CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761158Orig1s000

PRODUCT QUALITY REVIEW(S)

Breakthrough/Priority

Recommendation:
BLA: **Approval**

BLA/NDA Number: 761158
Review Number: 2, Addendum
Review Date: 7/16/2020

Addendum: The Assessment uploaded May 4, 2020 to Panorama still applies and is valid. This addendum is to update the facility status of the (b) (4) drug substance manufacturer from WITHHOLD to APPROVE and therefore to update the OPQ Recommendation from PENDING to APPROVE.

Drug Name/Dosage Form	BLENREP (belantamab mafodotin-blmf) / powder for injection
Strength/Potency	100 mg/vial
Route of Administration	Intravenous
Rx/OTC dispensed	Rx
Indication	(b) (4) treatment of adult patients with relapsed and refractory multiple myeloma (b) (4) (b) (4)
Applicant/Sponsor	GlaxoSmithKline Intellectual Property Development Ltd. England
US agent, if applicable	Jinali Dhebariya

Product Overview:

Belantamab mafodotin is a humanized, afucosyated immuno-conjugate that is specific for B-cell Maturation Antigen (BCMA). The antibody is conjugated to a microtubule disrupting agent monomethyl auristatin F (MMAF). Belantamab mafodotin binds to BCMA on multiple myeloma cells, delivering MMAF and inducing apoptosis.

Quality Review Team:

Discipline	**Reviewer**	**Office/Division**
Drug Substance	Anjali Shukla	OBP/DBRRII
Drug Product		
Immunogenicity		
SGD-1269 API	Ben Zhang / Su Tran	ONDP
Labeling	Scott Dallas /James Barlow	OBP/IO
Facility	Zhong Li / Thuy T. Nguyen	OPMA/DBM
Microbiology	Amy Devlin / Wendy Tan / Scott Nichols (DP) Zhong Li / Reyes Candau-Chacon (DS)	OPMA/DBM
Application Team Lead	William Hallett	OBP/DBRRII
Tertiary Assessment	Patrick Lynch	OBP/DBRRII

Submissions Reviewed:

Submission(s) Reviewed	Document Date
0047	05/07/2020

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: **APPROVAL**

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761158 for BLENREP manufactured by GlaxoSmithKline pending a final determination of the compliance status of the drug substance manufacturer (b) (4) The Office of Pharmaceutical Manufacturing Assessment recommendation is initially WITHOLD due to outcome of the pre-licensing inspection. The assessment was amended May 21, 2020 to **APPROVE** following the manufacturers remediation. The data submitted in this application are adequate to support the conclusion that the manufacture of BLENREP is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable: No PMCs from OPQ

A. Establishment Information:

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)			Approve - Based on Previous History
			Approve - Based on PAI/PLI
Human Genome Sciences, Inc. Rockville, MD, USA	3003782237	mAb Intermediate Manufacture; Testing (Release and Stability); WCB Storage Profile Code: **CBI**	Approve - Based on PAI/PLI
(b) (4)			Approve - Based on Previous History
GlaxoSmithKline LLC USA	3004055938	Working Cell Bank (WCB) Storage mAb Intermediate Storage Profile Code: **CBI**	Approve - Based on Previous History
(b) (4)			Approve - Based on Previous History

[redacted] (b) (4)			No Evaluation Necessary
			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History
GlaxoSmithKline Manufacturing SpA San Polo di Torrile, Italy	3002807114	Secondary packaging Leak detection of drug product Profile Code: **SVL**	Approve - Based on Previous History

B. Facilities:

Belantamab drug substance intermediate is manufactured by Human Genome Sciences (FEI: 3003782237). Cell banking operations occur at GlaxoSmithKline, Conshohocken, PA (FEI: 3004055938), (b) (4) (b) (4) (FEI: (b) (4)), and (b) (4) (FEI: (b) (4)).

A Pre-License Inspection was performed at Human Genome Sciences 1/22-29/2020. A 3 item 483 was issued. The firm was acceptable. In addition, a Pre-License Inspection was performed at (b) (4) (b) (4) A 9 item 483 was issued. The facility's status is currently **APPROVE – Based on PAI/PLI**. The pOAI status was downgraded to VAI (approval), following the successful completion of (3) consecutive batches of belantamab mafodotin DS to demonstrate the firm's readiness for commercial manufacturing.

William Hallett

Digitally signed by William Hallett
Date: 7/16/2020 10:16:29AM
GUID: 5317e2c20000ce395db4bc0c4cf39411
Comments: Addendum to May 4 2020 ATL memo to change status from PENDING to APPROVE

Patrick Lynch

Digitally signed by Patrick Lynch
Date: 7/16/2020 10:32:32AM
GUID: 54bfb193000693c35f4278034f85d77a

Breakthrough/Priority

Recommendation:
BLA: Approval (pending final determination of the compliance status of the (b) (4) Drug Substance Manufacturing facility)

BLA/NDA Number: 761158
Review Number: 1
Review Date: 5/4/2020

Drug Name/Dosage Form	BLENREP (belantamab mafodotin-blmf) / powder for injection
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US agent, if applicable	Jinali Dhebariya

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Drug Substance	Anjali Shukla	OBP/DBRRII
Drug Product		
Immunogenicity		
SGD-1269 API	Ben Zhang / Su Tran	ONDP
Labeling	Scott Dallas	OBP/IO
Facility	Zhong Li / Thuy T. Nguyen	OPMA/DBM
Microbiology	Amy Devlin / Wendy Tan / Scott Nichols (DP) Zhong Li / Reyes Candau-Chacon (DS)	OPMA/DBM
Application Team Lead	William Hallett	OBP/DBRRII
Tertiary Assessment	Patrick Lynch	OBP/DBRRII

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Wanda Nguyen	DROOD
Cross-disciplinary Team Lead	Bindu Kanapuru	DHM2
Medical Officer	Andrea Baines/Rachel Ershler	DHM2
Pharmacology/Toxicology	Liang Li / Lian Ma	DHM2
Clinical Pharmacology	George Shen / Lanre Okusanya	DHM2
Statistics	Zing Xu / Yute Wu	DHM2

1. Names:

a. Proprietary Name: BLENREP
b. Trade Name: BLENREP
c. Non-Proprietary Name/USAN: belantamab mafodotin-blmf
d. CAS Registry Number: 2050232-20-5
e. Common Name: n/a
f. INN Name: belantamab mafodotin
g. Compendial Name: n/a
h. OBP systematic name: CONJ: MAB HUMANIZED (IGG1) ANTI BAB60895 (BCMA_HUMAN); SGD 1269 (CB32667279)

Submissions Reviewed:

Submission(s) Reviewed	Document Date
0003: CMC Package #1	09/17/2019
0004	09/23/2019
0006: CMC Package #2	10/08/2019
0008	11/12/2019
0010: CMC Package #3	11/26/2019
0012	12/09/2019
0013	12/19/2019
0014	01/03/2020
0016	01/10/2020
0019	01/24/2020
0021	01/31/2020
0024	02/06/2020
0025	02/10/2020
0027	02/18/2020
0031	02/24/2020
0032	02/28/2020
0033	03/02/2020
0034	03/03/2020
0036	03/06/2020
0037	03/11/2020
0038	03/20/2020
0041	04/09/2020

Quality Review Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	II		(b) (4)	3	CDER DMF active	N/A	No review required as sufficient detail included in BLA.
	III			3	CDER DMF active	N/A	No review required as sufficient detail included in BLA.

