

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761065Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

**First Approval for Indication/Breakthrough/Priority Review:** for the treatment of HIV-1 infection in treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy.

**Recommendation: Approval**

**BLA STN 761065**  
**Review Number: 2**  
**Review Date:** February 22, 2018

<b>Drug Name/Dosage Form</b>	ibalizumab/injection (TROGARZO™)
<b>Strength/Potency</b>	200 mg/1.33 mL vial
<b>Route of Administration</b>	Intravenous infusion
<b>Rx/OTC dispensed</b>	Rx
<b>Indication</b>	Treatment of HIV-1 infection in treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy
<b>Applicant/Sponsor</b>	TaiMed Biologics USA Corp

**Product Overview**

Ibalizumab is a humanized IgG4, κ monoclonal antibody produced in a NS0 cell line. Ibalizumab binds with high affinity to an epitope on domain 2 of the CD4 T-cell coreceptor. CD4 is the primary receptor for the HIV-1 glycoprotein gp120. Ibalizumab blocks HIV-1 infection of CD4 T-cells by preventing the post-binding conformational change of CD4 that allows the fusion of the viral envelope with the T-cell membrane. By preventing the infection of CD4 T cells by HIV-1, ibalizumab may help reduce viral load and improve clinical outcomes in patients with HIV-1. During the BLA review, the Clinical Virology team observed that the HIV-1 envelope protein gp120 exhibit polymorphisms (several amino acid substitutions) of unknown significance, and that there are limited clinical data defining the resistance pathways for ibalizumab. Because ibalizumab is indicated for highly treatment-experienced patients, OND proposes three post-marketing requirements (PMRs 3283-3, 3283-4, and 3283-5) to identify the specific resistance pathways of ibalizumab and to assess the susceptibility of a patient’s virus to reduce the serious risk of developing multidrug resistant HIV-1 infection.

Ibalizumab drug substance and drug product are manufactured at WuXi AppTec (Wuxi, China). (b) (4)

[Redacted text block]

The drug substance (DS) contains ibalizumab at 150 mg/mL concentration, formulated in 10 mM L-Histidine, 5.2% sucrose, 52 mM sodium chloride, 0.045% polysorbate 80, pH 6.0, and stored at 2 °C to 8 °C. (b) (4)

[Redacted text block] (b) (4) For ibalizumab DS, the data provided in the BLA submission support an expiration dating period of (b) (4) months when stored at (b) (4) °C to (b) (4) °C.

Ibalizumab drug product manufacturing involves (b) (4). The container closure is a single (b) (4) 2 mL (b) (4) glass vial with a (b) (4) rubber stopper and aluminum flip-off seal. Ibalizumab is supplied at 200 mg/1.33 mL vial. (b) (4). For ibalizumab DP, the data provided in the BLA submission support an expiration dating period of 36 months when stored at 2°C to 8°C.

### Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Steven Bowen	DBRR III/OBP/OPQ
Drug Product	Steven Bowen	DBRR III/OBP/OPQ
Immunogenicity	Steven Bowen	DBRR III/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facility	Michael Shanks	DIA/OPF/OPQ
Microbiology (DS)	Bo Chi	DMA/OPF/OPQ
Microbiology (DP)	Virginia Carroll	
Business Process Manager	Anita Brown	RBPMB I/OPRO/OPQ
Team Lead for OBP	Ramesh Potla	DBRR III/OBP/OPQ
Tertiary Reviewer for OBP	Susan Kirshner	DBRR III/OBP/OPQ
Microbiology Team Lead (DS)	Reyes Candau-Chacon	DMA/OPF/OPQ
Microbiology Team Lead (DP)	Dupeh Palmer	DMA/OPF/OPQ
Microbiology Tertiary Reviewer	Patricia Hughes	DMA/OPF/OPQ
Facilities Team Lead	Peter Qiu	DIA/OPF/OPQ
Application Team Lead	Ramesh Potla	DBRR III/OBP/OPQ

### Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
RPM	Christian Yoder	DAVP/OAP/OND
Cross-disciplinary Team Lead	Adam Sherwat	DAVP/OAP/OND
Medical Officer	Virginia Sheikh	DAVP/OAP/OND
Pharm/Tox	David McMillan	DAVP/OAP/OND
Clinical Pharmacology	Qin Sun	DCPIV/OCP/OTS
Statistics	Karen Qi	DBIV/OB/OTS

#### 1. Names:

- a. Proprietary Name: Trogarzo
- b. Trade Name: Trogarzo
- c. Non-Proprietary Name/USAN: ibalizumab
- d. CAS Name: 680188-33-4
- e. Common Name: ibalizumab
- f. INN Name: ibalizumab

- g. Compendial Name: N/A
- h. OBP systematic name: MAB HUMANIZED (IGG4) ANTI P01730 (CD4\_HUMAN) [TMB355]
- i. Other names: TMB-355, WBP236, TNX-355, Hu5A8

### Submissions Reviewed

Submission(s) Reviewed	Document Date
Module 3 Rolling Submission	7/15/2016
Original BLA	5/3/2017
CMC amendment	5/11/2017
Response to IR 1 (OPF)	6/13/2017
Response to IR 2 (OBP)	6/27/2017
Response to IR 3 (OPF)	7/11/2017
Response to IR 4 (OBP & OPF)	8/11/2017
Response to IR 5 (OPF)	8/31/2017
Response to IR 6 (OPF)	9/12/2017
Sponsor's Response to Mid-cycle Comments	9/15/2017
Response to IR 7 (OBP & OPF)	9/18/2017
Response to IR 8 (OPF)	9/28/2017
Response to IR 9 (OBP)	9/29/2017
Response to IR 10 (OPF)	10/10/2017
Response to IR 11 (OBP & OPF)	10/13/2017
Revised Module 3 (1)	10/25/2017
Response to IR 12 (OPF)	10/27/2017
Response to IR 13 (OPF)	11/14/2017
Revised Module 3 (2)	11/28/2017
Response to IR 10 (OPF)	11/30/2017
Response to IR 13 (OBP)	12/15/2017
Response to IR 11 (OPF)	01/09/2018
Response to IR 14 (OBP & OPF)	1/18/2018
In-Use Stability Report (1)	1/19/2018
Response to IR 15 (OBP)	1/31/2018
In-Use Stability Report (2)	2/2/2018
Response to IR 16 (OBP)	2/12/2018
Response to IR 17 (OPF)	2/13/2018
Response to IR 18 (OBP)	2/23/2018

### 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 <sup>1</sup>	Status <sup>2</sup>	Comments
(b) (4)	III	(b) (4)	(b) (4)	3	N/A	Not reviewed. Sufficient information related to compatibility with the product is provided in the BLA.
	III			3	N/A	
	V			3	N/A	A previous review found the DMF adequate for (b) (4)

**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.** 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: None.

3. Consults: None

## Executive Summary

### I. Recommendations:

#### A. Recommendation and Conclusion on Approvability:

Recommendation: Approval.

The Office of Product Quality, CDER, recommends approval of BLA STN 761065 for Trogarzo (ibalizumab) manufactured by TaiMed Biologics USA Corp. The data submitted in this application are adequate to support the conclusion that the manufacture of Trogarzo 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. Approval Action Letter Language:

Manufacturing location:

- Drug Substance: Wuxi AppTec Biologics, Wuxi, China
- Drug Product: Wuxi AppTec Biologics, Wuxi, China
- Fill size and dosage form – 200 mg/1.33 mL in a single (b) (4) vial
- Dating period:
  - Drug Product: 36 months: 2-8 °C
  - Drug Substance: (b) (4) months: (b) (4) °C
  - Stability Option:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
- Exempt from lot release
  - Trogarzo is excepted from lot release per FR Doc. 95–29960

#### C. Benefit/Risk Considerations:

Trogarzo (ibalizumab) is for the treatment of HIV-1 infection in treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy.

