CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761035Orig1s000

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date: 11/12/2015
To: Administrative File, STN 761035/0
From: Ruth Moore, Ph.D., Chemist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA 761035 - Addendum to Facilities Review of 10/27/2015
US License: Pending
Applicant: Bristol-Myers Squibb (BMS) Company
Mfg Facility: Drug Substance: Bristol-Myers Squibb Corporation Inc., Syracuse, NY
FEI 1317461
Drug Product: Bristol-Myers Squibb Holdings Pharma Limited Liability Company, Manati, PR
FEI 2650089
Product: Elotuzumab for Injection
Dosage: 300 mg/vial and 400 mg/vial for intravenous administration by infusion after reconstitution. Sterile lyophilized product provided in single (b) (4) glass vials.
Indication: Treatment for Multiple Myeloma
Due Date: 11/13/2015

RECOMMENDATION: This submission is recommended for approval from a facility review perspective.

SUMMARY

The subject BLA proposes manufacture of Elotuzumab DS and DP, respectively, at Bristol-Myers Squibb (BMS) East Syracuse, NY facility, (FEI 1317461), and BMS Pharma Limited Liability Company, Manati, PR (FEI 2650089). Cell bank manufacture and testing will occur at (b) (4) Drug substance release and stability testing will be performed at BMS East Syracuse, and at (b) (4) (b) (4) is performed by BMS, Devens, MA (FEI 3008455069). The drug product is packaged at the BMS Manati, PR site.

An initial facilities review memo dated 10/27/2015 contained a pending recommendation for the facilities approval. This addendum documents the outcome of the inspection for the BMS Syracuse drug substance manufacturing facility, and provides the final recommendation on acceptability of the manufacturing facilities for manufacture of Elotuzumab in BLA 761035/0.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

- **3.2.S.2.1 DS Manufacturers.**
  The sites proposed for Elotuzumab DS manufacture, cell banking operations, and testing are presented below in Table 1.

TABLE 1. Proposed Sites for Elotuzumab DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
Bristol-Myers Squibb Company	6000 Thompson Rd East Syracuse, NY 13057	1317461	Elotuzumab DS manufacture, storage, release testing and stability testing (b) (4) (b) (4) (b) (4)
Bristol-Myers Squibb Company	36 Jackson Rd Devens, MA 01434	3008455069	DS testing - (b) (4) (b) (4) (b) (4)

***Reviewer Comment 1**: The facilities for manufacture of Elotuzumab DS are adequately described.*

- **Prior Inspection History for DS Manufacturing and Testing Sites**

  The prior inspection history for these sites was presented in the initial facility review memo dated 10/27/2015.

- **Current Prior Approval Inspection Decisions**
  BMS- Syracuse (FEI 1317461), Elotuzumab DS Manufacturing and Testing Site. Inspection conducted 10/5/205 to 10/9/2015 by CDER-OPF and CDER-OBP.
  A Pre-license inspection (PLI) of Bristol Myers-Squibb Company in East Syracuse, NY was completed in support of two breakthrough therapies, BLA 761035/0 for Elotuzumab (b) (4) (b) (4) The inspection was conducted in accordance with CP 7356.002M and ICH Q7. A comprehensive review of facilities, utilities, equipment, processes and procedures was conducted to evaluate product quality, compliance to commitments in the BLA and compliance to CGMPs. (b) (4) No observations were made and no Form FDA 483 was presented to BMS management at the conclusion of the inspection on October 9, 2015. (b) (4)

(b) (4)

The BMS manufacturing and testing facilities in East Syracuse were found to be acceptable from a CGMP perspective for manufacture of Elotuzumab DS under BLA 761035.

***Reviewer Comment 2**: The production and testing facilities associated with the manufacture of Elotuzumab DS are acceptable from a facilities assessment standpoint.*

DRUG PRODUCT FACILITIES

The sites proposed for manufacturing, testing, packaging and labeling of the drug product were described and evaluated in the initial facilities review memo dated 10/27/2015. The production and testing facilities associated with the manufacture of Elotuzumab DP were found to be acceptable from a facilities assessment standpoint.

CONCLUSION

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for the BMS East Syracuse (FEI 1317461) and BMS Manati (FEI 2650089) facilities proposed for Elotuzumab DS and DP manufacture. All proposed manufacturing and testing sites for BLA 761035/0 are recommended for approval from a facilities assessment standpoint.

Ruth A. Moore -S

Digitally signed by Ruth A. Moore -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ruth A. Moore -S, 0.9.2342.19200300.100.1.1=2001430890
Date: 2015.11.12 18:18:49 -05'00'

Ruth Moore Ph.D.
Chemist/ Compliance Officer
OPF Division of Inspectional Assessment Branch 1

Michael R. Shanks -S

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Date: 2015.11.12 21:27:33 -05'00'

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

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: 10/27/2015
To: Administrative File, STN 761035/0
From: Ruth Moore, Ph.D., Chemist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: Pending
Applicant: Bristol-Myers Squibb (BMS) Company
Mfg Facility: Drug Substance: Bristol-Myers Squibb Corporation Inc., Syracuse, NY
FEI 1317461
Drug Product: Bristol-Myers Squibb Holdings Pharma Limited Liability Company, Manati, PR
FEI 2650089
Product: Elotuzumab for Injection
Dosage: 300 mg/vial and 400 mg/vial for intravenous administration by infusion after reconstitution. Sterile lyophilized product provided in single (b) (4) glass vials.
Indication: Treatment for Multiple Myeloma
Due Date: 11/02/2015

RECOMMENDATION: Final recommendation on approval of this submission from a facility review perspective is pending the review of the EIR for the Pre-License Inspection (PLI) of the BMS East Syracuse facility.

SUMMARY

The subject BLA proposes manufacture of Elotuzumab DS and DP, respectively, at Bristol-Myers Squibb (BMS) East Syracuse, NY facility, (FEI 1317461), and BMS Pharma Limited Liability Company, Manati, PR (FEI 2650089). Cell bank manufacture and testing will occur at (b) (4). Drug substance release and stability testing will be performed at BMS East Syracuse, and at (b) (4) is performed by BMS, Devens, MA (FEI 3008455069). The drug product is packaged at the BMS Manati, PR site.

Elotuzumab (Empliciti™) is a humanized IgG1 monoclonal antibody produced in NSO cells. It is proposed for the treatment of patients with multiple myeloma. Elotuzumab drug product is manufactured as a lyophilized powder, and is presented at two strengths of 300 and 400 mg/vial.

The drug is administered intravenously by infusion after reconstitution with water for injection and dilution with normal saline or 5% dextrose in water.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

- **3.2.S.2.1 DS Manufacturers.**
  The sites proposed for Elotuzumab DS manufacture, cell banking operations, and testing are presented below in Table 1.

TABLE 1. Proposed Sites for Elotuzumab DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
Bristol-Myers Squibb Company	6000 Thompson Rd East Syracuse, NY 13057	1317461	Elotuzumab DS manufacture, storage, release testing and stability testing (b) (4)
Bristol-Myers Squibb Company	36 Jackson Rd Devens, MA 01434	3008455069	DS testing - (b) (4) (b) (4)

(b) (4)

***Reviewer Comment 1**: The facilities for manufacture of Elotuzumab DS are adequately described.*

- **Prior Inspection History for DS Manufacturing and Testing Sites**
  - Bristol-Myers Squibb Company (FEI 1317461). Elotuzumab DS Manufacturing and Testing Site.

(b) (4)

(b) (4)

- Bristol-Myers Squibb Devens, MA (FEI 3008455069) Elotuzumab DS Testing Site Inspection Conducted 6/25/15. PAI Coverage under (b) (4) and GMP coverage under (b) (4). No FDA Form 483 was issued. The inspection was classified NAI.

(b) (4)

- **Current Prior Approval Inspection Decisions**
  BMS- Syracuse (FEI 1317461), Elotuzumab DS Manufacturing and Testing Site. Inspection conducted 10/5/205 to 10/9/2015 by CDER-OPF and CDER-OBP.
  A Pre-license inspection (PLI) of Bristol Myers-Squibb Company in East Syracuse, NY was completed in support of two breakthrough therapies, BLA 761035/0 for Elotuzumab (b) (4) The inspection was conducted in accordance with CP 7356.002M and ICH Q7. A comprehensive review of facilities, utilities, equipment, processes and procedures was conducted to evaluate product quality, compliance to commitments in the BLA and compliance to CGMPs. (b) (4) (b) (4) (b) (4) No observations were made and no Form FDA 483 was presented to BMS management at the conclusion of the inspection on October 9, 2015. (b) (4) (b) (4)

  A final recommendation on the acceptability of the BMS manufacturing and testing facilities in East Syracuse for manufacture of Elotuzumab DS under BLA 761035/0 is pending.

Reviewer Comment 2: *The production and testing facilities associated with the manufacture of Elotuzumab DS are acceptable from a facilities assessment standpoint.*

- **3.2.S.2.2. Overview of Elotuzumab DS Manufacturing Operations Conducted at BMS.** Elotuzumab is produced from cell culture using an NS0 mouse myeloma-based cell line. The Elotuzumab manufacturing process is (b) (4)

19 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

CONCLUSION

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for the BMS East Syracuse (FEI 1317461) and BMS Manati (FEI 2650089) facilities proposed for Elotuzumab DS and DP manufacture. The final review of the EIR for the PLI fo BMS Syracuse is pending; an overall manufacturing recommendation will be provided via an addendum when a final inspection decision is made by CDER.

Ruth A. Moore -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ruth A. Moore -S, 0.9.2342.19200300.100.1.1=2001430890
Date: 2015.10.27 12:17:50 -04'00'

Ruth Moore Ph.D.
Chemist/ Compliance Officer
OPF Division of Inspectional Assessment
Branch 1

Zhihao Qiu -S

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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: 2015.10.27 12:20:54 -04'00'

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

Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum

Date: 10/15/2015

From: Ruth Moore, Ph.D., OPQ/OPF/DIA
Rachel Novak, Ph.D., OPQ/OBP/DBRR
Natalia Pripuzova, Ph.D., OPQ/OPF/DMA

To: BLA File, STN 761035/0

Through: Zhihao (Peter) Qiu, Ph.D., Branch Chief, OPQ/OPF/DIA Branch 1

Subject: Inspection waiver memo for manufacture of Elotuzumab drug product at the Bristol-Myers Squibb (BMS) facility in Manati, Puerto Rico

Applicant: Bristol Myers Squibb (BMS) Company

Facility: BMS Holdings Pharma Limited Liability Co.
Road 686, Km 2.3
Bo. Tierras Nuevas
Manati
Puerto Rico 00674, USA
FEI #2650089

Product: Elotuzumab (Impliciti) for Injection

Dosage: Lyophilized Powder, 300 mg/vial and 400 mg/vial Elotuzumab, for intravenous infusion after reconstitution.

Indication: Treatment of patients with relapse/refractory multiple myeloma (MM)

Waiver Recommendation

The Elotuzumab drug product will be manufactured in the [redacted] (b) (4) (b) (4) at BMS-Manati. The proposed commercial manufacturing scheme for Elotuzumab is [redacted] (b) (4) The facility was inspected by SJN-DO and CDER-OC from 5/05/2014–5/16/2014, and classified NAI. CGMP coverage was provided for SVS, SVL and [redacted] (b) (4) profiles during the inspection, and there were no concerns related to manufacture of sterile product by [redacted] (b) (4) methods at the facility. Based on the firm's compliance history and current acceptable GMP status, [redacted] (b) (4) BMS-Manati proposed for Elotuzumab [redacted] (b) (4) (b) (4) we recommend that inspection of BMS-Manati facility be waived for STN 761035/0.

