CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125370Orig1s000

MICROBIOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: December 20, 2010
To: Administrative File, STN 125370/0
From: Kalavati Suvarna, Ph.D., CDER/OC/DMPQ/MAPCB/BMT 12/20/2010
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT
Subject: Addendum to review memo dated November 10, 2010 12/20/10
US License: 1820
Applicant: Human Genome Sciences, Inc.
Mfg Facility: **For drug substance:** Human Genome Sciences, Inc., 14200 Shady Grove Road, Rockville, MD 20850, and Belward Large Scale Manufacturing (LSM), 9911 Belward Campus Drive, Rockville, MD 20850. FEI No. 1000303703.
Product: BENLYSTA® (Belimumab; HGS1006)
Dosage: Lyophilized powder for intravenous administration (80 mg/mL after reconstitution)
Indication: (b) (4) in adult patients with active, autoantibody-positive systemic lupus erythematosus.
Due Date: March 9, 2011

Recommendation for Approvability: The sponsor submitted an amendment 0009 dated 10/13/2010 describing updated in-process (b) (4) hold times and also an updated figure with the established hold times for (b) (4) (b) (4) Therefore, post-marketing commitment 2 stated in the original review dated November 10, 2010, is not needed. The BLA, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitment:

Post-marketing commitment 1: Please submit data supporting microbial control for the UF/DF membrane lifetime studies in a CBE-0 supplement by June 2012.

Assessment:

The validation of the in-process hold time limits based on the microbiological quality attributes of the [redacted] (b) (4); was performed (protocol PVP-06-029 report PVP-06-029R and report addendum PVP-06-029R-01). Results from this retrospective study were used to set in-process hold times based on the maximum hold time experienced at commercial scale. This approach was applied to all hold steps, including those with hold times [redacted] (b) (4) or less. Figure 3.2.S.2.5-14 in the submission was updated and the updated hold times were shown in bold text.

Figure 3.2.S.2.5-14. [redacted] (b) (4) in-process hold times.

[redacted] (b) (4)

Review comment: Microbial control was demonstrated at the end of established hold time.

SATISFACTORY

CONCLUSION:

I. Sections 3.2.S of the BLA pertaining to microbial control of the drug substance manufacturing process were reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective with the following post-marketing commitment:

Post-marketing commitment 1: Please submit data supporting microbial control for the UF/DF membrane lifetime studies in a CBE-0 supplement by June 2012.

The post-marketing commitment 2 in the original review dated November 10, 2010 was deleted based on information included in amendment 0009 dated 10/13/2010.

CC: DMPQ/BMT/Building 51, Suvarna
DMPQ/BMT/Building 51, Hughes
HFD-170, Bowen, Philantha
DMPQ/BMT/Building 51, eCTD Files (STN:125370)

Archived File: S:\archive\BLA\125370\STN125370.rev.mem.BLA.12-20-2010.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 11/30/2010
To: Administrative File, STN 125370/0
From: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/BMT 11/30/10
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT
Subject: New Biologic License Application (BLA): Review Memo
Applicant: Human Genome Sciences, Inc.
US License: 1820
Facility: Drug substance: Human Genome Sciences, Inc., Rockville MD (FEI = 1000303703)
Drug Product: [redacted] (b) (4))
Product: Benlysta® (belimumab)
Dosage: Lyophilized powder for intravenous infusion, 80 mg/mL after reconstitution
Indication: [redacted] (b) (4), in adult patients with active, autoantibody-positive systemic lupus erythematosus
PDUFA Date: December 9, 2010

Product Quality

The BLA, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective. The following post marketing commitments should be communicated to the firm:

1. Submit data supporting microbial control for the [redacted] (b) (4) lifetime studies in a Changes Being Effected (CBE-0) supplement by June 2012.

2. Provide data from three (3) batches of [redacted] (b) (4) demonstrating microbial control at the end of established hold time of [redacted] (b) (4) in a Changes Being Effected (CBE-0) supplement by June 2012.

3. Qualify the capper and validate the integrity of the belimumab drug product container closure in a helium leak test using 5 mL vials prepared at minimum and maximum sealing forces. Information and summary validation data of the helium leak test and the integrity of the belimumab drug product container closure will be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011. The preparation of the positive controls and sensitivity (breach size) of the helium leak test will be provided.

4. Provide quantitative data to demonstrate [redacted] (b) (4) The quantitative qualification data will be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011.

CGMP Facility Assessment

The BLA is recommended for approval from a CGMPS perspective.

The drug substance manufacturing facility, Human Genome Sciences, Inc., Rockville MD (FEI=1000303703) was inspected on 9/7-10/1/2010 by CDER inspectors and found to be acceptable from a CGMP perspective.

The inspection of the drug product facility, [redacted] (b) (4) was waived because this facility was inspected on [redacted] (b) (4) and is in compliance with CGMPs. The waiver memo signed by both the Office of Compliance and Office of Biotechnology Products is attached to this review.