The data submitted in this application support the conclusion that the manufacture of ibalizumab 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 production runs presented. From a product quality perspective, this product is approvable for human use. Review of manufacturing has identified that the methodologies used for drug substance and drug product manufacturing, release, and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents.

The current ibalizumab bulk drug substance (BDS) container is a (b) (4). The available stability data for ibalizumab BDS does not indicate that the current BDS container closure negatively impacts product quality. However, laboratory grade materials are not appropriate for use as the BDS container because the materials may not be sufficiently controlled to ensure consistent performance throughout the lifecycle of the product. To address this concern the sponsor agreed to Post-Marketing Commitment (PMC) 1 in section B below. PMC 1 is to develop, validate, and implement a new BDS container closure system using appropriate pharmaceutical grade materials.

The shipping qualification study for ibalizumab did not include an assessment of product quality after the shipment of ibalizumab drug product from Wuxi, China to the United States. Analytical testing should be performed on the product to assess product quality before and after shipping to evaluate the impact of the shipping conditions on ibalizumab drug product. To address this concern the sponsor agreed to PMC 2 in section B below. PMC 2 is to perform a drug product shipping study using the approved commercial shipping lane to evaluate the impact of shipment on product quality. Clinical trials were conducted in the United States supporting the safety and efficacy of drug shipped to the US.

The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. We also recommend approval of the commercial manufacture of ibalizumab drug substance and drug product at Wuxi AppTec Biologics in Wuxi, China. The OBP product quality and immunogenicity, DMA microbiological drug substance and drug product, DIA facility, and OBP labeling technical assessments are located as separate documents in Panorama.

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

**PMC 1:** To develop, validate, and implement an appropriate pharmaceutical grade container closure system for ibalizumab bulk drug substance.

The final study report(s) will be submitted according to 21 CFR 601.12 by October, 2019.

**PMC 2:** To perform a drug product shipping study using the approved commercial shipping lane to evaluate the impact of shipment on product quality.

The final study report(s) will be submitted by November, 2018.

**II. Summary of Quality Assessments:**

**A. CQA Identification, Risk and Lifecycle Knowledge Management**

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to both drug substance and drug product.

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

CQA	Risk	Origin	Control Strategy	Other
Aggregates (product related impurity)	Safety and efficacy	Protein aggregation on stability	(b) (4)	N/A
Acidic variants (product related impurity)	Safety and efficacy	(b) (4)	(b) (4)	N/A
Basic variants (Product related impurity)	Safety and efficacy	Oxidation	(b) (4)	N/A
Fragments (product related impurity)	Safety and efficacy	Degradation on stability	(b) (4)	N/A

Half-antibodies (product related variants)	Potential product- related species with IgG4 antibodies	Safety and Efficacy Potential impact on safety and efficacy not fully understood	(b) (4)	N/A
pH	Safety and efficacy	General CQA		N/A
Biological Activity	Efficacy	Intrinsic to molecule		N/A
Identity	Safety and efficacy	Intrinsic to molecule		N/AA

**B. Drug Substance [ibalizumab] Quality Summary**

**CQA Identification, Risk, and Lifecycle Knowledge Management**

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

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

CQA (type)	Risk	Origin	Control Strategy	Other
Residual NS0 Host Cell Protein (process related impurity)	Safety	Process related impurity (b) (4)	(b) (4)	N/A

			(b) (4)	
Residual NS0 Host Cell DNA (process related impurity)	Safety	Process related impurity (b) (4)		N/A
Bioburden	Safety	Contamination: Bioburden can be introduced throughout the manufacturing process		N/A
Endotoxin	Safety	Contamination: Endotoxin can be introduced throughout the manufacturing process		N/A
Mycoplasma	Safety	Contamination: Mycoplasma can be introduced during cell culture		N/A
(b) (4)	Safety	Process related impurity (b) (4)		N/A
Adventitious virus	Safety	Contamination: adventitious virus can be introduced during cell culture.		N/A
(b) (4)	Safety	Process related impurity, (b) (4)		N/A
(b) (4)	Safety	Process related impurity, (b) (4)		N/A

- **Description:**

Ibalizumab (TMB-355) is a humanized monoclonal IgG4 antibody that binds the CD4 co-receptor on T-cells to block entry of human immunodeficiency virus 1 (HIV-1). Ibalizumab consists of two identical gamma 4 heavy chains of 449 amino acids and two identical kappa light chains of 219 amino acids. The heavy and light chains are stabilized by multiple inter- and intra- chain disulfide bonds. The heavy chain constant region contains a single N-linked oligosaccharide chain, comprised primarily of neutral biantennary-type oligosaccharides. The primary amino acid sequence of ibalizumab is shown below. The IgG4 heavy chain hinge region sequence is not modified to prevent formation of half antibodies. The complementarity determining regions (CDR) are underlined and the N-linked glycosylation site at N299 of the heavy chain is shown in red. The heavy chain contains a C-terminal lysine residue, the variants of which are a potential source of heterogeneity.
- **Mechanism of Action (MoA):**

Ibalizumab binds with high affinity to an epitope on domain 2 of the CD4 T-cell coreceptor. CD4 is the primary receptor for the HIV-1 glycoprotein gp120. Ibalizumab blocks HIV-1 infection of CD4 T-cells by preventing the post-binding conformational change of CD4 that allows the fusion of the viral envelope with the T-cell membrane. By preventing the infection of CD4 T cells by HIV-1, ibalizumab may help reduce viral load and improve clinical outcomes in patients with HIV-1.
- **Potency Assay:**

The cell-cell fusion inhibition method for ibalizumab potency involves the co-culture of two HeLa cell lines:

  1. HL2/3 has been engineered to express gp120 on the cell surface and the transcriptional activator tat in the cytoplasm. The assay is run between passages 9 and 16.
  2. HeLa-CD4-LTR- $\beta$ -gal expresses CD4 on the cell surface and contains a LacZ reporter gene under the control of a tat-inducible LTR promoter. The assay is run between passages 4 and 12.

Co-culture of the two cell lines results in cell fusion mediated by interaction between gp120 on HL2/3 and CD4 on HeLa-CD4-LTR- $\beta$ -gal. After cell fusion, the cytoplasmic tat transcription factor binds to the LTR promoter of the reporter construct and drives expression of b-galactosidase. The cells are lysed and the chemiluminescence is measured. The level of chemiluminescent signal is proportional to the level of cell-cell fusion. Ibalizumab binds to CD4 on HeLa-CD4-LTR- $\beta$ -gal and prevents cell-cell fusion in a concentration dependent manner.
- **Reference Materials:**

A two-tier reference material system is in place, which is consistent with ICH Q6B. (b) (4)

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\_\_\_\_\_



- Container closure:  
The formulated bulk drug substance is (b) (4)  
(b) (4)  
(b) (4) PMC 1 is to implement a container closure system using pharmaceutical grade material. See the Benefit/Risk Considerations section for more information.
- Dating period and storage conditions:  
The data support an expiration dating period of (b) (4) months when stored at (b) (4) °C.