Summary

BLA STN 761035/0 was submitted by Bristol-Myers Squibb (BMS) and it provided information and data to support the manufacture of Elotuzumab for Injection, 300 mg/vial and 400 mg/vial. The manufacture of Elotuzumab drug substance is performed at BMS at East Syracuse, NY (FEI 1317461), and Elotuzumab drug product is manufactured at BMS Holdings Pharma, Manati, Puerto Rico (FEI 2650089). The current waiver recommendation is in regards to drug product manufacture at BMS-Manati, PR.

Facility Information

The drug product manufacturing process for Elotuzumab consists of (b) (4)

(b) (4)

Evaluation of criteria that may warrant inspection

(b) (4)

(b) (4)

(b) (4)

The proposed manufacturing scheme for Elotuzumab (b) (4)

(b) (4)

Signed:

Ruth Moore, Ph.D., DIA/OPF Reviewer Ruth A. Moore -S Digitally signed by Ruth A. Moore -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ruth A. Moore -S, 0.9.2342.19200300.100.1.1=2001430890 Date: 2015.10.15 14:51:14 -04'00' DATE _____

Rachel Novak, Ph.D., DBRR/OBP Reviewer Rachel L. Novak -S Digitally signed by Rachel L. Novak -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013719878, cn=Rachel L. Novak -S Date: 2015.10.16 12:41:14 -04'00' DATE _____

Natalia Pripuzova, Ph.D., DMA/OPF Reviewer 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=2900351935, cn=Natalia S. Pripuzova -S (Affiliate) Date: 2015.10.16 12:45:43 -04'00' DATE _____

Linan Ha, Ph.D., DBRR /OBP ATL Linan Ha -S Digitally signed by Linan Ha -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Linan Ha -S, 0.9.2342.19200300.100.1.1=1300429681 Date: 2015.10.19 19:39:24 -04'00' DATE _____

Patricia Hughes, Ph.D., DMA/OPF Branch Chief Patricia F. Hughestroost -S Digitally signed by Patricia F. Hughestroost -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300396542, cn=Patricia F. Hughestroost -S Date: 2015.10.20 07:43:40 -04'00' DATE _____

Zhihao Qiu, Ph.D., DIA/OPF Branch Chief 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=2000458274 Date: 2015.10.30 07:31:02 -04'00' DATE _____

Kathleen A. Clouse Strebel -S

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Date: 2015.10.30 01:17:09 -04'00'

Concur 10/30/2015

Kathleen Clouse, Ph.D. CONCUR DO NOT CONCUR DATE
Director, Division of Biotechnology Review and Research 1
Office of Biotechnology Products, Office of Pharmaceutical Quality, CDER

First Approval for Indication
Breakthrough, Priority Review

Recommendation: Approval

BLA 761035
Review # 01

Date: November 6, 2015

From: Linan Ha, Ph.D.
Team Leader, DBRR I/OBP

Through: Sarah Kennett, Ph.D.
Review Chief, DBRR I/OBP

Kathleen Clouse, Ph.D.
Director, DBRR I/OBP

Drug Name/Dosage Form	**Empliciti (elotuzumab)/for injection**
Strength/Potency	**300 mg/vial and 400 mg/vial**
Route of Administration	**Intravenous**
Rx/OTC Dispensed	**Rx**
Indication	**Treatment of patients with relapsed/refractory multiple myeloma (MM)**
Applicant/Sponsor	**Bristol-Myers Squibb Company**

Product Overview

Elotuzumab (Empliciti™) is a humanized IgG1 monoclonal antibody produced in NS0 cells. Elotuzumab targets Signaling Lymphocyte Activation Molecule Family 7 (SLAMF7). SLAMF7 is a glycoprotein expressed on myeloma and nature killer (NK) cells, but not on hematopoietic stem cells or normal solid tissues. Elotuzumab binds to SLAMF7 on the surface of myeloma cells and recruits NK cells through FcγRIIIa binding, which leads to the elimination of the myeloma cell via antibody–dependent cellular cytotoxicity (ADCC). Elotuzumab drug product is presented as a lyophilized powder in two strengths, 300 and 400 mg/vial. Elotuzumab is proposed for the treatment of multiple myeloma (MM) in patients who have received one or more prior therapies. Elotuzumab is administered in combination with lenalidomide and dexamethasone.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Rachel Novak	DBRR I/OBP/OPQ
Drug Product	Rachel Novak	DBRR I/OBP/OPQ
Immunogenicity	Rachel Novak	DBRR I/OBP/OPQ
Labeling	Jibril Abdus-Samad	OBP/OPQ
Facility	Ruth Moore	DIA/OPF/OPQ
Microbiology	Maria Jose Lopez- Barragan and Natalia Pripuzova	DMA/OPF/OPQ
Business Process Manager	Andrew Shiber	RBPMBI/ OPRO/OPQ
Team Lead for OBP	Linan Ha	DBRR I/OBP/OPQ
Tertiary Reviewer for OBP	Sarah Kennett	DBRR I/OBP/OPQ

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Natasha Kormanik	OHOP/DHP
Cross-disciplinary Team Lead	Albert Deisseroth	OHOP/DHP
Medical Officer	Nicole Gormley	OHOP/DHP
Pharm/Tox	Michael Manning	OHOP/DHOT
Clinical Pharmacology	Olanrewaju Okusanya	OTS/OCP/DCPV
Statistics	Chia-Wen Ko	OTS/OB/DBV

a. Names
   i. Proprietary Name: Empliciti
   ii. Trade Name: Empliciti
   iii. Non-Proprietary/USAN: elotuzumab
   iv. INN Name: elotuzumab
   v. OBP Systematic Name: MAB HUMANIZED (IGG1k) ANTI Q9NQ25 (SLAMF7_HUMAN)

b. Pharmacologic category: Therapeutic recombinant humanized monoclonal antibody

Submissions Reviewed

SUBMISSION(S) REVIEWED	DOCUMENT DATE
761035/1	May 27. 2015
761035/2	June 28, 2015
761035/6	August 12, 2015
761035/8	August 21, 2015
761035/11	September 4, 2015

761035/17	September 14, 2015
761035/24	October 1, 2015
761035/27	October 8, 2015
761035/30	October 14, 2015
761035/31	October 22, 2015
Received via email (response to IRs conveyed on October 21, and 23, 2015)	October 30, 2015
Received via email (response to IRs conveyed on October 29, and follow up to IR conveyed on October 23, 2015)	November 2, 2015
Received via email (follow up to IR conveyed on October 23, 2015)	November 4, 2015
Received via email (response to IR conveyed on November 3, 2015)	November 6, 2015

Quality Review Team-Signature Page

DISCIPLINE	REVIEWER	BRANCH/DIVISION	e-Signature
Product Quality	Rachel Novak	Division of Biotechnology Review and Research I	Rachel L. Novak -S Digitally signed by Rachel L. Novak -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013719878, cn=Rachel L. Novak -S Date: 2015.11.09 10:14:00 -05'00'
Microbiology (Drug Substance)	Maria Jose Lopez-Barragan	Division of Microbiology Assessment	Maria Jose Lopez Barragan -S (Affiliate) Digitally signed by Maria Jose Lopez Barragan -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=0012653737, cn=Maria Jose Lopez Barragan -S (Affiliate) Date: 2015.11.09 09:28:55 -05'00'
Microbiology (Drug Product)	Natalia Pripuzova	Division of Microbiology Assessment	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: 2015.11.09 09:37:44 -05'00'
Facilities	Ruth Moore	Division of Inspectional Assessment	Ruth A. Moore -S Digitally signed by Ruth A. Moore -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ruth A. Moore -S, 0.9.2342.19200300.100.1.1=2001430890 Date: 2015.11.09 08:00:41 -05'00'
Microbiology Quality Assessment Lead	Colleen Thomas	Division of Microbiology Assessment	Colleen Thomas -S Digitally signed by Colleen Thomas -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Colleen Thomas -S, 0.9.2342.19200300.100.1.1=2000334599 Date: 2015.11.07 14:11:37 -05'00'
Microbiology Team Lead	Patricia Hughes	Division of Microbiology Assessment	Patricia F. Hughestroost -S Digitally signed by Patricia F. Hughestroost -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300096547, cn=Patricia F. Hughestroost -S Date: 2015.11.07 14:59:34 -05'00'
Facilities Team Lead	Peter Qiu	Division of Inspectional Assessment	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: 2015.11.08 14:10:31 -05'00'
Application Technical Lead	Linan Ha	Division of Biotechnology Review and Research I	Linan Ha -S Digitally signed by Linan Ha -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Linan Ha -S, 0.9.2342.19200300.100.1.1=1300429681 Date: 2015.11.06 20:05:44 -05'00'
Review Chief	Sarah Kennett	Division of Biotechnology Review and Research I	Sarah B. Kennett -S Digitally signed by Sarah B. Kennett -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000597165, cn=Sarah B. Kennett -S Date: 2015.11.09 10:44:14 -05'00'
Division Director	Kathleen Clouse	Division of Biotechnology Review and Research I	Kathleen A. Clouse Strebel -S Digitally signed by Kathleen A. Clouse Strebel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300054511, cn=Kathleen A. Clouse Strebel -S Date: 2015.11.09 11:45:41 -05'00'

Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION: 351(a)**

2. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
[redacted]	[redacted]	[redacted] (b) (4)	Yes	Type III; Adequate information provided in the BLA for its intended use
[redacted]	[redacted]	[redacted]	Yes	Type III; Adequate information provided in the BLA for its intended use
[redacted]	[redacted]	[redacted]	Yes	Type III: Adequate information provided in the BLA for its intended use
[redacted]	[redacted]	[redacted]	Yes	Adequate information provided in the BLA for its intended use
[redacted]	[redacted]	[redacted]	Yes	Adequate information provided in the BLA for its intended use

B. Other Documents: None

3. CONSULTS: None

Integrated Review

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761035 for Empliciti (elotuzumab) manufactured by Bristol-Myers Squibb Company pending acceptable compliance checks. The data submitted in this application are adequate to support the conclusion that the manufacture of Empliciti 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: Bristol-Myers Squibb Company (FEI 1317461) East Syracuse, New York
  - Drug product: Bristol-Myers Squibb Holdings Pharma, Ltd. (FEI 2650089) Manati, Puerto Rico
- Fill size and dosage form: 300 mg/vial and 400 mg/vial
- Dating period:
  - Drug product: 36 months; 2-8°C
  - Drug substance: (b) (4)
- Exempt from lot release
  - Yes
  - Rationale if exempted: We exempt specified products according to 21 CFR 601.2a

c. Benefit/Risk Considerations

Empliciti is proposed for the treatment of MM in patients who have received one or more prior therapies. Empliciti is administered in combination with lenalidomide and dexamethasone. Nearly all MM patients receiving currently available treatment regimens relapse, leading to the development of progressive disease resistant to both immunomodulatory agents and proteasome inhibitors. Empliciti was found to significantly improve progression free survival in heavily treated MM patients. Therefore, Empliciti may address a currently unmet medical need.