(b) (4)	III	(b) (4)	3	CDER DMF active	N/A	No review required as sufficient detail included in BLA.
	III		3	CDER DMF active	N/A	No review required as sufficient detail included in BLA.
	III		3	CDER DMF active	N/A	No review required as sufficient detail included in BLA.
	III		3	CDER DMF active	N/A	Sufficient information related to (b) (4) process validations in BLA

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	119333	Commercial IND

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion: The sponsor is requesting categorical exclusion as listed in 21 CFR Part 25.31(a) as the biological product does not increase the use of the active moiety. GSK indicated they did not have any knowledge of extraordinary circumstances that might cause approval of this product to have a significant effect on the quality of the human environment.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: **APPROVAL** (**PENDING)**

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761158 for BLENREP manufactured by GlaxoSmithKline pending a final determination of the compliance status of the drug substance manufacturer, (b) (4) The Office of Pharmaceutical Manufacturing Assessment recommendation is WITHOLD pending due to outcome of the pre-licensing inspection. The assessment will be amended with the results of the manufacturers remediation. The data submitted in this application are adequate to support the conclusion that the manufacture of BLENREP is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

C. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance Intermediate: Human Genome Sciences, Rockville, MD
  - Drug Substance: (b) (4)
  - Drug Product: (b) (4)
- Fill size and dosage form: 100 mg / Powder for Injection
- Dating period:
  - Drug Product: 12 months: 2-8°C
  - Drug Substance: (b) (4) months: (b) (4) °C
  - Drug Substance Intermediate (belantamab): (b) (4) months: (b) (4) °C
  - Drug Substance intermediate (SGD-1269): Retest Period (b) (4) months: (b) (4) °C
  - Stability Option:
    - For stability protocols:
      - We have approved the stability protocol(s) in your license application for the purpose (b) (4) of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release:
  - Yes, BLENREP is exempted from lot release per FR 95-29960.

D. Benefit/Risk Considerations:

Belantamab mafodotin is an apoptosis-inducing immuno-conjugate that binds and induces apoptosis of BCMA-expressing multiple myeloma cells. The data submitted in this application support that the manufacture of belantamab mafodotin is well controlled and yields a consistently high-quality product. The conditions used in manufacturing have been sufficiently validated, and a consistent product is prepared from the multiple product runs presented. From a product quality perspective, this product is approvable for human use.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable: No PMCs from OPQ

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

Attributes	Impact	Source	Analytical method	Proposed control strategy
Antigen Binding	Represents MOA Impact on biological activity	(b) (4)	SPR	(b) (4)
FcγRIIIa Binding	Represents MOA Impact on biological activity		SPR	
Primary Structure	Proper sequence, including absence of amino acid substitutions, insertions, and deletions, is required to maintain stability, immunogenicity, safety and biological activity of the		SPR	
			Peptide mapping LC- MS/MS, intact and reduced mass analysis LC-MS	
Secondary and Tertiary Structure	Proper conformation is required to maintain stability, immunogenicity, safety and biological activity of the molecule.		SPR	
			Differential scanning calorimetry, Fourier transform infrared	
Glycosylation (b) (4)	Impact on biological activity, PK, immunogenicity, safety		HPLC-FLD ((b) (4) Profile)	
			LC-MS ((b) (4) Profile) Reduced CGE (b) (4)	
Disulfide bond configuration (b) (4)	Disulfide bond configuration has a potential to alter the secondary and tertiary structure of the mAb and impact immunogenicity, biological activity, safety and		SPR	
			Non-reduced and reduced Capillary Gel Electrophoresis	
			Non-reduced peptide mapping	

(b) (4)	PK. Additionally, changes in these could impact the reduction and conjugation of belantamab to belantamab mafodotin		Fluorescence assay kit	Stability Specification (SPR) Extended Characterization
Attributes	**Impact**	**Source**	**Analytical method**	**Proposed control strategy**
(b) (4) Isomerization	Structure-function relationship (SFR) studies have shown (b) (4) (b) (4) isomerization impact biological activity.	(b) (4)	SPR Peptide mapping LC- MS/MS	(b) (4)
Oxidation	SFR studies have shown (b) (4		SPR Peptide mapping LC- MS/MS	
Aggregation (Dimers and Multimers)	SFR studies have shown (b) (4 detected so there is a low risk to immunogenicity and safety		SEC Sedimentation Velocity Analytical Ultracentrifugation (SV- AUC)	
Fragmentation	Impact on biological activity and PK		SEC Reduced CGE Non-Reduced CGE	
Glycation	SFR studies show that glycation does not impact biological activity. Due to the complex nature of (b) (4)		cIEF	

	(b) (4) could pose a risk to patient safety.	(b) (4)	Peptide mapping LC- MS/MS	(b) (4)

B. Drug Substance Belantamab Mafodotin Quality Summary
CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Belantamab Mafodotin Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

Attributes	Impact	Source	Analytical method	Proposed control strategy
Appearance (color and clarity)	Impact on safety and immunogenicity	DS (b) (4) DS (b) (4)	Ph. Eur. Visual inspection, Turbidimeter	(b) (4)
Visible Particles	Impact on safety and immunogenicity	Intrinsic to the formulation	Ph. Eur./USP Visual evaluation	
Sub-visible Particles (b) (4)	Impact on safety and immunogenicity	Intrinsic to the formulation	Ph. Eur./USP HIAC, MFI	
pH	Impact on safety and immunogenicity	Intrinsic to the formulation	Ph. Eur./USP pH meter	
Osmolality	Impact on safety and immunogenicity	Intrinsic to the formulation	Ph. Eur./USP Osmometer	
Concentration	Impact on biological activity	Intrinsic to the formulation	Variable pathlength UV/VIS	
(b) (4)	(b) (4) which is regarded as less toxic and lower risk to patient safety (ICH Q3C)	DS (b) (4) (b) (4)	LC-UV	
(b) (4) Total Impurities	Impact on biological activity and safety	(b) (4) Process	HPLC	

- **Description:**
Belantamab is a recombinant, afucoylated humanized IgG1κ monoclonal antibody that binds B-cell maturation antigen (BCMA). The amino acid sequence of the variable domain was (b) (4) Belantamab consists of 4 polypeptide chains with 2 identical heavy chains, 451 amino acids each, and 2 identical light chains, 214 amino acids each, and a molecular weight of 146 kDa. The belantamab expression construct is expressed in a CHO cell line, (b) (4) Belantamab drug substance intermediate

is stored at (b) (4) °C, (b) (4) (b) (4)

SGD-1269, also called maleimidocaproyl monomethylauristatin F, or mc-MMAF, is a cytotoxic small molecule. It is manufactured via (b) (4)

Belantamab mafodotin drug substance is an antibody-drug conjugate that results from (b) (4) (b) (4) a target drug-antibody ratio (DAR) of four. The theoretical mass of 152 kDa is based on belantamab conjugated to an average of 4 SGD-1269 molecules. The (b) (4) drug substance is stored at (b) (4) °C, (b) (4)

- **Mechanism of Action (MoA):**
  Belantamab mafodotin binds to BCMA on the cell surface of malignant plasma B cells and is internalized. The mAb is degraded in the lysosome and active cytotoxic drug (cys-mcMMAF) is released inside the cell. Cys-mcMMAF inhibits microtubule formation by binding to α-tubulin and arresting mitosis, leading to apoptosis. Additionally, the antibody is afucosylated that increases binding to FcγRIIIa receptors and enhances recruitment and activation of immune effector cells.

- **Potency Assay:**
  There are three potency assays for belantamab mafodotin drug substance. The first is a cell-based assay that measures the viability of a human multiple myeloma cell line. The viability of the target cells are detected by luminescence and is dose-dependent on the activity of belantamab mafodotin and is reported as a relative percentage of the activity of the reference standard. The other two potency assays quantify belantamab mafodotin binding to BCMA and to FcγRIIIa by surface plasmon resonance (SPR).

- **Reference Materials:**
  (b) (4) GSK has a two-tiered reference standard system (b) (4) (b) (4) (b) (4)

- **Critical starting materials or intermediates:**
  (b) (4)

- **Manufacturing process summary:**
  (b) (4)

(b) (4)

- **Container closure:**
  Belantamab mafodotin drug substance is stored in (b) (4) containers with (b) (4) closures.

- **Dating period and storage conditions:**
  GSK conducted real-time, accelerated, and stressed stability studies on 3 intended-for-commercial lots and 6 clinical lots to support a proposed dating period of (b) (4) months when stored at (b) (4) °C.