**C. Drug Product [ibalizumab] 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	Risk	Origin	Control Strategy	Other
Osmolality	General CQA	Formulation	Tested at (b) (4) DP release and stability	N/A
Appearance	General CQA	Formulation	Tested at (b) (4) DP release and stability	N/A
Sterility/Container closure integrity	Safety	DP manufacturing, on stability	Tested at DP release and stability	N/A
Particulate matter	Safety	Particulates can be introduced throughout the manufacturing process and on stability	Tested at DP release and stability as per USP <788>	N/A
Endotoxin	Safety	Contamination: Endotoxin can be introduced throughout the manufacturing process	(b) (4) release and stability testing of (b) (4) DP.	N/A

- **Potency and Strength:**  
Ibalizumab is supplied at 200 mg/1.33 mL vial. Potency is defined as the percent activity relative to the current ibalizumab reference standard. The potency assay is the same as described in the DS section of this review memo.
- **Summary of Product Design:**  
Ibalizumab is supplied as a sterile, preservative-free solution in a single (b) (4) vial for intravenous infusion. The drug product formulation consists of 10 mM L-Histidine, 5.2% Sucrose, 52 mM sodium chloride, 0.045% polysorbate 80, pH 6.0. The extractable volume is 1.33 mL.
- **List of Excipients:**  
Excipients include 10 mM L-Histidine, 5.2% Sucrose, 52 mM sodium chloride, and 0.045% polysorbate 80.
- **Reference Materials:**  
The same reference material is used for DS and DP.
- **Manufacturing process summary:**



- Container closure:  
The primary container closure system for ibalizumab DP consists of a (b) (4) clear 2 mL (b) (4) glass vial (b) (4), 13-mm (b) (4) rubber stopper ( (b) (4) ), and a 13 mm Aluminum seal.
- Dating period and storage conditions:  
The dating period for ibalizumab DP is 36 months when stored at 2°C to 8°C, protected from light.

**D. Novel Approaches/Precedents:** None.

**E. Any Special Product Quality Labeling Recommendations:**

- Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
- Protect from light until use.
- Do not freeze.

**F. Establishment Information:**

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Manufacturing, Packaging, Quality Control Testing of the Drug Substance	WuXi Apptec Biopharmaceuticals Co., Ltd.	3010606982	Pre-License Inspection (8/2/2017)	VAI	Approve
DRUG PRODUCT					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Manufacturing and Quality Control Testing of the Drug Product	WuXi Apptec Biopharmaceuticals Co., Ltd.	3010606982	Pre-License Inspection (8/2/2017)	VAI	Approve
Labeling, Packaging, and Storage of Ibalizumab Drug Product	(b) (4)	(b) (4)	GMP Inspection (b) (4)	NAI	Approve
Ibalizumab Drug Product Final Identity Testing			GMP Inspection (b) (4)	VAI	Approve

**G. Facilities:**

Trogarzo™ (ibalizumab, TMB-355) DS and DP are manufactured at WuXi Apptec Biopharmaceuticals Co., Ltd. (FEI: 3010606982) in Wuxi, China. A Pre-license Inspection was performed at WuXi Apptec Biopharmaceuticals Co., Ltd. on 07/17 – 08/02/2017. A 23-item FDA Form 483 was issued, and the initial recommendation is withhold for this BLA. The final classification of acceptable (VAI) has been made after satisfactory resolution of inspectional

deficiencies by the firm. This was the first FDA inspection at WuXi Apptec Biopharmaceuticals Co. All other related manufacturing and testing facilities have an acceptable compliance status. This BLA application is recommended for approval from a facilities perspective.

## H. Lifecycle Knowledge Management:

### a. Drug Substance:

- i. Protocols:
  1. Validation of (b) (4) at commercial scale
  2. Requalification/annual retesting (b) (4)
  3. Post-approval DS stability protocol
- ii. Outstanding review issues/residual risk: PMC 1 is to implement a container closure system using pharmaceutical grade material. See the Benefit/Risk Considerations section for more information.
- iii. Future inspection points to consider:
  1. Adequacy of method verification for compendial methods used for DS lot release and stability testing.
  2. Re-inspect the manufacturing facility at WuXi Apptec Biopharmaceuticals Co., Ltd. (FEI: 3010606982) in Wuxi, China, about a year after the approval.

### b. Drug Product

- i. Protocols:
  1. Post-approval DP stability protocol
- ii. Outstanding review issues/residual risk: PMC 2 is to perform additional shipping validation studies. See the Benefit/Risk Considerations section for more information.
- iii. Future inspection points to consider:
  1. Adequacy of method verification for compendial methods used for DP lot release and stability testing.
  2. Re-inspect the manufacturing facility at WuXi Apptec Biopharmaceuticals Co., Ltd. (FEI: 3010606982) in Wuxi, China, about a year after the approval.



Ramesh  
Potla

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Susan  
Kirshner

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## **PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION**

**Reviewer: Virginia Carroll, PhD**  
**Acting Branch Chief: Patricia Hughes, PhD**

BLA: 761065/0  
Applicant: TaiMed Biologics USA Corp.  
US License Number: NA  
Submission Reviewed: Original BLA  
Product: ibalizumab (TROGARZO)  
Indication: HIV treatment of multi-drug resistant patients  
Dosage Form: Sterile solution for intravenous injection, 200 mg per vial (150 mg/mL)  
Manufacturing Sites: WuXi AppTec Biopharmaceuticals Co., Ltd. Wuxi, Jiangsu, China (FEI 3012672198)  
FDA Receipt Date: 5/3/2017  
Action Date: 4/3/2018

### **Conclusion and Approvability Recommendation**

The drug product part of this BLA, as amended, was reviewed from a sterility assurance and product quality microbiology perspective and is recommended for approval.

### **Review Addendum**

On November 30, 2017, a change in labeling was proposed to store diluted ibalizumab for 24 hours at 2-8°C or 4 hours at room temperature (20-25°C) prior to administration. The in-use microbial challenge study to support the post-dilution storage conditions is reviewed herein.

### **Product Quality Microbiology Assessment: Drug Product** **Drug Product Quality Microbiology Information Reviewed**

Sequence number	Date	Description
0062	November 14, 2017	In-use microbial challenge study (TMB-RD-R2017029)
0064	November 28, 2017	Update to 3.2.P.2.5

## **Module 3.2**

### **P.2.5 Microbiological Attributes**

#### Microbial challenge study to support the storage of the product post-dilution before injection

Prior to intravenous administration, 800 mg (maintenance dose) or 2000 mg (loading dose) ibalizumab is diluted in 250 mL of 0.9% saline. The sponsor proposed a post-dilution storage period of up to 4 hours at room temperature (20-25°C) or refrigerated for up to 24 hours (2-8°C). If refrigerated, the label states to ensure the diluted ibalizumab solution is at room temperature before administration. A summary of the study and the referenced report (TMB-RD-R2017029) was provided.

The microbial challenge study was performed with both doses of drug product diluted in 0.9% saline (3.25 and 8 mg/mL). The test panel of organisms included those in USP <51> (*E. coli*, *S. aureus*, *P. aeruginosa*, *C. albicans*, *A. brasiliensis*) plus *Enterobacter cloacae* and *Micrococcus luteus*. Samples were spiked with 0.1 mL of suspension resulting in <100 CFU/mL of each organism. Negative control (un-inoculated saline) and positive controls (inoculated saline) were included. Samples were stored at 2-8°C for 0, 4, 8, 16, 24, and 48 hours or 20-25°C for 0, 4, 8, 16, and 24 hours. The culture conditions were as follows: bacterial 35±2°C for 3 days, yeast 25±2°C for 5 days, mold 25±2°C for 7 days. Plate count results are summarized in Tables 5-8.

Results at 2-8°C show no growth of any organism over 48 hours compared to time 0 for both concentrations of diluted drug product, supporting a storage period of 24 hours at 2-8°C. Results at room temperature show no growth of organisms at 4 hours. At 8 hours, ≥0.5 log growth of *E. cloacae* was observed in both concentrations of diluted drug product (0.62 and 0.82 log increase) and continued to increase at 16 and 24 hours at room temperature (see results copied below).