The current potency assay for the release and stability testing of elotuzumab drug substance and drug product is a cell-based ADCC bioassay (b) (4) This assay assesses the ability of elotuzumab to elicit NK cell-mediated ADCC in SLAMF7-expressing target cells, and validation data were provided to

demonstrate adequate assay performance. However, this assay was developed during a late stage of development, and the acceptance criteria for this assay were derived from retrospective testing of release and stability samples. The cell-based ADCC assay and acceptance criteria to be approved under the BLA are sufficient to ensure adequate quality and safety of elotuzumab for the initial marketed product, because adequate information was provided to bridge the cell-based ADCC bioassay to the previous release/stability potency assay (SLAMF7 binding ELISA) and the binding assay data and to demonstrate that the ADCC bioassay is more sensitive than the SLAMF7 binding ELISA with respect to detecting product degradation. However, the sponsor was requested to re-evaluate the elotuzumab drug substance (DS) and drug product (DP) release and stability acceptance criteria when sufficient data from commercial manufacturing and testing become available to ensure the appropriateness of the initial specification. This re-evaluation will be performed as a PMC.

Cation exchange chromatography (CEX) is a stability indicating assay and is an important control for product-related impurities, such as (b) (4) (b) (4) However, the proposed DS and DP release and stability acceptance criteria were not sufficiently inclusive to provide adequate control over potential product degradation. The proposed specification provided a control over (b) (4) However, the specifications did not take into account the (b) (4) The proposed criteria (b) (4) (b) (4) Therefore, during the review cycle, the sponsor was requested to implement an appropriate control(s) to (b) (4) In response, the sponsor revised the control strategy (b) (4) This was considered to be acceptable for initial approval; however, given the limited data available (b) (4) the proposed acceptance criteria should be re-assessed when sufficient information becomes available. This re-assessment will be performed as a PMC.

The elotuzumab production cell line was developed (b) (4) (b) (4)

(b) (4)

[redacted] (b) (4) and a PMC was established to ensure that the sponsor will complete the ongoing studies to support the [redacted] (b) (4) of the MCB.

Validation of DS purification product [redacted] (b) (4) holds was performed. However, the [redacted] (b) (4) used as a surrogate solution in these studies [redacted] (b) (4) [redacted] The sponsor has committed to perform supplemental validation studies using an adequate surrogate to support the proposed [redacted] (b) (4) hold times for the [redacted] (b) (4) [redacted]. The sponsor committed to [redacted] (b) (4) [redacted]

The DP manufacturing process is well controlled and should consistently deliver DP of desired quality. The microbial retention data provided thus far and microbial control of the manufacturing process indicate that the risk of microbial penetration of the sterilizing filter is very low. However, additional data should be provided to further support the parameters for the sterilizing filter. A quality microbiology PMC for a confirmatory study will be implemented; the sponsor agreed to repeat the microbial retention filter validation [redacted] (b) (4) study in accordance with PDA Technical Report #26. The sponsor will perform a repeat microbial retention study for the sterilizing filter using a suitable surrogate solution or will perform the study using a modified process, a modified formulation [redacted] (b) (4) or a reduced exposure time for the challenge organism. If any filtration parameters are changed as a result of the study, the BLA file will be updated accordingly.

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

1. To re-evaluate elotuzumab drug substance lot release and stability specification acceptance criteria for the cell-based ADCC potency assay and cation exchange chromatography (CEX) assay after 30 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. To re-evaluate elotuzumab drug product lot release and stability specifications after 30 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.

3. To complete the ongoing studies to support the (b) (4) of the elotuzumab master cell bank (MCB). The results of the (b) (4) using multiple cells from the MCB will be provided in the final study report.

4. To perform supplemental validation studies using an adequate surrogate to support the proposed (b) (4) hold times for the (b) (4)

5. To repeat the microbial retention filter validation (b) (4) study in accordance with PDA Technical Report #26. Sponsor commits to providing a summary of the revised microbial retention filter validation study conducted with a modified process, a modified formulation (b) (4) or a reduced exposure time for the challenged organism used during the study. If any filtration parameters are changed as a result of the study, the BLA file will be updated accordingly.

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. For additional information see Appendix A (Drug Substance and Drug Product Quality Review: OBP Assessment).

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

CQA	Risk	Origin	Control Strategy	Other
[redacted]				
[redacted]				
[redacted]				

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[redacted]

	activity.		(b) (4) [redacted]	
Protein concentration	Potency and safety	(b) (4) [redacted]		
pH	Safety and efficacy		(b) (4) [redacted]	
Potency (ADCC)	Efficacy. ADCC is the proposed mechanism of action.	(b) (4) [redacted]		

			(b) (4)
SLAMF7 binding activity	Potency	(b) (4)	(b) (4)
Identity	Safety and efficacy	N/A	

B. Drug Substance: Elotuzumab Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

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. For additional information see Appendix A (Drug Substance and Drug Product Quality Review: OBP Assessment) and Appendix B (Drug Substance Microbiology Review: Division of Microbiology Assessment).

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

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

Viral Agents			[redacted] (b) (4)	
Bioburden	Safety; product quality due to degradation or modification of product by contaminating microorganisms	Bioburden can be introduced throughout the manufacturing process.	[redacted] (b) (4)	
Endotoxins	Safety	Endotoxins can be introduced throughout the manufacturing process.	[redacted] (b) (4)	
[redacted] (b) (4)				
Appearance (color, clarity, opalescence, particulates)	Safety and efficacy	N/A	Appearance is controlled by the formulation. Appearance is part of DS release and stability testing.	
Leachables/ extractables	Safety	Leachables and extractables could potentially be introduced by any product contact equipment, containers,	Extractable and leachable studies were performed on the DS container closure system and the (b) (4) used in DS manufacturing. Toxicology and risk assessments were performed for each extractable/leachable study.	

		and consumables.		
Osmolality	Safety	[redacted]	(b) (4)	
Polysorbate 80	Safety	[redacted]	(b) (4)	

a. Description

Elotuzumab is a humanized IgG1 monoclonal antibody consisting of (b) (4) (b) (4) heavy and light chains (b) (4) Elotuzumab contains (b) (4)

(b) (4)

For additional information see Appendix A.

b. Mechanism of action

SLAMF7 is a glycoprotein expressed on myeloma and Nature Killer (NK) cells, but not in normal tissues. Elotuzumab activates NK cells through binding to SLAMF7. Elotuzumab binds to myeloma cells via SLAMF7 and recruits and activates NK cells via an FcγRIIIa mediated pathway, which, in turn, leads to selective elimination of myeloma cells by ADCC activity. For additional information see Appendix A.

c. Potency Assay

Potency of elotuzumab is assessed using a cell based ADCC bioassay.

The cell based ADCC bioassay (b) (4) assesses the ability of elotuzumab to elicit NK cell-mediated ADCC in SLAMF7-expressing target cells. (b) (4)

(b) (4)

(b) (4)

[redacted]

For additional information see Appendix A.

d. Reference material(s)

(b) (4)

[redacted]

e. Critical starting materials or intermediates

A list of compendial and non-compendial (b) (4) materials was provided. Specifications for the non-compendial (b) (4) materials were provided.

(b) (4)

[redacted]

(b) (4)

[redacted]

f. Manufacturing process summary

(b) (4)

[redacted]

(b) (4)

For additional information see Appendix A and Appendix B.

g. Container closure

Elotuzuamb DS is filled into single- (b) (4) (b) (4) . For additional information see Appendix A

h. Dating period and storage conditions

(b) (4)

For additional information see Appendix A.

C. Drug Product [Empliciti] 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. For additional information on the characterization of Empliciti see Appendix A and Appendix C (Drug Product Microbiology Review: Division of Microbiology Assessement).

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management for DP CQAs that derived from DP manufacturing process and general DP attributes.

CQA	Risk	Origin	Control Strategy	Other
Sterility	Safety (infection) Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination could be introduced throughout DP manufacturing or through a container closure integrity failure.	Bioburden is controlled (b) (4) (b) (4) The sterilizing filter is integrity tested. Container closure components are sterilized. Validation data support sterility assurance of the finished DP. Sterility and endotoxin testing are included as part of the DP release specifications. Container closure integrity testing of DP samples is included in stability protocols.	
Endotoxin	Safety	Contamination could be introduced throughout DP manufacturing or through a container closure integrity failure.	The control strategies described for drug product sterility assurance also limit the introduction of endotoxin. The container closure components are (b) (4) The DP is tested for endotoxin at release.	
Particulate matter	Safety and immunogenicity	(b) (4)	(b) (4) particles are included in the DP release and stability specifications.	
Appearance (lyophilized cake)	Safety and efficacy	Appearance might be impacted by the formulation and the lyophilization processes.	Appearance of lyophilized cake is included in the DP release and stability specifications.	
Appearance (reconstituted	Safety and efficacy	Appearance might be impacted by the	Appearance of reconstituted solution is included in the DP release and stability specifications.	

solution)		formulation and by the reconstitution procedure.		
(b) (4)	Safety and efficacy	(b) (4)		
Reconstitution time	Efficacy	(b) (4)		
Container closure integrity	Safety	N/A	Container closure integrity testing is included in DP stability specification.	
Leachables/ extractables	Safety	Leachables and extractables could, potentially, be introduced by any product contact equipment, containers, and consumables.	Extractable and leachable studies were performed on the DP container closure system and the sterile filter used in DP manufacturing. Toxicology and risk assessments were performed for each extractable/leachable study.	

a. Potency and Strength

Potency is defined as the percent activity relative to elotuzumab reference standard. The potency assay is the same as described for the DS. Elotuzumab DP is provided in two strengths: 300 mg/vial and 400 mg/vial. The compositions of the two presentations are the same (b) (4) For additional information see Appendix A.

b. Summary of Product Design

Elotuzumab DP is supplied in single dose (b) (4) vials for administration by intravenous (IV) infusion. Elotuzumab for injection is reconstituted with sterile water for injection (SWFI) to obtain a solution with a protein concentration of 25 mg/mL. Prior to IV administration, the reconstituted solution is diluted with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP (b) (4) . For additional information see Appendix A.

c. List of Excipients: (b) (4) sodium citrate, (b) (4)% (w/v) sucrose, (b) (4)% (w/v) polysorbate 80, and water for injection. All excipients used in DP manufacturing meet compendial requirements. For additional information see Appendix A.

d. Reference material(s): DS and DP use the same reference material, see DS section d.

e. Manufacturing process summary:

The manufacturing process for elotuzumab DP includes (b) (4)

The process control strategy and the in-process and release testing provides assurance of (b) (4) processing, correct formulation, product homogeneity, consistent and accurate fill, and product quality.

The DP manufacturing process was validated. Validation included full scale validation with three lots of each presentation. Additional validation studies included:

- Validation of the preparation of components
- Validation of (b) (4) manufacturing process
- Shipping qualification study
- Process simulation and media fills
- Environmental monitoring qualification study

For additional information see Appendix A and Appendix C.

f. Container closure: Both 300 mg/vial and 400 mg/vial presentations use the same container closure system. It consists of a 20-cc Type I (b) (4) glass vial, a 20-mm gray (b) (4) stopper, and an aluminum (b) (4) seal with a (b) (4) (b) (4) seal cover. The two presentations differ only in the color of the (b) (4) seal cover. The cover for the 300 mg/vial presentation is ivory and the cover for the 400 mg/vial presentation is dark blue.

g. Dating period and storage conditions:

- For the 400 mg presentation, the BLA contained 36 months of real time stability data for three DP lots manufactured using (b) (4) DS, 18 months of real time stability data for three DP lots manufactured using (b) (4) DS, and 6 months of accelerated and stressed stability data for four DP lots derived from (b) (4) DS and six DP lots derived from (b) (4) DS.
- The 300 mg presentation was developed a later stage. All 300 mg presentation DP lots were manufactured using (b) (4) DS. The BLA contained 9 months of real time and 6 months of accelerated and stressed stability data for one DP lot manufactured prior to the PPQ campaign and 12 months of real time and 6 months of accelerated and stressed stability data for three DP registration lots.
- Photostability and freeze-thaw cycling data were provided for both presentations.
- The data provided in the BLA were sufficient to establish a 36 month shelf life for both the 400 mg and 300 mg presentations when stored at 2-8°C.
- The drug product stability commitment includes completing all on-going stability studies and placing the (b) (4) commercial lots for each presentation and at least (b) (4) thereafter on real time stability protocols. The stability commitment protocol is acceptable.

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

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations: None

F. Establishment Information

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
Function	**Site Information**	**DUNS/FEI Number**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**
(b) (4) (b) (4) DS manufacture, release and stability testing (b) (4) and storage	Bristol-Myers Squibb Company 6000 Thompson Road, East Syracuse, New York 13057, USA	1317461	Pre-license inspection required	PLI completed on 10/5/2015 was classified NAI. No item 483 was issued. The inspection covered the Quality, Facilities and Equipment, Production, Material and Laboratory Systems used to manufacture and test Elotuzumab DS	Pending compliance review
(b) (4) (b) (4) DS release and stability testing (b) (4) and storage	Bristol-Myers Squibb Company 38 Jackson Road, Devens, Massachusetts 01434, USA	3008455069	Acceptable based on profile and inspection history	NA	Acceptable
(b) (4)			Acceptable based on profile and inspection	NA	Acceptable

(b) (4)			history		
(b) (4)			Acceptable based on profile and inspection history	NA	Acceptable
			Acceptable based on profile and inspection history	NA	Acceptable
			Acceptable based on profile and inspection history	NA	Acceptable

DRUG PRODUCT

Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacture,	Bristol-Myers Squibb	2650089	Similar	Inspectional file review	Acceptable.

release and stability testing (b) (4) (b) (4) (b) (4) packaging; and labeling	Holdings Pharma, Ltd. Liability Company Road 686, Km 2.3, Bo. Tierras Nuevas, Manatí, Puerto Rico 00674, USA	(b) (4)	processes and most of the equipment at BMS-Manati are (b) (4)	shows there are no outstanding CGMP concerns. The current GMP status is acceptable.	Pre-license inspection waiver granted.
			Acceptable based on profile and inspection history	NA	Acceptable
Release and stability testing (b) (4) (b) (4)	Bristol-Myers Squibb Company 38 Jackson Road, Devens, Massachusetts 01434, USA	3008455069	Acceptable based on profile and inspection history	NA	Acceptable

For additional information see Appendix D (Facility Review: Division of Inspectional Assessment)

G. Lifecycle Knowledge Management

a. **Drug Substance**
   i. Protocols approved:
      - [redacted] (b) (4) cell bank comparability protocol
      - Annual GMP stability protocol
      - Primary and working reference standard requalification protocol
      - Working reference standard qualification protocol

      [redacted] (b) (4)
   ii. Outstanding review issues/residual risk: See PMCs
   iii. Future inspection points to consider: None at this time

b. **Drug Product**
   i. Protocols approved: Annual GMP stability protocol
   ii. Outstanding review issues/residual risk: See PMCs
   iii. Future inspection points to consider: None at this time

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
	Product Type			
1.	Recombinant Product	x		
2.	Naturally Derived Product		x	
3.	Botanical		x	
4.	Human Cell Substrate/Source Material		x	
5.	Non-Human Primate Cell Substrate/Source Material		x	
6.	Non-Primate Mammalian Cell Substrate/Source Material	x		
7.	Non-Mammalian Cell Substrate/Source Material		x	
8.	Transgenic Animal Sourced		x	
9.	Transgenic Plant Sourced		x	
10.	New Molecular Entity	x		
11.	PEPFAR Drug		x	
12.	PET Drug		x	
13.	Sterile Drug Product	x		
14.	Other_____		x	
	Regulatory Considerations			
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)		x	
16.	Comparability Protocol(s)		x	
17.	End of Phase II/Pre-NDA Agreements tem)		x	
18.	SPOTS		x	

	(Special Products On-line Tracking System				
19.	USAN Name Assigned		x		
20.	Other_____			x	
	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	
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 _____			x	

BLA STN 761035

EMPLICITI™ (elotuzumab)

Bristol-Myers Squibb

Rachel Novak, Ph.D., Product Quality Reviewer
Linan Ha, Ph.D., Team Leader
Division of Biotechnology Review and Research I
Office of Biotechnology Products

OBP CMC Review Data Sheet

1. **BLA#:** STN 761035

2. **REVIEW DATE:** October 29, 2015

3. **PRIMARY REVIEW TEAM:**

Medical Officer:	Nicole Gormley and Albert Deisseroth [Team Leader (TL) and CDTL]
Pharm/Tox:	Michael Manning and Chris Sheth (TL)
Product Quality Team:	Rachel Novak and Linan Ha (TL)
BMT or Facilities:	Maria Jose Lopez-Barragan, Natalia Pripuzova and Patricia Hughes (TL), Ruth Moore, Peter Qui (TL)
Clinical Pharmacology:	Olanrewaju Okusanya and Gene Williams (TL)
Statistics:	Chai-Wen Ko and Lei Nie (TL)
OBP Labeling:	Jibril Abdus-Samad
OBP RBPM:	Andrew Shiber
RPM:	Natasha Kormanik

4. **MAJOR GRMP DEADLINES**

Filing Meeting:	August 10, 2015
Mid-Cycle Meeting:	September 15, 2015
Wrap-Up Meeting:	November 9, 2015
Primary Review Due:	November 2, 2015
Secondary Review Due:	November 9, 2015
CDTL Memo Due:	November 16, 2015
PDUFA Action Date:	February 29, 2016

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

Communication/Document	Date
CMC Pre-BLA Meeting (WRO)	April 20, 2015
Filing letter	August 28, 2015
Information Request #1	September 3, 2015
Information Request #2	September 25, 2015
Information Request #3	October 2, 2015
Information Request #4	October 22, 2015

Information Request #5	October 23, 2015
Teleconference	October 27, 2015
Late cycle meeting	October 29, 2015
Information Request #6 (Follow-up to IR #5)	October 29, 2015

6. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
761035/1 (CMC Section, Rolling Submission)	May 27, 2015	Yes
761035/2 (Complete BLA package)	June 28, 2015	Yes
761035/17 (Response to IR#1)	September 14, 2015	Yes
761035/27 (Response to IR#2)	October 8, 2015	Yes
761035/30 (Response to IR#3)	October 14, 2015	Yes
Received via email (Response to IR#4)	October 26, 2015	Yes
Received via email (Response to IR#5)	October 27, 2015	Yes
Received via email (Follow-up to IR#3 and IR#5)	October 30, 2015	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

a. Proprietary Name: Emplicti
b. Trade Name: Emplicti
c. Non-Proprietary/USAN: elotuzumab
d. Common name: elotuzumab
e. INN Name: elotuzumab
f. Compendial Name: N/A
i. OBP systematic name: MAB HUMANIZED (IGG1k) ANTI Q9NQ25 (SLAMF7_HUMAN)
ii. CAS Registry Number: 915296-00-3

8. PHARMACOLOGICAL CATEGORY: Therapeutic recombinant humanized monoclonal antibody

9. DOSAGE FORM: For injection

10. STRENGTH/POTENCY:

(i) The concentration/strength of the Drug Product: 300 mg/vial and 400 mg/vial

(ii) Type of potency assay: A cell-based Antibody Dependent Cellular Cytoxicity (ADCC) assay is utilized to determine the potency of elotuzumab. ADCC activity is the main MOA for this product. Potency is reported as a percent of reference standard activity.

11. ROUTE OF ADMINISTRATION: Intravenous

12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
		(b) (4)	Yes	Type III; Adequate information provided in the BLA for its intended use
			Yes	Type III; Adequate information provided in the BLA for its intended use
			Yes	Type III: Adequate information provided in the BLA for its intended use
			Yes	Adequate information provided in the BLA for its intended use
			Yes	Adequate information provided in the BLA for its intended use

13. INSPECTIONAL ACTIVITIES

A Pre-licensure inspection of the Bristol-Myers Squibb (BMS) Drug Substance (DS) manufacturing facility in Syracuse, New York, USA was conducted on October 5-9, 2015 by Patricia Hughes (DMA, lead inspector), Maria Jose Lopez-Barragan (DMA), Ruth Moore (DIA), and Rachel Novak (OBP). (b) (4) No recommendations or 483 observations were identified. The recommendation by the inspection team was NAI.

An inspection of the Drug Product (DP) in Manati, Puerto Rico was waived by DIA.

14. CONSULTS REQUESTED BY OBP

None

15. QUALITY BY DESIGN ELEMENTS
None

16. PRECEDENTS
None

17. ADMINISTRATIVE
Signature Block

Discipline	Reviewer	Branch/Division	Signature
OBP- DS, DP, Immunogenicity	Rachel Novak	Division of Biotechnology Review and Research I	
Team Leader	Linan Ha	Division of Biotechnology Review and Research I	
Review Chief	Sarah Kennett	Division of Biotechnology Review and Research I	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation:

We recommend approval of STN 761035 for Empliciti (elotuzumab) manufactured by Bristol-Myers Squibb. The data submitted in this application are adequate to support the conclusion that the manufacture of Empliciti 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 the conditions specified in the package insert.

We recommend that the Empliciti DS be stored at [redacted] (b) (4) for (b) (4) months.

We recommend that the Empliciti DP be stored at 2-8°C for 36 months

II. List Of Deficiencies To Be Communicated

None

III. List Of Post-Marketing Commitments/Requirement

PMC#1: To re-evaluate elotuzumab drug substance lot release and stability specification acceptance criteria for the cell-based ADCC potency assay and cation exchange chromatography (CEX) assay after 30 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: To re-evaluate elotuzumab drug product lot release and stability specifications after 30 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#3: To complete the ongoing studies to support the [redacted] (b) (4) of the elotuzumab master cell bank (MCB). The results of the [redacted] (b) (4) using multiple cells from the MCB will be provided in the final study report.

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

Bristol-Myers Squibb states that this Biologic License Application qualifies for a categorical exclusion to the environmental assessment requirement under 21CFR 25.31(c), based on consideration of its effects when exposed to the environment. Elotuzumab is considered to be a nonhazardous, biodegradable product. The

environmental impact in terms of use and disposal is considered to be negligible and, therefore, does not require the preparation of an environmental assessment.

The claim of categorical exclusion is acceptable.

V. Primary Container Labeling Review

The CMC review of DP labeling was generated by Jibril Abdus-Samad, OBP.

VI. Review Of Common Technical Document-Quality Module 3.2

The review of Module 3.2 is provided below.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

The review of the immunogenicity assay validation is found below the DP section.

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

Elotuzumab is a humanized IgG1 monoclonal antibody consisting of (b) (4) (b) (4) heavy and light chains (b) (4) Elotuzumab contains (b) (4)

S. DRUG SUBSTANCE

3.2.S.1.1 Nomenclature

- Descriptive Name: Elotuzumab is a humanized recombinant monoclonal antibody (mAb) targeted against Signaling Lymphocytic Activation Molecule 7 (SLAMF7), also known as CS1, a cell surface glycoprotein. Elotuzumab consists of the complementarity-determining regions (CDRs) of the mouse antibody, MuLuc63, grafted onto human IgG1 heavy and kappa light chain framework regions.
- CAS Registry Number: 915296-00-3
- Generic Name (USAN, INN, JAN): Elotuzumab
- Trade Name: Empliciti
- Synonyms: HuLuc63; Anti-CS1
- Laboratory Codes:
  - BMS-901608-01 (also referred to as BMS-901608); (b) (4)

3.2.S.1.2 Structure

Elotuzumab has a theoretical mass of 148.1 kDa for the intact antibody. The light and heavy chains have masses of (b) (4) and (b) (4), respectively.

