CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761043Orig1s000

CHEMISTRY REVIEW(S)

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: July 11, 2017
To: Administrative File, STN 761043/0
From: Wayne Seifert, Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Zhihao (Peter) Qiu, Ph.D., Supervisory Consumer Safety Officer
CDER/OPQ/OPF/DIA, Branch 1 Chief
Subject: New Biologic License Application (BLA)
US License: 1727
Applicant: Human Genome Sciences, Inc. (A wholly owned subsidiary of GSK)
Mfg Facility: Drug Substance: Human Genome Sciences, Inc. (FEI: 3003782237)
Drug Product: Glaxo Operations UK Ltd. (FEI: 3002807078)
Product: BENLYSTA® (belimumab)
Dosage: Syringe within an autoinjector or a safety syringe device, 200 mg/1ml, Subcutaneous
Indication: Adult patients with active, autoantibody-positive systemic lupus erythematosus receiving standard therapy.
Due Date: July 22, 2017

RECOMMENDATION: This submission is recommended for approval from a facilities assessment perspective.

SUMMARY

The subject BLA proposes manufacture of belimumab DS at the Human Genome Sciences (HGS), Inc. facility in Rockville, Maryland (FEI: 3003782237) and DP at the Glaxo Operations UK Ltd. facility in Barnard Castle, County Durham, UK (FEI: 3002807078). Both locations are multi-product manufacturing facilities. The final dosage form for belimumab 200 mg solution for injection is composed of a 1 ml prefilled USP Type (b) glass syringe (PFS), with 27 gauge (b) (4) needle and rigid needle shield as the primary container closure system that is assembled into an autoinjector or a safety syringe device.

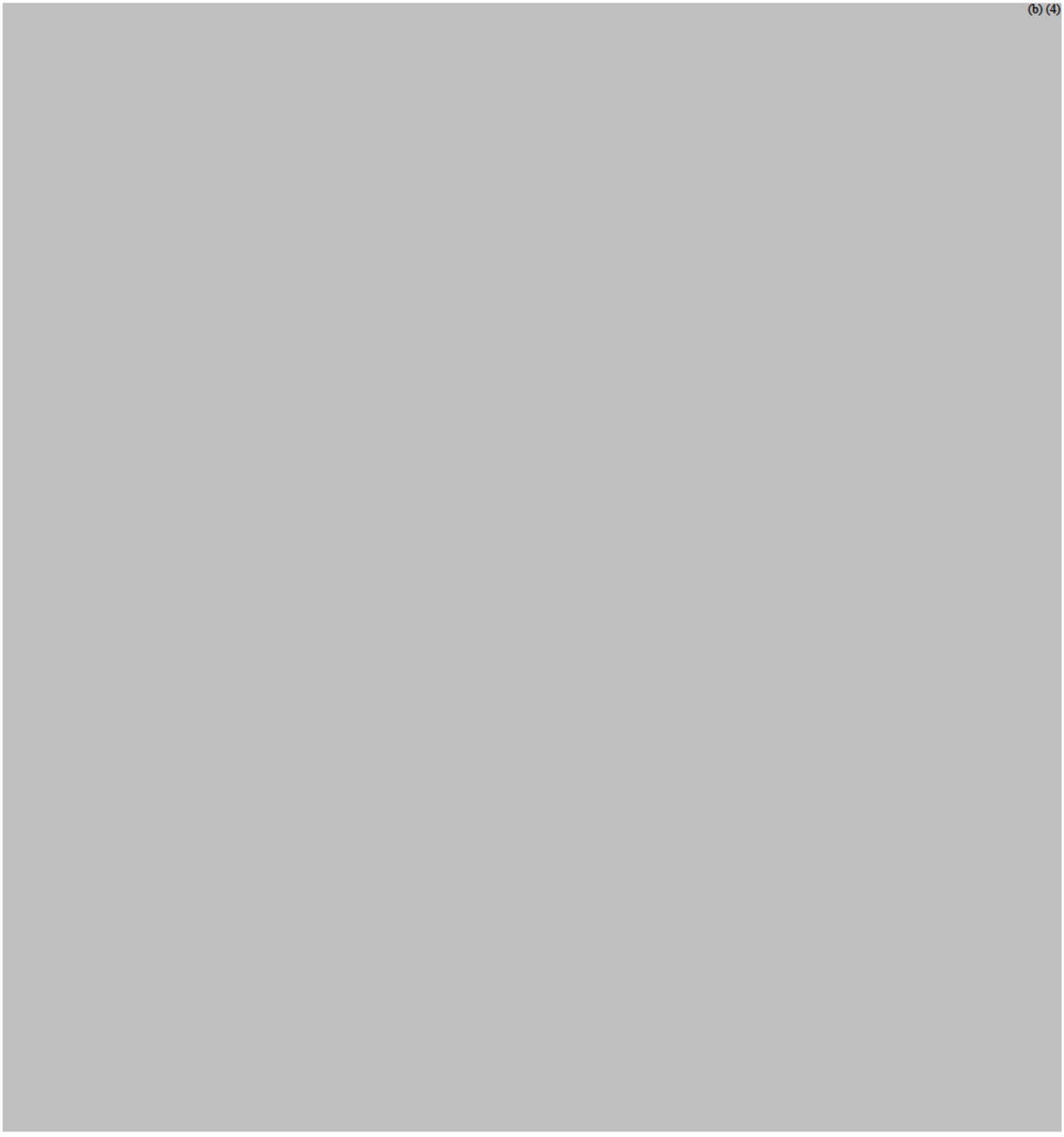
Belimumab is a recombinant, human IgG1λ monoclonal antibody that binds and antagonizes the biological activity of soluble B lymphocyte stimulator (BLyS) protein, a member of the tumor necrosis factor (TNF) ligand superfamily that promotes the survival of B lymphocytes. The BLyS antagonist, belimumab, was developed for the treatment of patients with SLE. Belimumab is expressed in NS0 cells (b) (4).

The facilities supporting DS manufacture, testing and storage are provided under Table 1, with facilities supporting Benlysta (belimumab) DP manufacture, testing and storage included under Table 3.

