPROVAL
March 9, 2011

Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, MD 20850

Attention: Diana J. Daly
Executive Director, Regulatory Affairs

Dear Ms. Daly:

Please refer to your Biologics License Application (BLA) dated June 9, 2010, received June 9, 2010, submitted under section 351 of the Public Health Service Act for Benlysta (belimumab) for injection.

We acknowledge receipt of your amendments dated July 20, August 10 and 27, September 15, 24, 27, and 30, October 6, 13, 19, 25, 26, and 27, November 3, 8, 10, 23, and 30, and December 1, 9, and 21, 2010, and January 28, February 8, 11, 14, 17, 23, and 25, and March 3 and 4, 2011.

We are issuing Department of Health and Human Services U.S. License No. 1820 to Human Genome Sciences, Rockville, Maryland, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce, or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product belimumab. Belimumab is indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

Under this license, you are approved to manufacture belimumab drug substance at Human Genome Sciences, Inc., in Rockville, Maryland. The final formulated product will be manufactured, filled, labeled, and packaged at [redacted] (b) (4) You may label your product with the proprietary name Benlysta and will market it as 120 mg in a 5-mL vial and 400 mg in a 20-mL vial.

Results of ongoing stability studies should be submitted throughout the dating period, as the data become available, including the results of stability studies from the first three production lots.

The dating period for the 120-mg vial of belimumab shall be 36 months from the date of manufacture when stored at 2° to 8°C. The dating period for the 400-mg vial of belimumab shall be 36 months from the date of manufacture when stored at 2° to 8°C. The dating period for drug

substance shall be 36 months when stored at -40° and/or -80°C. Belimumab drug product stability may be extended by inclusion of additional data for pilot lots and commercial lots in the Benlysta annual report.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You are not currently required to submit samples of future lots of belimumab 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 belimumab, 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 and with the minor editorial revision listed below.

- Replace "US License No. 0000" on the carton and container and the "US License No. XXXX" in the package insert and medication guide with "U.S. License No. 1820".

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, except with the revisions listed, 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. For administrative purposes, designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125370**."

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, except with the revisions listed above, 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*. 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 125370**." 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 4 years 11 months because necessary studies are impossible or highly impracticable. This is because too few children have the disease condition to study.

We are deferring submission of your pediatric study for ages 5 to 16 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1. Phase 2, multicenter study to evaluate the safety, efficacy, and pharmacokinetics of belimumab plus background standard therapy in 100 pediatric subjects ages 5 years to 17 years of age with active systemic lupus erythematosus (SLE).

Final Protocol Submission:	August 2011
Study Completion Date:	March 2016
Final Report Submission:	October 2016

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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 identify unexpected serious risks related to immunogenicity and negative pregnancy outcomes related to Benlysta (belimumab).

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

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

2. Develop improved immunogenicity assays that are less sensitive to product interference that are capable of detecting human anti-human antibodies (HAHA) in the presence of belimumab at ranges that would be expected to occur in patients receiving both high and low doses.

   The timetable you submitted on February 11, 2011, states that you will conduct these studies according to the following schedule:

   Final Protocol Submission: March 2012
   Final Report Submission: January 2013

3. Conduct a pregnancy registry to evaluate pregnancy outcomes for women exposed to Benlysta (belimumab) during pregnancy.

   The timetable you submitted on February 23, 2011, states that you will conduct this study according to the following schedule:

   Final Protocol Submission: July 2011
   Study Completion Date: October 2018
   Final Report Submission: April 2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks related to the potential for Benlysta (belimumab) to interfere with host responses to vaccinations, and to assess a signal of serious risks of mortality, infection, and malignancy with Benlysta (belimumab).

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

4. Conduct a randomized clinical trial to evaluate the effects of Benlysta (belimumab) treatment on host response to therapeutic vaccines. B cell-dependent antigens (e.g., pneumococcal polysaccharide vaccine) and T cell-dependent antigens (e.g., tetanus toxoid) will be evaluated.

The timetable you submitted on February 14, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	December 2011
Trial Completion Date:	March 2014
Final Report Submission:	September 2014

5. Conduct a randomized, placebo-controlled clinical trial with Benlysta (belimumab) in 5000 patients with active, autoantibody-positive systemic lupus erythematosus to evaluate Benlysta's long term safety profile including adverse events of special interest (e.g., mortality, malignancy, serious and opportunistic infections and depression/suicidality).

   The timetable you submitted on February 23, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	September 2011
Trial Completion Date:	May 2022
Interim Report Submission:	May 2019 (1 year data) May 2020 (2 year data)
Final Report Submission:	May 2023 (5 year data)

Submit the protocols to your IND 9970, 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 SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

6. Conduct a randomized, controlled clinical trial in patients with lupus nephritis to evaluate the efficacy and safety of Benlysta (belimumab).

   The timetable you submitted on February 23, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2012
Trial Completion:	January 2017
Final Report Submission:	October 2017

7. Conduct a randomized, controlled clinical trial to evaluate the efficacy and safety of Benlysta (belimumab) in African-American patients with SLE.

   The timetable you submitted on November 30, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	November 2011
Trial Completion Date:	July 2017
Final Report Submission:	January 2018

8. Submit a final report for the long-term, open-label, continuation trial LBSL99.

   The timetable you submitted on February 23, 2011, states that you will conduct this trial according to the following schedule:

Trial Completion Date:	May 2016
Final Report Submission:	December 2016

9. Submit a final report for the long-term, open-label, continuation trial C1066.

   The timetable you submitted on February 23, 2011, states that you will conduct this trial according to the following schedule:

Trial Completion Date:	May 2015
Final Report Submission:	December 2015

10. Submit a final report for the long-term, open-label, continuation trial C1074.

    The timetable you submitted on February 23, 2011, states that you will conduct this trial according to the following schedule:

Trial Completion Date:	March 2015
Final Report Submission:	October 2015

Submit clinical protocols to your IND 9970 for this product 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/trials 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**."

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

11. Submit data supporting microbial control for the UF/DF membrane lifetime studies in a CBE-0 supplement by June 2012.

    The timetable you submitted on December 21, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2010
Study Completion Date:	December 2011
Final Report Submission:	June 2012

12. Qualify the capper and validate the integrity of the belimumab drug product container closure in a (b) (4) prepared at minimum and maximum sealing forces. Information and summary validation data of the (b) (4) and the integrity of the belimumab drug product container closure should be submitted in a Changes Being Effected (CBE-0) supplement. Include the preparation of the positive controls and sensitivity (breach size) of the (b) (4)

The timetable you submitted on December 21, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2011
Study Completion Date:	April 2011
Final Report Submission:	June 2011

13. Provide quantitative data to demonstrate (b) (4) The quantitative qualification data should be submitted in a Changes Being Effected (CBE-0) supplement.

    The timetable you submitted on December 21, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2011
Study Completion Date:	April 2011
Final Report Submission:	June 2011

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

We acknowledge receipt of your submissions dated November 23, 2010, and February 23, 2011, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that at this time, a REMS is not necessary for Benlysta (belimumab) to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

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.

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

MEDWATCH-TO-MANUFACTURER PROGRAM

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.

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 instructions 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.

LETTERS 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 and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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 Philantha M. Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

/Curtis J. Rosebraugh, M.D., M.P.H./
Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling