

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761046Orig1s000

CHEMISTRY REVIEW(S)



BLA 761046: Priority Submission

Recommendation: Approval

BLA761046 Addendum-1 Review #02, June 21, 2016

Drug Name/Dosage Form	Zinplava (bezlotoxumab) / Injection
Strength/Potency	1000mg/Vial (25mg/mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Indication	Prevention of <i>Clostridium difficile</i> infection (CDI) recurrence in patients 18 years and older receiving antibiotic therapy for CDI
Applicant/Sponsor	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
US agent, if applicable	N/A

A. Names

- a. **Proprietary Name:** Zinplava
- b. **Trade Name:** Zinplava
- c. **Non-Proprietary/USAN:** Bezlotoxumab
- d. **CAS name:** 1246264-45-8
- e. **Common name:** MK-6072
- f. **INN Name:** Bezlotoxumab
- g. **OBP systematic name:** MAB HUMAN (IGG1) ANTIP18177
(TOXB_PEPDI)[MK6072]

Pharmacologic category: Therapeutic recombinant human monoclonal antibody (IgG1)

Product Overview

Bezlotoxumab is a human monoclonal antibody of IgG1/kappa isotype. It binds with *Clostridium difficile* toxin B. Binding of bezlotoxumab to toxin B blocks interaction of toxin B with target cell surface receptors, thereby preventing the intoxication pathways induced by toxin B in the cells and consequently preventing the damage and inflammation that lead to the symptoms of *Clostridium difficile* infection (CDI).

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Product Quality and Immunogenicity	William Hallett	Division of Biotechnology Review Research II
Manufacturing Facilities	Thuy Nguyen	Division of Inspectional Assessment
Microbiology Quality Assessment	Natalia Pripuzova	Division of Microbiology Assessment
Business Regulatory Process Manager	Melinda Bauerlien	OPRO/OPQ
Application Technical Lead	Rashmi Rawat	Division of Biotechnology Review Research II

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
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Cross-disciplinary Team Lead	Dmitri Iarikov	OND/DAIP
Clinical	Shrimant Mishra, Hiwot Hiruy	OND/DAIP
Non-Clinical	Luning (Ada) Zhuang, Jeffry Florian	OAP/DAIP
Clinical Microbiology	Kerian Grande Roche	OAP/DAIP
Clinical Pharmacology	Yang He, Seong Jang	CDER
Biometrics	Cheryl Dixon, Karen Higgins	OB/DBIV

Quality Review Team – Signature Page

DISCIPLINE	REVIEWER	DIVISION/OFFICE	e-SIGNATURE
Product Quality and Immunogenicity (Primary Reviewer)	William Hallett	DBRR II/OBP/OPQ	William H. Hallett -S Digitally signed by William H. Hallett -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001154757, cn=William H. Hallett -S Date: 2016.06.21 12:54:28 -04'00'
Microbiology Quality Assessment (Primary Reviewer)	Natalia Pripuzova	DMA/OPF/OPQ	Natalia S. Pripuzova -S (Affiliate) Digitally signed by Natalia S. Pripuzova -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000351935, cn=Natalia S. Pripuzova -S (Affiliate) Date: 2016.06.21 13:10:24 -04'00'
Microbiology Quality Assessment (Team Leader)	Colleen Thomas	DMA/OPF/OPQ	Colleen Thomas -S Digitally signed by Colleen Thomas -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000334597 Date: 2016.06.22 09:39:07 -04'00'
Manufacturing Facilities (Primary Reviewer)	Thuy Nguyen	DIA/OPF/OPQ	Thuy T. Nguyen -S Digitally signed by Thuy T. Nguyen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Thuy T. Nguyen -S, 0.9.2342.19200300.100.1.1=2000425639 Date: 2016.06.22 11:42:11 -04'00'
Manufacturing Facilities (Branch Chief)	Zhihao Qiu	DIA/OPF/OPQ	Zhihao Qiu -S Digitally signed by Zhihao Qiu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu -S, 0.9.2342.19200300.100.1.1=2000438274 Date: 2016.06.22 07:54:09 -04'00'
Product Quality Application Technical Lead and Team Leader	Rashmi Rawat	DBRRII/OBP/OPQ	Rashmi Rawat -S Digitally signed by Rashmi Rawat -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rashmi Rawat -S, 0.9.2342.19200300.100.1.1=0014137532 Date: 2016.06.21 12:20:37 -04'00'
Product Quality Acting Review Chief	Juhong Liu	DBRRII/OBP/OPQ	Juhong Liu -S Digitally signed by Juhong Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Juhong Liu -S, 0.9.2342.19200300.100.1.1=0010401517 Date: 2016.06.21 19:55:20 -04'00'



Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. Submission Reviewed:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
STN 761046, eCTD#0028	4/29/2016
STN 761046, eCTD#0032	5/31/2016
STN 761046, eCTD#0033	6/1/2016
STN 761046, eCTD#0034	6/17/2016

3. CONSULTS: *None*

Executive Summary

I. Recommendations

A Recommendation and Conclusion on Approvability

a. Recommendation

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761046 for Zinplava (bezlotoxumab) manufactured by Merck sharp & Dohme Inc. The data submitted in this application support the conclusion that the manufacture of Zinplava is well controlled and produces 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: (b) (4)
 - Drug Product: MSD Ireland (Carlow), Ireland
- Fill Size and Dosage Form
1000 mg/40 mL in single dose vial, Injection
- Dating Period:
 - Drug Product: 24 months; 2-8 °C
 - Drug substance: (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 extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12
- Exempt From Lot Release
 - Yes
 - Rationale for exemption: Specified Product (note: we exempt specified products according to CFR 601.2a)

c. Review Summary and Risk Benefit

The bezlotoxumab is a human monoclonal antibody that targets and neutralizes toxin B of *C. difficile*. It is indicated for the prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years and older receiving antibiotic therapy for CDI. The DS and DP manufacturing process are well controlled and capable of producing product of consistent quality. All manufacturing and testing facilities for the drug substance and drug product are deemed compliant. Merck submitted a data package containing the revised (b) (4) assay results for bezlotoxumab drug substance (DS) and drug product (DP). The revisions and reporting of the results were made according to the agreement made between FDA and Merck on March 25, 2016. The evaluation of the revised (b) (4) results for DS and DP in-process, release and stability show minimal change from the original reported values. All affected batch are found to be within the (b) (4) -assay acceptance criteria for release and stability after correction. Overall the revised results for (b) (4) assay did not the affect the initial conclusion regarding the manufacture, release, stability and shelf life determination of the bezlotoxumab drug substance and drug product. In addition to (b) (4) assay for assessing (b) (4) the final DS and DP control strategy also includes other (b) (4) assay that measure the (b) (4) in bezlotoxumab at release and during stability studies. Merck has also updated the appropriate sections of the BLA based on the agreements made between the Merck and the FDA during primary review cycle.

An issue of low endotoxin recovery was identified for the endotoxin assay used in the control of drug substance and drug product release. To ensure the product safety Merck has implemented an alternative control strategy for endotoxin assay until an adequately valid in vitro endotoxin assay is developed. The alternate endotoxin control strategy for the release of the DS include testing (b) (4) with an acceptance criterion of (b) (4). For control of the DP release the sponsor has implemented a rabbit pyrogen testing (RPT). Merck has agreed to develop a valid in vitro endotoxin assay for bezlotoxumab DS and DP release as a post marketing commitment.

There are some minor product quality issues identified during the BLA review, which do not preclude approval of the BLA and will be addressed as post marketing commitments.

