

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205004Orig1s000

PRODUCT QUALITY REVIEW(S)



Recommendation: Approval

NDA 205004 Review #4

Drug Name/Dosage Form	Bortezomib for Injection
Strength	3.5 mg/vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Fresenius Kabi USA, LLC
US agent, if applicable	Not applicable

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0023 (24), Amendment	April 28, 2017	DP
0025 (26), Resubmission	September 05, 2017	Revised MBR

Quality Review Team for Resubmission

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Anamitro Banerjee	OPQ/DNDP1/B2
Drug Product	Anamitro Banerjee	OPQ/DNDP1/B2
Process	Zhong Li	OPQ/OPF/DIA/IABI
Facility	Zhong Li	OPQ/OPF/DIA/IABI

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	10/23/2017	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Listed drug	NDA 21602	Velcade (bortezomib) for Injection
IND	IND 107868	Bortezomib for Injection

2. CONSULTS: None

Executive Summary

I. Recommendations

NDA 205004 is recommended for APPROVAL from a product quality standpoint. Include in the action letter the expiration date and the stability storage statement under item A.2. below.

A. Recommendation and Conclusion on Approvability

1. **Summary of Complete Response issues:** None
2. **Action letter language, related to critical issues such as expiration date**

Include the following statement in the action letter:

An expiration dating period of 24 months is granted for Bortezomib for Injection, when stored at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature], protected from light.

3. Benefit/Risk Considerations

This NDA was recommended for approval from the CMC perspective on October 23, 2015. The NDA was TENTATIVELY APPROVED by the agency due to patent issues. Since the tentative approval of the NDA, the applicant has proposed (b) (4) reconstitution time (NMT (b) (4) minutes) based on additional data available and updated Master Batch Records (based on recommendations by the FDA investigator). In addition, the DMF (b) (4) for the drug substance has been updated. All the updates were reviewed and were found to be acceptable.

No CMC deficiencies are identified at this time.

B. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	None
Non Proprietary Name of the Drug Product	Bortezomib for Injection
Non Proprietary Name of the Drug Substance	bortezomib
Proposed Indication(s) including Intended Patient Population	Indicated for treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy.
Duration of Treatment	(b) (4)
Maximum Daily Dose	1.3 mg/m ²
Alternative Methods of Administration	None



QUALITY ASSESSMENT
NDA 205004 Bortezomib for Injection
Fresenius Kabi USA, LLC



C. Biopharmaceutics Considerations

The biowaiver submitted in the original submission was granted per 21 CFR § 320.22(d) (see the Biopharmaceutics review dated February 17, 2015).

REVIEWER'S NAME:

Anamitro Banerjee, Ph. D.
Branch Chief (Acting), Branch II, Division of New Drug Products I

Thomas Oliver, Ph. D.
Division Director, Division of New Drug Products I

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Anamitro
Banerjee

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Thomas
Oliver

Digitally signed by Thomas Oliver
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**QUALITY ASSESSMENT****Recommendation: Approval****NDA 205004
Review #3**

Drug Name/Dosage Form	Bortezomib for Injection
Strength	3.5 mg/vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Fresenius Kabi USA, LLC
US agent, if applicable	Not applicable

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0016 (17), Resubmission	05/22/2015	Process and facility
0017 (18), Quality response to information request	07/31/2015	DS, DP and facility
0017 (18), Quality response to information request	10/09/2015	DP
0018 (19), Quality response to information request	10/16/2015	DP

Quality Review Team for Resubmission

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	OPQ/DNDP1/API
Drug Product	Janice Brown	OPQ/DNDP1/B2
Process	Zhong Li	OPQ/OPF/DIA/IABI
Microbiology	Erika Pfeiler	OPQ/OPF
Facility	Zhong Li	OPQ/OPF/DIA/IABI
Biopharmaceutics	Kelly Kitchens	OPQ/ONDP/DB2
Regulatory Business Process Manager	Rabiya Laiq	OPQ/OPRO/B1
Application Technical Lead	Janice Brown	OPQ/DNDP1/B2
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	See review #1	



