

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125370**

**CHEMISTRY REVIEW(S)**

# SUMMARY BLA125370 Belimumab



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration  
Office of Biotechnology Products / Office of Pharmaceutical Science  
Division of Monoclonal Antibodies

## The Quality Team Leader's Executive Summary

**From:** Marjorie A. Shapiro, Ph.D.  
Division of Monoclonal Antibodies (DMA), OPS, CDER

**Through:** Kathleen A. Clouse, Ph.D., Director, DMA, OPS, CDER

**To:** Sarah Okada, M.D., CDTL, DPARP, ODE II  
Badrul A. Chowdhury, M.D., Director, DPARP, ODE II

**BLA Number:** 125370/0  
**Product:** Benlysta® (belimumab)  
**Sponsor:** Human Genome Sciences

**Date of Review:** November 1, 2010  
**Due Date of CDTL Memo:** November 17, 2010

**I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY**

The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, recommends approval of STN 125730 for Benlysta® (belimumab) manufactured by Human Genome Sciences. The data submitted in this application are adequate to support the conclusion that the manufacture of Benlysta® (belimumab) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated and a consistent product was produced from the multiple production runs presented. We recommend that this product be approved for human use (under conditions specified in the package insert).

**II. APPROVAL LETTER INFORMATION**

The following should be communicated to sponsor in the approval letter:

The dating period for the 120 mg vial of *Benlysta*® (*belimumab*) drug product 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 *Benlysta*® (*belimumab*) drug product shall be 36 months from the date of manufacture when stored at 2° to 8°C. The date of manufacture shall be defined as the date <sup>(b) (4)</sup> of the formulated drug product. The dating period for bulk drug substance shall be 36 months when stored at -40° and/or -80°C. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of drug product and drug substance under 21 CFR 601.12.

**III. POST MARKETING COMMITMENTS AND/OR POST MARKETING REQUIREMENTS**

Post Marketing Requirement: Human Genome Sciences should explore the possibility of improving the screening, confirmatory and neutralizing immunogenicity assays implemented for the phase 3 studies. All assays are sensitive to the presence of various levels of belimumab such that true levels of immunogenicity cannot be assessed. It may be difficult to improve the sensitivity of the assays in the presence of belimumab so the PMR should focus on the feasibility to improve the assays rather than a requirement to improve the assays. If improved assays can be implemented, then the PMR could include an additional time frame to implement the assays.

<sup>(b) (4)</sup>

<sup>(b) (4)</sup> In addition, the draft package insert addresses this concern with the statement "The reported frequency for the group receiving 10 mg/kg may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentrations."

**IV. LIST OF DEFICIENCIES TO BE COMMUNICATED**

None

## V. EXECUTIVE SUMMARY

### A. Description of Benlysta® (belimumab) Drug Product and Drug Substance

Belimumab is a human IgG1, lambda first-in class therapeutic monoclonal antibody specific for B lymphocyte stimulator (BLyS; BAFF) that binds to soluble BLyS with high affinity

(b) (4)

Belimumab was derived from a phage display library generated by amplification of the VH, Vkappa and Vlambda transcripts from B cells pooled from 43 healthy donors and screened for binding to recombinant BLyS. The selected clone was reverse engineered to produce the full length IgG1 heavy chain and full length lambda light chain.

Belimumab has a typical antibody structure, composed of two identical H chains and two identical L chains, with a molecular weight of ~147 kDa. There is a typical heterogeneity at the H-chain N-terminus due to cyclization of glutamine to pyroglutamic acid and at the C-terminus of the H chain due to incomplete cleavage of the C-terminal lysine. This leads to a heterogeneous charge profile which does not impact the activity of belimumab. Belimumab also contains a typical heterogeneous N-linked glycosylation profile in the CH2 domain of the H chain.

(b) (4)

Belimumab drug product is supplied as a sterile, preservative-free lyophilized powder for reconstitution, dilution, and intravenous infusion provided in single-use glass vials with a latex-free rubber stopper and a flip-off seal. Any unused portion of the vial must be discarded.

There are two drug product dosage forms; a 120 mg vial (5 mL) and a 400 mg vial (20 mL).

The batch formula (b) (4) is: 80 g belimumab, 0.16 g citric acid monohydrate, 2.7 g sodium citrate dihydrate, (b) (4) sucrose, 0.4 g polysorbate 80 (b) (4)

Belimumab drug product is reconstituted with sterile Water for Injection (WFI) that is not supplied or packaged with the belimumab drug product.

The belimumab drug product overfill is (b) (4) for the 120 mg and 400 mg vial configurations, respectively. The overfill amount was calculated based on the USP and Ph. Eur. recommended excess volume. The overfill amounts allow for reconstitution volumes of 1.5 and 4.8 mL, which can be accurately measured using 3 and 5 mL syringes with minor graduations, respectively.

Both the 5 mL and 20 mL vials are USP and (b) (4) glass, (b) (4). Stoppers for both vial sizes are 20 mm, (b) (4) gray, (b) (4) rubber, lyophilization stopper; (b) (4). Seals are aluminum, 20 mm, white, flip-off (400 mg/vial) or aluminum, 20 mm, dark gray, flip-off (120 mg/vial).