ASSESSMENT

3.2.S.2. DRUG SUBSTANCE FACILITIES

(b) (4)



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Wayne Seifert
Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1

Wayne E. Seifert -S

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Mike Shanks
Biologist
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/s/

JONATHAN T DOW
07/27/2017

First Approval for Subcutaneous Administration of Belimumab for SLE

Recommendation: Approval

BLA 761043
Review 2
Review Date: 7/10/2017

Drug Name/Dosage Form	Benlysta (belimumab solution for injection)
Strength/Potency	200 mg/1.0 mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
Indication	SLE
Applicant/Sponsor	GlaxoSmithKline

Product Overview

Benlysta (belimumab) has the same active ingredient as Benlysta, but is intended for subcutaneous administration instead of intravenous administration. Belimumab is a human IgG1, lambda anti-BLyS monoclonal antibody. The main mechanism of action is binding to BLyS (BAFF), a B lymphocyte survival factor, and preventing its interaction with its receptor on B lymphocytes. Without the survival signals, B cells are depleted, including autoantibody expressing B cells. The manufacturing process is that same as for belimumab for intravenous administration (b) (4) (b) (4)

Note: At the time of the initial review, the proprietary name was Benlysta (b) (4). Since that time DMEPA determined that it would be acceptable to use the proprietary name Benlysta for both the iv and sc formulations.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance/Drug Product	Sean Fitzsimmons	OBP/DBRR1
Facilities	Wayne Seifert	OPF/DIA
Microbiology	Jessica Hankins	OPF/DMA
Business Regulatory Process Manager	Kelly Ballard	OPRO
Team Lead Facilities	Peter Qiu	OPF/DIA
Team Lead Microbiology	Patricia Hughes	OPF/DMA
Application Technical Lead	Marjorie Shapiro	OBP/DBRR1

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Jessica Lee	OND/DPARP
Cross-disciplinary Team Lead	Nikolay Nikolov	OND/DPARP
Medical Officer	Rosemarie Neuner	OND/DPARP
Pharm/Tox	Brett Jones/Tim Robison	OND/DPARP
Clinical Pharmacology	Sury Sista/Anshu Marathe	OCP/DCPII
Statistics	Ginto Pottackal/Greg Levin	OBE/BBII
CDRH	Keith Marin	CDRH

a. Names
   i. Proprietary Name: Benlysta
   ii. Trade Name: Benlysta
   iii. Non-Proprietary/USAN: belimumab
   iv. CAS name: 356547-88-1
   v. Common name: LymphoStat-B, monoclonal anti-BLyS
   vi. INN Name: belimumab
   vii. OBP systematic name: MAB HUMAN (IGG1) ANTI Q9Y275 (TN13B_HUMAN) [HGS1006]

b. Pharmacologic category: Therapeutic recombinant monoclonal antibody to the human B Lymphocyte Stimulator (BLyS)

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
761043.1 Original BLA submission	9/22/2016
761043.5 response to IR #2 11/10/2016	11/15/2016
761043.6 revised 356h	11/18/2016
761043.10 response to IR #2 11/10/2016	2/27/2017
761043.11 response to IR #4 2/9/2017	3/6/2017
761043.12 response to IR #6 3/9/2017	3/31/2017
761043.13 response to IR #7 4/6/17	4/24/2017
761043.12 response to IR #8 5/3/17	5/19/2017
761043.15 response to IR #9 5/15/17	6/2/2017
761043.16 response to IR #9 5/15/17 and #10 5/23/17	6/2/2017
761043.18 response to IR #11 6/9/17	6/14/17
761043.20 response to IR #12 6/16/17	6/23/17
761043.22 response to CMC PMCs 6/16/17	6/27/17
761043.24 response to IR #13 6/26/17	6/29/17
761043.24 response to IR #15 6/30/17	7/5/17

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

	TYPE			CODE[1]	STATUS[2]	COMMENTS
(b) (4)	Type III		(b) (4)	3	N/A	Information in BLA on device components reviewed by Keith Marin, CDRH
	Type III			3	N/A	
	Type III			3	N/A	
Files						
(b) (4)			(b) (4)	3	N/A	Information in BLA on device components reviewed by Keith Marin, CDRH
	510 (k)			3	N/A	

des for DMF
– Reviewed
to reference n

cate why the DMF was not reviewed, as
3 – Sufficient information in application; 4 –
er (explain under "Comments")

[2] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, Reference Listed Drug (RLD), or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Cross reference to other GSK submissions	STN 125370	BLA for belimumab iv formulation, which is the same manufacturing process as belimumab sc (b) (4)

		(b) (4)

3. CONSULTS:

DISCIPLINE/TOPIC	DATE REQUESTED	STATUS	RECOMMENDATION	REVIEWER
Device	11/15/2106	complete	approve	Keith Marin

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation
The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761043 for Benlysta, manufactured by Human Genome Sciences (a fully owned subsidiary of GlaxoSmithKline). The data submitted in this application are adequate to support the conclusion that the manufacture of Benlysta is well controlled and leads to a product that is pure and potent. We recommend that Benlysta be approved for human use under the conditions specified in the package insert.

b. Summary of Complete Response issues – none

c. Action letter language
- Manufacturing location:
  - Drug substance – Human Genome Sciences, Inc., Rockville, MD 20850
  - Drug product – Glaxo Operations UK Ltd., Barnard Castle, UK
- Fill size and dosage form – 200 mg/1.0 mL pre-filled syringe/autoinjector
- Dating period:
  - Drug product – 36 months; 2-8°C
  - Drug substance – (b) (4) months; (b) (4)
  - Stability
    - For stability protocols:
      Not applicable – data for drug substance and drug product support the requested expiration dating periods with no further extensions
- Exempt from lot release
  - Yes - specified product per 601.2a

d. Benefit/Risk Considerations
Benlysta (belimumab) is intended to deliver belimumab subcutaneously in the same population as Benlysta. It has the same active ingredient as Benlysta, first approved on March 9, 2011, for intravenous administration for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The benefit of Benlysta to SLE patients is that it provides flexibility of administration, reduces the time spent at a doctor's or infusion center and provides independence for patients. The higher concentration formulation does not result in higher levels of aggregates and the rates of immunogenicity between sc and iv delivery were comparable and low.

e. Environmental Assessment or Claim Of Categorical Exclusion

HGS requests a categorical exclusion under 21 CFG 25.31 (c). The applicant states they have no knowledge of any extraordinary circumstances that might have a significant effect on the quality of the human environment.

The claim of categorical exemption is accepted.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

1. Re-evaluate belimumab liquid drug product lot release acceptance criteria for osmolality, potency and protein concentration assays after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. HGS will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

   Final Report Submission: 03/20/2020

2. Establish a maximum hold time for the (b) (4) process and provide bioburden and endotoxin data supporting the maximum hold time from the first three batches of the 2017 manufacturing campaign.