C. Drug Product BLENREP (belantamab mafodotin-blmf) for injection, 100 mg/vial Quality Summary:

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

Attributes	Impact	Source	Analytical method	Proposed control strategy
Appearance (physical appearance of powder, color and clarity of the liquid)	Impact on safety and immunogenicity	DP (b) (4)	Ph. Eur. Visual inspection, Turbidimeter	(b) (4)
Visible Particles	Impact on safety and immunogenicity	Intrinsic to the formulation	Ph. Eur./USP Visual evaluation	
Sub-visible Particles (b) (4)	Impact on safety and immunogenicity	Intrinsic to the formulation	Ph. Eur./USP HIAC, MFI	
pH	Impact on safety and immunogenicity	Intrinsic to the formulation	Ph. Eur./USP pH meter	
Osmolality	Impact on safety and immunogenicity	Intrinsic to the formulation	Ph. Eur./USP Osmometer	
Concentration	Impact on biological activity	Intrinsic to the formulation	Variable pathlength UV/VIS	

Attributes	Impact	Source	Analytical method	Proposed control strategy (b) (4)
Drug Antibody Ratio (DAR)	Represents MOA Impact on biological activity	DS (b) (4)	HIC	
Sterility	mpact on safety (infection), purity, and efficacy (via degradation or modification of the product by microbial contamination)	Contamination may be introduced throughout the DP manufacturing process or failure of container closure integrity	USP Sterility Test Method	
Endotoxin	Safety (pyrogenic fever, increased immunogenicity risk) and purity	Raw materials, manufacturing process, or failure of container closure integrity	USP (b) (4) Test Method	
Container Closure Integrity	Impact on safety (maintenance of sterility during shelf life)	Container closure breaches during storage	(b) (4)	
Reconstitution Time	Impact on biological activity	DP (b) (4)	Reconstitution time	
Residual Moisture	Impact on biological activity	DP (b) (4)	Karl Fischer titration	
Weight variation	Impact on biological activity	DP (b) (4)	Dose uniformity by weight variation	
Elemental Impurities	Impact on safety and biological activity	Input Materials	ICP-MS	

Attributes	Impact	Source	Analytical method	Proposed control strategy
(b) (4) (b) (4)	(b) (4)	Stressed storage conditions for DS and DP	Peptide mapping LC-MS/MS	(b) (4)
			cIEF	

- Potency and Strength:
  BLENREP (belantamab mafodotin) for injection, is supplied at 100mg/vial. Potency of belantamab mafodotin is determined as a percent of cell growth inhibition, percent BCMA-antigen binding, and percent FcγRIIIa binding compared to the current reference standard. The potency assay is the same as described in the drug substance section of this review.

- Summary of Product Design:
  BLENREP is supplied as a sterile, preservative-free, white to yellow lyophilized powder in a single-dose vial containing 50mg/mL belantamab mafodotin.

- List of Excipients:
  Excipients include (b) (4) mM (b) (4) citric acid, (b) (4) mM trehalose, (b) (4) mM disodium edetate (EDTA), (b) (4) polysorbate 80, at pH 6.2.

- Reference Materials:
  The same reference material is used for drug substance and drug product.

- Manufacturing process summary:
  The manufacturing process of BLENREP includes (b) (4) (b) (4)

  The control strategy includes (b) (4) (b) (4)

  (b) (4)

- Container closure:

The container closure is filled into (b) (4) clear glass vials, sealed with 20 mm (b) (4) (b) (4) rubber stoppers, and secured by aluminum overseals with orange removable plastic caps.

- Dating period and storage conditions:
  The dating period for BENREP is 12 months at 2-8°C.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:
Store in a refrigerator at 2-8°C

F. Establishment Information:

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)			Approve - Based on Previous History
			Withhold - Based on PAI/PLI
Human Genome Sciences, Inc. Rockville, MD, USA	3003782237	mAb Intermediate Manufacture; Testing (Release and Stability); WCB Storage Profile Code: **CBI**	Approve - Based on PAI/PLI
(b) (4)			Approve - Based on Previous History
GlaxoSmithKline LLC USA	3004055938	Working Cell Bank (WCB) Storage mAb Intermediate Storage Profile Code: **CBI**	Approve - Based on Previous History
(b) (4)			Approve - Based on Previous History
			No Evaluation Necessary
			Approve - Based on Previous History

[redacted] (b) (4)			Approve - Based on Previous History
[redacted]			Approve - Based on Previous History
GlaxoSmithKline Manufacturing SpA San Polo di Torrile, Italy	3002807114	Secondary packaging Leak detection of drug product Profile Code: **SVL**	Approve - Based on Previous History

G. Facilities:

Belantamab drug substance intermediate is manufactured by Human Genome Sciences (FEI: 3003782237). Cell banking operations occur at GlaxoSmithKline, Conshohocken, PA (FEI: 3004055938), [redacted] (b) (4) (b) (4) (FEI: [redacted] (b) (4)), and [redacted] (b) (4) (FEI: [redacted] (b) (4)).

A Pre-License Inspection was performed at Human Genome Sciences 1/22-29/2020. A 3 item 483 was issued. The firm was acceptable. In addition, a Pre-License Inspection was performed [redacted] (b) (4) (b) (4) A 9 item 483 was issued. The facility's status is currently **withhold**. The pOAI status will be downgraded to VAL (approval), pending on the successful completion of (3) consecutive batches of belantamab mafodotin DS to demonstrate the firm's readiness for commercial manufacturing.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
-annual stability protocol
-qualification of new working cell bank
-concurrent validation [redacted] (b) (4) (b) (4)
in the belantamab manufacturing process
-validation of [redacted] (b) (4) belantamab mafodotin drug substance
- protocol for qualification of new belantamab working reference standard
- protocol for qualification of new belantamab mafodotin working reference standard
- [redacted] (b) (4) new facility

ii. Outstanding review issues/residual risk:
-n/a

iii. Future inspection points to consider:
-Follow-up on 483 observations
-Evaluate trending of release and in-process tests results

b. Drug Product

i. Protocols approved:
-annual stability protocol

ii. Outstanding review issues/residual risk: n/a

iii. Future inspection points to consider:
-Evaluate trending of release and in-process tests results

William Hallett

Digitally signed by William Hallett
Date: 5/04/2020 04:14:54PM
GUID: 5317e2c20000ce395db4bc0c4cf39411
Comments: Assessment will be amended once compliance status of (b) (4) facility is updated.

Patrick Lynch

Digitally signed by Patrick Lynch
Date: 5/05/2020 10:30:35AM
GUID: 54bfb193000693c35f4278034f85d77a

Breakthrough/Priority

Recommendation:
BLA: **Approval**

BLA/NDA Number: 761158
Review Number: 2, Addendum
Review Date: 7/16/2020

Addendum: The Assessment uploaded May 4, 2020 to Panorama still applies and is valid. This addendum is to update the facility status of the (b) (4) drug substance manufacturer from WITHHOLD to APPROVE and therefore to update the OPQ Recommendation from PENDING to APPROVE.

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Application Team Lead	William Hallett	OBP/DBRRII
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Submissions Reviewed:

Submission(s) Reviewed	Document Date
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I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: **APPROVAL**

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B. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable: No PMCs from OPQ

A. Establishment Information:

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)			Approve - Based on Previous History
			Approve - Based on PAI/PLI
Human Genome Sciences, Inc. Rockville, MD, USA	3003782237	mAb Intermediate Manufacture; Testing (Release and Stability); WCB Storage Profile Code: **CBI**	Approve - Based on PAI/PLI
(b) (4)			Approve - Based on Previous History
GlaxoSmithKline LLC USA	3004055938	Working Cell Bank (WCB) Storage mAb Intermediate Storage Profile Code: **CBI**	Approve - Based on Previous History
(b) (4)			Approve - Based on Previous History

(b) (4)			No Evaluation Necessary
			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History
GlaxoSmithKline Manufacturing SpA San Polo di Torrile, Italy	3002807114	Secondary packaging Leak detection of drug product Profile Code: **SVL**	Approve - Based on Previous History

B. Facilities:

Belantamab drug substance intermediate is manufactured by Human Genome Sciences (FEI: 3003782237). Cell banking operations occur at GlaxoSmithKline, Conshohocken, PA (FEI: 3004055938), (b) (4) (b) (4) (FEI: (b) (4)), and (b) (4) (FEI: (b) (4)).