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Belimumab drug substance is formulated in (b) (4) sodium citrate, (b) (4) sucrose, (b) (4) polysorbate 80, pH 6.5, at a concentration of (b) (4) belimumab/L.

The extinction coefficient specific for belimumab was determined to be (b) (4) AU\*mL\*mg\*cm<sup>-1</sup>.

The proposed action is subject to the categorical exclusion listed in 21 CFR Part 25.31(c). As stated in 21 CFR Part 25.31(c), action on an application for marketing approval of a biologic product is categorically excluded from environmental assessment requirements if the action is for a substance which occurs naturally in the environment, when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Human Genome Sciences does not have knowledge of any extraordinary circumstances that might cause this action to have a significant affect on the quality of the human environment.

### B. Clinical Trial Information

Indication: (b) (4) adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) in combination with standard therapy.

Route of Administration: Intravenous

The recommended dosage regimen is 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Belimumab should be infused over a 1-hour period. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a potentially life threatening infusion reaction

### C. Stability

Expiration dating of Benlysta® drug product is set for 36 months for both 120 and 400 mg vial configurations from the time of production when stored at 2-8°C.

For the 400 mg vial configuration, four pilot scale lots (b) (4) were placed on a formal registration cGMP stability study to establish the commercial expiry. In addition, 5 commercial-scale lots fully representative of commercial manufacturing (b) (4) were also placed on stability. HGS requested a (b) (4) expiration dating period based on supportive data from the pilot lots. Data are available for 60 months (3 lots) and 36 months (1 lot) for the pilot scale lots. The data available from the commercial lots are from 12 (2 lots), 18 (2 lots) and 24 (1 lot) months. While the pilot scale lots may be representative of the commercial lots, there are data for 24 months for only one commercial lot. We feel the combination of the supportive pilot lot data and the real time data from the commercial lots supports an initial expiration dating period of 36 months.

For the 120 mg/vial configuration, three pilot-scale stability lots were placed on a formal registration cGMP stability study to establish the commercial expiry. In addition, 3

## SUMMARY BLA125370 Belimumab

commercial-scale lots fully representative of commercial manufacturing were placed on stability. HGS requested a 36 month expiration dating period based on supportive data from the pilot lots. Data are available from 36 (1 lot) and 48 (2 lots) months for the pilot lots. The data available from the commercial lots are 12 (2 lots) and 24 (1 lot) months. While the pilot scale lots may be representative of the commercial lots, there are data for 24 months for only one commercial lot. We feel the combination of the supportive pilot lot data and the real time data from the commercial lots supports an initial expiration dating period of 36 months.

The belimumab drug product stability protocol will continue to collect data annually from 24 out to 60 months for the 5 commercial lots. Stability is monitored by appearance (b) (4) pH, protein concentration, SDS-PAGE, charge heterogeneity (IE-HPLC), SEC-HPLC, potency (inhibition of binding), reconstitution time, residual moisture, subvisible particulates and sterility. The stability protocol is acceptable and belimumab drug product stability may be extended by inclusion of additional data for pilot lot and commercial lots in the belimumab annual report.

The stability of belimumab during in-use periods was supported by post-reconstitution studies where samples were incubated for 8 hours at 2-8°C (upright and inverted positions).

A study of the compatibility and stability of belimumab with IV bags and infusion sets showed that belimumab is compatible with polyvinylchloride and polyolefin IV bags containing normal saline with tubing for intravenous delivery over an 8 hour storage period at ambient laboratory conditions.

Belimumab is not compatible with 5% dextrose IV diluent solutions. The Package Insert states that belimumab should not be used with dextrose.

The use of an in-line filter or peristaltic pump has no impact on product quality.

In addition, the use of a mechanical reconstitution device was found to be acceptable for the reconstitution of belimumab FDP (b) (4) 500 (b) (4) rpm for (b) (4)

Belimumab is sensitive to light exposure and should be stored protected from light. The belimumab drug product packaging is sufficient to protect the lyophilized drug product from light-induced degradation.

Belimumab drug product does not contain a preservative. Vials are single use.

Expiration dating of belimumab bulk drug substance is set for 36 months from the time of production when stored protected from light at -40°C and -80°C in (b) (4) containers. The primary stability lots were manufactured at HGS Belward Large Scale Manufacturing Facility in Rockville, MD. Storage of bulk drug substance is at either HGS (-40°C) or the contract drug product manufacturer (b) (4) (-80°C). Belimumab bulk drug substance stability has been studied at both temperatures including a combined study at both temperatures.

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The belimumab bulk drug substance stability protocol will continue to collect data for two additional time points at 48 and 60 months. Stability is monitored by appearance, pH, protein concentration, SDS-PAGE, charge heterogeneity (IE-HPLC), SEC-HPLC, potency (inhibition of binding) and bioburden. The stability protocol is acceptable and belimumab bulk drug substance stability may be extended by inclusion of the data in the belimumab annual report.

Degradation pathways for belimumab include aggregation and fragmentation, deamidation, oxidation, and loss of potency.