Cc:

WO22: Bowen
HFD-328, TFRB Blue Files (STN 125370)

Archived File: S:\archive\BLA\125370\125370.0.rev.mem.BLA.11.30.2010.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: **11/15/2010**
To: Administrative File, **STN 125370/0**
From: Bo Chi, Ph.D., CDER/OC/DMPQ/MAPCB/BMT BC 11/16/2010
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT PHH 11/30/10
Subject: New Biologic License Application (BLA)
Applicant: Human Genome Sciences, Inc.
US License: **1820**
Facility: [redacted] (b) (4)

Product: Benlysta® (belimumab)
Dosage: Lyophilized powder for intravenous infusion, 80 mg/mL after reconstitution
Indication: [redacted] (b) (4) in adult patients with active, autoantibody-positive systemic lupus erythematosus
PDUFA Date: December 9, 2010

Recommendation: The drug product part of this application, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective with the following two post-market commitments:

1. Qualify the capper and validate the integrity of the belimumab drug product container closure in a helium leak test using 5 mL vials prepared at minimum and maximum sealing forces. Information and summary validation data of the helium leak test and the integrity of the belimumab drug product container closure will be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011. The preparation of the positive controls and sensitivity (breach size) of the helium leak test will be provided.

2. Provide quantitative data to demonstrate [redacted] (b) (4) The quantitative qualification data will be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011.

Review Summary

Human Genome Sciences, Inc. (HGS) has submitted this BLA for belimumab drug product to treat adult patients with active, autoantibody positive system lupus erythematosus (SLE) who are receiving standard therapy. The drug substance is manufactured at HGS, Rockville, MD facility.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: November 10, 2010
To: Administrative File, STN 125370/0
From: Kalavati Suvarna, Ph.D., CDER/OC/DMPQ/MAPCB/BMT 11/10/2010
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT 11/30/2010
Subject: Original BLA
US License: 1820
Applicant: Human Genome Sciences, Inc.
Mfg Facility: **For drug substance:** Human Genome Sciences, Inc., 14200 Shady Grove Road, Rockville, MD 20850, and Belward Large Scale Manufacturing (LSM), 9911 Belward Campus Drive, Rockville, MD 20850. FEI No. 1000303703.
Product: BENLYSTA® (Belimumab; HGS1006)
Dosage: Lyophilized powder for intravenous administration (80 mg/mL after reconstitution)
Indication: [redacted] (b) (4) in adult patients with active, autoantibody-positive systemic lupus erythematosus.
Due Date: December 9, 2010

Recommendation for Approvability: The BLA, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitments:

Post-marketing commitment 1: Please submit data supporting microbial control for the [redacted] (b) (4) lifetime studies in a CBE-0 supplement by June 2012.

Post-marketing commitment 2: Please provide data from 3 batches of [redacted] (b) (4) demonstrating microbial control at the end of established hold time of [redacted] (b) (4) in a CBE-0 supplement by June 2012.

The Human Genome Sciences facilities at 9911 Belward Campus Drive, Rockville, MD 20850, and 14200 Shady Grove Road Rockville, MD 20850, were inspected from September 7, 2010 to October 1, 2010. A 10-item FDA form 483 was issued at the end of inspection. A recommendation was made to classify this inspection as VAI. The final inspection outcome is pending with Office of Compliance.

SUMMARY:

Belimumab is a recombinant, fully human IgG1λ monoclonal antibody, which binds to the soluble B lymphocyte stimulator (BLyS) protein and inhibits survival of B lymphocytes. The proposed indication for belimumab is [redacted] (b) (4) in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) in combination with standard therapy. The proposed commercial final drug product (FDP) is a lyophilized powder to be reconstituted with sterile water for injection (WFI), for intravenous (IV) infusion. The proposed dosing regimen is 10 mg/kg every 2 weeks for the first 3 doses, then every 4 weeks thereafter. The commercial product will be provided as a lyophilized powder for intravenous infusion in sterile single-use glass vials. Two configurations are available to accommodate dosing based on patient weight: 120 mg in a 5 mL vial and 400 mg in a 20 mL vial.

Belimumab is produced by mammalian cells (NS0 mouse myeloma) [redacted] (b) (4)

The manufacture and testing of bulk drug substance (BDS) and cell banks is performed at Human Genome Sciences, Inc., Traville facility, 14200 Shady Grove Road, Rockville, MD 20850. The manufacture of BDS using the [redacted] (b) (4) process, the in-process control tests and BDS release test, the unprocessed release test, stability tests, storage and shipment to fill-finish site is performed at the Human Genome Sciences, 9911 Belward Campus Drive, Rockville, MD 20850. Some select release and stability test are performed at the Belward small scale manufacturing facility at 9910 Belward Campus Drive, Rockville, MD 20850. [redacted] (b) (4)

The BLA was submitted in eCTD format. This review covers the evaluation of the drug substance aspects of the application from a microbial control and microbiology product quality perspective. The original submission and amendments to the original submission (eCTD sequence numbers: 0001 dated 7/20/2010; 0002 dated 8/10/2010; 0005 dated 9/24/2010; 0009 dated 10/13/2010; 0010 dated 10/19/2010; 0013 dated 10/27/2010; and 0015 dated 11/08/2010) are reviewed here.