A Pre-License Inspection was performed at Human Genome Sciences 1/22-29/2020. A 3 item 483 was issued. The firm was acceptable. In addition, a Pre-License Inspection was performed (b) (4) (b) (4) A 9 item 483 was issued. The facility's status is currently **APPROVE – Based on PAI/PLI**. The pOAI status was downgraded to VAI (approval), following the successful completion of (3) consecutive batches of belantamab mafodotin DS to demonstrate the firm's readiness for commercial manufacturing.

William Hallett

Digitally signed by William Hallett
Date: 7/16/2020 10:16:29AM
GUID: 5317e2c20000ce395db4bc0c4cf39411
Comments: Addendum to May 4 2020 ATL memo to change status from PENDING to APPROVE

Patrick Lynch

Digitally signed by Patrick Lynch
Date: 7/16/2020 10:32:32AM
GUID: 54bfb193000693c35f4278034f85d77a

BLA STN 761158

Belantamab mafodotin

Glaxo SmithKline LLC

Anjali Shukla, PhD, Product Quality Reviewer
William Hallett, PhD, Application Technical Lead
Division of Biotechnology Research and Review II
Office of Biotechnology Products

OBP CMC Review Data Sheet

1. BLA#: 761158
2. Review Date: March 5, 2020
3. Primary Review Team:

Clinical:	Rachel Ershler
	Andrea Baines
Nonclinical:	Natalie Simpson
Product Quality:	Anjali Shukla
	Zhong Li
	Amy Devlin
	Wendy Tan
Clinical Pharmacology:	Liang Li
	Guoxiang Shen
Statistics:	Qing Xu
OBP labeling:	Scott Dallas
RBPM:	Kelly Ballard

4. Major GRMP Deadlines:

Filing Meeting:	January 06, 2020
Mid-Cycle Meeting:	February 03, 2020
Late-Cycle Meeting:	March 30, 2020
Primary review due:	March 5, 2020
ATL Memo due:	March 5, 2020
PDUFA Action Date:	August 5, 2020

5. Communications with Sponsor and OND:

Communication/Document:	Date:
TCon with Sponsor	January 30, 2020
Mid-Cycle Meeting with OND	February 03, 2020
Mid-Cycle Meeting with Sponsor	February 11, 2020
Labeling Meeting with OND	February 27, 2020
Meeting with OND	March 02, 2020
TCon with Sponsor	March 03, 2020

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
Information Request Response 0008	11/12/2019	Yes
Information Request Response 0012	12/09/2019	Yes

Information Request Response 0021	01/31/2020	Yes (Review of OPMA IR responses in #0021 deferred to OPMA)
Information Request Response 0024	02/06/2020	Yes
Information Request Response 0027	02/18/2020	Yes
Information Request Response 0031	02/24/2020	Yes
Information Request Response 0032	02/28/2020	Yes
Information Request Response 0033	03/02/2020	Yes (Review of OPMA IR responses in #0033 deferred to OPMA)
Information Request Response 0034	03/03/2020	Yes

7. Drug Product Name/Code/Type:
   - a. Proprietary name: Blenrep
   - b. Trade name: Blenrep
   - c. Non-proprietary Name/USAN: Belantamab mafodotin
   - d. CAS name: 2050232-20-5
   - e. Common name: GSK2857916
   - f: INN name: Belantamab mafodotin
   - g. Compendial name: None
   - h. OBP systematic name: CONJ: MAB HUMANIZED (IGG1) ANTI BAB60895 (BCMA_HUMAN); SGD 1269 (CB32667279)
   - i. Other names

8. Pharmacological Category: B-cell maturation antigen (BCMA)-directed antibody and microtubule inhibitor conjugate
9. Dosage Form: Powder for injection
10. Strength/Potency: 100 mg
11. Route of Administration: Intravenous
12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			m 1.4.2	No review required as sufficient detail included in BLA. CDER DMF active
			m 1.4.2	No review required as sufficient detail included in BLA. CDER DMF active
			m 1.4.2	No review required as sufficient detail included in BLA. CDER DMF active

(b) (4)	m 1.4.2	No review required as sufficient detail included in BLA. CDER DMF active
	m 1.4.2	No review required as sufficient detail included in BLA. CDER DMF active
	m 1.4.2	No review required as sufficient detail included in BLA. CDER DMF active

13. Inspectional Activities:

Human Genome Sciences
9911 and 9910 Belward Campus Drive
Rockville, MD 20850
FEI: 3003782237
January 22-24, 27-29, 2020

(b) (4)

A pre-licensure inspection of the drug substance intermediate belantamab manufacturing facility Human Genome Sciences, Rockville, MD was conducted from January 22-24, 27-29, 2020 by Amy Devlin (OPMA, Lead Inspector), Thuy Nguyen (OPMA), Xiaoshi Wang (OBP) and Anjali Shukla (OBP). The inspection covered the five quality systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention and Laboratory Controls. A three-item FDA Form 483 was issued.

A pre-licensure inspection of the drug substance belantamab mafodotin manufacturing facility (b) (4) (b) (4) was conducted (b) (4) by Zhong Li (OPMA), William Hallett (OBP) and Chih-Jung Hsu (OBP). A 9 item FDA Form 483 was issued.

14. Consults Requested by OBP: None

15. Quality by Design Elements:

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

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

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation

The data submitted in BLA 761158 support the conclusion that the manufacturing process of Blenrep (belantamab mafodotin) is well controlled and leads to a product that is pure and potent. However, the recommendation for approval for human use is pending the approval of the DS manufacturing facility.

II.	List of Deficiencies to be Communicated	None
III.	List of Post-Marketing Commitments/Requirements	None
IV.	Review of Common Technical Document- Quality Module 1 A. Environmental Assessment of Claim of Categorical Exclusion	

The proposed action is subject to the categorical exclusion listed in 21 CFR Part 25.31(a). As stated in 21 CFR Part 25.31(a), action on an NDA or NDA supplement is categorically excluded from environmental assessment requirements if the action does not increase the use of the active moiety. GlaxoSmithKline does not have knowledge of any extraordinary circumstances that might cause this action to have a significant effect on the quality of the human environment.

V.	Primary Container Labeling Review Scott Dallas, OBP	Assessment performed by
VI.	Review of Common Technical Document- Quality Module 3.2	Refer below
VII.	Review of Immunogenicity Assays- Module 5.3.1.4	Refer below

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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	7/8/2020
Assessor:	Jim Barlow, RPh, Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Anjali Shukla, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research II
Application:	BLA 761158
Applicant:	GlaxoSmithKline Intellectual Property Development Ltd. England
Submission Dates:	November 14, December 5, 2019; and February 10, April 13 and July 8, 2020
Product:	Blenrep® (belantamab mafodotin-blmf)
Dosage form:	For injection
Strength and Container-Closure:	100 mg lyophilized powder in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application seeking an indication (b) (4) for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4) (b) (4) (b) (4)
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling submitted on July 8, 2020 are **acceptable** from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

CONCLUSION

The prescribing information, medication guide, container labels, and carton labeling submitted on July 8, 2020 were assessed and found to be **acceptable** from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The phrase "Manufactured by" will not be requested, because of space constraints with the label.

To Applicant: Revise the manufacturer information to appear with the name GlaxoSmithKline Intellectual Property Development Ltd. England and address of the applicant as appears on FDA form 356h. Please refer to 21 CFR 600.3(t) for the definition of a biologic product manufacturer, and to 21 CFR 610.60(a)(2) and 21 CFR 610.60(c) for additional information.

April 13, 2020: The applicant revised the manufacturer name to the name of the applicant as it appears on FDA form 356h.

FDA Response: The applicant's revision is acceptable.

[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60 (c) *Partial label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label.

Lot number or other lot identification (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: As currently presented, the location of lot number and expiration date are not clearly defined on the container label. Please confirm the inclusion and location of the lot number and expiration date [refer to 21 CFR 610.60(a)].

April 13, 2020: The applicant submitted a revised image with a lot and expiration date designation.

FDA Response: The applicant's presentation of the lot information is acceptable.

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: As currently presented, the location of lot number and expiration date are not clearly defined on the container label. Please confirm the inclusion and location of the lot number and expiration date [refer to 21 CFR 610.60(a)].