### D. Complexity

The manufacture of belimumab is a well controlled process. The quality attributes are consistent lot-to-lot. The final release specifications were based on an analysis of 10 commercial lots but lots manufactured since submission of the BLA all conform to the specifications. The specifications for both belimumab drug substance and drug product are justified. HGS narrowed some specifications for the commercial product based on their manufacturing experience. We find no need to require a further tightening of the specifications.

(b) (4)

The physicochemical attributes of belimumab include appearance, pH, osmolality, protein concentration, molecular weight, purity, charge heterogeneity, oxidation, deamidation, (b) (4)

Purity was assessed by several methods including SEC-HPLC (also a release method), analytical ultracentrifugation, reduced SDS-PAGE with Coomassie blue stain and silver stain, and reduced and non-reduced SDS-CGE. Purity levels for all methods (other than reducing SDS-PAGE and SDS-CGE) were found to be >99%.

Charge heterogeneity was assessed by capillary IEF and IE-HPLC (also a release method).

Biological activity and immunochemical properties were assessed by the in vitro potency assay, several ELISA assays, and inhibition of murine splenocyte and human B-cell proliferation.

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The in vitro potency assay assesses the ability of belimumab to inhibit europium (EU) labeled BLyS from binding to IM-9 cells which express all three BLyS receptors (See Mechanism of Action Section below), although two of the receptors (BR3 and TACI) are expressed at higher levels on the cell surface than the third (BCMA). Dilutions of the belimumab reference standard and samples are incubated with EU-BLyS and then IM-9 cells are added. The method is validated and the acceptance criterion is 75-133% relative potency.

Belimumab was forcibly degraded to produce oxidized, deamidated, aggregated, cross-linked and fragmented variants. These variants were purified and assessed in the potency assay. Only cross linked and fragmented variants consistently showed decreased potency outside the acceptance criteria. The other forms had decrease potency relative to the reference standard but fell within the acceptance criteria.

Process related impurities include [REDACTED] (b) (4)

[REDACTED] have been included as drug substance release methods during clinical development. Removal of these impurities was validated so these will no longer be included as part of release testing. Other than bioburden and endotoxin, which are part of in-process testing and release testing, removal of the other impurities has been adequately demonstrated.

Product related impurities include [REDACTED] (b) (4)

[REDACTED] (b) (4) Among these impurities, only fragments have a significant loss of biological activity. All are controlled by the manufacturing process. Aggregates and charge variants are assessed as part of release testing and have associated acceptance criteria.

### **E. Mechanism of Action**

BLyS (BAFF) is a member of the TNF ligand family that plays a role in B cell selection and survival and is expressed by many cells of the immune system. It is expressed as a cell surface trimer, which is cleaved by furin and released into circulation. There are three BLyS family receptors, BLyS receptor 3 (BR3, BAFF-R), transmembrane activator-1 and calcium modulator and cyclophilin ligand-interactor (TACI) and B cell maturation antigen (BCMA) displaying different levels of expression and patterns through B cell development and across B cell subsets. BLyS is the sole ligand for BR3 while both TACI and BCMA bind to BLyS and another member of the TNF ligand family, a proliferation-inducing ligand (APRIL). The interaction between BLyS and BR3 is necessary for newly formed and mature primary B cells whereas the interaction between BLyS and either TACI or BCMA plays a role in the actions of antigen-activated B cells, memory B cells and long-lived plasma cells.

The belimumab mechanism of action (MOA) is through blocking soluble BLyS binding to its three receptors. Thus it would have more activity directed towards blockade of the survival of naïve B cells, while memory B cells and plasma cells may still receive signals through TACI and BCMA via APRIL. By neutralizing the activity of BLyS, belimumab inhibits survival of B cells, and may preferentially affect autoreactive B cells.

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(b) (4) competition experiment demonstrated that belimumab can block BLyS binding to a BAFF-R-Fc fusion protein. A concentration of 31nM belimumab is required to achieve 50% inhibition.

Due to the fact that belimumab does not bind membrane BLyS HGS did not perform studies directly examining whether belimumab can participate in antibody effector functions, such as Antibody-Dependent Cellular Cytotoxicity or Complement-Dependent Cytotoxicity

### F. Manufacturing Process

Belimumab is expressed in an NS0 mouse myeloma cell line and manufactured using typical bioreactor and purification methods for therapeutic monoclonal antibodies.

(b) (4)

(b) (4) (b) (4)

Belimumab drug substance is formulated to (b) (4) in (b) (4) sodium citrate, (b) (4) sucrose, (b) (4) polysorbate 80, pH 6.5.

(b) (4)

(b) (4) (b) (4)

(b) (4)

### G. Comparability

There have been multiple comparability studies during the course of clinical development of belimumab for both drug substance and drug product.

Drug substance comparability: Pre-clinical and phase 1 studies used belimumab drug substance manufactured by the (b) (4) processes. Phase two studies used the (b) (4) process. Phase 3 studies used the (b) (4) and (b) (4) processes. The (b) (4) process is the proposed commercial process.

The associated belimumab drug product lots were also found comparable.