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

1. Re-evaluate MK-6072 DS and DP lot release and stability specifications after a minimum of 30 DS lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification



methods. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

2. Perform additional testing to support the clonality of the bezlotoxumab master cell bank (MCB).
3. Conduct a study to support the worst case cumulative hold times in the bezlotoxumab drug substance manufacturing process to demonstrate that the worst case cumulative hold time will not adversely affect the product quality of bezlotoxumab drug substance. These data are expected to demonstrate that there is no adverse impact to product quality (b) (4)

(b) (4)

Product Quality Microbiology (DMA)

1. Perform additional viability studies and a subsequent microbial retention study (b) (4)

(b) (4)

2. Develop a valid in vitro endotoxin assay for DP release testing. Studies will be performed to determine the most appropriate in vitro method for this purpose, including evaluation of sample preparation and pre-treatment, as well as alternate methodologies for endotoxin detection.

3. Perform Low Endotoxin Recovery (LER) studies (b) (4)

(b) (4)

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below provides a summary of product related critical quality attributes that are relevant to both drug substance and drug product. The table includes the identification of the various attributes along with their risk management. For additional information see Appendix A for the OBP product quality review addendum and Appendix B for the product quality microbiology review addendum.



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Identification of other CQAs specific to drug substance (e.g., process related impurities, adventitious agents, pH, appearance, etc.) or drug product are described in separate risk tables in section B, Drug Substance Quality Summary and section C, Drug Product Quality Summary.

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

CQA	Risk	Origin	Control Strategy	Other
(b) (4)				



(b) (4)





(b) (4)

B. Drug Substance [bezlotoxumab] Quality Summary

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

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

CQA	Risk	Origin	Control Strategy	Other
(b) (4)				



(b) (4)





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(b) (4)	Safety	(b) (4)	(b) (4) testing is part of DS in-process and release testing. The microbial control strategy appears to be adequate.	
	Safety		(b) (4) Sponsor commits to submit the results of LER studies (b) (4) as a PMC, within 3 months of product approval.	
(b) (4)				
pH	General CQA: Safety and efficacy	General CQA. Formulation	pH is controlled by the formulation process.	



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			pH is included in DS release and stability testing.	
(b) (4)				
Appearance: color	General CQA: Safety and efficacy	The color of the DS can be affected by all steps of the manufacturing process, storage conditions and exposure of light.	Color is controlled by the manufacturing process, including formulation. Color is part of DS release and stability testing.	
Appearance, Clarity/ Opalescence	General CQA: Safety and efficacy	The clarity of the DS can be affected by all steps of the manufacturing process.	Clarity is controlled by the manufacturing process, including formulation. Clarity is part of DS release and stability testing.	
Osmolality	Safety	Osmolality is most likely impacted by formulation. No change is expected on stability.	Osmolality is included in DS release testing.	

(b) (4)



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Identity	Safety and efficacy	N/A	Identity of the DS is controlled by release specifications. Identity tests at release include peptide map and toxin B-fragment binding ELISA assays.	
Leachables/extractables	Safety and efficacy (indirectly through effects on stability)	(b) (4) Leachables and extractables could potentially be introduced by any product contact equipment, containers and consumables.	Risk assessments for all (b) (4) materials were performed. Extractable assessments (b) (4) were conducted by the manufacturer vendor and were included in the BLA. Based on the risk assessment provided in the BLA, it was concluded that extractables from have no impact to the product quality and safety. An extractable study conducted on DS container indicates that (b) (4) (b) (4) bezlotoxumab is safe. Merck is also monitoring leachables in a stability study (b) (4) to assess DS container leachables.	

- a. Description:** Bezlotoxumab is a human monoclonal antibody (mAb) of the IgG1 κ isotype that binds the *C.difficile* toxin B. Bezlotoxumab has a molecular weight of approximately 148 kDa.
- b. Mechanism of action:** The primary mechanism of action (MOA) is neutralization of toxin B induced toxicity via direct binding (blocking). Bezlotoxumab binds toxin B with an affinity equilibrium dissociation constant (Kd) of 19 pM, and prevents its interaction with the cell surface and consequently inhibits the intoxication pathway that are induced by toxin B in the cells.
- c. Potency Assay:** The potency assays used to assess the biological activity of bezlotoxumab for release and stability include a Toxin B fragment 4 binding ELISA assay and a cell-based neutralization assay. The binding assay measures the ability of bezlotoxumab to bind to a *C. difficile* toxin B fragment 4, and the cell-based toxin neutralization assay measures the ability of the antibody to protect host cells from the toxin B induced toxicity. The potency is reported as % relative potency to a qualified reference standard.
- d. Reference material(s):** The current reference material lot WL00038529 was produced from clinical drug substance manufacturing process

(b) (4)

. The applicant commits to implement a two tier based strategy for establishing and maintaining future reference materials and plans to implement a new primary and secondary reference standard manufactured

using commercial process at later date. The qualification of the new primary reference material produced using commercial DS manufacturing is provided in the BLA.

e. Critical starting materials or intermediates:

(b) (4)

(b) (4)

Adequate testing for the identity, safety and genetic stability of the cell bank was performed. However, we noted this cell cloning procedure does not provide a high assurance of clonality of the MCB. The FDA communicated their concern to the applicant. The applicant acknowledged the concern regarding clonality and provided additional data demonstrating process and product consistency across a range of variations (b) (4) and genetic characterization of MCB, WCB and end of production cell banks. Although the data provided by the sponsor indicate that the current manufacturing process is not impacted by the clonality of the cell bank, however it did not address the impact of different manufacturing conditions and are, therefore, not robust enough to support lifecycle management of the product. Therefore we asked the sponsor to commit to perform additional testing to support the monoclonality of the master cell bank. The applicant agreed to perform additional testing of master cell bank to support clonality as a post marketing commitment.

(b) (4)

f. Manufacturing process summary: Bezlotoxumab drug substance is manufactured at

(b) (4)

(b) (4)

(b) (4)

using standard monoclonal antibody manufacturing processes. A single working cell bank vial is

g.

- h. **Dating period and storage conditions:** The data provided in the BLA support a shelf of (b) (4) months for bezlotoxumab drug substance when stored at (b) (4) °C.

The post-approval stability protocols and commitment (b) (4) on stability protocols are provided and found to be acceptable.

(See **appendix 1** for complete review of DS quality, manufacturing process and process controls and **appendix 2** for review of microbial control of DS manufacturing process and product quality)

C. Drug Product [Zinplava] Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs:

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

CQA	Risk	Origin	Control Strategy	Other
Sterility	Safety	Contaminants could be introduced throughout DP manufacturing or through a container closure integrity failure.	(b) (4) Adequate validation data supporting sterility assurance of the finished DP is provided in the BLA. Sterility testing of DP at release. Container closure integrity testing of DP samples on stability.	
Endotoxin	Safety	Contaminants could be introduced throughout DP manufacturing or due to integrity failure of the container closure.	The control strategies described for DP sterility assurance also limit the introduction of endotoxin. Sponsor commits to develop a valid in vitro endotoxin assay for DP release testing as a PMC within 24 months of product approval. Until a valid in vitro endotoxin assay is developed DP lot release will be based on results from Rabbit Pyrogen Testing (RPT).	
Particulate matter (sub-visible)	Safety and Immunogenicity	Sub-visible particulates could form throughout manufacturing or on storage. Might contain product- and process- related impurities	Sub-visible particles are included in the DP release and stability specifications.	
Appearance - Visible particulates	Safety and efficacy	Visible particulate might be impacted by the manufacturing	Visible particulate testing is included in the DP release and stability specifications.	