The amino acid sequence for the heavy and light chain of elotuzumab is below:

Figure 3.2.S.1.2-1: (b) (4) **Amino Acid Sequence of Elotuzumab Light Chain**

(b) (4)

Figure 3.2.S.1.2-2: (b) (4) **Amino Acid Sequence of Elotuzumab Heavy Chain**

(b) (4)

The structure of the (b) (4) is illustrated below:

Figure 3.2.S.1.2-2: (b) (4) Amino Acid Sequence of Elotuzumab Heavy Chain (continued)

(b) (4)

(b) (4)

3.2.S.1.3 General Properties

The major (b) (4) of elotuzumab has a measured (b) (4) (b) (4) of (b) (4) and a theoretical (b) (4) (b) (4) of (b) (4)

Elotuzumab is a humanized IgG1 monoclonal antibody targeted against SLAMF7, a glycoprotein expressed on myeloma cells at high levels. SLAMF7 is also expressed on Natural Killer (NK) cells (b) (4) The

mechanism of action for elotuzumab is ADCC mediated by NK cells. When elotuzumab is bound to SLAMF7 on myeloma cells, NK cells become activated via a CD16-mediated ADCC pathway, thereby enabling selective killing of myeloma cells. Elotuzumab has demonstrated potency in vivo based on anti-tumor effects in a mouse multiple myeloma xenograft tumor model and in vitro by antibody-dependent cellular cytotoxicity (ADCC) assays.

The potency assay used to assess the biological activity of elotuzumab for release and stability measures ADCC activity using an engineered NK cell line that acts as both the effector and target cell. See discussion in the relevant sections below.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The elotuzumab manufacturing sites and their responsibilities are listed in the following table.

Table 3.2.S.2.1-1: Drug Substance Manufacturing and Testing Sites Information

Site	Responsibility
Bristol-Myers Squibb Company[a] 6000 Thompson Road East Syracuse, New York 13057 USA	Drug Substance Manufacture (b) (4) Drug Substance Release Testing. Drug Substance Storage. Drug Substance Stability Testing. (b) (4)
Bristol-Myers Squibb Company 38 Jackson Road Devens, Massachusetts 01434 USA	Drug Substance Release Testing (b) (4) Drug Substance Storage. Drug Substance Stability Testing (b) (4) (b) (4)

(b) (4)

[a] BMS-Syracuse is qualified to perform all quality control (QC) testing of elotuzumab drug substance. (b) (4)

(b) (4)

Reviewer note: *BMS-Syracuse is the main release testing site;* (b) (4) *is noted as an*

alternate QC testing site; however, the submission does not contain method validation data for this testing facility to demonstrate comparable assay performances between the two QC testing sites. A request for this information was sent to the sponsor on 9/3/2015.

(b) (4)

3.2.S.2.2 Description of Manufacturing Process and Process Controls

(b) (4)

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(b) (4)

[redacted]

P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The elotuzumab DP is a sterilized, single-(b) (4) lyophilized powder that is a white to off-white cake. The DP comes in two presentations, 400 mg/vial and 300 mg/vial. For administration, the lyophilized DP is reconstituted with sterile water for injection (WFI) to a concentration of 25 mg/mL. For IV infusion, the reconstituted solution is diluted with 0.9% Sodium Chloride (USP) or 5% Dextrose (USP) [redacted] (b) (4)

Both presentations of DP are packaged in a 20 cc Type I glass vial with a 20 mm (b) (4) (b) (4) rubber stopper, and sealed with a 20 mm aluminum (b) (4) seal with (b) (4) button (blue for the 400 mg/vial presentation and ivory for the 300 mg/vial presentation).

The composition of the elotuzumab DP is summarized in the table below.

Table 3.2.P.1-1: Composition of Elotuzumab for Injection, 400 mg/Vial and Elotuzumab for Injection, 300 mg/Vial

Component	Quality Standard	Function	Quantity per Vial[a] 400 mg	Quantity per Vial[a] 300 mg
Elotuzumab (BMS-901608)	BMS Specification[b]	Active ingredient	(b) (4) mg	(b) (4) mg
Sodium Citrate[c]	USP, Ph Eur., JP	(b) (4)	21.5 mg	16.6 mg
Citric Acid Monohydrate	USP, Ph.Eur., JP		3.17 mg	2.44 mg
Sucrose	NF, Ph.Eur., JP		660 mg	510 mg
Polysorbate 80	NF, Ph.Eur., JP		4.40 mg	3.40 mg
Water for Injection[d]	USP, Ph Eur.		(b) (4)	—

USP = United States Pharmacopoeia
Ph Eur. = European Pharmacopoeia
NF = National Formulary
JP = Japanese Pharmacopoeia
(b) (4)

Reviewer comment: *All excipients in elotuzumab DP are USP/NF grade. This is adequate. Each presentation contains a (b) (4) overfill (b) (4) described in Section 3.2.P.2.2. An IR was conveyed to the sponsor on October 2, 2015 to clarify the (b) (4); see discussion in Section 3.2.P.2.2 for detailed information.*

3.2.P.2 Pharmaceutical Development
3.2.P.2.1 Components of the Drug Product

Elotuzumab (b) (4) contains (b) (4) elotuzumab in (b) (4) sodium citrate buffer, (b) (4)% (w/v) sucrose, and (b) (4)% (w/v) polysorbate 80, (b) (4). The (b) (4) is stored (b) (4) All excipients in (b) (4) meet compendial requirements (b) (4) (b) (4)

3.2.P.2.2 Drug Product
3.2.P.2.2.1 Formulation Development

During development, the formulation of elotuzumab evolved from a solution to a lyophilized DP. The summary of the formulation changes are provided in the table below.

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3.2.P.5.2 Analytical Procedures

The analytical methods used for release of the elotuzumab DP [redacted] (b) (4) as used for the DS release, [redacted] (b) (4) The drug content assay procedure is discussed together with validation study in Section 3.2.P.5.3 below. Compendial methods were used to measure [redacted] (b) (4)

Reviewer comment: *We defer to the DMA reviewer regarding the adequacy of the endotoxin and sterility assays.*

3.2.P.5.3 Validation of Analytical Procedures

See Section 3.2.S.4.3 for the discussion of the validation of the cell-based potency assay, (b) (4) [redacted], CEX, protein concentration and the SLAMF7 binding ELISA.

Drug Content Method Validation

This assay is used to determine the total drug content in each elotuzumab lyophilized DP batch.

[redacted] (b) (4)

Reviewer comment: *The data provided demonstrate that the drug content method is valid for its intended purpose.*

[redacted] (b) (4). *We defer to DMA to address the adequacy of the endotoxin and the sterility testing method validation.*

3.2.P.5.4 Batch Analyses

Batch analysis results were provided for the elotuzumab DP lots [redacted] (b) (4)

Reviewer comment: *The data provided in the Batch Analysis for the DP demonstrate a well-controlled manufacturing process.* [redacted] (b) (4) (b) (4)

3.2.P.5.5 Characterization of Impurities

The DP process does not introduce any [redacted] (b) (4) impurities into the product. See Section 3.2.S.3.2 for a discussion of the potential impurities in elotuzumab DS.

3.2.P.5.6 Justification of Specifications

[redacted] (b) (4)

(b) (4)

[redacted]

Color and Appearance of Lyophilisate

White to off-white whole cake or white to off-white fragmented cake

Color and appearance are visually inspected using the European Pharmacopeia procedure to describe the color and appearance. The acceptance criteria are based on data obtained from GMP batches at release and on stability stored at 2-8°C.

Reviewer comment: *This is acceptable.*

Appearance of Constituted Solution
Color: Colorless to slightly yellow
Visible Particulates: Liquid, essentially free of visible particles
Clarity: Clear to (b) (4) *opalescent*

The elotuzumab constituted solution is visually examined for color using a European Pharmacopeia (Ph. Eur. 2.2.2) procedure to describe the color of the solution using Ph. Eur. color standards. The elotuzumab constituted solution is visually examined for the presence of particles (particulates) using the European Pharmacopeia (Ph. Eur. 2.9.20) procedure. The elotuzumab constituted solution is visually examined for general clarity using the European Pharmacopeia (Ph.Eur. 2.2.1) procedure to describe the clarity (degree of opalescence) using Eur. Opalescence Reference Solutions I-IV.

The results for appearance of all the DP batches tested to date for release and for long-term stability samples stored at 2°C to 8°C have been colorless to slightly yellow, essentially free of particulates and clear to (b) (4) opalescent, (b) (4)

Reviewer comment: *The acceptance criteria for appearance of the elotuzumab DP are acceptable.*

Drug Content
400 mg/vial: (b) (4)
300 mg/vial:

To compensate for the potential (b) (4) the (b) (4) fill for the 400 mg/vial is (b) (4) mg/vial and the target for the 300 mg/vial is (b) (4) mg/vial.

Statistical analysis was performed on the content of the 400 mg/vial and 300 mg/vial presentations and was provided in Table 3.2.P.5.6.10-1 (not shown). (b) (4)

Reviewer comment: *The acceptance criteria are acceptable based on the data provided* (b) (4)

Particulate Matter

(b) (4)

(b) (4)

[redacted]

Reviewer comment: *This is acceptable.*

3.2.P.6 Reference Standards or Materials

The same reference standard is used for both elotuzumab DP and DS. See Section 3.2.S.5 for detailed information on the RS.

3.2.P.7 Container Closure System

The same container closure is used for both elotuzumab DP presentations. Elotuzumab for Injection, 300 mg/Vial, and Elotuzumab for Injection, 400 mg/Vial, are packaged in a 20 cc Type I (b) (4) glass vial and sealed with a 20-mm gray (b) (4) stopper and aluminum (b) (4) seal with (b) (4). For the 300 mg/vial presentation, the (b) (4) seal button color is ivory, and for the 400 mg/vial presentation, it is blue. The drug products are packaged in a paperboard folding carton.

3.2.P.7.1.1 Packaging Components Specifications

The specifications for the 20- c Type I (b) (4) glass vial are shown in the following table.

Table 3.2.P.7.1.1.1-1: Testing Standard for 20-cc Type I (b) (4) Glass Vial

(b) (4) Packaging Component	Test	Analytical Procedure	Critical Attribute	Acceptance Criteria
Vial - 20-cc	Description by visual examination	Visual Examination	Style Color	Round Tubing (b) (4)
	Identification	Conforms to United States Pharmacopeia and European Pharmacopoeia	Material	Type I Glass
	Dimensional examination	Use suitable calipers, gauges or optical comparators to assess dimensions	Dimensions: - Overall height - External body diameter - Flange outside diameter	 68.0 ± 0.5 mm 26.75 ± 0.25 mm 19.94 ± 0.25 mm

The specifications for the 20 mm (b) (4) gray (b) (4) lyophilization stopper (b) (4) (b) (4)

(b) (4)

[redacted]

3.2.P.8 Stability

Registrational studies for stability are being conducted with six batches of elotuzumab DP, three for the 400 mg/vial presentation and three for the 300 mg/vial presentation. Six additional 400 mg/vial batches and one additional 300 mg/vial batch are being assessed to support the stability of the DP. All the DP batches on stability except Batch STAB15Feb13 were manufactured at BMS-Manati. All the stability samples are stored in the commercial [redacted] (b) (4) package components and assessed using the proposed specifications. Stability samples are stored at the [redacted] (b) (4) BMS-New Brunswick.