   Final Report Submission: 03/16/2018

3. Conduct a (b) (4) test method qualification study using one additional lot of belimumab drug substance.

   Final Report Submission: 08/17/2018

4. Conduct the (b) (4) qualification study using two additional lots of belimumab drug substance.

   Final Report Submission: 08/17/2018

5. Conduct a low endotoxin recovery study for the belimumab drug product using spiked LAL Reagent Water (LRW) as a control for at least two time points other than the initial spike (e.g., 24 hours and 48 hours). Provide the LER study report to the Agency.

   Final Report Submission: 03/16/2018

The final report submission dates were found to be acceptable by Sean Fitzsimmons and Jessica Hankins.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Much of the knowledge regarding product attributes was obtained from the original development of belimumab for intravenous administration. The quality attributes for

belimumab for subcutaneous administration are the same and details of the data supporting the CQA identification, risk and lifecycle knowledge management can be found in BLA 123750.

Table 1: Drug Substance API CQA Identification, Risk and Lifecycle Knowle

CQA (Type)	Risk	Origin		
Aggregate (Dimer and Higher Order) (Product Variant)	Impact on biological activity, immunogenicity, PK/PD, and safety	Predominantly covalent dimers and no higher order aggregate. May be formed during DS and DP manufacture and storage.	(b) (4)	(b) (4)
Fragmentation (Product impurity)	Impact on biological activity, immunogenicity, PK/PD, and safety	May be formed during DS and DP manufacture and storage.		Cross-linked H-L chains and H-H chains have reduced potency.
Deamidation (Product variant)	Impact on efficacy and PK/PD	(b) (4)		(b) (4)

		(b) (4)	(b) (4)		(b) (4)
Fc glycosylation	Impact on efficacy, PK and safety	Intrinsic to molecule and cell culture			(b) (4)
Fab glycosylation	Impact on efficacy, PK and safety	Intrinsic to molecule and cell culture			
BLys (Potency)	MOA - Impact on efficacy	Intrinsic to molecule Impacted by fragments and cross linked molecules			
Oxidation	Potential impact on	DS and DP manufacture:			(b) (4)

(Product variant)	biological activity and PK/PD	(b) (4)	(b) (4) (b) (4)
Primary Sequence	Impact on efficacy, safety and immunogenicity	Expression construct and cell line	
Secondary and Tertiary Structure	Impact on efficacy, PK/PD and immunogenicity	Expression construct and cell line	

B. Drug Substance [belimumab] Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Visual Appearance: color and opalescence	Impact on safety and immunogenicity	May be affected by cell culture, (b) (4)	(b) (4)	

(General)			(b) (4)	
Protein Quantity (General)	Impact on efficacy	DS manufacture (b) (4)		
Host Cell Proteins (Process Impurity)	Impact on safety and immunogenicity	Cell Culture		(b) (4)
DNA (Process Impurity)	Impact on safety and immunogenicity	Cell Culture		
(b) (4) (Process Impurity)	Impact on safety and immunogenicity	(b) (4)		
(b) (4) (Process Impurity)	Impact on safety and immunogenicity	Cell Culture		
(b) (4) (Process Impurity)	Impact on safety	Cell Culture		

			(b) (4) (b) (4)
(b) (4) (Process Impurity)	Impact on safety	Cell Culture	
Endotoxin (Contaminant)	Impact on safety	Raw materials or contamination during manufacturing	
Bioburden (Contaminant)	Impact on safety and efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials or contamination during manufacturing	

a. Description
Belimumab MAB HUMAN (IGG1) ANTI Q9Y275 (TN13B_HUMAN) [HGS1006] is a human IgG1, lambda anti-BLyS (BAFF) monoclonal antibody produced in (b) (4) cells. It has an average molecular weight of 147 KDa and a pI of ~8.6. It has the typical structure of an IgG1 antibody with 4 interchain disulfide bonds and 12 intrachain disulfide bonds and typical N-linked glycan structures in the heavy chain.

b. Mechanism of action
BLyS, a member of the TNF super family, regulates B cell maturation, function, survival and homeostasis. Belimumab inhibits the binding of BLyS to its receptors, and therefore inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin producing plasma cells.

c. Potency Assay
The potency assay is an inhibition of europium-labeled BLyS binding to IM-9 cells, a human B Lymphoblast cell line. Replicates of belimumab reference standard and sample dilutions are incubated with EU-BLyS and then IM-9 cells are added to the belimumab/Eu-BLyS complexes. After further incubation, europium fluorescence is determined. There is an inverse relationship between levels of fluorescence and levels of belimumab in the

ed

d. (b) (4)

e. (b) (4)

f. Manufacturing process summary (b) (4)

(b) (4)

g. (b) (4)

h. Dating period and storage conditions
(b) (4) months at (b) (4) °C.

C. Drug Product [belimumab] Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin		Other
Appearance (General)	Measure of purity, impact on product safety and immunogenicity		(b) (4)	
pH (General)	Impact on product stability and conformation	(b) (4)		(b) (4)
Osmolality (General)	Potential impact on therapeutic dose			
Particulate matter (visible and sub-visible) (General)	Impact on product safety and efficacy			
Weight variation	Impact on efficacy	DP manufacture		

(General)			(b) (4)	
Plunger depth (General)	Impact on efficacy	DP manufacture		(b) (4)
Deliverable Volume (General)	Impact on efficacy	DP manufacture		
Protein Quantity (General)	Impact on efficacy	DP manufacture (b) (4)		
Endotoxin (Contaminant)	Impact on safety and immunogenicity	Contamination may be introduced throughout DP manufacturing process.		
Sterility (Contaminant)	Impact on safety and efficacy (due to degradation or modification of	Contamination may be introduced throughout DP manufacturing.		

	the product)		(b) (4)	
Container Closure Integrity (Contaminant)	Impact on safety	May be impacted by storage conditions.		

a. Potency and Strength
Benlysta is supplied as Belimumab injection for subcutaneous use (200 mg/1.0 mL) as a single-use, sterile liquid drug product in two formats both containing a p

P

(b) (4)

A

(b) (4)

(b) (4)

b.

- Product quality attributes are retained during manufacture, device assembly, transport, shelf life, and use.
- Product is manufactured by a robust and reproducible process that provides a high assurance of quality.
- Provided as a sterile, low-endotoxin product packaged in a container closure system that ensures product integrity for the intended shelf life.
- Product is self-administered subcutaneously via an autoinjector or safety syringe to deliver a 1.0 mL volume containing a single dose of 200 mg belimumab.