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QUALITY ASSESSMENT
NDA 205004 Bortezomib for Injection
Fresenius Kabi USA, LLC



Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Refer to reviews #1 and #2

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	[REDACTED]	(b) (4)	Adequate	10/23/2015	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Listed drug	NDA 21602	Velcade (bortezomib) for Injection
IND	IND 107868	Bortezomib for Injection

2. CONSULTS: None



Executive Summary

I. Recommendations

NDA 205004 is recommended for APPROVAL from a product quality standpoint. Include in the action letter the expiration date and the stability storage statement under item A.2. below.

A. Recommendation and Conclusion on Approvability

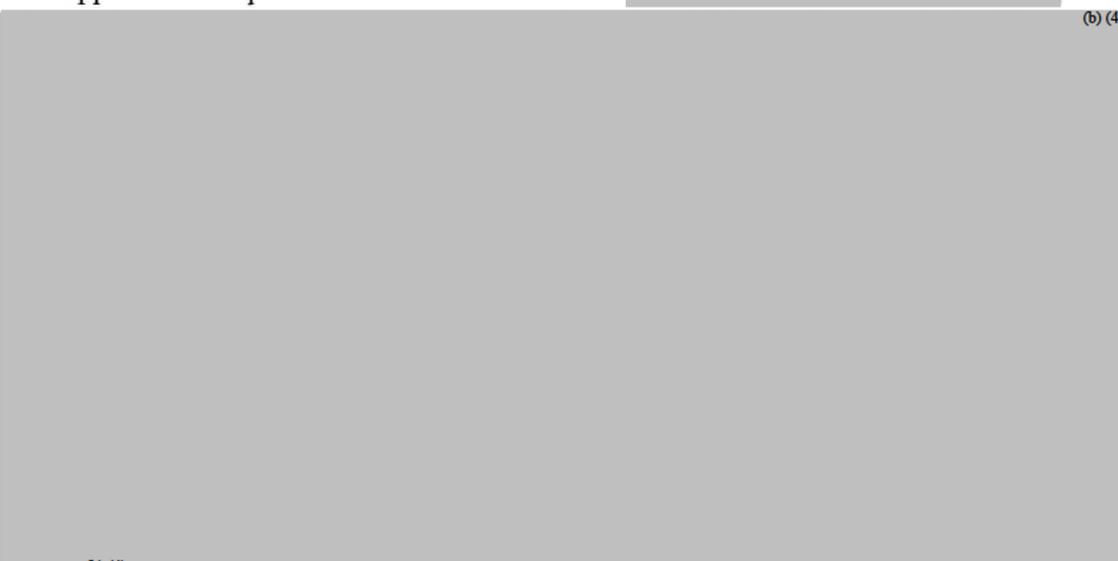
- 1. Summary of Complete Response issues: None**
- 2. Action letter language, related to critical issues such as expiration date**

Include the following statement in the action letter, if applicable for a tentative approval:

An expiration dating period of 24 months is granted for Bortezomib for Injection, when stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature], protected from light.

3. Benefit/Risk Considerations

The review of this NDA is based primarily on chemistry, manufacturing and controls and clinical pharmacology/biopharmaceutics data. In this third review cycle for this NDA. The applicant has updated the DMF to reflect that (b) (4)



(b) (4) The drug product issues have been satisfactorily addressed and the review has recommended approval of the NDA.

The process, microbiology and biopharmaceutics review continue to recommended approval of the NDA submission. Pharmacology/Toxicology has no concerns with the



QUALITY ASSESSMENT
NDA 205004 Bortezomib for Injection
Fresenius Kabi USA, LLC



excipients and impurities in the drug product at the defined levels. The applicant has satisfactorily resolved the withhold recommendation from the Office of Process and Facilities. The cGMP status for all manufacturing sites is acceptable. Therefore, there are no outstanding regulatory issues for this NDA. This NDA is recommended for approval from a product quality standpoint.