(b) (4)

[redacted]

There are real-time stability data for 400 mg/vial presentation batches stored at the recommended storage temperature of 2-8°C for 36 months [redacted] (b) (4), 18 months [redacted] (b) (4) and 12 months [redacted] (b) (4). All DP stability samples were also stored for up to 6 months at 25°C/60%RH (accelerated). Seven lots were stored for up to three months at 40°C/75%RH (stressed).

For the 300 mg/vial presentation stability data are available for long term storage conditions through 9 months (one batch) and 6 months (three batches), for accelerated storage conditions through 3-6 months (four batches) and for stressed conditions through up to 6 months (three batches).

The long-term and accelerated protocols for the 400 mg/vial registration batches are provided in the tables below; the 300 mg/vial protocols are similar.

(b) (4)

Reviewer comment: *Potency testing using the cell based assay was performed retrospectively for the 400 mg/vail presentation until the 18 month time points. No additional cell based potency tests are indicated for time points post 18 months. Considering that the cell based potency assay is included in the post-approval stability commitment, and the stability protocols initiated after the implementation of the assay will provide more applicable data, this approach is acceptable.*

Information on the batches used in the stability studies were provided in Table 3.2.P.8.1.2-1 (not shown). For the 400 mg/ vial, three DP batches OK66509, 1F64992 and 1A67291 were put on stability (long-term and accelerated) prior to initiation of the registration batches and will be assessed up to 60 months. The same is true for 300 mg/vial batch 3H65098.

The stability data are summarized as follows:
Long-term stability (2-8°C)

(b) (4)

- Lots 2K71727, 2K72803 and 2K72604 of the 400 mg/vial presentation have been tested using the cell based-bioassay. All were within the acceptance criteria through 18 months.
- There were no overall trends in size variants over the course of the study. (b) (4) These samples were still within acceptance criteria.

Accelerated storage (25°C/60%RH)

- No notable trends or changes were observed in appearance, concentration, pH, constitution time, water content, cell-based potency, SLAMF7 binding, (b) (4) particulates or charged profile for either presentation.
- There was (b) (4) but all samples were within the acceptance criteria for up to 6 months for the 400 mg/vial and 300 mg/vial.

Stressed storage resulted in (b) (4) These results further support that the (b) (4) assays are stability indicating.

There were no notable differences between the upright and inverted storage conditions.

Reviewer Comment: *Due to the limited amount of stability data provided for the 300 mg/vial presentations and the lack of clinical experience, the sponsor was asked (in the IR on 9/25/2015) to provide a stability update on this presentation. The sponsor responded on 10/8/2015 with 12 month time points for long-term storage for the 300 mg/vial presentation. The data demonstrate no trends or changes in the elotuzumab DP for up to 12 months.*

Based on the adequate long term 36 months stability data obtained from the three DP lots derived from (b) (4), a 36-month shelf life at 2-8°C was proposed for both elotuzumab DP presentations.

Reviewer Comment: *The proposed shelf life is acceptable,* (b) (4)

Photostability studies were performed in accordance with ICH Q1B for both the 300 mg/vial and the 400 mg/vial presentations (b) (4) (b) (4)

To determine the effects of frozen storage on the elotuzumab DP, the 300mg/vial and 400 mg/vial DP samples were [redacted] (b) (4)

Freeze/thaw studies were performed on the elotuzumab DP [redacted] (b) (4) (b) (4)

3.2.P.8.2 Post-approval Stability Protocol and Commitment

[redacted] (b) (4)

Table 3.2.P.8.2-1: Post-Approval Stability Protocol for Elotuzumab for Injection, 300 mg/vial and 400 mg/vial

[redacted] (b) (4)

Table 3.2.P.8.2-1: Post-Approval Stability Protocol for Elotuzumab for Injection, 300 mg/vial and 400 mg/vial

(b) (4)

[redacted]

Table 3.2.P.8.2-1: Post-Approval Stability Protocol for Elotuzumab for Injection, 300 mg/vial and 400 mg/vial

(b) (4)

Reviewer comment: *The post-approval stability commitment and protocols are acceptable.*

(b) (4)

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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:	10/28/2015
To:	Administrative File, STN 761035/0
From:	Maria Jose Lopez Barragan, PhD., Reviewer, CDER/OPQ/OPF/DMA/BIV
Through:	Patricia F. Hughes, PhD., Acting Branch Chief, CDER/OPQ/OPF/DMA/BIV
Subject:	New Biologic License Application (BLA)
US License:	1713
Applicant:	Bristol-Myers Squibb Company
Facilities:	Bristol-Myers Squibb Company; 6000 Thompson Road, East Syracuse, NY; FEI: 1317461 (Drug Substance Manufacture)
Product:	Elotuzumab (Empliciti®)
Dosage:	400 mg and 300 mg/vial of lyophilized powder for intravenous injection
Indication:	Advanced Multiple Myeloma
Due date:	11/30/2015

Recommendation for approvability: The drug substance part of BLA 761035 is recommended for approval from a microbial control and microbiology product quality perspective with one post-marketing commitment:

1. The sponsor has committed to [redacted] (b) (4)

Summary

Bristol-Myers Squibb Company has submitted BLA 761035 to obtain approval of elotuzumab. Elotuzumab is a humanized recombinant anti-CS1 monoclonal IgG1 antibody for treatment of [redacted] (b) (4) multiple myeloma.

BLA 761035 was submitted in eCTD format as a rolling BLA. The original application was submitted on 05/27/2015 and contained module 1, module 3 and the related quality summary document in module 2.3; remaining module 2 and modules 4 and 5 were submitted on 06/29/2015 in amendment 0001. This review contains the assessment of elotuzumab bulk drug substance from a microbiological quality perspective.

Drug Substance Quality Microbiology Information Reviewed

IR Submission Date	Description	eCTD Sequence	Date
Not applicable	Original BLA	0000	05/27/2015
08/21/2015	Amendment	0010	09/04/2015
09/03/2015	Amendment	0016	09/14/2015
09/24/2015	Amendment	0023	10/01/2015

Review Narrative

S. DRUG SUBSTANCE

S.1. General Information

Elotuzumab is a humanized recombinant monoclonal IgG antibody targeted against SLAMF7 (CS1), a glycoprotein highly expressed in myeloma cells. Elotuzumab antibody has a theoretical mass of 148.1 kDa [redacted] (b) (4)

The description is satisfactory

S.2. Manufacture

S.2.1. Manufacture(s)

The following facilities are involved in the manufacture, release testing, and stability testing of Elotuzumab drug substance:

Site	Responsibilities
Bristol-Myers Squibb Company, 6000 Thompson Road, East Syracuse, NY 13057, USA FEI: 1317461	• Drug substance manufacture • DS release testing • Storage and stability testing
Bristol-Myers Squibb Company, 38 Jackson Road, Devens, MA 01434 USA FEI: 3008455069	• DS release testing • Storage and stability testing

[redacted] (b) (4)

S.2.2. Description of Manufacturing Process and Process Controls

[redacted] (b) (4)

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(b) (4)

Satisfactory

S.4.4. Batch Analysis

Results from over 90 lots (b) (4) of elotuzumab drug substance were used to develop DS specifications. Data for bioburden and endotoxin are shown in Table 3.2.S.4.4.2-5 submitted by sponsor and all batches showed bioburden levels below (b) (4) and endotoxin < (b) (4) (b) (4) commercial retained batches (b) (4) manufactured in BMS-Syracuse (b) (4) were further tested using the (b) (4)t endotoxin test method and in all cases endotoxin levels were < (b) (4)

> *Reviewer's comment: (b) (4) was not qualified for endotoxin testing in elotuzumab DS (b) (4) therefore, data obtained using this technique should not be considered. Endotoxin was further monitored in (b) (4) batches using the qualified (b) (4) technique and in all cases endotoxin remained below (b) (4).*

Satisfactory

S.4.5. Justification of Specifications

Bioburden Test Specification

The proposed bioburden acceptance criterion for elotuzumab is ≤ (b) (4) and all lots met specifications at release and stability time points. Elotuzumab DS is stored at (b) (4)

Endotoxin Test Specification

The proposed acceptance criterion for endotoxin is ≤ (b) (4) of elotuzumab (b) (4) Considering the highest proposed commercial dose (10 mg/kg) the maximum allowed endotoxin contribution would be (b) (4) The maximum dose used in clinical trials was (b) (4) in which the maximum contribution of endotoxin would be (b) (4)

> *Reviewer's comments: bioburden specifications are adequate based on recommended storage conditions (b) (4) The endotoxin DS specification is adequate (b) (4) . The maximum endotoxin contribution for the recommended commercial elotuzumab dose (10 mg/kg) is (b) (4) providing a (b) (4) safety margin over the maximum recommended endotoxin limit of (b) (4)*

Satisfactory

S.5. Reference Standards

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

S.6. Container Closure System

(b) (4)

[redacted]

Satisfactory

S.7. Stability

S.7.1. Stability Summary and Conclusions

Stability studies were performed in (b) (4) registrational commercial DS batches ((b) (4) at manufacture scale produced according to (b) (4) (b) (4) additional batches (b) (4) were used for further stability studies. All samples under study were stored in (b) (4) and all were manufactured in BMS-East Syracuse at the intended commercial scale.

All stability studies have been performed in accordance with ICH Q1A (R2) and Q5C. Additional stability studies under stress conditions of (b) (4) were conducted on (b) (4) DS batches (b) (4)

(b) (4)

Reviewer's comments: photo stability studies are deferred to OBP.

S.7.2. Post-Approval Stability Protocol and Stability Commitment

The sponsor commits to (b) (4)

(b) (4)

S.7.3. Stability Data

Reviewer's comment: no microbial attributes (bioburden or endotoxin) data was monitored during the stability studies. Microbial quality data is not required during stability studies for drug substance (b) (4)

Satisfactory

cGMP Status

Refer to Panorama for cGMP status of the relevant facilities.

Conclusion

I. The Drug Substance section of this BLA as amended was reviewed from a microbial control and microbiology product quality perspective and it is recommended for approval.

II. Non-microbial information and data from the Drug Substance section of this BLA should be also reviewed by OBP.

III. A pre-license inspection was conducted at BMS-East Syracuse in October 5th to 9th 2015 by OPF/DMA (Patricia F. Hughes and Maria Jose Lopez Barragan), OBP (Rachel Novak) and DIA (Ruth Moore).

FDA Information Request for STN 761035/0 submitted on 08/21/2015. Sponsor responses in amendment 0010 (09/04/2015)

1. Description of the Manufacturing Process and Process Controls (Section 3.2.S.2.2)

(b) (4)

2. Process Validation and/or Evaluation (Section 3.2.S.2.5)

(b) (4)

(b) (4)

3. Analytical Procedures (Section 3.2.S.4.2)

   a. Provide a description of the bioburden and endotoxin testing methods for DS release samples.

FDA Information Request for STN 761035/0 submitted on 09/03/2015. Sponsor responses in amendment 0016 (09/14/2015)

(b) (4)

FDA Information Request for STN 761035/0 submitted on 09/24/2015. Sponsor responses in amendment 0023 (10/01/2015)

(b) (4)

Maria Jose Lopez Barragan, Primary Reviewer

Patricia F. Hughes, Acting Branch Chief

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

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Natalia Pripuzova, Ph.D.
ACTING BRANCH CHIEF: Patricia Hughes, Ph.D.