Table 5 Growth of Microorganisms in Diluted 800 mg Ibalizumab at 2-8 °C

Time point (hours)		Inoculum concentration	0	4	8	16	24	48	
microorganisms	<i>E. coli</i> (ATCC 8739)	CFU/mL	5	0	0	0	0	0	0
		Log <sub>10</sub>	0.70	0.00	0.00	0.00	0.00	0.00	0.00
	<i>S. aureus</i> (ATCC 6538)	CFU/mL	25	0	0	0	0	0	0
		Log <sub>10</sub>	1.40	0.00	0.00	0.00	0.00	0.00	0.00
	<i>P. aeruginosa</i> (ATCC 9027)	CFU/mL	20	0	0	3	8	0	0
		Log <sub>10</sub>	1.30	0.00	0.00	0.48	0.88	0.00	0.00
	<i>C. albicans</i> (ATCC 10231)	CFU/mL	3	0	0	5	0	0	0
		Log <sub>10</sub>	0.48	0.00	0.00	0.70	0.00	0.00	0.00
	<i>A. brasiliensis</i> (ATCC 16404)	CFU/mL	3	0	0	0	0	0	0
		Log <sub>10</sub>	0.48	0.00	0.00	0.00	0.00	0.00	0.00
	<i>E. cloacae</i> (ATCC 13047)	CFU/mL	10	3	3	0	0	0	0
		Log <sub>10</sub>	1.00	0.48	0.48	0.00	0.00	0.00	0.00
	<i>M. luteus</i> (ATCC 10240)	CFU/mL	80	0	0	0	0	0	0
		Log <sub>10</sub>	1.90	0.00	0.00	0.00	0.00	0.00	0.00
	Un-inoculated control (0.9% normal saline)			0	0	0	0	0	0
				0.00	0.00	0.00	0.00	0.00	0.00

Table 6 Growth of Microorganisms in Diluted 2000 mg Ibalizumab at 2-8 °C

Time point (hours)		Inoculum concentration	0	4	8	16	24	48	
microorganisms	<i>E. coli</i> (ATCC 8739)	CFU/mL	5	0	0	0	0	3	0
		Log <sub>10</sub>	0.70	0.00	0.00	0.00	0.00	0.48	0.00
	<i>S. aureus</i> (ATCC 6538)	CFU/mL	25	0	0	0	0	0	0
		Log <sub>10</sub>	1.40	0.00	0.00	0.00	0.00	0.00	0.00
	<i>P. aeruginosa</i> (ATCC 9027)	CFU/mL	20	3	5	5	3	0	0
		Log <sub>10</sub>	1.30	0.48	0.70	0.70	0.48	0.00	0.00
	<i>C. albicans</i> (ATCC 10231)	CFU/mL	3	0	0	0	0	0	0
		Log <sub>10</sub>	0.48	0.00	0.00	0.00	0.00	0.00	0.00
	<i>A. brasiliensis</i> (ATCC 16404)	CFU/mL	3	0	0	3	3	3	0
		Log <sub>10</sub>	0.48	0.00	0.00	0.48	0.48	0.48	0.00
	<i>E. cloacae</i> (ATCC 13047)	CFU/mL	10	3	0	0	0	0	0
		Log <sub>10</sub>	1.00	0.48	0.00	0.00	0.00	0.00	0.00
	<i>M. luteus</i> (ATCC 10240)	CFU/mL	80	0	5	0	0	0	0
		Log <sub>10</sub>	1.90	0.00	0.70	0.00	0.00	0.00	0.00
	Un-inoculated control (0.9% normal saline)			0	0	0	0	0	0
				0.00	0.00	0.00	0.00	0.00	0.00

**Table 7 Growth of Microorganisms in Diluted 800 mg Ibalizumab at 25 ±2°C**

Time point (hours)		Inoculum concentration	0	4	8	16	24	
microorganisms	<i>E. coli</i> (ATCC 8739)	CFU/mL	5	0	3	0	0	0
		Log <sub>10</sub>	0.70	0.00	0.48	0.00	0.00	0.00
	<i>S. aureus</i> (ATCC 6538)	CFU/mL	25	0	0	0	3	0
		Log <sub>10</sub>	1.40	0.00	0.00	0.00	0.48	0.00
	<i>P. aeruginosa</i> (ATCC 9027)	CFU/mL	20	0	0	3	5	3
		Log <sub>10</sub>	1.30	0.00	0.00	0.48	0.70	0.48
	<i>C. albicans</i> (ATCC 10231)	CFU/mL	3	0	0	0	0	0
		Log <sub>10</sub>	0.48	0.00	0.00	0.00	0.00	0.00
	<i>A. brasiliensis</i> (ATCC 16404)	CFU/mL	3	0	0	0	0	0
		Log <sub>10</sub>	0.48	0.00	0.00	0.00	0.00	0.00
	<i>E. cloacae</i> (ATCC 13047)	CFU/mL	10	3	3	13	2.3×10 <sup>2</sup>	1.4×10 <sup>2</sup>
		Log <sub>10</sub>	1.00	0.48	0.48	1.10	2.37*	2.13*
	<i>M. luteus</i> (ATCC 10240)	CFU/mL	80	0	0	0	0	0
		Log <sub>10</sub>	1.90	0.00	0.00	0.00	0.00	0.00
Un-inoculated control (0.9% normal saline)			0	0	0	0	0	
			0.00	0.00	0.00	0.00	0.00	

Note: \* More than 0.5 log<sub>10</sub> unit higher than the initial inoculum

**Table 8 Growth of Microorganisms in Diluted 2000 mg Ibalizumab at 25 ±2 °C**

Time point (hours)		Inoculum concentration	0	4	8	16	24	
microorganisms	<i>E. coli</i> (ATCC 8739)	CFU/mL	5	0	3	0	0	0
		Log <sub>10</sub>	0.70	0.00	0.48	0.00	0.00	0.00
	<i>S. aureus</i> (ATCC 6538)	CFU/mL	25	0	3	3	0	0
		Log <sub>10</sub>	1.40	0.00	0.48	0.48	0.00	0.00
	<i>P. aeruginosa</i> (ATCC 9027)	CFU/mL	20	0	5	5	5	3
		Log <sub>10</sub>	1.30	0.00	0.70	0.70	0.70	0.48
	<i>C. albicans</i> (ATCC 10231)	CFU/mL	3	0	3	0	0	0
		Log <sub>10</sub>	0.48	0.00	0.48	0.00	0.00	0.00
	<i>A. brasiliensis</i> (ATCC 16404)	CFU/mL	3	0	1.5	3	3	0
		Log <sub>10</sub>	0.48	0.00	0.18	0.48	0.48	0.00
	<i>E. cloacae</i> (ATCC 13047)	CFU/mL	10	3	3	20	6.2×10 <sup>2</sup>	4.5×10 <sup>2</sup>
		Log <sub>10</sub>	1.00	0.48	0.48	1.30	2.79*	2.65*
	<i>M. luteus</i> (ATCC 10240)	CFU/mL	80	0	0	0	0	0
		Log <sub>10</sub>	1.90	0.00	0.00	0.00	0.00	0.00
Un-inoculated control (0.9% normal saline)			0	0	0	0	0	
			0.00	0.00	0.00	0.00	0.00	

Note: \* More than 0.5 log<sub>10</sub> unit higher than the initial inoculum

*Reviewer's Comment: Inoculum was low (3-5 CFU/mL) for three of seven organisms (E. coli, C. albicans, A. brasiliensis), however, this was acceptable because growth was not observed for the same three organisms at the higher temperature which is considered worst-case. The applicant has compared log values to initial inoculum control rather than time 0, but actual CFU values were provided for analysis. In general, storage of diluted drug product for 4 hours at room temperature does not require microbial challenge data. The proposed post-dilution storage time of 24 hours at 2-8°C or 4 hours at room temperature is acceptable for ibalizumab.*

## SATISFACTORY

### **CGMP Status**

The assessment of manufacturing facilities is documented in panorama.

### **Conclusion**

- I. The BLA was reviewed from a product quality microbiology perspective and is recommended for approval.
- II. Product quality aspects other than microbiology should be reviewed by OBP.
- III. No inspection follow-up items were identified.