- Product is non-interactive with packaging components.

c. List of Excipients
Sodium Chloride 6.7 mg/mL
L-Arginine Hydrochloride 5.3 mg/mL
L-Histidine, Monohydrochloride 1.2 mg/mL
L-Histidine 0.65 mg/mL
Polysorbate 80 0.1 mg/mL

d.

e.

f.

(b) (4)

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

(RNS) that is preassembled onto the syringe. The RNS is composed (b) (4)

(b) (4) After

filling, the PFS is sealed with 1 mL long rubber plunger stopper (b) (4)

(b) (4)

g. Expiration Date & Storage Conditions
The shelf life for DP is 36 months at 2-8°C.

D. Novel Approaches/Precedents

None

E. Any Special Product Quality Labeling Recommendations

F. Establishment Information

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
	SITE INFORMATION	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
(b) (4)	Human Genome Sciences, Inc. (A wholly owned subsidiary of GSK) Belward Large Scale Manufacturing (LSM) Facility 9911 Belward Campus Drive Rockville, MD 20850	034062104/ 3003782237	Inspection waived	NA	Approve based on inspection and compliance history
	(b) (4)		Inspection waived	NA	Approve based on inspection and compliance history

(b) (4)					
(b) (4)			Inspection waived	NA	Approve based on inspection and compliance history
(b) (4)			Inspection waived	NA	Approve based on inspection and compliance history
G PRODUCT					
	INFORMATION			**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**

Manufacture of the Syringe DP, Release and Stability Testing, Autoinjector Assembly and Testing, Safety Syringe Assembly and Testing, Labelling and Packaging of Supply, DP Batch Release	Glaxo Operations UK Ltd. Harmire Road Barnard Castle County Durham UK DL12 8DT	228472833/ 3002807078	Inspection scheduled for 06/26/2017 – 07/04/2017	To be determined	Recommendation pending outcome of PLI. Previous inspection and compliance history is satisfactory.
DP release and stability testing	Glaxo Operations UK Ltd. Gunnels Wood Road Stevenage Hertfordshire UK SG1 2NY	218783633/ 3009763376	Inspection waived	NA	Approve based on inspection and compliance history

G. Facilities
Prior Inspection History

Drug Substance

Human Genome Sciences, Inc. (FEI: 3003782237) - DS Manufacture and Testing Facility

- A surveillance inspection was conducted by BLT-DO between April 4-11, 2016 of the HGS Belward Large Scale Manufacturing Facility. Quality, Production, Facilities and Equipment and Laboratory Systems were covered. A 3- item Form FDA 483 was issued. The inspection was classified VAI.
- (b) (4)
- (b) (4)

(b) (4)

(b) (4)

(b) (4)

D

Glaxo Operations UK Ltd. (FEI: 3002807078) – DP Manufacturer, Testing and Release

- The PLI for BLA 761043 belimumab (Benlysta) was conducted between 06/26/2017 – 07/04/2017 by CDER-DIA. The inspection included all six systems for BLA 761043. A 4-Item FDA form 483 was issued for 1) Equipment used in

the manufacturing process is not adequately maintained; 2) Corrective action was not taken in a timely manner to mitigate glove and sleeve integrity failures; 3) Testing for GMP utilities is not adequate; and the reference standard used in drug product identification testing is not adequately controlled. 7-items were

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4) This inspection was conducted in response to BLA supplement 125370/36 to add this laboratory as the back-up DP testing laboratory for Benlysta (belimumab) for the US market. Quality and Laboratory Systems were covered. The inspection resulted in no Form FDA 483, with five discussion items. The inspection was classified NAI.

H. Lifecycle Knowledge Management

a. Drug Substance

i. Protocols approved
Annual GMP stability – no extension of shelf life is needed

ii. Outstanding review issues/residual risk
None

iii. Future inspection points to consider
PAI was waived, so the sc manufacturing process should be examined at the next inspection.

b. Drug Product

i. Protocols approved
Annual GMP stability – no extension of shelf life is needed

ii. Outstanding review issues/residual risk
none

iii. Future inspection points to consider
PAI scheduled for 06/26/2017 – 07/04/2017; future inspectional items will be determined based on the inspection.

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity		X	
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		

14.	Other_____			
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)			X
16.	Comparability Protocol(s)		X	
17.	End of Phase II/Pre-NDA Agreements tem)			X
18.	SPOTS (Special Products On-line Tracking System			X
19.	USAN Name Assigned	X		
20.	Other_____			
Quality Considerations				
21.	Drug Substance Overage			
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements	X		
27.	Real Time Release Testing (RTRT)		X	
28.	Parametric Release in lieu of Sterility Testing		X	

29.	Alternative Microbiological Test Methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial Analytical Procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other _____				

Marjorie Shapiro

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Jessica Hankins, Ph.D.
ACTING BRANCH CHIEF: Patricia Hughes, Ph.D.

BLA:	761043
Applicant:	Human Genome Sciences, Inc. (GlaxoSmithKline)
US License Number:	1820
Submission Reviewed:	BLA
Product:	belimumab (Benlysta®)
Indication:	Adult patients with active, autoantibody-positive systemic lupus erythematosus receiving standard therapy.
Dosage Form:	solution for subcutaneous injection (200 mg/1 mL)
Manufacturing Site:	Drug Substance: Human Genome Sciences, Inc. Belward Large Scale Manufacturing Facility 9911 Belward Campus Dr. Rockville, MD, USA (FEI: 300382237) Drug Product: Glaxo Operations UK Ltd. Harmire Rd. Barnard Castle County Durham DL12 8DT United Kingdom (FEI: 3003722390)
FDA Receipt Date:	September 22, 2016
Action Date:	July 22, 2017

Conclusion and Approvability Recommendation

The BLA, as amended, was reviewed from a product quality microbiology and sterility assurance perspective. No issues were identified that would preclude approval. This review evaluates responses to information requests sent to the sponsor on 6/16/2017, 6/26/2017, and 6/30/2017. The responses to the information request will be documented in an addendum to this review memo. There are 4 post-marketing commitments:

1. Establish a maximum hold time for the [redacted] (b) (4) process and provide bioburden and endotoxin data supporting the maximum hold time from the first three batches of the 2017 manufacturing campaign.

2. Conduct a [redacted] (b) (4) test method qualification study using one additional lot of belimumab drug substance.

3. Conduct the [redacted] (b) (4) qualification study using two additional lots of belimumab drug substance.

4. Conduct a low endotoxin recovery study for the belimumab drug product using spiked LAL Reagent Water (LRW) as a control for at least two time points other than the initial spike (e.g., 24 hours and 48 hours). Provide the LER study report to the Agency.