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

II. Summary of Quality Assessments

The current application for Bortezomib for Injection 3.5 mg lyophilized powder is submitted as a 505(b)(2) NDA. This is a new formulation of an approved Bortezomib for Injection. The innovator product, Velcade (bortezomib) for Injection from Millennium Pharmaceuticals, Inc. (NDA 21602) is a single-use vial containing 3.5 mg of bortezomib as a lyophilized powder.

This is the third review cycle for this NDA.

A. Drug Substance [bortezomib] Quality Summary

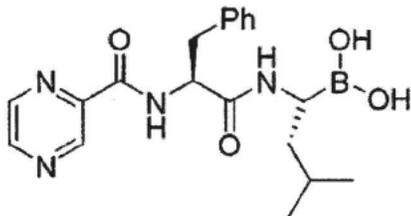
The applicant cross-referenced the CMC information for bortezomib drug substance to DMF (b) (4). DMF (b) (4) was reviewed and found adequate (see multiple reviews in DARRTS, the most current by Hari Sarker on 23-Oct-2015).

1. Chemical Name or IUPAC Name/Structure



The chemical structure of bortezomib was confirmed by Mass spectroscopy, ¹H NMR, ¹³C NMR, COSY, IR, UV, XRPD, and DSC.

(b) (4)



Bortezomib as boronic acid
 $C_{19}H_{25}BN_4O_4$
MW: 384.24

2. Properties/CQAs Relevant to Drug Product Quality

The drug substance (b) (4) Bortezomib is hygroscopic, and exists in polymorph (b) (4). The polymorphism information is not critical since the drug product dosage form is an injection after reconstitution. Bortezomib is sensitive to metal, oxygen and light. Bortezomib drug substance is unstable and readily degrades at room temperature.

(b) (4)

. Bortezomib, as the monomeric boronic acid, has aqueous solubility of 3.3 – 3.8 mg/mL in the pH range of 2.0 – 6.5.

3. List of starting materials (source: DMF review #1)

- (b) (4) (starting material)

The holder has identified (b) (4) as a starting material. This material is commercially available from different sources. The holder states that they purchase this material from the following manufacturers/suppliers.

(b) (4)

The holder states that their (b) (4) may alternatively purchase this material from their (b) (4).

- (b) (4) (starting material)



The holder states that [redacted] (b) (4) is commercially available and they purchase it from the following manufacturers/suppliers:

[redacted] (b) (4)

The holder states that their [redacted] (b) (4) may alternatively purchase this material from their [redacted] (b) (4).

- [redacted] (b) (4) (intermediate)

According to DMF review #2, the holder acknowledged that [redacted] (b) (4) is an intermediate, and not a starting material as originally proposed in the original DMF.

4. Suppliers of starting materials (site):

See #3 - List of starting materials for starting material supplier information.

5. Summary of Synthesis

Information on the synthesis, controls, reagents, solvents, and auxiliary materials employed in the production of the bortezomib drug substance along with the release specification is described in DMF [redacted] (b) (4).

6. Process

a. Sterilization processes of the sterile bulk, as applicable

Not applicable. The drug substance is not sterile.

b. Critical equipment

DMF [redacted] (b) (4): No critical equipment is specified in DMF review #1.

7. Container Closure

Drug Substance is packaged at [redacted] (b) (4) (described in DMF review #2) in the following container closure:

[redacted] (b) (4)

8. Retest Period & Storage Conditions



Retest period for bortezomib is (b) (4) months when stored (b) (4)
(b) (4)

B. Drug Product [bortezomib for injection] Quality Summary

1. Strength

Each single-dose vial of bortezomib contains 3.5 mg of bortezomib as a sterile lyophilized powder for reconstitution.