Date:	27 October, 2015
BLA:	761035
Applicant:	Bristol-Myers Squibb Company
US License Number:	1713
Submission Reviewed:	Original BLA (Breakthrough Therapy Designation)
Product:	Elotuzumab (Humanized anti-CS1 Monoclonal IgG1 antibody)
Indication:	(b) (4) Multiple Myeloma
Dosage Form:	400 mg/vial and 300 mg/vial, lyophilized powder supplied in vials.
Manufacturing Sites:	Bristol-Myers Squibb Holdings Pharma, Ltd. Liability Company, Manati, PR, USA (FEI: 2650089)
FDA Receipt Date:	29 June 2015
Action Date:	1 December 2015

Approvability Recommendation: The BLA was reviewed from drug product quality microbiology prospective. No issues were identified that preclude approval. However, the sponsor has been asked to conduct the following post-marketing commitment (PMC): perform a repeat microbial retention study for the sterilizing filter validation using a suitable surrogate solution, modified process, modified formulation, or a reduced exposure time for the challenge organism. Sponsor has agreed to complete these studies by April 2016.The PMC agreement will be documented in an addendum to this review memo.

Summary: BLA761035, Module 3, "Quality", was submitted in electronic format on 27-May-2015 as a part of the rolling submission to license elotuzumab for treatment of patients with (b) (4) multiple myeloma. Elotuzumab is designated as breakthrough therapy. Elotuzumab is a humanized anti-CS1 monoclonal IgG1 antibody targeting SLAMF7, glycoprotein expressed on myeloma and Natural Killer (NK) cells. The single-(b) (4) lyophilized drug product (DP) is presented at the two strengths of 300 mg/vial and 400 mg/vial and is administered intravenously by infusion after reconstitution with water for injection and dilution with normal saline or 5% dextrose in water. The drug substance (DS) is manufactured and quality control (QC) tested at the Bristol-Myers Squibb facility located in East Syracuse, New York, USA. The DP is manufactured and QC tested at the Bristol-Myers Squibb facility located in Manati, PR.

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	27 May 2015	Original BLA
0005	12 August 2015	Response to IR
0007	21 August 2015	Response to IR
0016	14 September 2015	Response to IR
0029	22 October 2015	Response to IR

Drug Product Review

Module 3.2

P.1 Description and Composition of the Drug Product

Elotuzumab for injection is a non-pyrogenic lyophilized powder that is white to off-white whole or fragmented cake that is provided in 2 strengths. Elotuzumab for Injection, 400 mg/vial, and Elotuzumab for Injection, 300 mg/vial, are single-(b) (4) sterile lyophilized products. Elotuzumab for injection is reconstituted with sterile water for injection (SWFI) to obtain a solution with a protein concentration of 25 mg/mL. Prior to administration, the reconstituted solution is diluted with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP (b) (4) The composition of DP is described in the Table 3.2.P.1-1 below copied from the submission.

Table 3.2.P.1-1: Composition of Elotuzumab for Injection, 400 mg/Vial and Elotuzumab for Injection, 300 mg/Vial

Component	Quality Standard	Function	Quantity per Vial[a] 400 mg	Quantity per Vial[a] 300 mg
Elotuzumab (BMS-901608)	BMS Specification[b]	Active ingredient	(b) (4) mg	(b) (4) mg
Sodium Citrate[c]	USP. Ph.Eur., JP	(b) (4)	21.5 mg	16.6 mg
Citric Acid Monohydrate	USP. Ph.Eur., JP		3.17 mg	2.44 mg
Sucrose	NF. Ph.Eur., JP		660 mg	510 mg
Polysorbate 80	NF, Ph.Eur., JP		4.40 mg	3.40 mg
Water for Injection[d]	USP. Ph.Eur.			(b) (4)
			—	—

(b) (4)

***Reviewer's comment**: This information is provided in this review memo for reference. Sponsor does not propose storage of the reconstituted DP (with concentration of 25 mg/mL) after initial reconstitution of the lyophilized DP with SWFI. For details please refer to **Section P.2.5**, Microbiology Data in Support of the Proposed Label Storage Statement.*

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container Closure Integrity

The results of the container closure integrity test (CCIT) for Elotuzumab for Injection, 400 mg/vial are applicable to both DP presentations. CCIT of the (b) (4) packaging components was performed (b) (4)

***Reviewer's question:** Please provide data on the results of the CCIT (study date and run number) conducted to qualify the (b) (4) controls (both positive and negative). Please provide the worst-case (b) (4) process parameters validated with CCIT.*

Response Summary (0005):

(b) (4)

Microbiology Data in Support of the Proposed Label Storage Statement

In order to simulate potential contamination during infusion preparation elotuzumab infusions were inoculated with 7 challenge microorganisms (listed in Table 3.2.P.2.5.2-1 copied below from the submission). (b) (4)

(b) (4)

Table 3.2.P.2.5.2-1: Challenge Microorganisms and Inoculum Verification of the Microorganisms Used for the 2°- 8°C (b) (4)

(b) (4)

(b) (4)

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The facilities involved in the manufacture, release testing, release, packaging, labeling, and market-life stability testing of DP are provided in Table 3.2.P.3.1-1 below.

Table 3.2.P.3.1-1: Site and Responsibilities

Site	Responsibility
Bristol-Myers Squibb Holdings Pharma, Ltd. Liability Company Road 686, Km 2.3 Bo. Tierras Nuevas Manati, Puerto Rico 00674 USA	Manufacture, release and stability testing (b) (4) [redacted], release, (b) (4) packaging, and labeling
(b) (4) [redacted]	
Bristol-Myers Squibb Company 38 Jackson Road Devens, Massachusetts 01434 USA	Release and stability testing (b) (4) [redacted]
(b) (4) [redacted]	

P.3.2 Batch Formula

The batch size for the commercial manufacture of DP may vary within the proposed range outlined in Table 3.2.P.3.2-1, copied below from the submission.

Table 3.2.P.3.2-1: Proposed Commerical Batch Sizes for the Manufacture of Elotuzumab for Injection, 300 mg/Vial and 400 mg/Vial for BMS-Manati

Product	Proposed Commercial Batch Size[a]			
	Minimum		Maximum	
	Weight (kg)	Theoretical Number of Vials[b]	Weight (kg)	Theoretical Number of Vials[b]
Elotuzumab for Injection, 300 mg/Vial	117	16,544	156	22,058
Elotuzumab for Injection, 400 mg/Vial	117	12,784	156	17,045

[a] Validated batch sizes

(b) (4) [redacted]

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4) [redacted]

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(b) (4)

Reviewer's comment: *The method validation for CCIT reviewed here was described under Section **3.2.P.8.3.7**, Analytical Procedures and in amendment 0004. The results demonstrated that the method is capable of consistently detecting breaches of* (b) (4)

SATISFACTORY

P.5.4 Batch Analysis

A total of 2 batches (b) (4) DP were produced for clinical and stability studies during the period of (b) (4). A total of (b) (4) batches of 400 mg/vial and (b) (4) batch of 300 mg/vial of DP have been manufactured at BMS-Manati for clinical and stability studies during the period of (b) (4) (b) (4) batches of 300 mg/vial and (b) (4) batches of 400 mg/vial of DP have been manufactured at BMS-Manati for process validation and stability studies during the period of (b) (4). All of the lots met release specifications for sterility. The endotoxin levels for the total of (b) (4) batches of DP produced ranged from (b) (4)

SATISFACTORY

P.5.6 Justification of Specifications

The compendial method to evaluate DP sterility complies with USP <71> requirements. The endotoxin specification for commercial DP is ≤ (b) (4) The maximum proposed commercial dose for DP is 10 mg/kg. The total potential maximum endotoxin is (b) (4) Therefore the endotoxin contribution from the DP is not more than (b) (4)

The lyophilized DP is reconstituted in WFI and then further diluted with either 0.9% Sodium Chloride Injection or Dextrose 5% Water (D5W). The final DP infusion concentration can range from (b) (4) and the worst case for administration of endotoxin from the infusion fluid would occur (b) (4) as it would contain the highest volume of infusion fluid. The maximum allowable volumes of infusion fluids are (b) (4) of patient weight and the infusion diluents have endotoxin limits of not more than (b) (4)

The total potential maximum endotoxin administered from DP infusion at 10 mg/kg is:
Maximum endotoxin <u>from infusion fluid</u>: (b)
Maximum total endotoxin (b) (4)
<u>The total</u> Maximum endotoxin from infused elotuzumab dose is (b) (4)

Reviewer's comment: *The total maximum endotoxin from the infused elotuzumab dose is* (b) (4) (b) (4)

(b) (4)

SATISFACTORY

P.7 Container Closure System

The DP container closure system and corresponding DMF reference are shown in the Tables 3.2.P.7.1-1 and 3.2.P.7.3-1 copied below.
For the 300 mg/vial presentation, the (b) (4) seal button color is ivory, and for the 400 mg/vial presentation, it is blue. The DP is packaged in a paperboard folding carton.
The glass vials are manufactured f (b) (4) (b) (4)

Table 3.2.P.7.1-1: (b) (4) Packaging Components for Elotuzumab for Injection

Component	Description
Vial	20-cc Type I (b) (4) glass vial (b) (4)
Stopper	20-mm gray (b) (4) lyophilization stopper
(b) (4) Seal	20-mm aluminum crimp seal with (b) (4) button Ivory (b) (4) button for Elotuzumab for Injection, 300 mg/Vial Blue (b) (4) button for Elotuzumab for Injection, 400 mg/Vial

Table 3.2.P.7.3-1: Drug Master File References

Component	Vendor	DMF Number
20-cc Type I (b) (4) glass vial	(b) (4)	
20-cc Type I (b) (4) glass vial		
20 mm (b) (4) gray (b) (4) lyophilization stopper with (b) (4)		

SATISFACTORY

P.8 Stability

P.8.2 Post-Approval Stability Commitment

Microbiological post-approval stability tests include Bacterial Endotoxin and CCIT. They are (b) (4)

P.8.3 Stability Data

The stability studies on DP, 300 mg/vial and 400 mg/vial include long-term storage conditions (5°C for up to 36 months), accelerated conditions (25°C/60% RH for up to 6 months) and stress conditions (40°/75% RH). Stability samples were stored in the upright or inverted positions. Registrational stability studies are being conducted on six batches of DP, 400 mg/Vial, and three batches of DP, 300 mg/Vial and have demonstrated that the DP is stable at 5°C. In addition, stability studies are being conducted on six more batches of DP, 400 mg/Vial, and on one more batch of DP, 300 mg/Vial. Real-time stability data are available for DP, 400 mg/Vial, stored at the 5°C for 12 months (two batches), 18 months (three batches), 24 months (one batch), 36 months (three batches). Based on up to 36 months of real-time data from ongoing stability studies at the long-term condition of 5°C, a shelf-life of 36 months is proposed for DP, 300 and 400 mg/Vial.

Reviewer's comments: *CCIT results are available for initial, 12, 24, and 36 months; Sterility and Endotoxin tests results are available only for initial time point of the long-term storage at 5°C. There have been no out of specification results. The reminder of the stability data should be reviewed by OBP.*

Module 1

Labeling Review: Prescribing Information

The prescribing information indicates that lyophilized DP reconstituted in WFI. Once the reconstitution is completed 16 mL from 400 mg vial and 12 mL from 300 mg vial used to further dilute DP with (b) (4) either 0.9% Sodium Chloride Injection or Dextrose 5% Water (D5W). The DP infusion must be completed within 24 hours of reconstitution of the DP lyophilized powder. If not used immediately, the infusion solution may be stored under refrigeration conditions: 2°C to 8°C (36°F-46°F) and protected from light for up to 24 hours (a maximum of 8 hours of the total 24 hours can be at room temperature: 20°C to 25°C [68°F-77°F] and room light).