Virginia  
Carroll

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Patricia  
Hughes Troost

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Date: 2/14/2018 10:37:19AM  
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**Date:** 1/24/2018  
**To:** Administrative File, STN 761065/0  
**From:** Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV  
**Endorsement:** Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead,  
CDER/OPQ/OPF/DMA/Branch IV  
**Subject:** Addendum to review memo for New Biologic License Application (BLA)  
STN 761065 dated September 14, 2017  
**Applicant:** TaiMed Biologics USA Corp.  
**US License:** 2057  
**Facility:** WuXi AppTec Biopharmaceuticals Co., Ltd.  
WuXi, Jiangsu Province, P.R.China  
FEI: 3012672198  
**Product:** ibalizumab (TMB-355)  
**Dosage:** 150 mg/mL, liquid in vials, intravenous infusion  
**Indication:** Treatment of HIV patients with Multi-Drug Resistance  
**Action Date:** March 3, 2018

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**Recommendation:** The drug substance part of this BLA is recommended for approval from quality microbiology perspective.

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**Review Addendum**

The following studies and information were submitted to the Agency after the interim review and are reviewed herein:

1. Qualification of the DS sample for the bioburden test using 30 mL test volume.
2.  (b) (4)
3. Update the BLA as committed

**Assessment**

**Qualification of the DS sample for the bioburden test using 30 mL test volume**

In the amendment dated 1/18/2018 (Sequence 72), the applicant provided bioburden qualification data for the drug substance (DS) sample using 30 mL test volume. Report VD2739-MVR, "Supplemental method verification report for bioburden analysis for WBP236 drug substance (membrane filtration)" was provided and reviewed. The qualification study used one DS lot (Lot 236170607).

The acceptance criteria for the study are:

- Microbial recovery in the testing group of each spike test is between 50-200% (including 50-200%)
- No microorganism growth in the negative control
- Positive control group has 10-100 CFU/filter

During the qualification study, challenge microorganism in 0.1 mL volume (not more than 100 CFU) was added to 30 mL ibalizumab DS sample and filtered. The positive controls are prepared by filtering 30 mL of sodium chloride-peptone buffer solution and 0.1 mL of the test strain. The negative control was prepared by filtering sodium chloride-peptone buffer solution. Each filter was rinsed with 100mL of pH7.0 sterile sodium chloride-peptone buffer solution 3 times.

The challenge organisms are provided in the table below:

Test strains information for sample:

Strain Name	Outer Number	Internal Number	Passages Number
<i>Pseudomonas aeruginosa</i>	ATCC9027	BPa17013	4
<i>Staphylococcus aureus</i>	ATCC6538	BSa17018	4
<i>Bacillus subtilis</i>	ATCC6633	BBs17010	4
<i>Candida albicans</i>	ATCC10231	FCa17012	4
<i>Aspergillus brasiliensis</i>	ATCC16404	FAb17015	4
<i>Moraxella (moraxella) osloensis</i> *	NA	20170615B02	NA
<i>Mycosphaerella</i> sp. *	NA	20170629A08	NA

\*: This two dominate environmental isolates were isolated from WuXi manufacturing facility.

The incubation conditions used are provided in the table below:

Table 3.1-1 Actual incubation conditions used in each experiment

Strain/Experiment group	Medium	Incubation temperature	Incubation time
<i>Staphylococcus aureus</i>	TSA	30-35°C	3 days
<i>Pseudomonas aeruginosa</i>	TSA	30-35°C	3 days
<i>Bacillus subtilis</i>	TSA	30-35°C	3 days
<i>Moraxella (moraxella) osloensis</i>	TSA	30-35°C	3 days
<i>Mycosphaerella</i> sp.	SDA	20-25°C	5 days
<i>Candida albicans</i>	TSA	30-35°C	5 days
	SDA	20-25°C	5 days
<i>Aspergillus brasiliensis</i>	TSA	30-35°C	5 days
	SDA	20-25°C	5 days
Sample Control Group	TSA	30-35°C	5 days
	SDA	20-25°C	5 days
Negative Control Group	TSA	30-35°C	5 days
	SDA	20-25°C	5 days

The study results are:

- Microbial recovery in the testing group of each spike test was between 58-159%
- No microorganism growth in the negative control
- Positive control group has 11-77 CFU/filter

All the results met the acceptance criteria.

*Reviewer comment: The bioburden specification for DS has been changed from (b) (4) CFU/ (b) (4) mL to (b) (4) CFU/ (b) (4) mL. The sponsor provided supplemental bioburden qualification data for the increased test volume. All the results met the acceptance criteria. The supplemental bioburden qualification study used only one lot. Qualification data using samples from two additional lots will not be requested because the risk of having inhibitory effect due to the increased test volume is very low. Previously submitted qualification data of the 10-mL test volume using samples from three DS lots showed no inhibitory effect. In addition, the bioburden test uses the membrane filtration method*

(b) (4)

Satisfactory

(b) (4)



*Satisfactory*

Update the BLA as committed

All the committed updates of the BLA have been verified.

*Satisfactory*

**Conclusion**

- I. The drug substance part of this BLA is recommended for approval from quality microbiology perspective

- II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the OBP reviewer.
- II. See Panorama for compliance status of the facilities.



Bo  
Chi

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Reyes  
Candau-Chacon

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**First Approval for Indication/Breakthrough/Priority Review:** for the treatment of HIV-1 infection in treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy.

**Recommendation:** Pending

**BLA STN 761065**  
**Review Number: 1**  
**Review Date:** September 28, 2017

<b>Drug Name/Dosage Form</b>	ibalizumab/injection (TROGARZO™)
<b>Strength/Potency</b>	200 mg/1.33 mL vial
<b>Route of Administration</b>	Intravenous infusion
<b>Rx/OTC dispensed</b>	Rx
<b>Indication</b>	Treatment of HIV-1 infection in treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy
<b>Applicant/Sponsor</b>	TaiMed Biologics USA Corp

### Product Overview

Ibalizumab is a humanized IgG4, κ monoclonal antibody produced in a NS0 cell line. Ibalizumab binds with high affinity to an epitope on domain 2 of the CD4 T-cell coreceptor. CD4 is the primary receptor for the HIV-1 glycoprotein gp120. Ibalizumab blocks HIV-1 infection of CD4 T-cells by preventing the post-binding conformational change of CD4 that allows the fusion of the viral envelope with the T-cell membrane. By preventing the infection of CD4 T cells by HIV-1, ibalizumab may help reduce viral load and improve clinical outcomes in patients with HIV-1.

Ibalizumab drug substance and drug product are manufactured at WuXi AppTec (Wuxi, China). (b) (4)

The drug substance (DS) contains ibalizumab at 150 mg/mL concentration, formulated in 10 mM L-Histidine, 5.2% Sucrose, 52 mM sodium chloride, 0.045% polysorbate 80, pH 6.0, and stored at 2 °C to 8 °C. (b) (4)

(b) (4) For ibalizumab DS, the data provided in the BLA submission support an expiration dating period of (b) (4) months when stored at (b) (4) °C.

Ibalizumab drug product manufacturing involves (b) (4). The container closure is a single (b) (4) 2 mL (b) (4) glass vial with a (b) (4) 1 rubber stopper and aluminum flip-off seal. Ibalizumab is supplied at 200 mg/1.33 mL vial. (b) (4). For ibalizumab DP, the data

provided in the BLA submission support an expiration dating period of 36 months when stored at 2°C to 8°C.

### Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Steven Bowen	DBRR III/OBP/OPQ
Drug Product	Steven Bowen	DBRR III/OBP/OPQ
Immunogenicity	Steven Bowen	DBRR III/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facility	Michael Shanks	DIA/OPF/OPQ
Microbiology (DS)	Bo Chi	DMA/OPF/OPQ
Microbiology (DP)	Virginia Carroll	
Business Process Manager	Anita Brown	RPMB I/OPRO/OPQ
Team Lead for OBP	Ramesh Potla	DBRR III/OBP/OPQ
Tertiary Reviewer for OBP	Susan Kirshner	DBRR III/OBP/OPQ
Microbiology Team Lead (DS)	Reyes Candau-Chacon	DMA/OPF/OPQ
Microbiology Team Lead (DP)	Dupez Palmer	DMA/OPF/OPQ
Microbiology Tertiary Reviewer	Patricia Hughes	DMA/OPF/OPQ
Facilities Team Lead	Peter Qiu	DIA/OPF/OPQ
Application Team Lead	Ramesh Potla	DBRR III/OBP/OPQ

### Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
RPM	Christian Yoder	DAVP/OAP/OND
Cross-disciplinary Team Lead	Adam Sherwat	DAVP/OAP/OND
Medical Officer	Virginia Sheikh	DAVP/OAP/OND
Pharm/Tox	David McMillan	DAVP/OAP/OND
Clinical Pharmacology	Qin Sun	DCPIV/OCP/OTS
Statistics	Karen Qi	DBIV/OB/OTS

#### 1. Names:

- a. Proprietary Name: Trogarzo
- b. Trade Name: Trogarzo
- c. Non-Proprietary Name/USAN: ibalizumab
- d. CAS Name: 680188-33-4
- e. Common Name: ibalizumab
- f. INN Name: ibalizumab
- g. Compendial Name: N/A
- h. OBP systematic name: MAB HUMANIZED (IGG4) ANTI P01730 (CD4\_HUMAN) [TMB355]
- i. Other names: TMB-355, WBP236, TNX-355, Hu5A8

### Submissions Reviewed

Submission(s) Reviewed	Document Date
Module 3 Rolling Submission	7/15/2016
Original BLA	5/3/2017
CMC amendment	5/11/2017
Response to IR 1 (OPF)	6/13/2017
Response to IR 2 (OBP)	6/27/2017
Response to IR 3 (OPF)	7/11/2017
Response to IR 4 (OBP & OPF)	8/11/2017
Response to IR 5 (OPF)	8/31/2017
Response to IR 6 (OPF)	9/12/2017
Sponsor's Response to Mid-cycle Comments	9/15/2017
Response to IR 7 (OBP & OPF)	9/18/2017
Response to IR 8 (OPF)	9/28/2017
Response to IR 9 (OBP)	9/29/2017

### Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

Letters of authorization to review the drug master files for the cell culture media (b) (4) and components of the drug substance and drug product container closure systems have been requested. As of the date of this report the letters of authorization have not been received. This will be reviewed in an addendum to this report.

B. Other documents: None.

3. Consults: None

## Executive Summary

### I. Recommendations:

#### A. Recommendation and Conclusion on Approvability:

Recommendation: Pending.

At this time, a recommendation cannot be made from the product quality perspective because of the deficiencies listed below:

1. The Sponsor has not submitted the errata to address the discrepancies observed between the information submitted in the BLA and manufacturing and testing operations conducted at the Wuxi facility. In the CMC amendment dated 09/15/2017, the Sponsor stated that the errata will be provided as a separate submission, but did not indicate a timeline for this submission. In a subsequent teleconference on 9/26/2017 the Sponsor was unable to clarify when the errata would be submitted. The complete list of all discrepancies between the BLA and the manufacturing and testing operations at the Wuxi facility is necessary before a substantive review can be completed.
2. All sections of the BLA need to be updated with current information. Changes to the application that the Sponsor is proposing in response to Agency comments need to be integrated into all relevant sections of the BLA. All information that is inaccurate or no longer relevant needs to be removed.
3. The Sponsor is not submitting the documentation to electronic common technical document (eCTD) appropriately. This is resulting in multiple versions of the same document appearing within the same section of the eCTD. To correct this the Sponsor was advised in the teleconference on 9/26/2017 to contact the FDA ESUB group to resolve the electronic submission issues for this BLA.
4. Letters of authorization to review the drug master files (DMFs) for the cell culture media (b) (4) and the components of the container closure systems for the drug substance and drug product were requested and have not yet been provided. These letters of authorization are needed to evaluate whether the components of the cell culture media are adequately controlled and whether the container closure systems are compatible with ibalizumab DS and DP.
5. In the teleconference held on 9/26/2017 the Sponsor committed to provide a list of action items and a proposed timeline to the agency early in the week of October 3<sup>rd</sup>. This list has yet to be provided.
6. Complete summary data and information for two additional successful media fills, as requested, will be reviewed prior to approval. We acknowledge that the relevant study results were planned to be submitted by October 15, 2017.

7. Currently the review of the PLI at WuXi, DS and DP manufacturer, is under review and pending the firm's response to a RAI. Satisfactory resolution of the FDA-483 items regarding the WuXi PLI is required for BLA 761065 approval.

A recommendation of approvability will be made in an addendum to this review memo upon the receipt and review of all pending information from the Sponsor.

## **B. Approval Action Letter Language:**

Manufacturing location:

- Drug Substance: Wuxi AppTec Biologics, Wuxi, China
- Drug Product: Wuxi AppTec Biologics, Wuxi, China
- Fill size and dosage form – 200 mg/1.33 mL in a single (b) (4) vial
- Dating period:
  - Drug Product: 36 months: 2-8 °C
  - Drug Substance: (b) (4) months: (b) (4) °C
- Exempt from lot release
  - Yes
  - Rationale, if exempted: specified product
  - We exempt specified products according to 21 CFR 601.2a.

## **C. Benefit/Risk Considerations:**

Trogarzo (ibalizumab) is for the treatment of HIV-1 infection in treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy.

A review of benefit-risk assessment will be documented in the addendum to this report once all outstanding information has been reviewed.

## **B. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:**

Potential post marketing commitments/requirements will be documented in the addendum to this report once all outstanding information has been reviewed.

## **II. Summary of Quality Assessments:**

### **A. CQA Identification, Risk and Lifecycle Knowledge Management**

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to both drug substance and drug product.

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

CQA	Risk	Origin	Control Strategy	Other
Aggregates (product related impurity)	Safety and efficacy	Protein aggregation on stability	(b) (4)	<i>The proposed release and stability acceptance criteria should be revised to be in agreement with clinical and manufacturing experience.</i>
Acidic variants (product related impurity)	Safety and efficacy	(b) (4)	(b) (4)	<i>The proposed release and stability acceptance criteria should be revised to be in agreement with clinical and manufacturing experience.</i>
Basic variants (Product related impurity)	Safety and efficacy	Oxidation	(b) (4)	<i>The proposed release and stability acceptance criteria should be revised to be in agreement with clinical and manufacturing experience.</i>
Fragments (product related impurity)	Safety and efficacy	Degradation on stability	(b) (4)	NA
Half-antibodies (product related variants)	Potential product-related species with IgG4 antibodies	Safety and Efficacy Potential impact on safety and efficacy not fully	(b) (4)	NA

		understood	(b) (4)	
pH	Safety and efficacy	General CQA		NA
Biological Activity	Efficacy	Intrinsic to molecule		<i>The proposed release and stability acceptance criteria should be revised to be in agreement with clinical and manufacturing experience.</i>
Identity	Safety and efficacy	Intrinsic to molecule		NA

**B. Drug Substance [ibalizumab] Quality Summary**

**CQA Identification, Risk, and Lifecycle Knowledge Management**

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

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

CQA (type)	Risk	Origin	Control Strategy (b) (4)	Other
Residual NS0 Host Cell Protein (process related impurity)	Safety	Process related impurity (b) (4)		NA
Residual NS0 Host Cell DNA (process related impurity)	Safety	Process related impurity (b) (4)		NA
Bioburden	Safety	Contamination: Bioburden can be introduced throughout the manufacturing		NA

		process	testing of DS and DP.	
Endotoxin	Safety	Contamination: Endotoxin can be introduced throughout the manufacturing process	(b) (4)	NA
Mycoplasma	Safety	Contamination: Mycoplasma can be introduced during cell culture		NA
(b) (4)	Safety	Process related impurity (b) (4)		NA
Adventitious virus	Safety	Contamination: adventitious virus can be introduced during cell culture.		NA
(b) (4)	Safety	Process related impurity, (b) (4)		NA
(b) (4)	Safety	Process related impurity, (b) (4)		NA