Product Quality Microbiology Assessment

Quality Microbiology Information Reviewed

Sequence number	Date	Description
0019	06/23/17	Response to information request
0023	06/29/17	Response to information request

[redacted] (b) (4)

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Jessica Hankins

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Patricia Hughes Troost

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First Approval for Subcutaneous Administration of Belimumab for SLE

Recommendation: Approval

BLA 761043
Review 1
Review Date: 6/19/2017

Drug Name/Dosage Form	Benlysta (b) (4) (belimumab solution for injection)
Strength/Potency	200 mg/1.0 mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
Indication	SLE
Applicant/Sponsor	GlaxoSmithKline

Product Overview

Benlysta (b) (4) (belimumab) has the same active ingredient as Benlysta, but is intended for subcutaneous administration instead of intravenous administration. Belimumab is a human IgG1, lambda anti-BLyS monoclonal antibody. The main mechanism of action is binding to BLyS (BAFF), a B lymphocyte survival factor, and preventing its interaction with its receptor on B lymphocytes. Without the survival signals, B cells are depleted, including autoantibody expressing B cells. The manufacturing process is that same as for belimumab for intravenous administration (b) (4) (b) (4)

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance/Drug Product	Sean Fitzsimmons	OBP/DBRR1
Facilities	Wayne Seifert	OPF/DIA
Microbiology	Jessica Hankins	OPF/DMA
Business Regulatory Process Manager	Kelly Ballard	OPRO
Team Lead Facilities	Peter Qiu	OPF/DIA
Team Lead Microbiology	Patricia Hughes	OPF/DMA
Application Technical Lead	Marjorie Shapiro	OBP/DBRR1

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Jessica Lee	OND/DPARP
Cross-disciplinary Team Lead	Nikolay Nikolov	OND/DPARP
Medical Officer	Rosemarie Neuner	OND/DPARP
Pharm/Tox	Brett Jones/Tim Robison	OND/DPARP
Clinical Pharmacology	Sury Sista/Anshu Marathe	OCP/DCPII
Statistics	Ginto Pottackal/Greg Levin	OBE/BBII
CDRH	Keith Marin	CDRH

a. Names
   i. Proprietary Name: Benlysta (b) (4)
   ii. Trade Name: Benlysta
   iii. Non-Proprietary/USAN: belimumab
   iv. CAS name: 356547-88-1
   v. Common name: LymphoStat-B, monoclonal anti-BLyS
   vi. INN Name: belimumab
   vii. OBP systematic name: MAB HUMAN (IGG1) ANTI Q9Y275 (TN13B_HUMAN) [HGS1006]

b. Pharmacologic category: Therapeutic recombinant monoclonal antibody to the human B Lymphocyte Stimulator (BLyS)

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
761043.1 Original BLA submission	9/22/2016
761043.5 response to IR #2 11/10/2016	11/15/2016
761043.6 revised 356h	11/18/2016
761043.10 response to IR #2 11/10/2016	2/27/2017
761043.11 response to IR #4 2/9/2017	3/6/2017
761043.12 response to IR #6 3/9/2017	3/31/2017
761043.13 response to IR #7 4/6/17	4/24/2017
761043.12 response to IR #8 5/3/17	5/19/2017
761043.15 response to IR #9 5/15/17	6/2/2017
761043.16 response to IR #9 5/15/17 and #10 5/23/17	6/2/2017

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

	TYPE			CODE[1]	STATUS[2]	COMMENTS
(b) (4)	Type III		(b) (4)	3	N/A	Information in BLA on device components reviewed by Keith Marin, CDRH
	Type III			3	N/A	
	Type III			3	N/A	
Files						
(b) (4)			(b) (4)	3	N/A	Information in BLA on device components reviewed by Keith Marin, CDRH
	510 (k)			3	N/A	

des for DMF
– Reviewed
to reference n

cate why the DMF was not reviewed, as
3 – Sufficient information in application; 4 –
er (explain under "Comments")

[2] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, Reference Listed Drug (RLD), or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Cross reference to other GSK submissions	STN 125370	BLA for belimumab iv formulation, which is the same manufacturing process as belimumab sc (b) (4)

		(b) (4)

3. CONSULTS:

DISCIPLINE/TOPIC	DATE REQUESTED	STATUS	RECOMMENDATION	REVIEWER
Device	11/15/2106	complete	approve	Keith Marin

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation
The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761043 for Benlysta (b) (4), manufactured by Human Genome Sciences (a fully owned subsidiary of GlaxoSmithKline) pending acceptable compliance checks and responses to outstanding information requests regarding drug substance and drug product microbiology. The data submitted in this application are adequate to support the conclusion that the manufacture of Benlysta (b) (4) is well controlled and leads to a product that is pure and potent. We recommend that Benlysta (b) (4) be approved for human use under the conditions specified in the package insert.

b. Summary of Complete Response issues – none

c. Action letter language
- Manufacturing location:
  - Drug substance – Human Genome Sciences, Inc., Rockville, MD 20850
  - Drug product – Glaxo Operations UK Ltd., Barnard Castle, UK
- Fill size and dosage form – 200 mg/1.0 mL pre-filled syringe/autoinjector
- Dating period:
  - Drug product – 36 months; 2-8°C
  - Drug substance – (b) (4) months; (b) (4) C
  - Stability
    - For stability protocols:
      Not applicable – data for drug substance and drug product support the requested expiration dating periods with no further extensions
- Exempt from lot release
  - Yes - specified product per 601.2a

d. Benefit/Risk Considerations
Benlysta (b) (4) (belimumab) is intended to deliver belimumab subcutaneously in the same population as Benlysta. It has the same active ingredient as Benlysta, first approved on March 9, 2011, for intravenous administration for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The benefit of Benlysta (b) (4) to SLE patients is that it provides flexibility of administration, reduces the time spent at a doctor's or infusion center and provides independence for patients. The higher concentration formulation does not result in higher levels of aggregates and the rates of immunogenicity between sc and iv delivery were comparable and low.

e. Environmental Assessment or Claim Of Categorical Exclusion
HGS requests a categorical exclusion under 21 CFG 25.31 (c). The applicant states they have no knowledge of any extraordinary circumstances that might have a significant effect on the quality of the human environment.

The claim of categorical exemption is accepted.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

1. Re-evaluate belimumab liquid drug product lot release acceptance criteria for osmolality, potency and protein concentration assays after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. HGS will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

2. Establish a maximum hold time for the (b) (4) process and provide bioburden and endotoxin data supporting the maximum hold time from the first three batches of the 2017 manufacturing campaign.