April 13, 2020: The applicant submitted a revised image with a lot and expiration date designation.

FDA Response: The applicant's presentation of the expiration date information is acceptable.

Beyond Use Date (Multiple-dose containers) (container label)	Acceptable
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Product Strength (container label)	Acceptable
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: The Rx Only statement appears prominent in bold font on the principal display panel. Decrease the prominence by debolding the Rx Only statement.

April 13, 2020: The applicant debolded the Rx Only statement.

FDA Response: The applicant's revision is acceptable.

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The container label could be considered a partial label per 21 CFR 610.60(c), and space constraints inhibit the ability to include a Medication Guide statement. The omission of the statement on the container label is acceptable.

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Please confirm there is no text on the ferrule and cap overseal of the vials. Refer to USP General Chapters: <7> Labeling (Ferrules and Cap Overseals).

April 7, 2020: The applicant responded via email that there is no text on the ferrule and cap overseal of the vials.

FDA Response: The applicant's response is acceptable.

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Please confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located per 21 CFR 610.60(e).

April 7, 2020: The applicant responded via email that a labeled container allows the end user to visually inspect the drug product.

FDA Response: The applicant's response is acceptable.

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

***NDC numbers* (container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Revise the statement, [redacted] "Dosage: See Prescribing Information."

April 13, 2020: The applicant revised the Dosage statement to read "Dosage: See Prescribing Information".

FDA Response: The applicant's revision is acceptable.

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
Space constraints limit the inclusion of an ingredient statement.

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Revise and bold the statement from, [redacted] to "**Store refrigerated at 36°F to 46°F (2°C to 8°C).**" We recommend this to increase prominence of this important information and minimize the risk of the storage information being overlooked.

April 13, 2020: The applicant revised the Storage statement to read "**Store refrigerated at 36°F to 46°F (2°C to 8°C).**"

FDA Response: The applicant's revision is acceptable.

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	✓ Yes ☐ No ☐ N/A

[redacted] Agent	Acceptable
Regulation: 21 CFR 201.57(c)(17)(iv)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: [redacted] we recommend including the statement in bold red font on the side panel of the container label, "**CAUTION: [redacted] Agent**".

April 13, 2020: The applicant included the statement "**CAUTION: [redacted] Agent.**".

July 8, 2020: To be consistent with OSHA terminology, the Agency is changing "**CAUTION: [redacted] Agent**" to read "**CAUTION: Hazardous Drug**".

FDA Response: The applicant's revision is acceptable.

Package[6] Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Revise the manufacturer information to appear with the name, GlaxoSmithKline Intellectual Property Development Ltd. England, and address of the applicant as appears on FDA form 356h. Please refer to 21 CFR 600.3(t) for the definition of a biologic product manufacturer, and to 21 CFR 610.61(b)(2) and 21 CFR 610.64 for additional information.
April 13, 2020: The applicant revised the manufacturer's name and address as requested.

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

FDA Response: The applicant's revision is acceptable.

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The carton displays a "No Preservative" statement.

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Revise and bold the statement from, (b) (4) (b) (4) to "**Store refrigerated at 36°F to 46°F (2°C to 8°C).**" We recommend this to increase prominence of this important information and minimize the risk of the storage information being overlooked.

April 13, 2020: The applicant revised the statement to read "Store refrigerated at 36°F to 46°F (2°C to 8°C)."

FDA Response: The applicant's revision is acceptable.

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
No additional handling statements are needed.

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Dr. Shukla confirmed the rubber stopper is not made with natural rubber latex. Thus, no additional statements are required to be added to the carton labeling.

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Please include an ingredient statement, refer to 21 CFR 610.61(n) and 21 CFR 201.100(b), and include preparation instructions, refer to 21 CFR 201.5(g). Consider including a statement similar to: Each 100 mg per vial requires reconstitution with 2 mL of Sterile Water for Injection, USP, to obtain a concentration of 50 mg/mL. Each mL of reconstituted solution contains belantamab mafodotin-xxxx (50 mg), citric acid (0.42 mg), disodium edetate dihydrate (0.019 mg), polysorbate 80 (0.2 mg), trehalose dihydrate (75.6 mg), and trisodium citrate dihydrate (6.7 mg).

April 13, 2020: The applicant revised the inactive ingredient statement as requested.

FDA Response: The applicant's revision is acceptable.

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The source of the antibody is not a safety issue.

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

The carton displays a "No U.S. standard of potency" statement which is acceptable.

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: To Applicant: The Rx Only statement appears prominent in bold font on the principal display panel. Decrease the prominence by debolding the Rx Only statement. April 13, 2020: The applicant debolded the Rx Only statement. FDA Response: The applicant's revision is acceptable.

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	✓ Yes ☐ No ☐ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Revise the statement, (b) (4) (b) (4) to "Dosage: See Prescribing Information."

April 13, 2020: The applicant revised the dosage statement to read "Dosage: See Prescribing Information."

FDA Response: The applicant's revision is acceptable.

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	✓ Yes ☐ No ☐ N/A

Medication Guide (package labeling)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: We note the inclusion of a Medication Guide as part of the labeling submission; however, the Medication Guide statement is missing from the principal display panel of the container label and carton labeling. Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner. Ensure the Medication Guide statement appears in accordance with 21 CFR 208.24(d).

April 13, 2020: The applicant included a Medication Guide statement on the principal display panel.

FDA Response: The applicant's revision is acceptable.

(b) (4) **Agent**	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: (b) (4) (b) (4) (b) (4) we recommend including the statement in bold red font on the side panel of the container label, "**CAUTION:** (b) (4) **Agent**".

April 13, 2020: The applicant included the statement "**CAUTION:** (b) (4) **Agent.**" on the principal display panel.

July 8, 2020: To be consistent with OSHA terminology, the Agency is changing "**CAUTION:** (b) (4) **Agent**" to read "**CAUTION: Hazardous Drug**".

FDA Response: The applicant's revision is acceptable.

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Dr. Shukla confirmed the product strength as 100 mg/vial.

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Reconstituted product in a vial:
Dr. Shukla confirmed the drug product can be reconstituted with 2 mL of Sterile Water for Injection, USP, to yield a concentration of 50 mg/mL. The reconstituted solution should not be shaken or frozen, (b) (4) and can be swirled gently to reconstitute. The reconstituted solution is clear to opalescent, colorless to yellow to brown liquid.

Diluted infusion solution:
Dr. Shukla confirmed the reconstituted drug product can be diluted in 0.9% Sodium Chloride Injection to a final concentration of 0.2 mg/mL to 2 mg/mL. The compatibility studies were completed with infusion bags made of polyvinyl chloride and polyolefin. The diluted infusion solution (infusion bag with the drug product) should not be shaken or frozen, (b) (4) (b) (4) and can be mixed by gently inversion. Dr. Shukla confirmed the diluted infusion solution should be clear and colorless.

Storage:
Dr. Shukla confirmed from a stability perspective and the microbiology team from a microbiology perspective confirmed the data support that 1) storage of the reconstituted solution in a vial for up to 4 hours under refrigerated or room temperature conditions, 2) storage of the diluted infusion solution in an infusion bag up to 24 hours under refrigerated condition, and 3) storage of the diluted infusion solution in an infusion bag up to 6 hours at room temperature.

Infusion bags:
Dr. Shukla confirmed the compatibility studies were with infusion bags made of polyvinyl chloride and polyolefin, and the results were acceptable.

To Applicant: Your compatibility studies support PVC and PO bags. Thus, the label was updated to include this information. (The following sentence was inserted: The infusion bags must be made of polyvinyl chloride (PVC) or polyolefin (PO).)

April 13, 2020: The applicant included the proposed sentence to state the infusion bags must be made of PVC or PO.

FDA Response: The applicant's revision is acceptable.

To Applicant: Revised to include the verbatim statement per 21 CFR 201.57(c)(3)(iv). (The following sentence was included: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.)

April 13, 2020: The applicant accepted FDAs' verbatim statement per 21 CFR 201.57(c)(3)(iv).

FDA Response: The applicant's revision is acceptable.