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		process and storage conditions		
Appearance – Color, Clarity and degree of opalescence	Safety and efficacy	Manufacturing process, formulation, and storage conditions	Appearance testing is included in DP release stability specifications.	
pH	Safety and efficacy	pH is most likely impacted by formulation and compounding. No change on stability is expected.	pH is included in both DP release and stability specifications. pH is controlled by testing the final formulation	
Osmolality	Safety	Osmolality is most likely impacted by formulation and compounding. No change is expected on stability.	Osmolality is included in DP release testing.	

(b) (4)

Identity	Safety and efficacy	General CQA	DP release specifications include identity testing by peptide map and toxin B fragment-4 binding ELISA.	
Container closure integrity	Safety	CQA, might be impacted by storage conditions.	Container closure integrity testing is included in the DP stability specification. Container closure integrity testing is performed using a validated dye ingress test.	
Leachables/extracta	Safety	(b) (4) leachables and	The sponsor provided a risk assessment of extractables /	



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bles		extractables could potentially be introduced by any product contact equipment, containers and consumables.	leachables for the DP process product (b) (4), (b) (4) and the container closure. Stability studies to assess the leachables from the DP container closure and their impact to product quality are also ongoing under long term accelerated and stress storage conditions. (b) (4)	
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- a. **Potency and Strength:** Zinplava is supplied as 1000 mg/40 mL (25 mg/mL) solution in single-dose vials for intravenous injection.
- b. **Description/Commercial Image:** Zinplava is a preservative free, clear to moderately opalescent, colorless to pale yellow solution. Zinplava is provided in sterile, (b) (4) vial (b) (4).
- c. **List of Excipients:** Each mL of Zinplava contains bezlotoxumab (1,000 mg), sodium chloride (351 mg), sodium citrate dihydrate (190 mg), citric acid monohydrate (32 mg), polysorbate 80 (10 mg), diethylenetriaminepentaacetic acid (0.31 mg), and Water for Injection, USP.. Additionally, the vial may contain NaOH to adjust the pH to 6.0.
- d. **Reference material(s):** Same as drug substance
- e. **Manufacturing Process:** Bezlotoxumab drug product is manufactured at Merck, Sharp, and Dohme (MSD) in Carlow, Ireland. For the manufacture of Zinplava, (b) (4).
(b) (4)
- f. **Container Closure:** The container closure system for Zinplava drug product includes (b) (4).
(b) (4)

g. Expiration Date & Storage Conditions: The stability data in the BLA support a shelf life of 24 months for Zinplava drug product when stored at 2 - 8°C.

h. List of co-packaged components: N/A

*(See **appendix 1** for review addendum of DS and DP quality, manufacturing process and process controls and **appendix 2** for review addendum of microbial control of DP manufacturing process and product quality and **appendix 3** for review addendum of inspectional assessment of facilities)*

D. Novel Approaches/Precedents

None

E. Any Special Product Quality Labeling Recommendations

Store in a refrigerator at 2-8°C,

Protect from light

Do not freeze

Do not shake

F. Establishment Information

The compliance status of the DS manufacturing facility, (b) (4) was deemed satisfactory during pre-licensure inspection conducted in (b) (4).

Bezlotoxumab drug product is manufactured at MSD Ireland. This compliance status of this facility is considered acceptable based on the last inspection that was conducted by FDA (b) (4).

The compliance status of the DS and DP testing sites and DP packaging and labeling sites is also considered acceptable based on their prior inspectional history.

(See appendix 3 for the review of bezlotoxumab DS and DP manufacturing facilities by division of inspectional assessment reviewer, Thuy Nguyen)

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Table 1 and 2 below list the DS and DP manufacturing sites, their responsibilities and addresses:

TABLE 1. Proposed Sites for Bezlotoxumab DS Manufacture, Cell Banking and Testing Operation

Site Name	Address	FEI Number	Responsibilities
(b) (4)			
Merck Sharp & Dohme Corp.	770 Sunnyside Pike West Point, Pennsylvania 19486 U.S.	2510592	MCB and WCB storage
(b) (4)			
Merck Sharp & Dohme	Ballinacurra Road	3002808087	DS release and stability testing
Schering-Plough Brinny Company	Inishannon, County Cork Ireland		
(b) (4)			

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Table 4. Manufacturing, Testing, Packaging, and Release Sites for MK-6072 Drug Product

Site Name	Address	FEI Number	Responsibilities
MSD Ireland (Carlow)	Dublin Road Carlow, Ireland	3008694906	DP manufacturing • DP release and stability testing
(b) (4)			
Merck Sharp & Dohme Schering-Plough Brinny Company	Ballinacurra Road Inishannon, County Cork Ireland	3002808087	DP release and stability testing
(b) (4)			
Merck Sharp & Dohme Corp.	4633 Merck Road Wilson, North Carolina	1036761	Packaging and Labeling Final DP release
	27893		
(b) (4)			



G. Lifecycle Knowledge Management

B. Drug Substance

- a. Protocols approved: Annual GMP stability protocol, stability protocols

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

- b. Outstanding review issues/residual risk: See PMC

- c. Future inspection points to consider: TBD

C. Drug Product

- a. Protocols approved: Annual GMP stability protocol and stability protocols

(b) (4)

- b. Outstanding review issues/residual risk: See PMCs

- c. Future inspection points to consider: N/A

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	



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8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity	X		
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		
14.	Other_____			N/A
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)		X	
16.	Comparability Protocol(s)		X	
17.	End of Phase II/Pre-NDA Agreements tem)			
18.	SPOTS (Special Products On-line Tracking System		X	
19.	USAN Name Assigned	X		
20.	Other_____			N/A
Quality Considerations				
21.	Drug Substance Overage		X	
22.	Design Space	Formulation	X	
23.		Process	X	
24.		Analytical Methods	X	
25.		Other	X	
26.	Other QbD Elements	X		
27.	Real Time Release Testing (RTRT)		X	
28.	Parametric Release in lieu of Sterility Testing		X	
29.	Alternative Microbiological Test Methods	X		

**QUALITY REVIEW BLA 761046 (Bezlotoxumab)**

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

BLA: STN 761046

Bezlotoxumab

**Manufacturer: Merck, Sharp, and Dohme Corp.,
a subsidiary of Merck & Co., Inc.**

Reviewer: William Hallett, Ph.D.
Team Leader: Rashmi Rawat, Ph.D.

Division of Biotechnology Research and Review II
Office of Biotechnology Products

Product Quality Review Data Sheet

(Includes only information updated since the initial review finalized on April 22, 2016)

- 1. BLA #:** STN 761046
- 2. REVIEW #:** 2 (Addendum 1)
- 3. REVIEW DATE:** June 21, 2016
- 4. REVIEWER(s):** William Hallett, Ph.D.
Rashmi Rawat, Ph.D., Team Leader

5. COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS SINCE THE FINALIZATION OF THE INITIAL REVIEW:

<u>Communication/Documents</u>	<u>Date</u>
Information Request #6	5/27/2016

6. SUBMISSION(S) REVIEWED UNDER THIS ADDENDUM:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
STN 761046, eCTD#0028	4/29/2016
STN 761046, eCTD#0032	5/31/2016
STN 761046, eCTD#0033	6/1/2016
STN 761046, eCTD#0034	6/17/2016

17. ADMINISTRATIVE**Signature Block**

William Hallett, Ph.D. Division of Research and Review II, Office of Biotechnology Products

Rashmi Rawat, Ph.D., Division of Research and Review II, Office of Biotechnology Products

I. Recommendation

The data submitted in the Biologics License Application (BLA) support the conclusion that the manufacture of Zinplava (bezlotoxumab, MK-6072) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs at manufacturing sites presented. It is recommended that Zinplava (bezlotoxumab) be approved for human use (under conditions specified in the package insert).