#### **H. Immunogenicity**

The immunogenicity assays used for the phase 1 and 2 clinical studies are not adequate to assess immunogenicity. If patient samples from phase 1 and 2 studies were not reassessed in the validated phase 3 immunogenicity assays, these data should not be included in the overall assessment of immunogenicity.

The phase 3 immunogenicity studies include a screening assay, an inhibition assay and a neutralization assay. A positive result in the screening assay will be assessed in the inhibition assay and a positive result in the inhibition assay will be assessed in the neutralization assay. A negative result in either of the first two assays will not proceed to the subsequent assay. Overall the phase 3 immunogenicity assays were adequately qualified and validated, but there are concerns that in the presence of belimumab, the assays cannot adequately assess the real immunogenicity of belimumab.

The screening assay is an electrochemiluminescence (ECL) bridging assay where a belimumab Fab is both the capture and detection reagent. The capture Fab is biotin labeled for binding to a streptavidin coated plate, while the detection Fab is conjugated with a sulfo-tag which provides the signal. An acid dissociation step is used to dissociate belimumab from anti-drug antibodies (ADA), but can also dissociate BLYS-belimumab complexes. The positive control is a polyclonal anti-belimumab antibody raised in cynomolgus monkeys immunized with belimumab Fab and purified on a belimumab Fab immunoaffinity column. The negative control is pooled normal human serum. The sensitivity of the assay is dependent upon the levels of ADA present in the sample. The limit of detection (LOD) for this assay is 100 ng/mL in the presence of 2 µg/mL belimumab. This is an appropriately sensitive assay. However, in the presence of 40 µg/mL belimumab, the LOD is only 2 µg/mL ADA. Thus, knowledge of the level of product present in serum samples at the time of sampling is crucial for interpretation of the immunogenicity data in this assay.

The confirmatory assay is based on the screening assay, but includes the use of unlabeled competitors to diminish the signal observed in the first assay. This assay design can distinguish between a true positive (ADA) and a false positive (BLYS-belimumab complexes). The unlabeled competitors are belimumab and a soluble BLYS receptor (TACI-Fc). In this design, excess belimumab will inhibit either ADA or the complex from binding while the TACI-Fc soluble receptor will only inhibit ADA binding. The LOD is 250 ng/mL in the presence of BLYS at 25 µg/mL and belimumab at 10 µg/mL, but is 1 µg/mL in the presence of BLYS at 100 µg/mL and belimumab at 10 µg/mL. The assay is not valid in the

## SUMMARY BLA125370 Belimumab

presence of belimumab at 40 µg/mL where ADA at concentrations of 2 µg/mL cannot be detected.

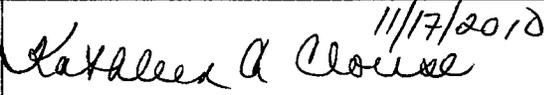
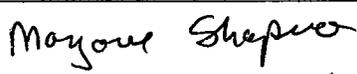
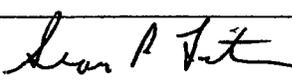
The neutralization assay uses a BR3-Fc-biotin as the capture agent. Labeled BLyS will bind to this receptor, but when belimumab is mixed with the labeled BLyS, binding is inhibited and no signal is detected. In the presence of neutralizing ADA, belimumab will not be able to bind to BLyS and inhibit the signal. The LOD of this assay is 400 ng/mL, however it is extremely sensitive to the presence of belimumab.

### I. Protocols and SOPs in BLA

The following protocols and SOPs are included in the BLA and will be approved upon approval of the BLA. Implementation of the protocols and SOPs will not require a Prior Approval Supplement.

- [REDACTED] (b) (4)
- Drug Substance stability protocol - expiration dating period can be extended in the annual report
- Drug Product stability protocol - expiration dating period can be extended in the annual report
- Comparability protocol to us [REDACTED] (b) (4)  
[REDACTED] (b) (4)
- SOP to qualify a new WCB
- SOP to qualify a new reference standard.
- The Summer Seasonal Shipping protocol for belimumab drug product is acceptable. The data from this study will be submitted to the Annual Report.

### VI. SIGNATURE BLOCK (BLA ONLY)

Name and Title	Signature and Date
Kathleen A. Clouse, Ph.D. Director Division of Monoclonal Antibodies	 11/17/2010
Marjorie A. Shapiro Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies	 11/16/2010
Sean P. Fitzsimmons, Ph.D. Primary Reviewer, Staff Scientist, Division of Monoclonal Antibodies	 11-16-2010



# **Review Cover Sheet**

**BLA STN 125370/0**

**BENLYSTA (belimumab)**

**Human Genome Sciences, Inc.**

**Sean Fitzsimmons, Ph.D.**  
**Division of Monoclonal Antibodies, HFD-123**

# Product Quality Review Data Sheet

1. **BLA#** STN 125370/0
2. **REVIEW #:** 1
3. **REVIEW DATE:** 23-November-2010
4. **REVIEWERS:** Sean Fitzsimmons, Ph.D.  
Marjorie Shapiro, Ph.D., Team Leader
5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS:**