3. Conduct a (b) (4) test method qualification study using one additional lot of belimumab drug substance. In addition, conduct the kinetic chromogenic bacterial endotoxin qualification study using two additional lots of belimumab drug substance.

4. Conduct a low endotoxin recovery study for the belimumab drug product using spiked LAL Reagent Water (LRW) as a control for at least two time points other than the initial spike (e.g., 24 hours and 48 hours). Provide the LER study report to the Agency.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Much of the knowledge regarding product attributes was obtained from the original development of belimumab for intravenous administration. The quality attributes for belimumab for subcutaneous administration are the same and details of the data supporting the CQA identification, risk and lifecycle knowledge management can be found in BLA 123750.

Table 1: Drug Substance API CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin		
Aggregate (Dimer and Higher Order) (Product Variant)	Impact on biological activity, immunogenicity, PK/PD, and safety	Predominantly covalent dimers and no higher order aggregate. May be formed during DS and DP manufacture and storage.	(b) (4	(b) (4)
Fragmentation (Product impurity)	Impact on biological activity, immunogenicity, PK/PD, and safety	May be formed during DS and DP manufacture and storage.		Cross-linked H-L chains and H-H chains have reduced potency.
Deamidation (Product variant)	Impact on efficacy and PK/PD	(b) (4)		(b) (4)

		(b) (4)	(b) (4)	(b) (4)	
Fc glycosylation	Impact on efficacy, PK and safety	Intrinsic to molecule and cel culture			
Fab glycosylation	Impact on efficacy, PK and safety	Intrinsic to molecule and cel culture			(b) (4)
BLys (Potency)	MOA - Impact on efficacy	Intrinsic to molecule Impacted by fragments and cross linked molecules			
Oxidation	Potential impact on	DS and DP manufacture:			(b) (4)

(Product variant)	biological activity and PK/PD	(b) (4)	(b) (4) (b) (4)
Primary Sequence	Impact on efficacy, safety and immunogenicity	Expression construct and cell line	
Secondary and Tertiary Structure	Impact on efficacy, PK/PD and immunogenicity	Expression construct and cell line	

B. Drug Substance [belimumab] Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Visual Appearance: color and opalescence	Impact on safety and immunogenicity	(b) (4)	(b) (4)	

(General)				
Protein Quantity (General)	Impact on efficacy	DS manufacture (b) (4)	(b) (4)	
Host Cell Proteins (Process Impurity)	Impact on safety and immunogenicity	Cell Culture		(b) (4)
DNA (Process Impurity)	Impact on safety and immunogenicity	Cell Culture		
(b) (4) (Process Impurity)	Impact on safety and immunogenicity	(b) (4)		
(b) (4) (Process Impurity)	Impact on safety and immunogenicity	Cell Culture		
(b) (4) (Process Impurity)	Impact on safety	Cell Culture		

(b) (4) (Process Impurity)	Impact on safety	Cell Culture	(b) (4)
Endotoxin (Contaminant)	Impact on safety	Raw materials or contamination during manufacturing	
Bioburden (Contaminant)	Impact on safety and efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials or contamination during manufacturing	

a. Description
Belimumab MAB HUMAN (IGG1) ANTI Q9Y275 (TN13B_HUMAN) [HGS1006] is a human IgG1, lambda anti-BLyS (BAFF) monoclonal antibody produced in (b) (4) cells. It has an average molecular weight of 147 KDa and a pI of ~8.6. It has the typical structure of an IgG1 antibody with 4 interchain disulfide bonds and 12 intrachain disulfide bonds and typical N-linked glycan structures in the heavy chain.

b. Mechanism of action
BLyS, a member of the TNF super family, regulates B cell maturation, function, survival and homeostasis. Belimumab inhibits the binding of BLyS to its receptors, and therefore inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin producing plasma cells.

c. Potency Assay
The potency assay is an inhibition of europium-labeled BLyS binding to IM-9 cells, a human B Lymphoblast cell line. Replicates of belimumab reference standard and sample dilutions are incubated with EU-BLyS and then IM-9 cells are added to the belimumab/Eu-BLyS complexes. After further incubation, europium fluorescence is determined. There is an inverse relationship between levels of fluorescence and levels of belimumab in the

ted

d. (b) (4)

e. (b) (4)

f. Manufacturing process summary (b) (4)

(b) (4)

g. Container closure
(b) (4)

h. Dating period and storage conditions
(b) (4) months at (b) (4) C.

C. Drug Product [belimumab] Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin		Other
Appearance (General)	Measure of purity, impact on product safety and immunogenicity	DP manufacture (b) (4)	(b) (4)	
pH (General)	Impact on product stability and conformation	DS manufacture (b) (4)		(b) (4)
Osmolality (General)	Potential impact on therapeutic dose	DS manufacture (b) (4)		
Particulate matter (visible and sub-visible) (General)	Impact on product safety and efficacy	DP manufacture (b) (4)		
Weight variation	Impact on efficacy	DP manufacture		

(General)			(b) (4)
Plunger depth (General)	Impact on efficacy	DP manufacture	(b) (4)
Deliverable Volume (General)	Impact on efficacy	DP manufacture	
Protein Quantity (General)	Impact on efficacy	DP manufacture (b) (4)	
Endotoxin (Contaminant)	Impact on safety and immunogenicity	Contamination may be introduced throughout DP manufacturing process.	
Sterility (Contaminant)	Impact on safety and efficacy (due to degradation or modification of	Contamination may be introduced throughout DP manufacturing.	

	the product)		(b) (4)	
Container Closure Integrity (Contaminant)	Impact on safety	May be impacted by storage conditions.		

a. Potency and Strength
Benlysta (b) (4) is supplied as Belimumab injection for subcutaneous use (200 mg/1.0 mL) as a single (b) (4) sterile liquid drug product in two formats both c

(b) (4)

(b) (4)

(b) (4)

b.

(b) (4)

- Product quality attributes are retained during manufacture, device assembly, transport, shelf life, and use.
- Product is manufactured by a robust and reproducible process that provides a high assurance of quality.
- Provided as a sterile, low-endotoxin product packaged in a container closure system that ensures product integrity for the intended shelf life.
- Product is self-administered subcutaneously via an autoinjector or safety syringe to deliver a 1.0 mL volume containing a single dose of 200 mg belimumab.