I recommend an expiry of (b) (4) months for bezlotoxumab drug substance when stored at (b) (4) °C.

I recommend an expiry of 24 months for bezlotoxumab drug product when stored at 2-8°C.

The post-approval stability protocols are acceptable.

II. List of Deficiencies to be Communicated

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

III. List of Post-Marketing Commitments

Same as listed in the primary review dated 4/22/2016.

IV. Review of Common Technical Document-Quality Module 3.2

Review:

Background: (b) (4) method used to assess bezlotoxumab (MK-6072) purity (b) (4) is a (b) (4) method. (b) (4)

The sponsor submitted a meeting package to FDA on 25-March-2016 (STN 761046 eCTD 0025) and a teleconference was held on 30-March-2016 to discuss the impact of this deviation on bezlotoxumab process and product quality. The following strategy was proposed by Merck and agreed to by FDA:

1. Apply correction factors (b) (4)
2. Perform re-test of stability samples (b) (4)
3. Re-evaluate (b) (4) acceptance criteria and shelf-life based on results obtained using correction factor and retesting of accelerated and stress stability samples.
4. Re-test all other impacted samples.

All re-tests are performed on retain samples that were stored at (b) (4) °C since the initial test.

(b) (4)

Reviewer Comment: Because the use of the correction factors is a mathematical calculation, the corrections made by applying this correction factor are uniform and repeatable.

(b) (4)

(b) (4)

Therefore, the conclusion made to studies whose results were corrected using the correction factors remain the same.

(b) (4)

The following table was produced by the primary reviewer. It summarizes the sections of the BLA that were impacted by the changes to the (b) (4) result, the nature of the change, and the reviewer conclusions on the impact of these changes.

eCTD Section	Changes Provided	Impact of Change on Conclusions
3.2.S.2.5.2 Process Validation and/or Evaluation – Process Performance Qualification	Change in (b) (4) results for release and homogeneity testing	No impact
3.2.S.2.6.3 Manufacturing Process Development – Analytical Comparability	Change to release and stability results	No impact
3.2.S.2.6.4 Manufacturing Process Development – Process Characterization	Changes to purity profiles (b) (4)	No impact
3.2.S.3.1 Elucidation of Structure and Other Characteristics	(b) (4)	No impact
3.2.S.4.1 Specification	No change to DS release or stability specifications	No impact
3.2.S.4.2 Analytical Procedures	Bridging data slightly changed	No impact
3.2.S.4.3 Validation of Analytical Procedures	‘Robustness’ added to validation package, robustness data adequate	No impact
3.2.S.4.4 Batch Analysis	(b) (4)	No impact
3.2.S.4.5 Justification of Specification	See below	No impact
3.2.S.5 Reference Standards or Materials	Updated results for qualification of New PRS	No impact
3.2.S.7.1 Stability Summary and Conclusions	See below	No impact
3.2.S.7.3.2 Stability Data – Ancillary Studies	Changes with initial results (b) (4) for PPQ lots are the updated release results from Batch Analysis	No impact
3.2.P.2.3 Manufacturing Process Development	Impacted results limited to the across the lot results provided for PPQ lot 0000405037. (b) (4)	No impact
3.2.P.2.3.2 Manufacturing Process Development – Analytical Comparability	Impacted results limited to release and stability results reported in 3.2.P.2.3.2. No change in sponsor’s analytical comparability conclusions.	No impact
3.2.P.3.5 Process Validation	Filling PPQ results changed	No impact

and/or Evaluation		
3.2.P 5.1 Specification	Sponsor revised the DP stability acceptance criteria (b) (4) to match what is used for Release. Previously, the sponsor had different stability acceptance criteria that accounted for increased degradation during storage	Specifications Changed
3.2.P 5.4 Batch Analysis	Release results for the 3 PPQ lots (000405036A, 0000405037, 0000405039) and 3 development lots (WL00052908, WL00052909, WL00052111) were updated.	No impact
3.2.P 5.6 Justification of Specifications	DP release specifications did not change. DP stability specifications changed to match the release settings.	No impact
3.2.P 8.1 Stability Summary and Conclusions	See below	No impact
3.2.P 8.3.2 Stability Data – Ancillary Studies	Impacted results are limited to the (b) (4) stability data for the formal stability study (FSS) lots.	No impact

The evaluation of the impact to this corrective action on the affected sections of the BLA is discussed below in detail.

3.2.S.2.5 Process Validation and/or Evaluation

3.2.S.2.5.2 Process Validation and/or Evaluation – Process Performance Qualification

The (b) (4) results are limited to the (b) (4) results for release and homogeneity testing. The corrected values were recalculated (b) (4).

Reviewer Comment: The four PPQ lots had homogeneity (beginning, middle, and end) and release (the middle sample point) results were corrected (b) (4). The changes made with the correction factors shifted the values, the results still demonstrated DS homogeneity during (b) (4) and compliance with the release acceptance criteria. Therefore, this is acceptable.

3.2.S.2.6.3 Manufacturing Process Development

3.2.S.2.6.3 Manufacturing Process Development – Analytical Comparability

(b) (4)

3.2.S.3.1 Characterization

3.2.S.3.1 Elucidation of Structure and Other Characteristics

The impacted (b) (4) results in this section were limited to the results reported for characterization generated from one PPQ lot and one RS lot. (b) (4)

Reviewer Comment: The correction in purity is due to recalculation using the (b) (4) correction factors and is similar to the change observed elsewhere in the updated data. The corrected PPQ (b) (4) results are used in several locations in the BLA.

3.2.S.4.1 and 3.2.S.4.5 Specification and Justification of Specification

3.2.S.4.1 Specification

The following table shows the final DS release and stability specification:

Table 1 Commercial Release and Stability Specifications for MK-6072 Drug Substance

Attribute	Acceptance Criterion		Method
	Release	Stability	
Description			
Physical Appearance	Opalescence: ≤ (b) (4), Color: ≤ (b) (4)		Ph. Eur. 2.2.1 Ph. Eur. 2.2.2
Identification			
Peptide Map	Comparable to reference	Not tested	(b) (4)
Binding ELISA	Positive	Not tested	Direct-binding ELISA
Potency			
Binding ELISA	(b) (4) % of reference		Direct-binding ELISA
Toxin Neutralization Bioassay	(b) (4) % of reference		Cell-based functional assay
Assay			
Protein Concentration	(b) (4)		UV Spectrophotometry
Purity			

(b) (4)

Attribute	Acceptance Criterion		Method
	Release	Stability	
Impurities			
Product-Related Substances/Impurities			
(b) (4)	(b) (4)		(b) (4)
Process-Related Substances/Impurities			
(b) (4)	Not tested		(b) (4)
	Not tested		
	Not tested		
Excipients			
(b) (4)	Not tested		(b) (4)
(b) (4)			(b) (4)
Pharmaceutical Technical Tests			
pH	5.7–6.3		Ph. Eur. 2.2.3 USP <791>
Osmolality	300–380 mOsm/kg	Not tested	Ph. Eur. 2.2.35 USP <785>
Microbial Quality			
Bacterial Endotoxin ^a	(b) (4) EU/mg		Ph. Eur. 2.6.14 USP <85>
Bioburden	(b) (4) cfu/10 mL		Ph. Eur. 2.6.12 USP <61>

^a Bacterial endotoxin testing is performed (b) (4)

Reviewer Comment: The DS specifications were updated following completion of the initial review. The updates to the specifications were based on commitments by the sponsor to update the acceptance criteria for the (b) (4), (b) (4)

The sponsor also updated the release and stability acceptance criteria (b) (4)

(b) (4) the sponsor's proposed acceptance criterion was (b) (4). My analysis showed the range based on mean $\pm$ 3SD using the commercial method on clinical lots was (b) (4)%. Therefore, in IR#6, sent 5/27/2016, we asked the sponsor to adjust the acceptance criteria to (b) (4)%.