To Applicant: The paragraph was revised based upon data submitted for the drug product in the infusion bag.
(The revisions applied to the identifying characteristics and particulate matter of the infusion solution to read: The diluted infusion solution should be clear and colorless. Discard if particulate matter is observed.)

April 13, 2020: The applicant included the proposed statements from FDA.

FDA Response: The applicant's revisions are acceptable.

To Applicant: Please insert the appropriate filter pore size. (The comment applied to the sentence: Filtration of the diluted solution is not required; however, if the diluted solution is filtered, use a polyethersulfone (PES)-based filter.)

April 13, 2020: The applicant inserted a reference to the pore size of 0.2 microns.

FDA Response: The applicant's revision is acceptable.

To Applicant: Please include the statement "Do Not Freeze" to reinforce that the infusion solution should not be frozen.
The bullet information was revised to read:
If the diluted infusion solution of BLENREP is not used immediately, store refrigerated at 36ºF to 46ºF (2ºC to 8ºC) for up to 24 hours. **Do not freeze**. Once removed from refrigeration, administer the diluted infusion solution of BLENREP within 6 hours (including infusion time).

April xxxx

FDA Response: The applicant's revisions are acceptable.

July 8, 2020: The firm revised as requested and included "**Do not freeze**" to reinforce that the infusion should not be frozen in the "Dilution" subsection of the DOSAGE and ADMINISTRATION section.

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Dr. Shukla confirmed the identifying characteristics of the lyophilized powder as a "white to yellow" color.

To Applicant: Revised to include the identifying characteristics per 21 CFR 201.57(c)(4). to read:
For injection: 100 mg of belantamab mafodotin-xxxx as a white to yellow lyophilized powder in a single-dose vial for reconstitution.

April 13, 2020: The applicant inserted the identifying characteristics, white to yellow, as requested by FDA.

FDA Response: The applicant's revision is acceptable.

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Dr. Shukla confirmed the wording in the first paragraph concerning the drug substance (DS) was acceptable, which also states the antibody is produced in a mammalian cell line (Chinese Hamster Ovary), the molecular weight of the DS is 152 kDa, and approximately 4 molecules of mafodotin are attached to each antibody molecule. Dr. Shukla also confirmed the figure of the structure for Belantamab mafodotin-blmf submitted April 13, 2020 was acceptable.

Dr. Shukla confirmed the drug product is preservative-free, the pH is 6.2, there is no U.S. standard of potency, and the qualitative and quantitative information was correct.

To Applicant: The first paragraph was revised to include the pharmacologic class per 21 CFR 201.57(c)(12). (The first sentence was revised to read "Belantamab mafodotin-xxxx is a B-cell maturation antigen (BCMA)-directed antibody and microtubule inhibitor conjugate".)

To Applicant: Revised to include additional structural information concerning the drug product. (The following sentence was inserted into the second paragraph: Approximately 4 molecules of mafodotin are attached to each antibody molecule.)

To Applicant: Revised to include the proper name and dosage formulation per 21 CFR 201.57(c)(12). (To read in part: TRADENAME (belantamab mafodotin-xxxx) for injection is a sterile, preservative-free ….)

April 13, 2020: The applicant accepted FDAs' three proposed revisions as indicated above to Section 11.

FDA Response: The applicant's revisions are acceptable.

Full Prescribing Information	
15 & 16 Cytotoxic Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: Tradename is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Pharm tox has confirmed the drug product is hazardous and the appropriate reference and hazardous statements have been included in Sections 2, 15 and 16.
July 8, 2020: OBP Confirmed that sections 2, 15 and 16 contained "hazardous statement" in text.

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Dr. Shukla confirmed the rubber stopper is not made with natural rubber latex. Dr. Shukla confirmed the drug product does not need to be protected from light, freezing or shaking.

To Applicant: Revised to include the dosage formulation and identifying characteristics per 21 CFR 201.57(c)(17). (Revised the first sentence in Section 16 to read:
TRADENAME (belantamab mafodotin-xxxx) for injection, is a sterile, preservative-free, white to yellow lyophilized powder for ….)

April 13, 2020: The applicant included the dosage formulation and identifying characteristics as requested by the FDA.

FDA Response: The applicant's revisions are acceptable.

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: Revised the "manufacturer by" information to appear with the name and address of the applicant as appears on FDA form 356h. Please refer to 21 CFR 600.3(t) for the definition of a biologic product manufacturer. Also per 21 CFR 201.1(i) and 21 CFR 201.100(e), the name and location of business listed here (street address, city, state, and zip code) is required in labeling. Please insert your address information. (Revised the manufacturer's name to read, GlaxoSmithKline Intellectual Property Development Ltd. England, which is the applicant name on the FDA form 356h. The applicant will need to include the address information).

April 13, 2020: The applicant revised the manufactured by statement as requested.

FDA Response: The applicant's revision is acceptable.

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

MEDICATION GUIDE	
STORAGE AND HANDLING	**Acceptable**

Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
Not applicable: The product is administered in a healthcare setting, so storage and handling information does not need to be conveyed in a medication guide.

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Revise the "manufacturer by" information to appear with the name and address of the applicant as appears on FDA form 356h. Please refer to 21 CFR 600.3(t) for the definition of a biologic product manufacturer. Also per 21 CFR 201.1(i) and 21 CFR 201.100(e), the name and location of business listed here (street address, city, state, and zip code) is required in labeling. Please insert your address information.

April 13, 2020: The applicant revised the manufacturer name and address information as requested.

FDA Response: The applicant's revisions are acceptable.

Patient Information Labeling Evaluation (N/A)

APPENDIX C. Acceptable Labels and Labeling
Prescribing Information and Medication Guide (submitted on July 8, 2020 \\cdsesub1\evsprod\bla761158\0058\m1\us\114-labeling\1141-draft\draft-clean.docx)

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James Barlow

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Anjali Shukla

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: **4/10/2020**
To: Administrative File, **STN 761158/0**
From: Zhong Li, Ph.D., Reviewer, CDER/OPQ/OPMA/DBM/Branch 1
Through: Reyes Candau-Chacon, Ph.D., Quality Assessment Lead, OPMA/DBM/Branch 2
Subject: New Biologic License Applications (BLA)
US License: 2148
Applicant: GlaxoSmithKline Intellectual Property Development Ltd. England (GSK)
Facilities: Human Genome Sciences, Inc. *(FEI: 3003782237; mAb intermediate manufacturer)*
(b) (4) *(FEI:* (b) (4) *; ADC DS manufacturer)*
(b) (4) *(FEI:* (b) (4) *; DP manufacturer)*
Product: Belantamab Mafodotin (GSK2857916)
Dosage: Lyophilized Powder (100 mg/vial) for Intravenous Injection after Reconstitution
Indications: Treatment of adult patients with relapsed and refractory multiple myeloma
Due date: PDUFA date 4/2/2020 (Primary Review due 3/5/2020)

Recommendation: The drug substance part of this BLA is recommended for approval from a microbial control and microbiology product quality perspective.

Review Summary

GSK has submitted BLA 761158/0 to license belantamab mafodotin and the associated monoclonal antibody (mAb) intermediate, antibody-drug conjugate (ADC) drug substance (DS), and drug product (DP) manufacturing processes.

The CMC sections of the BLA were submitted in (5) waves (from 9/17/2019 to 11/26/2019) in eCTD under a Real-Time Oncology Review (RTOR) Pilot program. The BLA was submitted as a rolling BLA, which was completed on December 5, 2019. This review contains an assessment of the mAb intermediate and ADC DS sections from a microbiological quality perspective. For review of the DP aspects of the application, please see the review by Dr. Amy Devlin. The submission and amendments reviewed for the mAb intermediate and ADC DS are provided in the table below:

eCTD Sequence	Date	Description
0003	09/17/2019	Presubmission: Real-Time Oncology Review Pilot – Batch 2
0004	09/23/2019	Quality Information Amendment: Responses to FDA Questions 19 Sep 2019
0010	11/26/2019	Presubmission: Real-Time Oncology Review Pilot – Batch 5
0011	12/05/2019	Original BLA
0019	01/24/2020	Response to Information Request
0036	03/06/2020	Response to Information Request
0037	03/11/2020	Response to Information Request
0041	04/09/2020	Response to Information Request

REVIEW NARRATIVE

S. Belantamab (*mAb intermediate*)

S.1. General Information

Belantamab, an intermediate in the manufacture of belantamab mafodotin, is a recombinant afucosylated humanized IgG1κ monoclonal antibody specific for B-cell maturation antigen (BCMA). The antibody is N-linked glycosylated on each heavy chain at asparagine (Asn) N301 with afucosylated structures composed of N-acetyl-glucosamine, mannose, and galactose. The polypeptide molecular mass is 146 kDa and the carbohydrate molecular mass is approximately 3 kDa resulting in a total estimated molecular mass of 149 kDa for belantamab.