- Product is non-interactive with packaging components.

c. List of Excipients
Sodium Chloride 6.7 mg/mL
L-Arginine Hydrochloride 5.3 mg/mL
L-Histidine, Monohydrochloride 1.2 mg/mL
L-Histidine 0.65 mg/mL
Polysorbate 80 0.1 mg/mL

d.

e. (b) (4)

f. (b) (4) (b) (4) with staked 27G (b) (4) needle and rigid needle shield (RNS) that is preassembled onto the syringe. The RNS is composed (b) (4) (b) (4). After filling, the PFS is sealed with 1 mL long rubber plunger stopper (b) (4) (b) (4)

g. Expiration Date & Storage Conditions
The shelf life for DP is 36 months at 2-8°C.

D. Novel Approaches/Precedents

None

E. Any Special Product Quality Labeling Recommendations

F. Establishment Information

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
Manufacture of BDS, Testing of WCB, In-process control testing, unprocessed bulk, BDS release testing Storage of GMP reference standard, MCB and WCB, Storage and shipment of BDS Secondary testing	Human Genome Sciences, Inc. (A wholly owned subsidiary of GSK) Belward Large Scale Manufacturing (LSM) Facility 9911 Belward Campus Drive Rockville, MD 20850	034062104/ 3003782237	Inspection waived	NA	Approve based on inspection and compliance history
(b) (4)			Inspection waived	NA	Approve based on inspection and compliance history

(b) (4)					
(b) (4)			Inspection waived	NA	Approve based on inspection and compliance history
(b) (4)			Inspection waived	NA	Approve based on inspection and compliance history
PRODUCT					
FUNCTION	**INFORMATION**	**DUNS/FEI NUMBER**		**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**

Manufacture of the Syringe DP, Release and Stability Testing, Autoinjector Assembly and Testing, Safety Syringe Assembly and Testing, Labelling and Packaging of Supply, DP Batch Release	Glaxo Operations UK Ltd. Harmire Road Barnard Castle County Durham UK DL12 8DT	228472833/ 3003722390	Inspection scheduled for 06/26/2017 – 07/04/2017	To be determined	Recommendation pending outcome of PLI. Previous inspection and compliance history is satisfactory.
DP release and stability testing	Glaxo Operations UK Ltd. Gunnels Wood Road Stevenage Hertfordshire UK SG1 2NY	218783633/ 3009763376	Inspection waived	NA	Approve based on inspection and compliance history

G. Facilities
Prior Inspection History

Drug Substance

Human Genome Sciences, Inc. (FEI: 3003782237) - DS Manufacture and Testing Facility

- A surveillance inspection was conducted by BLT-DO between April 4-11, 2016 of the HGS Belward Large Scale Manufacturing Facility for profiles CBI and CTX. Quality, Production, Facilities and Equipment and Laboratory Systems were covered. A 3-

(b) (4)

- (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Drug Product

Glaxo Operations UK Ltd. (FEI: 3002807078) – DP Manufacturer, Testing and Release

- The PLI for BLA 761043 belimumab (Benlysta (b) (4)) will be conducted between 06/26/2017 – 07/04/2017.
- A surveillance inspection was conducted between May 22 – June 2, 2017. A 3-item Form FDA483 was issued for 1) Equipment and utensils are not cleaned and maintained at appropriate intervals to prevent malfunctions and contamination that would alter the safety, identity, strength, quality or purity of the drug product; 2) (b) (4) support areas are deficient

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Glax

(b) (4)

(b) (4) This inspection was conducted in response to BLA supplement 125370/36 to add this laboratory as the back-up DP testing laboratory for Benlysta (belimumab) for the US market. Quality and Laboratory Systems were covered. The inspection resulted in no Form FDA 483, with five discussion items. The inspection was classified NAI.

H. Lifecycle Knowledge Management

a. Drug Substance

i. Protocols approved
Annual GMP stability – no extension of shelf life is needed

ii. Outstanding review issues/residual risk
None

iii. Future inspection points to consider
PAI was waived, so the sc manufacturing process should be examined at the next inspection.

b. Drug Product

i. Protocols approved
Annual GMP stability – no extension of shelf life is needed

ii. Outstanding review issues/residual risk
none

iii. Future inspection points to consider
PAI scheduled for 06/26/2017 – 07/04/2017; future inspectional items will be determined based on the inspection.

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
	Product Type			
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity		X	
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		

14.	Other_____			
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)			X
16.	Comparability Protocol(s)		X	
17.	End of Phase II/Pre-NDA Agreements tem)			X
18.	SPOTS (Special Products On-line Tracking System			X
19.	USAN Name Assigned	X		
20.	Other_____			
Quality Considerations				
21.	Drug Substance Overage			
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements	X		
27.	Real Time Release Testing (RTRT)		X	
28.	Parametric Release in lieu of Sterility Testing		X	

29.	Alternative Microbiological Test Methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial Analytical Procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other _____				

Marjorie Shapiro

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Patricia Hughes Troost

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Thuy Thanh Nguyen

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Kathleen Clouse Strebel

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Jessica Hankins, Ph.D.
ACTING BRANCH CHIEF: Patricia Hughes, Ph.D.

BLA:	761043
Applicant:	Human Genome Sciences, Inc. (GlaxoSmithKline)
US License Number:	1820
Submission Reviewed:	BLA
Product:	belimumab (Benlysta®)
Indication:	Adult patients with active, autoantibody-positive systemic lupus erythematosus receiving standard therapy.
Dosage Form:	solution for subcutaneous injection (200 mg/1 mL)
Manufacturing Site:	Drug Substance: Human Genome Sciences, Inc. Belward Large Scale Manufacturing Facility 9911 Belward Campus Dr. Rockville, MD, USA (FEI: 300382237) Drug Product: Glaxo Operations UK Ltd. Harmire Rd. Barnard Castle County Durham DL12 8DT United Kingdom (FEI: 3003722390)
FDA Receipt Date:	September 22, 2016
Action Date:	July 22, 2017

Conclusion and Approvability Recommendation

The BLA was reviewed from a product quality microbiology and sterility assurance perspective. No issues were identified that would preclude approval; however, responses to an information request are pending. The responses to the information request will be documented in an addendum to this review memo. There are 3 post-marketing commitments:

1. Establish a maximum hold time for the [redacted] (b) (4) process and provide bioburden and endotoxin data supporting the maximum hold time from the first three batches of the 2017 manufacturing campaign.

2. Conduct a (b) (4) test method qualification study using one additional lot of belimumab drug substance. In addition, conduct the (b) (4) (b) (4) qualification study using two additional lots of belimumab drug substance.

3. Conduct a low endotoxin recovery study for the belimumab drug product using spiked LAL Reagent Water (LRW) as a control for at least two time points other than the initial spike (e.g., 24 hours and 48 hours). Provide the LER study report to the Agency.