The sponsor's response to IR#6 argued that upper limit for the (b) (4) was too restricting, and recommended an upper limit of (b) (4)%. The sponsor's recommended upper limit (b) (4) release and stability is acceptable.

3.2.S.4.5 Justification of Specification

The release acceptance criteria for (b) (4) is based on a statistical analysis (tolerance interval) approach based on the product experience (b) (4). The product experience includes the lots which were generated with (b) (4) and tested using the commercial (b) (4) method. No (b) (4) material was tested with the commercial method or used for justification of specification. (b) (4)

The stability acceptance criteria (b) (4) (b) (4) (b) (4) is within the proposed release acceptance criteria; therefore, the stability acceptance criteria are the same as the release acceptance criteria.

Reviewer Comment: *The specification for release and stability of the drug substance did not change as a result of the (b) (4) changes.* (b) (4) (b) (4)

The sponsor's proposed release and stability specifications for the (b) (4) method provide adequate control of the product and are acceptable.

3.2.S.4.2 and 3.2.S.4.3 Analytical Procedures and Validation of Analytical Procedures

The corrected (b) (4) results impacted the data used in the bridging studies between Development 1 and Development 2, and between Development 2 and Commercial, but the conclusion of both bridging studies did not change.

Reviewer Comment: *The malfunctioning equipment was used during Development 2 and Commercial, so bridging studies using either method had their data updated.*

The validation of the (b) (4) method (in 3.2.S.4.3.9) was impacted by the corrected (b) (4) data. The robustness data used previously only (b) (4) the impacted instrument. Therefore, the robustness data will be replaced with a supplemental robustness evaluation (b) (4) (b) (4)

Reviewer Comment: *All other validation data other than robustness was performed using the (b) (4) that was not impacted (b) (4) therefore, those validation results remain unchanged. The update to the robustness section completes the validation of the (b) (4) method.*

3.2.S.4.4 Batch Analysis

The update to the Batch Analysis data is limited to a correction release results for the bezlotoxumab DS PPQ lots.

Reviewer Comment: These corrected results are due to a recalculation using the (b) (4) correction factors. These corrected values are the same corrected values to the PPQ data that was been implemented throughout the BLA. The results for all four PPQ batches were the same, so all four batches report release results (b) (4). The PPQ batches are similar to each other and within the acceptance criteria.

3.2.S.5 Reference Standards or Materials

The impacted (b) (4) results are limited to the results reported for qualification of the new primary reference standard and for stability monitoring of the current PRS lot. The two results were corrected using the (b) (4) correction factors. The corrected New PRS (b) (4) result is (b) (4)%, and the corrected Current PRS result is (b) (4)%.

Reviewer Comment: The correction factors provided a minor update to the purity of the two PRS results, and these minor changes do not affect the adequacy of the reference standard.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

The impacted (b) (4) results include the (b) (4) and (b) (4) stability data. The (b) (4) data were updated using (b) (4) correction factor, while the (b) (4) stability data below were corrected by retesting of the retain samples. These changes result in updated statistics and trending data. The sponsor concluded that there was no substantive impact on trends, conclusions, or on their shelf-life proposal.

For the (b) (4) data, a statistically significant change was not observed (b) (4).

Reviewer Comment: The (b) (4) data (b) (4) show no trending data, indicating that this product is stable by this test at the recommended storage condition.

(b) (4)

Reviewer Comment: The negative trend observed with the (b) (4) (b) (4) demonstrates that this method is stability indicating. The original data also demonstrated that the method was stability indicating, though it was observed on (b) (4) and not on (b) (4). In addition to (b) (4) assay, other methods are also stability indicating at this time point; (b) (4). These data indicate that the product is losing stability after (b) (4). However, the (b) (4) stability data support the routine handling and shipping of the DS

(b) (4). The change in stability data following retesting is acceptable.

3.2.S.7.3 Stability Data

The ICH stability studies (b) (4) for the 4 PPQ lots (379473, 383557, 383560, and 390203) were updated as referenced in the summary section above. The updates were made using the (b) (4) correction factors (b) (4), and the retain samples were retested for (b) (4) stability results.

Reviewer Comment: Only samples that were tested on the affect instrument were recalculated. Samples that were tested on the other instrument have their results listed as “No change”. The changes here are captured in the review of the Stability Summary and Conclusions above.

3.2.S.7.3.2 Stability Data – Ancillary Studies

The impacted (b) (4) results in this section are limited to the initial result for the (b) (4) studies for the DS PPQ lots because these studies used the PPQ release data for the initial stability result, and these results were already described above as corrected. None of the results other than the initial stability results were affected.

Reviewer Comment: The corrected release results were reviewed earlier in this review. No other samples in the Ancillary studies were impacted. The corrected results do not impact the review of the (b) (4) shipping stability study.

Drug Product

3.2.P.2.3 Manufacturing Process Development

(b) (4)

Reviewer Comment: The comparability acceptance criteria are based on (b) (4) tolerance intervals, so altering the results is expected to change the acceptance criteria. The corrected values all fall within the updated comparability acceptance criteria and the changes do not impact the conclusion of the study; therefore, these data are acceptable.

3.2.P.3.5 Process Validation and/or Evaluation

The impacted results in 3.2.P.3.5 are limited to the reported PPQ results (b) (4). During PV, (b) (4) the vials was assessed by the (b) (4) method (b) (4) (b) (4) to determine the uniformity of the process, and these values were corrected via the correction factor.

Reviewer Comment: The corrected results do not affect the outcome of the PV study; therefore, these results are acceptable.

3.2.P.5.1 and 3.2.P.5.6 Specification and Justification of Specifications

Table 1 Commercial Release and Stability Specifications for MK-6072 Drug Product

Attribute	Acceptance Criterion		Method
	Release	Stability	
Description			
Physical Appearance	Opalescence: (b) (4) Color: (b) (4) Visible Particles: Essentially free of visible particles		Ph. Eur. 2.2.1 Ph. Eur. 2.2.2 Ph. Eur. 2.9.20
Identification			
Peptide Map	Comparable to reference	Not tested	(b) (4)
Binding ELISA	Positive	Not tested	Direct-binding ELISA
Potency			
Binding ELISA	(b) (4) % of reference		Direct-binding ELISA
Toxin Neutralization Bioassay	(b) (4) % of reference		Cell-based functional assay
Assay			
Protein Concentration	(b) (4)		UV spectrophotometry
Purity			
(b) (4)			

Table 1 Commercial Release and Stability Specifications for MK-6072 Drug Product

Attribute	Acceptance Criterion		Method
	Release	Stability	
Impurities			
Product-Related Substances/Impurities			(b) (4)
(b) (4)			
Excipients			
(b) (4)	Not tested		(b) (4)
(b) (4)	(b) (4)	HPLC-CAD	
Pharmaceutical Technical Tests			
Container-Closure Integrity ^a	Not tested	Conforms	Dye ingress
pH	5.7–6.3		Ph. Eur. 2.2.3 USP <791>
Osmolality	300–380 mOsm/kg	Not tested	Ph. Eur. 2.2.35 USP <785>
Subvisible Particulates			Ph. Eur. 2.9.19 USP <787>
(b) (4)			
(b) (4)			
Extractable Volume	(b) (4)	Not tested	Ph. Eur. 2.9.17
Microbial Quality			
Bacterial Endotoxin	(b) (4)	Not tested	Ph. Eur. 2.6.14 USP <85>
(b) (4)		Not tested	USP <151>
Sterility	No growth		Ph. Eur. 2.6.1 USP <71>

Reviewer Comment: The DP specifications were updated following completion of the initial review. The updates to the specifications were based on commitments by the sponsor to update the acceptance criteria for the Toxin Neutralization Bioassay, Binding ELISA, (b) (4).