[redacted] (b) (4)

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(b) (4)

[redacted]

CC: DMPQ/BMT/Building 51, Suvarna
DMPQ/BMT/Building 51, Hughes
HFD-170, Bowen, Philantha
DMPQ/BMT/Building 51, eCTD Files (STN:125370)

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Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CDER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications. You cannot have multiple indications under supplement submissions. If the sponsor submits multiple indications under a supplement, you must unbundle the submission.

CDER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125370/0 Product: Belimumab Applicant: Human Genome Sciences, Inc.

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date: July 21, 2010
Committee Recommendation (circle one): File RTF

RPM: _____
(signature/date)

Attachments:

- ❑ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - ____ Part A – RPM
  - __√__ Part B – Product/CMC/Facility Reviewer(s): Kalavati Suvarna (DS), Chi Bo (DP)
  - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____ _____
  - ____ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____ _____ _____ _____
- ❑ Memo of Filing Meeting

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y	
❑ Novel Excipients	N	OBP Lead; no novel excipients
❑ Executed Batch Records	Y	OBP Lead
❑ Method Validation Package	Y	For endotoxin and bioburden methods; OBP lead for other methods
❑ Comparability Protocols	Y N	OBP Lead

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y N	
Drug Substance [3.2.S]		
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	Y N	Defer to OBP
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	Y	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	Y N	Defer to OBP
❑ control of critical steps and intermediates o justification of specifications o analytical method validation o reference standards o stability	Y	OBP Lead. Bioburden and endotoxin related information is included.

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	Microbial control is discussed and data are presented
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	Defer to OBP
❑ characterization of drug substance	Y N	Defer to OBP
❑ control of drug substance o specification o justification of specs. o analytical procedures o analytical method validation o batch analyses o consistency (3 consecutive lots) o justification of specs.	Y	Microbiology information included; OBP lead on other aspects.
❑ reference standards	Y N	Defer to OBP
❑ container closure system	Y	Description, container-closure integrity, sterilization information included.
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y	Bioburden testing; OBP lead on other stability test
Drug Product [3.2.P]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y	
❑ controls of critical steps and intermediates	Y	
❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o other needed validation data	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	
❑ control of drug product (justification of specifications; analytical method validation)	Y	
❑ container closure system [3.2.P.7] ○ specifications (vial, elastomer, drawings) ○ availability of DMF ○ closure integrity ○ administration device(s)	Y	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	Y	
Diluent (vials or filled syringes) [3.2P′]		Diluent sterile Water for Injection (WFI) is not supplied.
❑ description and composition of diluent	Y N	
❑ pharmaceutical development	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance: ○ 3 consecutive lots ○ other needed validation data	Y N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system ○ specifications (vial, elastomer, drawings) ○ availability of DMF ○ closure integrity	Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results		
Other components to be marketed (full description and supporting data, as listed above):		Not applicable.
❑ other devices	Y N	
❑ other marketed chemicals (e.g. part of kit)	Y N	
Appendices for Biotech Products [3.2.A]		
❑ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation and storage ○ sterilization of equipment and materials ○ procedures and design features to prevent contamination and cross-contamination	Y	
❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of	Y N	OBP Lead

CTD Module 3 Contents	Present?	If not, justification, action & status
production ❑ novel excipients	Y N	OBP Lead
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y N Y N Y N	OBP Lead
Literature references and copies [3.3]	Y N	OBP Lead

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review? ❑ legible ❑ English (or translated into English) ❑ compatible file formats ❑ navigable hyper-links ❑ interpretable data tabulations (line listings) & graphical displays ❑ summary reports reference the location of individual data and records ❑ all electronic submission components usable	Y Y Y Y Y Y Y Y	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	Y	
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 N	OBP Lead
includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	OBP Lead
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	OBP Lead
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	OBP Lead
certification that all facilities are ready for inspection	Y	Facilities listed; certification that they are ready for inspection is included.
data establishing stability of the product through the proposed dating period and a	Y N	OBP Lead

Examples of Filing Issues	Yes?	If not, justification, action & status
stability protocol describing the test methods used and time intervals for product assessment.		
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: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility ❑ ❑	Y Y Y N Y	OBP lead
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	Y N	OBP lead
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	Not applicable; original BLA

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Fileable

Recommendation (circle one): File RTF

7/15/2010 7/15/2010

Reviewer: Kalavati Suvarna; Bo Chi Type (circle one): Product (Chair) Facility (DMPQ)

(signature/ date)

Concurrence:

Branch/Lab Chief: _____ Division Director: _____ 7/16

(signature/ date) (signature/ date)