Product Quality Microbiology Assessment

Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	9/22/16	Original BLA application
0004	11/15/16	Response to information request
0011	03/05/17	Response to information request
0012	03/31/17	Response to information request
0016	06/02/17	Response to information request

(b) (4)

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Jessica Hankins

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BLA STN 761043

Belimumab

Human Genome Sciences
(Wholly owned subsidiary of GSK)

OBP, Product Reviewer
Sean Fitzsimmons

OPF/DMA, DS/DP Microbiology Reviewer
Jessica Hankins

OPF/DIA, Facilities Reviewer
Wayne Seifert

OPRO RBPM
Kelly Ballard

ATL
Marjorie Shapiro

OPQ CMC BLA Review Data Sheet

1. **BLA#:** STN 761043

2. **REVIEW DATE:** June 12, 2017

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Rosemarie Neuner
CDTL: Nikolay Nikolov
Pharm/Tox: Brett Jones/Tim Robinson
Product Quality Team: Sean Fitzsimmons/Marjorie Shapiro
CMC Microbiology: Jessica Hankins/Patricia Hughes
Facilities: Wayne Seifert/Peter Qiu
Clinical Pharmacology: Sury Sista/Anshu Marathe
Statistics: Ginto Pottackal/Greg Levin
OBP Labeling: Vicky Borders-Hemphill
RPM: Kelly Ballard and Melinda Bauerlien

4. **MAJOR 21st Century Review DEADLINES**
Filing Meeting: November 9, 2016
Mid-Cycle Meeting: February 16, 2017
Wrap-Up Meeting: June 19, 2017
Primary Review Due: June 18, 2017
Secondary Review Due: June 25, 2017
CDTL Memo Due: June 2, 2017
PDUFA Action Date: July 22, 2017

5. **COMMUNICATIONS WITH APPLICANT AND OND:**

Communication/Document	Date
Information Request	February 9, 2017
Information Request	April 6, 2017
Information Request	May 3, 2017
Information Request	May 23, 2017

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
SD 11 (eCTD 0011)	March 6, 2017	Yes
SD 13 (eCTD 0013)	April 24, 2107	Yes
SD 15 (eCTD 0015)	May 19, 2017	Yes
SD 16 (eCTD 0016)	June 2, 2017	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Benlysta (b) (4)
   b. Trade Name: Benlysta (b) (4)
   c. Non-Proprietary/USAN: belimumab
   d. CAS name: 356547-88-1
   e. Common name: LymphoStat-B, monoclonal anti-BLyS, LSB
   f. INN Name: belimumab
   g. OBP systematic name: MAB HUMAN (IGG1) ANTI Q9Y275 (TN13B_HUMAN) [HGS1006]
   h. Other Names: GSK1550188, HGS1006

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

9. **DOSAGE FORM:** Liquid

10. **STRENGTH/POTENCY:**
   a. The concentration of Benlysta (belimumab) drug product is 200 mg per 1 mL dose
   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 (b) (4) % of reference standard.

11. **ROUTE OF ADMINISTRATION:** Subcutaneous

			Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			yes	Sufficient information in the BLA reviewed by CDRH
			yes	Sufficient information in the BLA reviewed by CDRH
			yes	Sufficient information in the BLA reviewed by CDRH
			Yes	Sufficient information in the BLA reviewed by CDRH
			Yes	Sufficient information in the BLA reviewed by CDRH

13. INSPECTIONAL ACTIVITIES

Belimumab DS will be manufactured at Human Genome Sciences (HGS) Inc., Rockville, Maryland (FEI: 3003782237) and Benlysta (b) (4) (belimumab) DP at Glaxo Operations UK Ltd., Barnard Castle, UK (FEI: 3002807078). The belimumab DS manufacturing process in the Large Scale Manufacturing (LSM) facility at HGS is similar to the belimumab DS process described in BLA 125370/0, dosage form lyophilized (b) (4) are shared between BLA 125370/0 (b) (4) and BLA 761043/0 (b) (4).

The most recent inspection of the HGS facility was conducted by BLT-DO from 4/4 - 11/2016 for profile code CBI that resulted in a VAI conclusion. Inspection coverage for the LSM facility includes a PAI conducted by CDER-DIA from 7/20 - 24/26/2015, and BLT-DO from 10/29/2013 to 11/05/2013 for profile code CBI. The inspections resulted in a VAI and NAI conclusion, respectively.

Based on the compliance history of the firm, the current GMP status, and the fact that HGS has been approved to manufacture other Agency approved products, with the process steps between belimumab DS manufacture for BLA 125370/0 (b) (4) and BLA 761043/0 (b) (4) overall the same, the pre-license inspection of the HGS manufacturing facility in Rockville, Maryland (FEI: 3003782237) is waived for BLA 761043/0 (action date 07/22/2017).

The DP facility inspection is scheduled for June 06/26/2017 – 07/04/2017 and approval will be pending an acceptable inspection and compliance check.

14. CONSULTS REQUESTED BY OBP

Dr. Keith Marin, CDRH, reviewed the prefilled syringe and autoinjector devices for this product. CDRH recommends approval.

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
	Design of Experiments
	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS

None

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The data submitted in this Biologics License Application support the conclusion that the manufacture of Benlysta (b) (4) (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. The Office of Biotechnology Products recommends that Benlysta (b) (4) (belimumab) be approved for human use under conditions specified in the package insert, contingent upon a successful drug product facility inspection.

We recommend an expiration dating period of (b) (4) months for Benlysta (b) (4) drug substance when stored at (b) (4) °C.

We recommend an expiration dating period of 36 months for Benlysta (b) (4) drug product when stored at 2-8°C.

II. List Of Deficiencies To Be Communicated

None

III. List Of Post-Marketing Commitments/Requirement

1. Re-evaluate belimumab drug product lot release acceptance criteria for osmolality, potency and protein concentration assays after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. HGS will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment or Claim Of Categorical Exclusion

HGS requests a categorical exclusion under 21 CFG 25.31 (c). The applicant states they have no knowledge of any extraordinary circumstances that might have a significant effect on the quality of the human environment.

The claim of categorical exemption is accepted.

V. Primary Container Labeling Review

Primary container labeling review was performed by Vicky Borders-Hemphill, OBP.

VI. Review Of Common Technical Document-Quality Module 3.2

The review of module 3.2 is provided below.

VII. Review of Immunogenicity Assays – Module 5.3.1.4

The review of module 5.3.1.4 is provided below.

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Sean Fitzsimmons

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Marjorie Shapiro

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