As a result of the corrected (b) (4) data, the sponsor also updated the DP release acceptance criteria (b) (4) to the same acceptance criteria used for the DS. The DP stability acceptance criteria (b) (4) are also the same as the DS release and stability acceptance criteria. The sponsor proposed a stability acceptance criterion (b) (4), however, we felt this acceptance criterion was too broad given their product experience, and the sponsor updated the acceptance criteria (b) (4). This tightened acceptance criterion, and the DP release and stability acceptance criteria in total, are acceptable.

There is no change the DP release acceptance criteria for (b) (4) assay. However, the DP stability acceptance criteria (b) (4) were revised to align with the release acceptance criteria.

Table 23 Commercial Release and Stability Specifications for MK-6072 Drug Product (b) (4)

Attribute	Original Acceptance Criterion		Revised Acceptance Criterion		Method
	Release	Stability	Release	Stability	
(b) (4)					

The (b) (4) stability acceptance criteria did not change, and still provides a different acceptance criterion ((b) (4)) than the release acceptance criterion ((b) (4)).

3.2.P.5.6 Justification of Specifications

There is no change to the DP release acceptance criteria. There is a change to the DP stability acceptance criteria (b) (4). The sponsor based the acceptance criteria for stability on the 95% Confidence Interval (b) (4). For the (b) (4) acceptance criteria, (b) (4) was outside the proposed release acceptance criterion (b) (4) therefore, a separate stability acceptance criterion of (b) (4) was proposed. (b) (4) (b) (4) is within the proposed release acceptance criterion, so the stability acceptance criterion was set to align with the release acceptance criterion.

Reviewer Comment: I agree with the sponsor's approach to setting the DP release and stability acceptance criteria. (b) (4), (b) (4)

(b) (4) The sponsor's data show that the potency is maintained (b) (4) The sponsor also has a PMC to update the acceptance criteria for all methods following the manufacture of 30 DS lots. This (b) (4) purity test is also supported by (b) (4), so the sponsor has (b) (4) methods to measure purity. The (b) (4) acceptance criteria for DP release and stability is acceptable.

3.2.P.5.4 Batch Analysis

The impacted (b) (4) results in this section are limited to the release results from the 3 PPQ lots (000405036A, 0000405037, 0000405039) and 3 Development lots sourced from (b) (4) DS (WL00052908, WL00052909, WL00052111).

Reviewer Comment: The corrected results were updated using the correction factor. The corrected results demonstrate that the lots are comparable and all within the acceptance criteria. These results are acceptable.

3.2.P.8 Stability

The impacted (b) (4) results reported in 3.2.P.8 are limited to figures and discussions for the (b) (4) (000405036A, 0000405037, 0000405039, WL00052908, WL00052909, WL00052111), the (b) (4) shipping stability studies (WL00052908, WL00052909, WL00052111), the (b) (4) stressed stability studies (000405036A, 0000405037, 0000405039, WL00052908, WL00052909, WL00052111). The sponsor revised the statistics and trending figures, and concluded that the changes to the stability data had no impact on trends, conclusions, or shelf-life proposal.



***Reviewer Comment:** The updates to the stability data do not change the conclusions from what they were prior to correcting the (b) (4) results. The changes in the stability results following correction (b) (4) are minor, and show no meaningful differences. These corrected results support the previous conclusion regarding its stability indicating properties of the (b) (4) (b) (4) method. These results support that the product is stable under the long-term storage conditions when assessed by the (b) (4) method. Updated stability data support the proposed shelf-life of 24 months of the DP (b) (4); therefore, these results are acceptable.*

3.2.P.8.3 Stability Data

3.2.P.8.3.1 Stability Data – ICH Stability Studies

The (b) (4) stability results reported for samples stored at (b) (4) were corrected. The (b) (4) data were corrected (b) (4). The (b) (4) were corrected by retesting retain samples that were stored at (b) (4). The affected lots are WL00052111 (b) (4) WL00052908 (b) (4) WL00052909 (b) (4), 000405036A (b) (4), 000405037 (b) (4), and 000405039 (b) (4).

3.2.P.8.3.2 Stability Data – Ancillary Studies

The impacted (b) (4) results in this section of the BLA are limited to the (b) (4) stability data for the bezlotoxumab formal stability study (FSS) lots. The retain samples, stored at (b) (4) were retested on instruments that had undergone (b) (4)

Reviewer Comment: *The corrected results do not impact the conclusions of the ICH or the Ancillary stability studies. The sponsor's correction of the stability data is acceptable.*



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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

Date: 7 June, 2016
To: Administrative File, STN 125377/83
From: Natalia Pripuzova, Ph.D., Reviewer, CDER/OPQ/OPF/DMA/ Branch IV
Endorsement: Colleen Thomas, Ph.D., QAL, CDER/OPQ/OPF/DMA/Branch IV
Applicant: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
US License Number: 0002
Submission Reviewed: Original BLA
Product: Bezlotoxumab (25mg/ml)
Indication: Prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI
Dosage Form: 25mg/ml, liquid for i/v injection, supplied in vials.
Manufacturing Sites:
Drug Substance: (b) (4)
Drug Product: MSD Ireland (Carlow), Carlow, County Carlow, Ireland (FEI: 3008694906)
FDA Receipt Date: 23 November 2015
Action Date: 23 July 2016

Approvability Recommendation: This is an addendum to the primary review. The BLA, as amended, was reviewed from drug substance and drug product quality microbiology prospective and is recommended for approval.

Summary: BLA761046 was submitted in electronic format on 23-November-2015 to license bezlotoxumab for the prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI. Bezlotoxumab (MK-6072) is a fully human monoclonal antibody (mAb) of the IgG1/kappa isotype subclass that binds with high

affinity to *Clostridium difficile* (*C. difficile*) toxin B. This memo is an addendum to the product quality microbiology review for the drug substance and drug product dated 04 May 2016. This memo covers responses to information requests sent after the primary review goal date.

Product Quality Microbiology Assessment: Drug Substance

Drug Substance Quality Microbiology Information Reviewed

Sequence number	Date	Description
0032	31 May 2016	Response to IR (BLA update)

Module 3.2

S.2.2 Description of Manufacturing Process and Process Controls

(b) (4)

Reviewer's comment: Sponsor updated the BLA as proposed in the response to IR dated April 18, 2016, Response 2 (seq. 0026).

SATISFACTORY

S.2.4 Controls of Critical Steps and Intermediates

(b) (4)

Reviewer's comments: Sponsor updated the BLA as proposed in the response to IR dated April 18, 2016, Response 2 (seq. 0026).

SATISFACTORY

S.4 Control of Drug Substance

S.4.1. Specification

Updated with revised DS release criterion for (b) (4) (b) (4)
(b) (4)

Reviewer's comments: Sponsor updated the BLA as proposed in the response to IR dated April 18, 2016, Response 2 (seq. 0026).

SATISFACTORY

S.4.2. Analytical Procedures

Updated to reflect (b) (4) testing (b) (4)
(b) (4)

Reviewer's comments: Sponsor updated the BLA as proposed in the response to IR dated April 18, 2016, Response 2 (seq. 0026).

SATISFACTORY

S.4.3. Validation of Analytical Procedures

Updated to reflect (b) (4) testing (b) (4)

Reviewer's comments: Sponsor updated the BLA as proposed in the response to IR dated April 18, 2016, Response 2 and 3 (seq. 0026).