<u>Communication/Document</u>	<u>Date</u>
Type C pre-BLA meeting	08-Mar-2010
Filing Review memo (45 days)	09-Aug-2010
74 day letter	20-Aug-2010
Information Request Letter	14-Sep-2010
HGS Inspection (and 483)	07-Sep-2010 to 01-Oct-2010
Telecon 1 (CMC)	22-Oct-2010
Telecon 2 (CMC)	29-Oct-2010
6. **SUBMISSION(S) REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
STN 125370/0/Original Submission	09-June-2010
STN 125370/0.3/Amendment	27-Aug-2010
STN 125370/0.4/Amendment	15-Sep-2010
STN 125370/0.6/Amendment	27-Sep-2010
STN 125370/0.12/Amendment	26-Oct-2010
STN 125370/0.13/Amendment	27-Oct-2010
STN 125370/0.14/Amendment	03-Nov-2010
7. **NAME & ADDRESS OF APPLICANT:**

**Name:** Human Genome Sciences, Inc.  
**Address:** 14200 Shady Grove Road  
Rockville, MD 20850  
USA  
FDA registration number:  
**Representative:** Diana J. Daly  
**Telephone:** (240) 314-4416
8. **DRUG PRODUCT NAME/CODE/TYPE:**
  - a) Proprietary Name: BENLYSTA
  - b) Non-Proprietary/USAN: belimumab
  - c) Code name: HGS1006

- c) Code name: HGS1006
- d) CAS registry number: 356547-88-1
- e) Common names: Lymphostat B, monoclonal anti-BLyS, LSB
- f) Drug Review Status: Fast-track
- g) Chemical Type: human IgG1 $\lambda$  recombinant monoclonal antibody
- h) NDC: 49401-104-01 (120 mg/vial), 49401-104-02 (400 mg/vial)
- i) ATC code: L04AA26

9. **PHARMACOLOGIC CATEGORY:** Therapeutic recombinant monoclonal antibody to the human B Lymphocyte Stimulator (BLyS)

10. **DOSAGE FORM:** Lyophilized

11. **STRENGTH/POTENCY:**

- a) The concentration of Benlysta (belimumab) Drug Product is 120 mg/vial and 400 mg/vial
- b) Potency is defined as a percent relative to the reference standard, using a cell-based inhibition of binding assay dependent on the ability of Benlysta to inhibit binding of Europium-labeled BLyS to the B lymphoblastoid cell line IM-9, which expresses the three known BLyS receptors. The potency specification is 75-133% of reference standard.
- c) The expiry periods for 400 mg/vial and 120 mg/vial drug products are 36 months and 36 months respectively, when stored at 2°-8°C and protected from light.
- d) Benlysta is filled into either 5 ml or 20 ml glass vials (containing 120 or 400 mg of active ingredient respectively).

12. **ROUTE OF ADMINISTRATION:** Intravenous administration.

13. **ACID (Animal Component Information Database)**

Raw materials used in the manufacture of belimumab that may be of animal origin were identified and assessed in section 3.2.S.2.3.2- Control of Source and Starting Materials of Biological Origin. (b) (4)

*Raw Material:*

*Vendor:*

*Source:*

*Raw Material:*

*Vendor:*

Source:

(b) (4)

14. **PRIMARY STRUCTURE, PHARMACOLOGICAL CATEGORY, MAIN SPECIES MOLECULAR WEIGHT, HOST SOURCE, MAIN GLYCOSYLATION STRUCTURE/S:**

Belimumab is a human IgG1, lambda first-in class therapeutic monoclonal antibody specific for B lymphocyte stimulator (BLyS; BAFF) produced in NSO cells. It is composed of two (b) (4) heavy chains and two (b) (4) light chains. In total, belimumab contains (b) (4) and has an approximate molecular weight of 147.0 kDa. (b) (4)

15. **RELATED/SUPPORTING DOCUMENTS:**

**DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED
(b) (4)	III		(b) (4)
	III		
	V		
	V		

16. **CONSULT STATUS:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Environmental Assessment	Approve	09-Nov-2010	Sean Fitzsimmons
DMA Carton and vial labeling	Pending		Kimberly Raines
BMT– memo for Drug Substance Review	Approve	10-Nov-2010	Kalavati Suvarna
BMT– memo for Drug Product Review	Approve	10-Nov-2010	Bo Chi
EIR for HGS	Approve	01-Nov-2010	Suvarna/Fitzsimmons/ Graham/Dougherty/ Obenhuber

17. **Inspectional Activities**

A pre-license inspection of the facility for the manufacture of belimumab was conducted following a request by the Biotech Manufacturing Team, Office of Compliance, CDER under FACTS assignment #1200750 (Inspection No. TFRB-10-11; OP ID 4962039). The inspection covered the manufacturing operations for BLA STN 125370 for belimumab drug substance at Human Genome Sciences Inc., 9911 Belward Campus Drive, Rockville, MD 20850 and 14200 Shady Grove Road Rockville, MD 20850. The inspection was conducted in accordance with applicable sections of CP 7356.002M, Inspection of Licensed Therapeutic Drug Products and ICH Q7A. This inspection was limited to the manufacture of belimumab. This inspection covered the following main systems: Quality, Facilities and Equipment, Production, Materials, and Laboratory. A 10 item FDA Form 483 was issued to Ms. Sarah Thomas, Vice President, Quality, on October 1, 2010. Observations made during the inspection pertain to inadequate document control, deviation management, failure to follow SOPs, lack of clarity in batch records, operator errors, training, equipment cleaning, changeover cleaning verification, manufacturing process consistency, and tracking of expired laboratory reagents/chemicals. In addition, 5 recommendations were made to the firm. The closeout occurred on October 1, 2010 and no objections were raised. It is recommended that the inspection be classified as VAI. The firm intends to address the cited observations.