S.2. Manufacture

(b) (4)

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S.4.5.2.1.14 Bioburden

The manufacture of belantamab mafodotin DS is controlled to provide a low bioburden product, to facilitate manufacture of the sterile drug product. The total viable count method includes both TAMC and TYMC and is performed in accordance with USP <61> and Ph. Eur. 2.6.12. The acceptance criterion is the same for both, TAMC and TYMC, and corresponds to (b) (4)

SATISFACTORY

S.5 Reference Standards or Materials

Reviewer's comment: *This section is deferred to OBP.*

S.6 Container Closure System

(b) (4)

(b) (4) (*See **S.6. Container Closure System_belantamab***.)

S.7 Stability

Bioburden and endotoxin are not included in the stability program.

Reviewer's comment: *This section is deferred to OBP.*

cGMP Status

Refer to Panorama for cGMP status of the relevant facilities.

Conclusion

I. The belantamab mAb and belantamab mafodotin drug substance sections of BLA 761158 were reviewed from a microbial control and microbiology product quality perspective and is recommended for approval.

II. Information and data in this submission not related to microbial control of the belantamab mAb and belantamab mafodotin drug substance should be reviewed by an OBP reviewer.

III. Refer to Panorama for cGMP status of the relevant facilities.

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Zhong Li

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Reyes Candau-Chacon

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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Pharmaceutical Manufacturing Assessment
Division of Biotechnology Manufacturing

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewers: Wendy Tan, Ph.D and Amy Devlin, Ph.D.
Acting Quality Assessment Lead: Candace Gomez-Broughton, Ph.D.

BLA:	761158/0
Applicant:	GlaxoSmithKline Intellectual Property Development Ltd. England
US License Number:	2148
Product:	Belantamab Mafodotin 100 mg powder for Injection
Indication:	(b) (4) treatment for multiple myeloma
Dosage Form:	Powder for Injection, 100 mg, intravenous
Facility:	(b) (4) (FEI: (b) (4))
FDA Receipt Date:	December 5, 2019
Action Date:	June 5, 2020

Conclusion and Approvability Recommendation

The drug product portion of BLA STN 761158/0, as amended, was reviewed from a sterility assurance and quality microbiology perspective, and it is recommended for approval. Refer to the memo from Dr. Zhong Li for an assessment of the drug substance section of the BLA.

REVIEW SUMMARY

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0003	09/17/2019	Original BLA
0010	11/26/2019	Amendment
0011	12/05/2019	Amendment
0016	01/10/2020	Amendment (Response to IR)
0033	03/02/2020	Amendment (Response to IR)

0041	04/09/2020	Amendment (Response to IR)

1.14 LABELING

2 Dosage and Administration

(b) (4)

Label Section (b) (4) states the following regarding DP storage following reconstitution in 2 mL of Sterile Water for Injection, USP:

(b) (4)

In addition, Section (b) (4) states the following regarding storage of reconstituted DP that has been diluted into an intravenous infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP prior to injection:

(b) (4)

Reviewer Comment: *Sterile WFI is not co-packaged with the drug product. Microbial challenge studies supporting the post-reconstitution and post-dilution hold periods are described in P.2.5.*

MODULE 3.2 – GSK 2857916 (BELANTAMAB MAFODOTIN FOR INJECTION, 100 MG)

P.1 Composition of the Drug Product

GSK 2857916 DP is a sterile, preservative-free, lyophilized powder for intravenous infusion provided in single-use, (b) (4) glass vial. The powder in each vial is reconstituted with 2 mL of sterile WFI (not co-packaged with product). The composition of GSK 2857916 DP was provided in Table 1 in Module P.1 (table not shown herein). Each vial contains (b) (4) mg belantamab mafodotin DS, (b) (4) mg trisodium citrate dihydrate, (b) (4) mg citric acid, (b) (4) mg trehalose dihydrate, (b) (4) mg disodium edetate dihydrate (EDTA), (b) (4) mg polysorbate 80, and (b) (4) mL WFI (b) (4) (b) (4)

Reviewer Comment*: The composition of GSK 2857916 DP was adequately described.*

—SATISFACTORY—

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.4. Container Closure System (CCS)

1. Container Closure System

(b) (4)

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(b) (4)

SATISACTORY

P.5 Control of Drug Product

P.5.1 Specifications

The Specification microbiology quality criteria were included in Table 1 of P.5.1, and are summarized in the table below. Endotoxin testing will be performed by the (b) (4) method. The endotoxin value will be recorded (b) (4) (b) (4) Sterility will be assessed by the (b) (4) method.

SPECIFICATION CRITERIA FOR MICROBIOLOGY QUALITY*

Contaminants		
Bacterial Endotoxin[1]	USP <85>, Ph. Eur. 2.6.14	Release: (b) (4) EU/mL
Sterility[1]	USP <71>, Ph. Eur. 2.6.1	Release: Pass

Note:

1. The product is reconstituted with 2.0 mL of Water for Injection (WFI).

**The information in this table was taken from data presented in Table.1 of P.5.1.*

Reviewer Comment: *The specification criteria for microbiology quality were adequately described and are acceptable. Endotoxin release specification was (b) (4) EU/mL in Sequence 0041.*

P.5.2 ANALYTICAL PROCEDURES

5.2.1 Sterility

Reviewer Comment: *The release specification indicated that sterility testing will be performed upon release.*

The procedures for sterility testing were described in P.5.2 and are in accord with the requirements of USP <71> and Ph. Eur. 2.6.1. The sterility test is performed by the (b) (4) method for GSK

(b) (4)

(b) (4) The acceptance

criterion is (b) (4) (b) (4)

Reviewer Comment: *The sterility testing method was adequately described and complies with USP <71>.*

—SATISFACTORY—

5.2.2 Endotoxin Testing

Endotoxin testing is performed by the (b) (4) method per the requirements of USP <85> and Ph. Eur. 2.6.12. (b) (4) (b) (4)

Reviewer Comment: *The endotoxin testing method was adequately described and complies with USP <85> and Ph. Eur. 2.6.14.*

—SATISFACTORY—

P.5.3 VALIDATION OF ANALYTICAL PROCEDURES

P.5.3.1 Bacterial Endotoxins

Determination of product inhibition-enhancement of the LAL endotoxin assay performed by the (b) (4) (b) (4) method was conducted in accord with the requirements of USP <85>. The table below shows the results of the endotoxin assay inhibition-enhancement testing.

GSK 2857916 Inhibition-Enhancement Oualification

(b) (4)

This table is a copy of Table 1 of P.5.3.2

As outlined in the table above, endotoxin recovered was between (b) (4)% of the known concentration (b) (4) (b) (4) (b) (4) (b) (4) Inhibition/enhancement qualification testing results showed that the test requirements and acceptance criteria were met. The method is qualified for the detection of endotoxin in drug product samples.

Reviewer Comment: *Adequate evidence was presented that inhibition-enhancement did not occur for formulated BDP batches 9D007, 9D008, and 9D009.*

P.5.3.2 Sterility

Sterility test method qualification was described in P.5.3. ATCC challenge species specified in USP <71> (*Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Clostridium sporogenes, Candida albicans, Aspergillus brasiliensis*) were inoculated to a level of NMT (b) (4) CFU (b) (4) in GSK 2857916. The growth of inocula added to GSK 2857916 was compared to that for inocula added to (b) (4) The assay procedures were the same as those described above in the review for P.5.2.