SATISFACTORY

S.4.5. Justification of Specifications

Updated with revised release acceptance criterion and justification for (b) (4) (b) (4)
(b) (4)

Reviewer's comments: Sponsor updated the BLA as proposed in the response to IR dated April 18, 2016, Response 2 (seq. 0026).

SATISFACTORY

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0032	31 May 2016	Response to IR (BLA update)

Module 3.2

P.5 Control of Drug Product

P.5.1 Specifications

Updated to include DP release acceptance criterion for Pyrogen Testing and with revised DP release acceptance criterion for bacterial endotoxin (b) (4)

Reviewer's comments: Sponsor updated the BLA as proposed in the response to IR dated April 18, 2016, Response 1 and 5 (seq. 0026).

SATISFACTORY

P.5.2 Analytical Procedures

Updated to reflect the addition of Pyrogen testing to the DP release panel (see Table 1, copied below from the submission, for the major attributes of the method).

Table 1 Major Attributes of the Method

Attribute	Description
Assay Summary	(b) (4)
Compendial References	
Critical Equipment	
Critical Materials	
Controls	
Sample	
Acceptance Criteria	
Reportable Results	

(b) (4)

Reviewer's comments: Sponsor updated the BLA as proposed in the response to IR dated April 18, 2016, Response 1 and 5 (seq. 0026).

P.5.3 Validation of Analytical Procedures

Updated to reflect the addition of Pyrogen testing to the DP release panel. New section added to describe the verification of the Rabbit Pyrogen test method.

Reviewer's comments: Sponsor updated the BLA as proposed in the response to IR dated April 18, 2016, Response 1 and 5 (seq. 0026).

P.5.6 Justification of Specifications

Updated to include DP release acceptance criterion for Rabbit Pyrogen Testing. Updated with revised DP release acceptance criterion for bacterial endotoxin (b) (4)

Reviewer's comment: Sponsor updated the BLA as proposed in the response to IR dated April 18, 2016, Response 1 and 5 (seq. 0026).

SATISFACTORY

Conclusion

- I. The BLA, as amended, 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.

Archived File: 761046.rev.mem.BLA.06-07-2016.doc

NATALIA PRIPUZOVA

(REVIEWER)

06/07/2016

COLLEEN THOMAS (QUALITY ASSESMENT LEAD)

06/07/2016



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

Date: 5/22//2016
To: Administrative File, STN 761046
From: Thuy T. Nguyen, Facility Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: 0002
Applicant: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Mfg. Facility: Drug Substance: (b) (4)
Drug Product: MSD Ireland (Carlow), FEI: 3008694906
Product: Bezlotoxumab Injection
Dosage: 40 mL of 25 mg/mL
Indication: The treatment of patients with Clostridium difficile infection (CDI) and (b) (4) for the prevention of CDI recurrence
Due Date: 5/30/2016

RECOMMENDATION: The application is recommended for approval from a facilities assessment standpoint.

SUMMARY

This assessment is an addendum for 5/1/2016 facilities Review of BLA 761046. In the 5/1/2016 Review a final facilities recommendation was not made because the preapproval inspection was on going for the (b) (4) proposed for DS manufacturing and testing site. No FDA 483 was issued and the inspection was classified as NAI. All listed facilities are now currently in state of compliance and the application is recommended for approval from a facilities assessment standpoint.

CONCLUSION

As amended, all manufacturing, packaging and testing sites listed in the submission are recommended for approval from a facilities assessment standpoint.

BLA 761046 Bezlotoxumab Amended Memo

Thuy T. Nguyen, M.P.H.
Facility Reviewer
OPF Division of Inspectional Assessment
Branch 1

Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JONATHAN T DOW
11/03/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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

Date: 5/22//2016
To: Administrative File, STN 761046
From: Thuy T. Nguyen, Facility Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: 0002
Applicant: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Mfg. Facility: Drug Substance: (b) (4)
Drug Product: MSD Ireland (Carlow), FEI: 3008694906
Product: Bezlotoxumab Injection
Dosage: 40 mL of 25 mg/mL
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Due Date: 5/30/2016

RECOMMENDATION: The application is recommended for approval from a facilities assessment standpoint.

SUMMARY

This assessment is an addendum for 5/1/2016 facilities Review of BLA 761046. In the 5/1/2016 Review a final facilities recommendation was not made because the preapproval inspection was on going for the (b) (4) proposed for DS manufacturing and testing site. No FDA 483 was issued and the inspection was classified as NAI. All listed facilities are now currently in state of compliance and the application is recommended for approval from a facilities assessment standpoint.

CONCLUSION

As amended, all manufacturing, packaging and testing sites listed in the submission are recommended for approval from a facilities assessment standpoint.

BLA 761046 Bezlotoxumab Amended Memo

Thuy T. Nguyen -S

Digitally signed by Thuy T. Nguyen -S
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ou=People, cn=Thuy T. Nguyen -S,
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Thuy T. Nguyen, M.P.H.
Facility Reviewer
OPF Division of Inspectional Assessment
Branch 1

Zhihao Qiu -S

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Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

BLA STN 761046

Bezlotoxumab

**Merck Sharp & Dohme Corp.,
a subsidiary of Merck & Co., Inc.**

**William Hallett PhD, Product Quality Reviewer
Rashmi Rawat PhD, Team Leader
Division of Biotechnology Research and Review II
Office of Biotechnology Products**

OBP CMC Review Data Sheet

1. **BLA#:** STN 761046
2. **REVIEW DATE:** 4/22/2016
3. **PRIMARY REVIEW TEAM:**

Medical Officer:	Dmitri Iarikov, Shrimant Mishra, Hiwot Hiruy
Pharm/Tox:	Luning (Ada) Zhuang, Jeffry Florian
Product Quality:	William Hallett, Rashmi Rawat
Product Quality, Microbiology:	Natalia Pripuzova, Patricia Hughes
BMT or Facilities:	Thuy Nguyen
Clinical Pharmacology:	Yang He, Seong Jang
Clinical Microbiology:	Kerian Grande Roche
Statistics:	Cheryl Dixon, Karen Higgins
OBP Labeling:	Jibril Abdus-Samad
RPM:	Christopher Davi
4. **MAJOR GRMP DEADLINES**

Filing Meeting:	Jan 22, 2016
Mid-Cycle Meeting:	March 22, 2016
Wrap-Up Meeting:	May 9, 2016
Primary Review Due:	April 22, 2016
Secondary Review Due:	May 6, 2016
PDUFA Action Date:	July 23, 2016
5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
CMC Pre-BLA Meeting	9/24/2015
Filing Letter	2/5/2016
Information Request #1	2/26/2016
Information Request #2	3/16/2016
Information Request #3	4/1/2016
Information Request #4	4/6/2016
Information Request #5	4/18/2016

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

Submission	Date Received	Review Completed (Yes/No)
STN 761046/0	11/23/2015	Yes
STN 761046 /0012 (response to IR #1)	03/04/2016	Yes
STN 761046 / 0013 (response to IR #1)	3/8/2016	Yes
STN 760146 / 0014 (response to IR #1)	3/11/2016	Yes
STN 761046 / 0019 (b)(4) issue)	3/21/2016	Yes
STN 761046 / 0021 (response to IR #2)	3/24/2016	Yes
STN 761045 / 0022 (mtg background package)	3/25/2016	Yes
STN 761046 / 0025 (response to IR #3)	4/8/2016	Yes
STN 761046 / 0023 (response to IR #4)	4/12/2016	Yes
STN 761046 /0027 (response to IR #5)	4/20/2016	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**