Reviewer's comment: *Data on the potential contamination during infusion preparation of elotuzumab infusions in 0.9% sodium chloride injection (NS) and 5% dextrose injection (D5W) in infusion bags were described and reviewed under* ***Section P.2.5.2,*** *Microbiology Data in Support of the Proposed Label Storage Statement. Sponsor does not propose storage of the reconstituted DP (with concentration of 25 mg/mL) after initial reconstitution of the lyophilized DP with SWFI. Enough information is provided on the growth promotion of the reconstituted and diluted DP to support labeling.*

SATISFACTORY

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.

DP Quality Microbiology Information Requests Sent

27 July 2015 – response in amendment 0005

Section 3.2.P.2.5. Container Closure Integrity

1) Please provide summary CCIT results (study date and run number) obtained from the qualification of the (b) (4) and describe the (b) (4) controls (both positive and negative). Please provide the worst-case (b) (4) process parameters validated with the CCIT.

Section 3.2.P.2.5.3. Rabbit Pyrogen Test

1) Please provide justification for the administered dose based on the maximum dose of DP per day per kg of body weight of a human.

2) Please submit the protocol report for Rabbit Pyrogen Test. The report should include the following: number of rabbits used for testing of each lot and rabbit temperature rise data.

Section 3.2.P.3.4.1. (b) (4) Test Methods: Bioburden

Please provide the sample volume for the bioburden test performed for the bulk DP (b) (4) (b) (4)

Section 3.2.P.3.5.2.4. Validation of (b) (4)

1) There is no information provided in the submission about the (b) (4)

2) Please provide the (b) (4) validation report, containing the following information: the viability results that demonstrated that the DP has a bactericidal effect on (b) (4)
It appears that the microbial retention study was conducted by (b) (4) We recommend that the challenge study (b) (4)

Section 3.2.P.3.5.2.5. Process Simulation and Media Fills

Please provide the following additional information regarding the Media Fill runs:

(b) (4)

Section 3.2.P.5.3. Validation of Analytical Procedures
Please provide CCIT method validation data.

12 August 2015 – response in amendment 0007

Section 3.2.P.3.5.2.4. Validation of (b) (4)

(b) (4)

03 September 2015 – response in amendment 0016

Appendix 3.2.A.1.4.2. Environmental Monitoring of the Manufacturing Area.

The description of the environmental monitoring program should be moved from **Appendix 3.2.A.1.4.2** to **Section 3.2.P.3.3**, *Description of the Manufacturing Process and Process Controls.*

Section 3.2.P.3.5.2.4. Validation of Sterile Filtration
Your commitment to provide a summary of the revised microbial retention filter validation study conducted with a modified process, a modified formulation, or a reduced exposure time for the challenged organism by April 2016 is acceptable. Please also submit the study protocol for the Agency review prior to conducting the study. Please provide a timeframe for providing this proposed protocol.

09 October 2015 – response in amendment 0029

1) Some of the information related to microbial control and (b) (4) filling provided in **Section 3.2.P.3.5** should also be provided in ***Section 3.2.P.3.3*** and/or ***3.2.P.3.4*** of the submission. Please update the appropriate sections with the following information:

(b) (4)

Section 3.2.P.3.5. Process validation and/or evaluation

(b) (4)

Section 3.2.P.8.3.7, Analytical Procedures

6) The positive controls for container closure integrity testing (CCIT) are prepared by (b) (4)

(b) (4)

NATALIA PRIPUZOVA
(REVIEWER)
10/27/2015

COLLEEN THOMAS
(ACTING QUALITY ASSESSMENT LEAD)
10/27/2015

PATRICIA HUGHES (ACTING BRANCH CHIEF)
10/27/2015

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: 10/27/2015
To: Administrative File, STN 761035/0
From: Ruth Moore, Ph.D., Chemist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: Pending
Applicant: Bristol-Myers Squibb (BMS) Company
Mfg Facility: Drug Substance: Bristol-Myers Squibb Corporation Inc., Syracuse, NY
FEI 1317461
Drug Product: Bristol-Myers Squibb Holdings Pharma Limited Liability Company, Manati, PR
FEI 2650089
Product: Elotuzumab for Injection
Dosage: 300 mg/vial and 400 mg/vial for intravenous administration by infusion after reconstitution. Sterile lyophilized product provided in single (b) (4) glass vials.
Indication: Treatment for Multiple Myeloma
Due Date: 11/02/2015

RECOMMENDATION: Final recommendation on approval of this submission from a facility review perspective is pending the review of the EIR for the Pre-License Inspection (PLI) of the BMS East Syracuse facility.

SUMMARY

The subject BLA proposes manufacture of Elotuzumab DS and DP, respectively, at Bristol-Myers Squibb (BMS) East Syracuse, NY facility, (FEI 1317461), and BMS Pharma Limited Liability Company, Manati, PR (FEI 2650089). Cell bank manufacture and testing will occur at (b) (4). Drug substance release and stability testing will be performed at BMS East Syracuse, and at (b) (4) is performed by BMS, Devens, MA (FEI 3008455069). The drug product is packaged at the BMS Manati, PR site.

Elotuzumab (Empliciti™) is a humanized IgG1 monoclonal antibody produced in NSO cells. It is proposed for the treatment of patients with multiple myeloma. Elotuzumab drug product is manufactured as a lyophilized powder, and is presented at two strengths of 300 and 400 mg/vial.

The drug is administered intravenously by infusion after reconstitution with water for injection and dilution with normal saline or 5% dextrose in water.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

- **3.2.S.2.1 DS Manufacturers.**
  The sites proposed for Elotuzumab DS manufacture, cell banking operations, and testing are presented below in Table 1.

TABLE 1. Proposed Sites for Elotuzumab DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
Bristol-Myers Squibb Company	6000 Thompson Rd East Syracuse, NY 13057	1317461	Elotuzumab DS manufacture, storage, release testing and stability testing (b) (4) (b) (4)
Bristol-Myers Squibb Company	36 Jackson Rd Devens, MA 01434	3008455069	DS testing - (b) (4) (b) (4) (b) (4)

***Reviewer Comment 1**: The facilities for manufacture of Elotuzumab DS are adequately described.*

- **Prior Inspection History for DS Manufacturing and Testing Sites**

(b) (4)

(b) (4)

- Bristol-Myers Squibb Devens, MA (FEI 3008455069) Elotuzumab DS Testing Site Inspection Conducted 6/25/15. PAI Coverage under (b) (4) and GMP coverage under (b) (4). No FDA Form 483 was issued. The inspection was classified NAI.

(b) (4)

- **Current Prior Approval Inspection Decisions**
  BMS- Syracuse (FEI 1317461), Elotuzumab DS Manufacturing and Testing Site. Inspection conducted 10/5/205 to 10/9/2015 by CDER-OPF and CDER-OBP.
  A Pre-license inspection (PLI) of Bristol Myers-Squibb Company in East Syracuse, NY was completed in support of two breakthrough therapies, BLA 761035/0 for Elotuzumab (b) (4) The inspection was conducted in accordance with CP 7356.002M and ICH Q7. A comprehensive review of facilities, utilities, equipment, processes and procedures was conducted to evaluate product quality, compliance to commitments in the BLA and compliance to CGMPs. (b) (4) No observations were made and no Form FDA 483 was presented to BMS management at the conclusion of the inspection on October 9, 2015.

(b) (4)

A final recommendation on the acceptability of the BMS manufacturing and testing facilities in East Syracuse for manufacture of Elotuzumab DS under BLA 761035/0 is pending.

***Reviewer Comment 2**: The production and testing facilities associated with the manufacture of Elotuzumab DS are acceptable from a facilities assessment standpoint.*

- **3.2.S.2.2. Overview of Elotuzumab DS Manufacturing Operations Conducted at BMS.**
  Elotuzumab is produced from cell culture using an NS0 mouse myeloma-based cell line. The Elotuzumab manufacturing process is (b) (4)

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(b) (4)

[redacted]

DRUG PRODUCT FACILITIES

- **3.2.P.3.1. DP Manufacturers.**
  The sites proposed for Elotuzumab DP manufacture, testing, packaging, and labeling are presented below in Table 3.

TABLE 3. Sites Proposed for Elotuzumab Drug Product Manufacture and Testing

Site Name	Address	FEI Number	Responsibilities
Bristol-Myers Squibb Holdings Pharma, Ltd. Liability Company	Road 686 KM 2.3 BO Tierras Nuevas, Manati PR 00674	2650089	Elotuzumab DP manufacture; release testing and stability testing (b) (4) (b) (4) (b) (4) packaging and labeling
[redacted]			(b) (4)
Bristol-Myers Squibb Company	38 Jackson Road Devens, Massachusetts USA 01434	3008455069	DP release and stability testing (b) (4) (b) (4)

- **Prior Inspection History for DP Manufacturing and Testing Sites**
  - Bristol-Myers Squibb Holdings Pharma Ltd. Liability Company (FEI 2650089) Elotuzumab DP Manufacturing, Testing, Packaging and Labeling Site.
    - Inspection Conducted 5/05/2014 to 5/16/2014 by SJN-DO. Inspection coverage was given in accordance with CP #7356.002, Drug Process Inspection, CP #7356.002A, Sterile Drug Process Inspection – Small Volume Parenteral, and CP #7356M, Inspection of Licensed Therapeutic Drug Products. The inspection was classified NAI, and included coverage of profiles SVL, SVS and (b) (4)
    - Inspection Conducted 01/09 to 01/19/2012 by SJN-DO. Inspection coverage was given in accordance with CP #7356.002, Drug Process Inspection; CP #7356.002A, Sterile Drug Process Inspection – Small Volume Parenteral; and CP #7356.021, Drug Quality Reporting System NDA Field Alert Reporting. (b) (4) .The inspection verified that the firm implemented corrective actions to previous-inspection listed observations, and concluded that there were no other objectionable conditions. No FDA-483 was issued at the conclusion of the inspection; the inspection was classified NAI.

  - Bristol-Myers Squibb Devens, MA (FEI 3008455069) Elotuzumab DS Testing Site Inspection Conducted 6/25/15. PAI Coverage under (b) (4) and GMP coverage under (b) (4). No FDA Form 483 was issued. The inspection was classified NAI.

(b) (4)

- **Current Prior Approval Inspection Decisions**

  A PAI waiver was recommended for the BMS Manati Drug Product Manufacturing Facility for BLA 761035/0. The approved inspection waver memo is on file.

  The Elotuzumab drug product will be manufactured in the (b) (4) (b) (4) at BMS-Manati. The proposed commercial manufacturing scheme for Elotuzumab is (b) (4) The facility was inspected by SJN-DO and CDER-OC from 5/05/2014–5/16/2014, and classified NAI. CGMP coverage was provided for SVS, SVL and (b) (4) profiles during the inspection, and there were no concerns related to manufacture of sterile product by (b) (4) methods at the facility. Facility design, utilities, equipment, cleaning, sanitization, (b) (4) and other procedures for prevention of contamination and cross-contamination during manufacture of Elotuzumab DP described in the submission were reviewed and found to be adequate.

Reviewer Comment 11. *The production and testing facilities associated with the manufacture of Elotuzumab DP are acceptable from a facilities assessment standpoint.*

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(b) (4)

***Reviewer Comment 19**: The general description of other products manufactured at BMS Manati is acceptable.*

CONCLUSION

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for the BMS East Syracuse (FEI 1317461) and BMS Manati (FEI 2650089) facilities proposed for Elotuzumab DS and DP manufacture. The final review of the EIR for the PLI fo BMS Syracuse is pending; an overall manufacturing recommendation will be provided via an addendum when a final inspection decision is made by CDER.

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