The data for testing conducted with three GSK 2857916 lots, 8D001, 8D002, and 8E003, were provided in P.5.3. A summary is presented in the table below. The data show that GSK 2857916 did not inhibit the growth of the ATCC challenge species under the testing conditions used and demonstrated that the USP <71> (b) (4) method is adequate for sterility testing of GSK 2857916.

RESULTS OF STERILITY TESTING QUALIFICATION FOR GSK 2857916 LOTS 8D001, 8D002, and 8E003.

Challenge Organism (media)	Acceptance Criteria	Batch 8D001 Result	Batch 8D002 Result	Batch 8E003 Result
B. subtilis ATCC 6633 (b) (4) *C. albicans* ATCC 10231 (b) (4) *A. brasiliensis* ATCC 16404 (b) (4) *C. sporogenes* ATCC 19404 (b) (4) *S. aureus* ATCC 6538 (b) (4) *P. aeruginosa* ATCC 9027 (b) (4) *B. cereus* (environmental isolate) (b) (4)	(b) (4)	Pass Pass Pass Pass Pass Pass Pass	Pass Pass Pass Pass Pass Pass Pass	Pass Pass Pass Pass Pass Pass Pass
Inoculum Challenge Level	(b) (4) Colony Forming Units (CFU)	Pass	Pass	Pass
Negative Controls for the (b) (4) media were negative.				

**This table is a copy of Table 1 from P.5.3.*

Reviewer Comment: *Qualification of sterility testing was adequately described and is acceptable.*

—SATISFACTORY—

P.5.6 JUSTIFICATION OF SPECIFICATIONS

2.1.15. Bacterial Endotoxin

1. Endotoxin Specification Value. The draft label (Module 1.14.1) states a recommended dosage of 2.5 mg/kg body weight administered intravenously every 3 weeks and a maximum dose of 3.4 mg/kg body weight. Given the endotoxin specification of (b) (4) EU/mL, the maximum administered endotoxin level calculates as 3.4 mg/kg X (b) (4) EU/mg = (b) (4) EU/kg (for a 70 kg individual, equivalent to 70 kg X (b) (4) EU/kg = (b) (4) EU). These values are well within the 5 EU/kg daily limit (350 EU for a 70 kg individual) stated in USP <85>.

Reviewer Comment: *The specification endotoxin value is within the recommended limit stated in USP <85> and is acceptable. The administered endotoxin levels are also well within the recommended limit if the levels added by sterile WFI (USP specification criterion (b) (4) as well as GSK 2857916 DP are considered.*

Maximum Endotoxin contributed by GSK 2857916 DP for 70 kg individual: = (b) (4) EU
(see calculation above)
Endotoxin contributed by 2 mL sterile WFI: 2 mL X (b) (4) EU/mL: = (b) (4) EU
Endotoxin contributed by (b) (4) mL X (b) (4) EU/mL = (b) (4) EU
TOTAL: = (b) (4) EU

The calculated sum of (b) (4) EU is still within the (b) (4) EU limit for a 70 kg individual stated in USP <85>. There is a (b) (4)-fold safety factor.

2. Low Endotoxin Recovery (LER). (b) (4) (b) (4) The procedures for investigating the potential for LER were presented in P.5.3.2 and the Sequence 0016 response to Question 12. To perform the LER studies, (b) (4) (b) (4)

(b) (4)

LER STUDY RESULTS FOR GSK 2857916 DP LOTS SLBW3623 (1), SLBZ4949 (2), and SLBZ108 (3).

(b) (4)

*This table is a copy of Table 3 from P.5.3.2.1

Reviewer Comment: *Based on the spike recovery data presented above, adequate evidence was provided*

(b) (4)

(b) (4)

—SATISFACTORY—

Sterility

As stated in P.5.6.2.1.16, the belantamab mafodotin DP is confirmed to be sterile following the method of testing (USP <71>) specified during its qualification, found in P.5.3. Sterility is performed on release only, not on stability.

Reviewer Comment*: The purpose of the sterility is adequate.*

—SATISFACTORY—

Pyrogens

Using the rabbit challenge method, pyrogen testing was conducted following the procedures outlined in USP <151>. Testing was performed with samples from lots 9D007, 9D008, and 9D009. For each batch, three rabbits were inoculated. The Sequence 0016 response to question 2, in the attachments, it was stated that the amount of injected GSK 2857916 DP was 3.4 mg/kg of body weight, corresponding to (b) (4) mL/kg of a (b) (4) mg/mL GKS 2857916 solution. This dose is equivalent to the human high dose of 3.4 mg/kg indicated on the label. Results of the testing are indicated in the table below. For all post-inoculation time points (1.0, 1.5, 2, 2.5, and 3 hours) for all animals there was either no temperature increase or a maximum temperature increase of (b) (4) °C. All animals tested remained within the (b) (4) (b) (4) °C temperature increase acceptance criterion (b) (4)

Lot Number	Rabbit	Weight (kg)	Final Dose (mL)	Non-inoculated control temp.	T = 60 minutes	T = 90 minutes	T = 120 minutes	T = 150 minutes	T = 180 minutes	Max. Temp. Increase at any interval
9D007	(b) (4)									
9D007										
9D007										
9D008										
9D008										
9D008										
9D009										
9D009										
9D009										

**Data in this table was taken from Sequence 0016 response to question 2 in the attachments section of the submitted response.*

Reviewer Comment: *As amended, adequate information was provided that GSK 2857916 DP manufactured at the described commercial scale is nonpyrogenic as assessed by the USP <151> rabbit pyrogen test.*

—SATISFACTORY—

P.7 CONTAINER CLOSURE SYSTEM

As described in P.7, the container closure system (CCS) consists of the following:

- (b) (4) glass, clear vials. Overall height 40 mm; external diameter 22 mm; internal mouth diameter 12.6 mm.
- (b) (4) 20 mm gray (b) (4) rubber, (b) (4) stoppers.
- (b) (4) 20 mm, orange (b) (4) aluminum flip-off crimp caps.

Reviewer Comment: *The container closure system was adequately described. As indicated in P.3.5 of the BLA, DMF (b) (4) was referenced (b) (4) and was adequate for the (b) (4) family.*

—SATISFACTORY—

P.8.2. POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

The proposed expiry for GSK 2857916 DP is 12 months under 2-8°C storage conditions. For post-approval stability assessment, (b) (4) (b) (4) (b) (4) annual testing will be conducted (b) (4)

Reviewer Comment: *The commitment to conduct annual stability testing of GSK 2857916 DP for CCIT* (b) (4) *is adequate from a microbiology quality assessment perspective.*

—SATISFACTORY—

P.8.3. STABILITY DATA

Stability Data

Tables 15-31 in P.8.3 provide stability data for PPQ lots 9D007, 9D008, and 9D009. These lots met the criterion for microbial control at the initial 0 month interval, but data for the 12 month time point are not yet available. CCIT data for DP batches 8D001, 8D002, and 8E003 were provided in Tables 1-12. For all three batches, the acceptance criteria for CCI were achieved. Twelve month CCIT data for the clinical batch 8K006 were not provided at the time of the BLA submission. Data only out to 3 months of stability testing is presented in Tables 13 and 14 for the clinical batch in P.8.3.

Reviewer Comment: *The data provided for DP batches 8D001, 8D002, and 8E003 indicate that the stability criteria for microbiology quality was maintained for these lots through a 12 month test point. Evaluation of chemical stability data for these lots is deferred to the OBP reviewer.*

Container Closure Integrity Testing (CCIT)

Container closure integrity testing (CCIT) is perfomed using the dye ingress assay. Drug product vials (b) (4)

—SATISFACTORY—

cGMPs

The assessment of manufacturing facilities is documented in Panorama and in the facilities assessment review for this application.

CONCLUSION

- **The drug product part of the BLA, as amended, was reviewed from a sterility assurance and microbial product quality perspective and is recommended for approval.**

- **Product quality aspects other than microbiology should be reviewed by OBP.**

INFORMATION REQUESTS

IR Submitted 12/20/2019.
Responses received 01/03/2020 in Sequence 0014, 01/10/2020 in Sequence 0016, and 02/24/2020 in Sequence 0031.

(b) (4)

4 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

Wendy Tan

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KELLY R BALLARD
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