- Description:**  
Ibalizumab (TMB-355) is a humanized monoclonal IgG4 antibody that binds the CD4 co-receptor on T-cells to block entry of human immunodeficiency virus 1 (HIV-1). Ibalizumab consists of two identical gamma 4 heavy chains of 449 amino acids and two identical kappa light chains of 219 amino acids. The heavy and light chains are stabilized by multiple inter- and intra- chain disulfide bonds. The heavy chain constant region contains a single N-linked oligosaccharide chain, comprised primarily of neutral biantennary-type oligosaccharides. The primary amino acid sequence of ibalizumab is shown below. The IgG4 heavy chain hinge region sequence is not modified to prevent formation of half antibodies. The complementarity determining regions (CDR) are underlined and the N-linked glycosylation site at N299 of the heavy chain is shown in

red. The heavy chain contains a C-terminal lysine residue, the variants of which are a potential source of heterogeneity.

- Mechanism of Action (MoA):  
Ibalizumab binds with high affinity to an epitope on domain 2 of the CD4 T-cell coreceptor. CD4 is the primary receptor for the HIV-1 glycoprotein gp120. Ibalizumab blocks HIV-1 infection of CD4 T-cells by preventing the post-binding conformational change of CD4 that allows the fusion of the viral envelope with the T-cell membrane. By preventing the infection of CD4 T cells by HIV-1, ibalizumab may help reduce viral load and improve clinical outcomes in patients with HIV-1.
- Potency Assay:  
The cell-cell fusion inhibition method for ibalizumab potency involves the co-culture of two HeLa cell lines:

1. HL2/3 has been engineered to express gp120 on the cell surface and the transcriptional activator tat in the cytoplasm. The assay is run between passages 9 and 16.

2. HeLa-CD4-LTR- $\beta$ -gal expresses CD4 on the cell surface and contains a LacZ reporter gene under the control of a tat-inducible LTR promoter. The assay is run between passages 4 and 12.

Co-culture of the two cell lines results in cell fusion mediated by interaction between gp120 on HL2/3 and CD4 on HeLa-CD4-LTR- $\beta$ -gal. After cell fusion, the cytoplasmic tat transcription factor binds to the LTR promoter of the reporter construct and drives expression of b-galactosidase. The cells are lysed and the chemiluminescence is measured. The level of chemiluminescent signal is proportional to the level of cell-cell fusion. Ibalizumab binds to CD4 on HeLa-CD4-LTR- $\beta$ -gal and prevents cell-cell fusion in a concentration dependent manner.

- Reference Materials:  
A two-tier reference material system is in place, which is consistent with ICH Q6B. The



(b) (4)



**C. Drug Product [ibalizumab] 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

<b>CQA</b>	<b>Risk</b>	<b>Origin</b>	<b>Control Strategy</b>	<b>Other</b>
Osmolality	General CQA	Formulation	Tested at (b) (4) DP release and stability	<i>The proposed release and stability acceptance criteria should be revised to be in agreement with clinical and manufacturing experience.</i>
Appearance	General CQA	Formulation	Tested at (b) (4) DP release and stability	NA

Sterility/Container closure integrity	Safety	DP manufacturing, on stability	Tested at DP release and stability	NA
Particulate matter	Safety	Particulates can be introduced throughout the manufacturing process and on stability	Tested at DP release and stability as per USP <788>	NA
Endotoxin	Safety	Contamination: Endotoxin can be introduced throughout the manufacturing process	(b) (4) release and stability testing of (b) (4) DP.	NA

- Potency and Strength:**  
Ibalizumab is supplied at 200 mg/1.33 mL vial. Potency is defined as the percent activity relative to the current ibalizumab reference standard. The potency assay is the same as described in the DS section of this review memo.
- Summary of Product Design:**  
Ibalizumab is supplied as a sterile, preservative-free solution in a single (b) (4) vial for intravenous infusion. The drug product formulation consists of 10 mM L-Histidine, 5.2% Sucrose, 52 mM sodium chloride, 0.045% polysorbate 80, pH 6.0. The extractable volume is 1.33 mL.
- List of Excipients:**  
Excipients include 10 mM L-Histidine, 5.2% Sucrose, 52 mM sodium chloride, and 0.045% polysorbate 80.
- Reference Materials:**  
The same reference material is used for DS and DP.
- Manufacturing process summary:**

(b) (4)



(b) (4)

- Container closure:  
The primary container closure system for ibalizumab DP consists of a (b) (4) clear 2 mL (b) (4) glass vial (b) (4), 13-mm (b) (4) rubber stopper (b) (4), and a 13 mm Aluminum seal.
- Dating period and storage conditions:  
The dating period for ibalizumab DP is 36 months when stored at 2°C to 8°C, protected from light.

**D. Novel Approaches/Precedents:** None.

**E. Any Special Product Quality Labeling Recommendations:**

- Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
- Protect from light until use.
- Do not freeze.

**F. Establishment Information:**

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTI ONAL OBSERVA TIONS	FINAL RECOMMEND ATION
Manufacturi	WuXi Apptec	3010606982	Pre-License	VAI/OAI	PENDING

ng, Packaging, Quality Control Testing of the Drug Substance	Biopharmaceuti cals Co., Ltd.		Inspection (8/2/2017)		Approve/Withho ld
DRUG PRODUCT					
FUNCTION	SITE INFORMATI ON	DUNS/FEI NUMBER	PRELIMINA RY ASSESSME NT	INSPECTI ONAL OBSERVA TIONS	FINAL RECOMMEN DATION
Manufacturin g, Packaging, Quality Control Testing of the Drug Product	WuXi Apptec Biopharmaceut icals Co., Ltd.	3010606982	Pre-License Inspection (8/2/2017)	VAI/OAI	PENDING Approve/Withh old
Identity Testing	WuXi AppTec	1000122198	GMP Inspection (4/17/2015)	VAI	Approve
Identity Testing	(b) (4)	(b) (4)	GMP Inspection (b) (4)	NAI	Approve

**G. Facilities:**

Trogarzo™ (ibalizumab, TMB-355) DS and DP are manufactured at WuXi Apptec Biopharmaceuticals Co., Ltd. (FEI: 3010606982). A Pre-license Inspection was performed at WuXi Apptec Biopharmaceuticals Co., Ltd. on 07/17 – 08/02/2017. A 23-item Form FDA 483 was issued. The recommendation for the firm is **pending (approve/withhold)**; however, the inspection is **pending final classification**. Currently, the WuXi Apptec Biopharmaceuticals Co., Ltd. (FEI: 3012672198/3010606982) site has an unacceptable compliance and is recommended as a pending (approve/withhold) .

**H. Lifecycle Knowledge Management:**

**a. Drug Substance:**

i. Protocols :

1. Validation of (b) (4) at commercial scale
2. Qualification/annual retesting (b) (4)
3. Post-approval DS stability protocol

- ii. Outstanding review issues/residual risk: See “Recommendation” section for outstanding review issues.
- iii. Future inspection points to consider: See 483 observations in the establishment information section and DIA review.

**b. Drug Product**

- i. Protocols:
  - 1. Post-approval DP stability protocol
- ii. Outstanding review issues/residual risk: See “Recommendation” section for outstanding review issues.
- iii. Future inspection points to consider: See 483 observations in the establishment information section and DIA review.