18. **Recommendations on BLA Approvability**

The data submitted in this Biologics License Application support the conclusion that the manufacture of Benlysta™ (belimumab) is well controlled, and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in

manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. It is recommended that Benlysta™ (belimumab) be approved for human use (under conditions specified in the package insert).

## **QUALITY UNIT ASSESSMENT**

### **I. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY MODULE 3.2 BODY OF DATA**

The review of module 3.2 is provided below. A review of the product immunogenicity assays and a comparability protocol is included at the end of the primary review document. Questions submitted to HGS for two CMC-related telecons on 10-22-2010 and 10-29-2010 are also included at the end of the review. A consult review regarding the validation reports for pharmacokinetic and pharmacodynamic assays was provided as a separate memorandum to the clinical pharmacology review team.

### **II. REVIEW OF COMMON TECHNICAL DOCUMENT MODULE 1**

#### **a) ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION**

HGS has submitted a categorical exclusion under 21 CFR 25.31 (c). The applicant states that to its knowledge, no extraordinary circumstances exist. The drug substance and intermediates are not derived from plants or animals taken from the wild. There is not information indicating that additional environmental information is warranted.

*The claim of categorical exemption is accepted.*

#### **PACKAGE INSERT**

CMC review and comments on the package insert were provided directly to the team and are incorporated in the approved package insert.

#### **b) DRUG PRODUCT LABEL**

CMC review of the Drug Product Label was generated under a separate consult to Kimberly Raines.

### **III. LIST OF APPROVED REQUESTS and SOPs**

- a) Qualification of Working cell banks. (b) (4)
- b) Reprocessing of Bulk Drug Substance (BDS) (b) (4)  
(3.2.S.2.2.3)
- c) Request to remove specifications for (b) (4) (b) (4)  
(b) (4) 3.2.S.3.2)
- d) Reference standard qualification SOP OCG-2457 (3.2.S.5.4)
- e) Suitability of GMP run (b) (4) for commercial use  
(3.2.S.4.4)
- f) Proposal to submit summer seasonal shipping data for Bulk Drug Substance (BDS) to the  
BLA annual report (3.2.S.2.5.1.4.3)
- g) BDS stability protocol M0606022 for establishing commercial expiry (3.2.S.7)

- h) BDS stability protocol M0608007 to be used for support of the commercial expiry (3.2.S.7).
- i) BDS stability protocol M0610003 as the post-approval commitment stability protocol (3.2.S.7).
- j) FDP 400 mg/vial stability protocols SP0060154-P01, M0605010, and M0607003 for establishing commercial expiry (3.2.P.8.2)
- k) FDP 120 mg/vial stability protocols M0606009, M0606013 and M0607004 for establishing commercial expiry (3.2.P.8.2)
- l) FDP 400 mg/vial stability protocol M0608003 stability commitment for commercial batches (3.2.P.8.2)
- m) FDP 120 mg/vial stability protocol M0608005 stability commitment for commercial batches (3.2.P.8.2)
- n) FDP 400 mg/vial protocol M0610004 and 120 mg/vial stability protocol M0610005 for stability of annual batches (3.2.P.8.2)
- o) GMP lot <sup>(b) (4)</sup> for is suitable for release and commercial distribution (3.2.S.2.5.1.1 and 3.2.S.4.4)

**III. LIST OF DEFICIENCIES TO BE COMMUNICATED**

There are no CMC-related deficiencies precluding approval of this BLA.

**ADMINISTRATIVE**

**A. Reviewers' Signatures**

Product Reviewer: Sean P. Fitzsimmons, Ph.D. *Sean Fitz 11/23/10*

**B. Endorsement Block**

Product Division Team Leader: Marjorie Shapiro, Ph.D. *Marjorie Shapiro 11/23/10*  
 Product Division Director: Kathleen A. Clouse, Ph.D. *Kathleen A. Clouse 11/29/2010*

**C. cc Block**

OBP Office Director: Steven Kozlowski, M.D.  
 Clinical Division Director DPARP: Badrul Chowdhury



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service  
**Center for Drugs Evaluation & Research - Food & Drug Administration**  
Division of Monoclonal Antibodies  
NIH Campus, Building 29B  
29B Lincoln Drive, Bethesda MD 20892  
Telephone (301) 827-0850  
Facsimile (301) 827-0852

## Memorandum

**Date:** 8-26-2010  
**From:** Sean Fitzsimmons, Ph.D. *Sean Fitz 10-14-2010*  
**Through:** Marjorie Shapiro, Ph.D., Lab Chief, Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies *M. Shapiro 10/14/10*  
**To:** File BLA STN:125370  
**Sponsor:** Human Genome Sciences  
**Drug:** Belimumab (Benlysta)  
**Subject:** Bioanalytical Method Validation for Assay used to Detect belimumab.