- a. Proprietary Name: Zinplava
- b. Code Name: MK-6072
- c. Trade Name: Zinplava
- d. Non-Proprietary/USAN: bezlotoxumab
- e. CAS name: anti-(Clostridium difficile toxin B)
Immunoglobulin G1 (human monoclonal γ -chain), disulfide with human monoclonal κ -chain, dimer
- f. Common name: bezlotoxumab
- g. INN Name: bezlotoxumab
- h. Compndial Name: n/a
- i. OBP systematic name: MAB HUMAN (IGG1) ANTIP18177
(TOXB_PEPDI)[MK6072]
- j. CAS Registry Number: 1246264-45-8

8. **PHARMACOLOGICAL CATEGORY:** Therapeutic recombinant human monoclonal antibody9. **DOSAGE FORM:** Injection10. **STRENGTH/POTENCY:**

- (i) The concentration/strength of the Drug Product: Each drug product vial contains 25 mg/mL bezlotoxumab for a total of 1000 mg/ 40 mL per vial.
- (ii) Type of potency assay (s): Potency is defined as the percent activity relative to the reference standard, using a cell based toxin neutralization bioassay that measures the ability of the bezlotoxumab to protect host cells from toxicity of the *C. Difficile* toxin B; and a binding ELISA assay that measures the ability of the antibody to bind to toxin B.

11. **ROUTE OF ADMINISTRATION:** Intravenous

12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)				Type V No review required as all the relevant information related to compatibility with the product was in the BLA. CBER DMF is active
				Type II No review required as all the relevant information related to compatibility with the product was in the BLA CBER DMF is active
				Type III No review required as all the relevant information related to compatibility with the product was in the BLA CDER DMF is active
				Type III No review required as all the relevant information related to compatibility with the product was in the BLA CDER DMF is active
				Type V No review required as all the relevant information related to compatibility with the product was in the BLA CDER DMF is active
				Type V No review required as all the relevant information related to compatibility with the product was in the BLA CDER DMF is active

13. INSPECTIONAL ACTIVITIES

A pre-licensure inspection of drug substance manufacturing facility, (b) (4) will be conducted on (b) (4), by Patricia Hughes (DMA, lead inspector), Natalia Pripuzova (DMA), Thuy Nguyen (DIA), Collen Thomas (DIA), William Hallett (OBP), and Cyrus Agarbi (OBP). The inspection will cover the manufacturing operations for the bezlotoxumab drug substance at (b) (4) under BLA STN 761046. This inspection will be limited to the manufacturing and testing of bezlotoxumab. This PLI will cover the following five quality systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls.

The requirement for conducting a PLI for the drug product manufacturing facility was waived based on the recent inspectional history of the drug product manufacturing facility.

14. CONSULTS REQUESTED BY OBP

None

15. QUALITY BY DESIGN ELEMENTS

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

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

16. PRECEDENTS

None

17. ADMINISTRATIVE

Signature Block

Name and Title	Office/Division	Signature
William Hallett, Product Quality Reviewer	Office of Biotechnology, DBRR II	William H. Hallett -S Digitally signed by William H. Hallett -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001154757, cn=William H. Hallett -S Date: 2016.04.22 17:20:24 -0400
Rashmi Rawat, Product Quality Team Leader	Office of Biotechnology, DBRR II	Rashmi Rawat -A Digitally signed by Rashmi Rawat -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rashmi Rawat -A, 0.9.2342.19200300.100.1.1=0014137532 Date: 2016.04.22 17:26:31 -0400

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The data submitted in the Biologics License Application support the conclusion that the manufacture of Zinplava (bezlotoxumab) is well controlled and leads to a product that is pure and potent. The bezlotoxumab product is free from endogenous and adventitious infectious agents sufficient to meet parameters recommend by FDA. The conditions used for manufacturing bezlotoxumab have been sufficiently validated, and consistent products have been manufactured from the multiple production runs presented. It is recommended that Zinplava (bezlotoxumab) be approved for human use (under conditions specified in the package insert) provided the following issues are sufficiently addressed prior to the Action Date:

- Revisions to the (b) (4) purity specification and results for the in-process, release and stability testing of bezlotoxumab drug substance and drug product (b) (4)
(b) (4)
(b) (4)
- Inspection of the drug substance manufacturing facility, (b) (4)
(b) (4)
- Revisions of the proposed acceptance criteria in BLA for the potency assays (b) (4)
(b) (4)
bezlotoxumab drug substance and drug product lot release and stability specification as agreed upon during the primary review cycle (April 20, 2016, eCTD seq. 0027).
- Description of packaging and labeling activities for the drug product manufacturing process as agreed upon during the primary review cycle (April 20, 2016, eCTD seq. 0027).

With the exceptions noted above, I recommend approval of the proposed lot release and shelf-life specifications for bezlotoxumab drug substance and drug product. Merck will re-evaluate drug substance and drug product lot release and stability specifications when 30 drug substance lots have been manufactured using the commercial process

I recommend an expiry of (b) (4) months for bezlotoxumab drug substance when stored at (b) (4) °C.

I recommend an expiry of 24 months for bezlotoxumab drug product when stored at 2-8°C.

The post-approval stability protocols are acceptable.

II. List of Deficiencies to Be Communicated

None

III. List of Post-Marketing Commitments/Requirement

PMC#1: Re-evaluate MK-6072 DS and DP lot release and stability specifications after a minimum of 30 DS lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

PMC#2: Perform additional testing to support the clonality of the bezlotoxumab master cell bank (MCB).

PMC#3: Conduct a study to support the worst case cumulative hold times in the bezlotoxumab drug substance manufacturing process to demonstrate that the worst case cumulative hold time will not adversely affect the product quality of bezlotoxumab drug substance. These data are expected to demonstrate that there is no adverse impact to product quality (b) (4)

(b) (4)

(b) (4)

IV. Review of Common Technical Document - Quality Module I

A. Environmental Assessment or Claim of Categorical Exclusion

A claim for a categorical exclusion is being made under 21 CFR 25.31 (c) for substances that occur naturally in the environment. The composition of bezlotoxumab drug substance is a nonhazardous, biodegradable product that will be catabolized into naturally occurring amino acids and is not expected to result in any significant risk to the environment. To the sponsor's knowledge, no extraordinary circumstances, as described in 21 CFR 25.21, exist that would result in significant impact to the environment from the discharge of this substance.

V. Primary Container Labeling Review

The primary and secondary container labeling review was performed by Jibril Abdus-Samad, OBP.

VI. Review of Common Technical Document-Quality Module 3.2

This document contains the review of the information provided on bezlotoxumab drug substance (section 3.2.S), drug product (section 3.2.P), adventitious agents safety evaluation (3.2.A), and the batch records (3.2.R).

Bezlotoxumab drug substance is manufactured at

(b) (4)

(b) (4)

Bezlotoxumab drug product is manufactured at Merck, Sharp, and Dohme (MSD) in Carlow, Ireland. The manufacturing process of bezlotoxumab drug product includes (b) (4)

(b) (4). The container closure is a single-use, (b) (4) vial (b) (4).
(b) (4).

VII. Review of Immunogenicity Assays- Module 5.3.1.4

A review of the product immunogenicity assays is included at the end of the primary review document. Immunogenicity testing includes a typical 3-tiered assay approach consisting of an anti-drug antibody (ADA) screening assay, a confirmatory assay, and a neutralizing antibody assay. The ADA screening assay has sufficient drug tolerance. It detects (b) (4) of ADA in the presence of up to (b) (4) of bezlotoxumab in the serum. The neutralizing assay is a cell based assay has a sensitivity of (b) (4) of NAb in up to (b) (4) of bezlotoxumab in the serum.

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/s/

WILLIAM H HALLETT
04/22/2016

RASHMI RAWAT
04/22/2016