Susan  
Kirshner

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Center for Drug Evaluation and Research  
Office of Pharmaceutical Quality  
Office of Process and Facilities  
Division of Microbiology Assessment  
WO Building 22  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

## **PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION**

**Reviewers: Virginia Carroll, PhD and Bo Chi, PhD**  
**Quality Assessment Lead: Dupeh Palmer, PhD**

BLA: 761065/0  
Applicant: TaiMed Biologics USA Corp.  
US License Number: NA  
Submission Reviewed: Original BLA  
Product: ibalizumab (TROGARZO)  
Indication: HIV treatment of multi-drug resistant patients  
Dosage Form: Sterile solution for intravenous injection, 200 mg per vial (150 mg/mL)  
Manufacturing Sites: WuXi AppTec Biopharmaceuticals Co., Ltd. Wuxi, Jiangsu, China (FEI 3012672198)  
FDA Receipt Date: 5/3/2017  
Action Date: 10/3/2017

### **Conclusion and Approvability Recommendation**

The drug product part of this BLA, as amended, was reviewed from a sterility assurance and product quality microbiology perspective. The recommendation for approval cannot be made until additional media fill information and data are submitted and reviewed and the BLA is appropriately amended.

### **Review Addendum**

Two additional media fills [REDACTED] (b) (4) of ibalizumab at WuXi AppTec will be submitted to the Agency by October 15, 2017 and will be reviewed in an addendum.

Appropriate updates to Module 3 of the BLA are currently pending.

## **Product Quality Microbiology Assessment: Drug Product**

### **Drug Product Quality Microbiology Information Reviewed**

<b>Sequence number</b>	<b>Date</b>	<b>Description</b>
0010	May 3, 2017	Original BLA
0017	June 13, 2017	Response to IR
0025	July 11, 2017	Response to IR
0039	August 31, 2017	Response to IR
0041	September 12, 2017	Response to IR
0046	September 18, 2017	Response to IR

## **Module 3.2**

### **P.1 Description and Composition of the Drug Product**

Ibalizumab is a sterile solution for intravenous injection. It is provided at a concentration of 150 mg/mL in 2 mL clear glass vials. Each vial is filled with (b) (4) mL of product to deliver 1.33 mL per vial to provide 200 mg ibalizumab.

The composition of the drug product per 1 mL is shown in the table below. The pH is adjusted to 6.0.

**Table 3.2.P.1.3 Quantities of Ingredients Used in Ibalizumab Drug Product Vial**

<b>Ingredient</b>	<b>Amount Per 1-mL Vial</b>
Ibalizumab	150 mg
Sucrose	52 mg
Sodium Chloride	3.04 mg
Polysorbate 80	(b) (4)
L-histidine	1.55 mg
	(b) (4)

The quantities of ingredients used for drug product vials were clarified in an amendment (sequence 0025):

**Table 1. Quantities of Ingredients in ibalizumab Drug Product Per Vial**

<b>Ingredients</b>	<b>Amount per vial (Label claim 1.33 mL/vial)</b>
Ibalizumab	200 mg
Sucrose	69.2 mg
Sodium Chloride	4.04 mg
Polysorbate 80 (b) (4)	0.60 mg
(b) (4)	
L-histidine	2.06 mg
(b) (4)	Adjust pH to 6.0
	(b) (4)

*Reviewer's Comments: Table 3.2.P.1.3 lists amounts per 1 mL, but the drug product is provided in 2 mL vials at an extractable volume of 1.33 mL/vial. The vials are overfilled to (b) (4) mL.*

*The grades and vendors of sodium chloride and polysorbate 80 differed between sections 3.2.A.3 and 3.2.P.1.2 and were clarified in an amendment (sequence 0025). The components listed in Table 3.2.P.1.2 (not shown) were used in a mixing study for process characterization. See section 3.2.P.2.1 below for components of ibalizumab drug product.*

*According to the label, ibalizumab is administered as a single loading dose of 2000 mg (10 vials) with a maintenance dose of 800 mg (4 vials) in 250 mL saline.*

## **P.2 Pharmaceutical Development**



## P.8 Stability

### P.8.1 Stability Summary and Conclusions

Two clinical lots and three validation lots are currently on the stability protocol. A commercial shelf-life of 3 years at 2-8° is proposed. Available long-term stability data at 5°C for sterility and endotoxin is summarized below. The acceptance criteria were no growth in the sterility test and (b) (4) EU/mL for the endotoxin test. The CCIT method was implemented in lieu of sterility at months 33 and 36 for the first lot and will be applied for all future stability time points.

DP Lot #	DP Lot	Manufacturing Date	Stability Data (months)
1	201403001	March 2014	0, 12, 24, 33*, 36*
2	201505012	June 2015	0, 12
3	201509019	Sept 2015	0, 12
4	201509020	Sept 2015	0, 12
5	201509021	Sept 2015	0, 12

\*Sterility replaced with CCIT method in June 2016

The following was submitted in an amendment (sequence 0017):

It was confirmed that sterility is performed at release and CCIT will be performed once every 12 months and at expiry. It was proposed that CCIT be performed at release/time 0 instead of sterility. The sponsor requested clarification from the Agency on the approach.

The following was submitted in an amendment (sequence 0025):

It was confirmed that sterility will be tested at product release and CCIT will be performed in lieu of sterility testing for stability samples once every 12 months and at expiry.

*Reviewer's Comment: The acceptance criteria for endotoxin at release (b) (4) upon the Agency's request. The endotoxin specification for stability is not updated, but endotoxin testing is not required for stability samples.*

### **P.8.2 Post-Approval Stability Commitment**

The five manufactured lots of ibalizumab DP are on the stability program for 3 years. Newly manufactured lots will be placed on the same stability program, stored at 2-8°C for 3 years. Testing is performed at WuXi AppTec.

*Reviewer's Comment: Removal of the endotoxin and sterility testing on stability was requested. The response will be reviewed in the addendum.*

### **P.8.3 Stability Data**

Stability data was presented in tables for the five DP lots. Sterility, CCIT, and endotoxin results for the 5°C storage condition are summarized below.

DP Lot	Month	Sterility/CCIT*	Endotoxin (≤3.5 EU/mL)
201403001	0	No growth	<0.5 EU/mL
	12	No growth	<0.5 EU/mL
	24	No growth	<0.3 EU/mL
	33*	Pass	<0.3 EU/mL
	36*	Pass	<0.3 EU/mL
201505012	0	No growth	<0.5 EU/mL
	12	No growth	<0.3 EU/mL
201509019	0	No growth	<0.3 EU/mL
	12	No growth	≤0.3 EU/mL
201509020	0	No growth	<0.3 EU/mL
	12	No growth	<0.3 EU/mL
201509021	0	No growth	<0.3 EU/mL
	12	No growth	<0.3 EU/mL

*Reviewer's Comment: Stability results for sterility, CCIT, and endotoxin met the acceptance criteria. No post-dilution study was required because the diluted drug product must be used  $\leq 4$  hours after dilution.*

SATISFACTORY

### **CGMP Status**

The assessment of manufacturing facilities is documented in panorama.

### **Conclusion**

- I. The BLA was reviewed from a product quality microbiology perspective. The recommendation for approval cannot be made until additional media fill information and data is submitted and reviewed and the BLA is appropriately amended.
- II. Product quality aspects other than microbiology should be reviewed by OBP.
- III. No inspection follow-up items were identified.

**DP Quality Microbiology Information Requests Sent and Date**

**May 26, 2017 (response 0017)**

Your 351(a) BLA appears to be incomplete and does not contain all of the information necessary to support a substantive review of ibalizumab from a sterility assurance perspective. Refer to the FDA responses that were provided in the meeting minutes from the CMC Type B Teleconferences on September 4, 2015 and February 3, 2016 and to the 1994 Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products. Please submit your responses to the following information requests prior to June 16, 2017. All translations of documents should be certified.



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