### Pharmacokinetic Assays

The assays to quantify belimumab levels in human serum were performed by HGS for all studies. Two assay formats were used to detect belimumab in clinical studies: an ELISA was used to detect belimumab in serum samples from the Phase 1 and 2 clinical studies of IV-administered belimumab, while an ECL-based PK assay was used to detect belimumab in serum samples from both Phase 3 IV studies and the Phase 1 and 2 clinical studies of SC-administered belimumab. The main advantage in switching to the ECL platform was that it allowed the PK assay to have a greater dynamic range of quantification and higher sample throughput than was possible with the ELISA. Subsequent to use in Phase 3 studies, the specifications for the control and standard curve samples in the Phase 3 ECL assay were modified and the modified assay was shown to be comparable to the previous version of the assay. Table 2.7.1-3 provides an overview of the PK assays, assay performance characteristics and the report titles for qualification and validation studies.

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

BLA/NDA Number: 125370    Applicant: Human Genome Sciences    Stamp Date:

Established/Proper Name:    BLA/NDA Type:

**Belimumab**

On initial overview of the BLA/NDA application for filing:

<b>CTD Module 1 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
Cover Letter	Y	
Form 356h completed	Y	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y	
<input type="checkbox"/> PI –non-annotated	Y	
<input type="checkbox"/> PI –annotated	Y	
<input type="checkbox"/> PI (electronic)	Y    N	
<input type="checkbox"/> Medication Guide	Y    N	
<input type="checkbox"/> Patient Insert	Y	
<input type="checkbox"/> package and container	Y	
<input type="checkbox"/> diluent	Y    N	Not necessary
<input type="checkbox"/> other components	Y    N	Not necessary
<input type="checkbox"/> established name (e.g. USAN)	Y	
<input type="checkbox"/> proprietary name (for review)	Y	

<b>Examples of Filing Issues</b>	<b>Yes?</b>	<b>If not, justification, action &amp; status</b>
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
<input type="checkbox"/> legible	Y	
<input type="checkbox"/> English (or translated into English)	Y	
<input type="checkbox"/> compatible file formats	Y	
<input type="checkbox"/> navigable hyper-links	Y	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing arrangement	Y    N	Not Necessary

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

<b>CTD Module 2 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
<input type="checkbox"/> Drug Substance	Y	
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y	
<input type="checkbox"/> Novel Excipients	Y	
<input type="checkbox"/> Executed Batch Records	Y	
<input type="checkbox"/> Method Validation Package	Y	
<input type="checkbox"/> Comparability Protocols	Y N	Not sure what is needed here

<b>CTD Module 3 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	Y	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	
<input type="checkbox"/> description of manufacturing process and process control	Y	
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest		
<input type="checkbox"/> purification		
<input type="checkbox"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	Y	
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input type="checkbox"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and intermediates	Y	
<input type="checkbox"/> justification of specifications		
<input type="checkbox"/> stability		

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

<b>CTD Module 3 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
<ul style="list-style-type: none"> <li><input type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions)</li> <li><input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)</li> <li><input type="checkbox"/> characterization of drug substance</li> <li><input type="checkbox"/> control of drug substance               <ul style="list-style-type: none"> <li><input type="checkbox"/> specifications</li> <li><input type="checkbox"/> justification of specs.</li> <li><input type="checkbox"/> analytical procedures</li> <li><input type="checkbox"/> analytical method validation</li> <li><input type="checkbox"/> batch analyses</li> </ul> </li> <li><input type="checkbox"/> reference standards</li> <li><input type="checkbox"/> container closure system</li> <li><input type="checkbox"/> stability               <ul style="list-style-type: none"> <li><input type="checkbox"/> summary</li> <li><input type="checkbox"/> post-approval protocol and commitment</li> <li><input type="checkbox"/> pre-approval                   <ul style="list-style-type: none"> <li><input type="checkbox"/> protocol</li> <li><input type="checkbox"/> results</li> <li><input type="checkbox"/> method validation</li> </ul> </li> </ul> </li> </ul>	<p align="center">Y</p>	
<p><b>Drug Product [3.2.P] [Dosage Form]</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> description and composition</li> <li><input type="checkbox"/> pharmaceutical development               <ul style="list-style-type: none"> <li><input type="checkbox"/> preservative effectiveness</li> <li><input type="checkbox"/> container-closure integrity</li> </ul> </li> <li><input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)</li> <li><input type="checkbox"/> batch formula</li> <li><input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)</li> <li><input type="checkbox"/> controls of critical steps and intermediates</li> <li><input type="checkbox"/> process validation including aseptic processing &amp; sterility assurance:               <ul style="list-style-type: none"> <li><input type="checkbox"/> Filter validation</li> <li><input type="checkbox"/> Component, container, closure depyrogenation</li> </ul> </li> </ul>	<p align="center">Y</p> <p align="center">Y</p> <p align="center">Y    N</p> <p align="center">Y</p> <p align="center">Y</p> <p align="center">Y</p> <p align="center">Y</p> <p align="center">Y</p> <p align="center">Y</p>	<p align="center">Not Necessary</p>

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> <li>and sterilization validation               <ul style="list-style-type: none"> <li>○ Validation of aseptic processing (media simulations)</li> <li>○ Environmental Monitoring Program</li> <li>○ Lyophilizer validation</li> <li>○ Other needed validation data (hold times)</li> </ul> </li> <li><input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)</li> <li><input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)</li> <li><input type="checkbox"/> reference standards or materials</li> <li><input type="checkbox"/> container closure system [3.2.P.7]               <ul style="list-style-type: none"> <li>○ specifications (vial, elastomer, drawings)</li> <li>○ availability of DMF &amp; LOAs</li> <li>○ administration device(s)</li> </ul> </li> <li><input type="checkbox"/> stability               <ul style="list-style-type: none"> <li><input type="checkbox"/> summary</li> <li><input type="checkbox"/> post-approval protocol and commitment</li> <li><input type="checkbox"/> pre-approval                   <ul style="list-style-type: none"> <li>○ protocol</li> <li>○ results</li> <li>○ method validation</li> </ul> </li> </ul> </li> </ul>	<p align="center">Y</p> <p align="center">Y</p> <p align="center">Y</p> <p align="center">Y</p> <p align="center">Y</p>	
<p>Diluent (vials or filled syringes) [3.2P']</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> description and composition of diluent</li> <li><input type="checkbox"/> pharmaceutical development               <ul style="list-style-type: none"> <li>○ preservative effectiveness</li> <li>○ container-closure integrity</li> </ul> </li> <li><input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)</li> <li><input type="checkbox"/> batch formula</li> <li><input type="checkbox"/> description of manufacturing process for production through</li> </ul>	<p align="center">Y    N</p>	<p align="center">Not Necessary</p>

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

<b>CTD Module 3 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	Not Necessary
<input type="checkbox"/> controls of critical steps and intermediates	Y N	Not Necessary
<input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> <li><input type="checkbox"/> Filter validation</li> <li><input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation</li> <li><input type="checkbox"/> Validation of aseptic processing (media simulations)</li> <li><input type="checkbox"/> Environmental Monitoring Program</li> <li><input type="checkbox"/> Lyophilizer sterilization validation</li> <li><input type="checkbox"/> Other needed validation data (hold times)</li> </ul>	Y N	Not Necessary
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	Not Necessary
<input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	Not Necessary
<input type="checkbox"/> reference standards	Y N	Not Necessary
<input type="checkbox"/> container closure system <ul style="list-style-type: none"> <li><input type="checkbox"/> specifications (vial, elastomer, drawings)</li> <li><input type="checkbox"/> availability of DMF &amp; LOAs</li> </ul>	Y N	Not Necessary
<input type="checkbox"/> stability <ul style="list-style-type: none"> <li><input type="checkbox"/> summary</li> <li><input type="checkbox"/> post-approval protocol and commitment</li> <li><input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <li><input type="checkbox"/> protocol</li> <li><input type="checkbox"/> results</li> </ul> </li> </ul>		
Other components to be marketed (full description and supporting data, as listed above):		
<input type="checkbox"/> other devices	Y N	Not Necessary
<input type="checkbox"/> other marketed chemicals (e.g. part	Y N	Not Necessary

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

<b>CTD Module 3 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
of kit)		
Appendices for Biotech Products [3.2.A]		
<input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <li><input type="checkbox"/> manufacturing flow; adjacent areas</li> <li><input type="checkbox"/> other products in facility</li> <li><input type="checkbox"/> equipment dedication, preparation, sterilization and storage</li> <li><input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination</li> </ul>	Y	
<input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <li><input type="checkbox"/> avoidance and control procedures</li> <li><input type="checkbox"/> cell line qualification</li> <li><input type="checkbox"/> other materials of biological origin</li> <li><input type="checkbox"/> viral testing of unprocessed bulk</li> <li><input type="checkbox"/> viral clearance studies</li> <li><input type="checkbox"/> testing at appropriate stages of production</li> </ul>	Y	
<input type="checkbox"/> novel excipients	Y N	Not Necessary
USA Regional Information [3.2.R]		
<input type="checkbox"/> executed batch records	Y	
<input type="checkbox"/> method validation package	Y	
<input type="checkbox"/> comparability protocols	Y	
Literature references and copies [3.3]	Y	

<b>Examples of Filing Issues</b>	<b>Yes?</b>	<b>If not, justification, action &amp; status</b>
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y	

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

<b>Examples of Filing Issues</b>	<b>Yes?</b>	<b>If not, justification, action &amp; status</b>
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	<b>Y</b>	
Certification that all facilities are ready for inspection	<b>Y</b>	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	<b>Y</b>	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	<b>Y</b>  <b>Y</b> <b>N</b> <b>Y</b>	Not applicable, tests used are specified   Not Necessary
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	<b>Y</b>	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	<b>Y</b>	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	<b>Y</b>	