2. Description/Commercial Image

Bortezomib for injection is supplied as a sterile single-dose vial containing 3.5 mg of bortezomib, 10.5 mg boric acid, and 25 mg glycine as a sterile lyophilized powder. For each 3.5 mg single-dose vial of bortezomib for injection, reconstitute with 3.5 mL of 0.9% sodium chloride. The final bortezomib concentration is after reconstitution is 1 mg/mL. Bortezomib contains no antimicrobial preservative. Reconstituted bortezomib should be administered within 8 hours of preparation. When reconstituted as directed, bortezomib may be stored at (b) (4) 25°C (b) (4) 77°F). The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to 8 hours in a syringe; however, total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting.

3. Summary of Product Design

The subject of the current NDA application is a new formulation of approved Bortezomib for Injection. The route of administration, dosage form and strength of the proposed drug product are the same as the listed drug, Velcade (bortezomib) for Injection. The proposed drug product is a single dose sterile lyophilized powder containing 3.5 mg/vial of bortezomib in a 10 mL vial. The applicant's Bortezomib for Injection is intended for administration as a 3-5 second bolus intravenous injection after reconstitution with (b) (4) mL commercially available 0.9% Sodium Chloride Injection, USP. The subcutaneous route of administration and all relevant information in the listed drug package insert has been carved out of the applicant's labeling and the administration of the proposed drug product is for intravenous use only.

4. List of Excipients

The excipients in Bortezomib for Injection are 10.5 mg boric acid and 25 mg glycine. (b) (4) The levels of excipients are within maximum daily dose of bortezomib in the FDA inactive ingredient database.

The excipients used in the manufacture of the proposed drug product include the following:

- Boric Acid, NF
- Glycine, USP
- [REDACTED] (b) (4)
- Water [REDACTED] (b) (4)
- [REDACTED] (b) (4)

[REDACTED] (b) (4)
[REDACTED] water (b) (4)
(b) (4) removed during the lyophilization process. [REDACTED] (b) (4)
[REDACTED]

5. Process Selection (Unit Operations Summary)

a. Sterilization processes of the drug product, as applicable

The manufacturing process for bortezomib for injection consists of [REDACTED] (b) (4)
[REDACTED] (b) (4)

b. Critical equipment

All product contact equipment used in the [REDACTED] (b) (4) filling operation.

6. Container Closure

Bortezomib for Injection will be filled into Type I USP amber glass vials. Vials are closed with gray [REDACTED] (b) (4) rubber, [REDACTED] (b) (4) stoppers and capped with aluminum crimped flip-off seals.

7. Expiration Date & Storage Conditions

An expiration dating period of 24 months is granted for Bortezomib for Injection, when stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature], protected from light.

8. List of co-packaged components

There are no co-packaged components.



9. Final Discipline Recommendations

DISCIPLINE	REVIEWER	FINAL RECOMMENDATION
Drug Substance	Hari Sarker	Approval
DMF Reviewer	Ying Lin	Adequate
DMF Reviewer	Hari Sarker	Adequate
Drug Product	Janice Brown	Approval
Process	Zhong Li	Approval
Microbiology	Erika Pfeiler	Approval
Facility	Zhong Li	Approval
Biopharmaceutics	Kelly Kitchens	Approval
Application Technical Lead	Janice Brown	Approval

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	None
Non Proprietary Name of the Drug Product	Bortezomib for Injection
Non Proprietary Name of the Drug Substance	bortezomib
Proposed Indication(s) including Intended Patient Population	Indicated for treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy.
Duration of Treatment	(b) (4)
Maximum Daily Dose	1.3 mg/m ²
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Classification:
 - Drug Substance: N/A
 - Drug Product: N/A

2. Biowaivers/Biostudies
 - Biowaiver Requests

The biowaiver submitted in the original submission was granted per 21 CFR § 320.22(d) (see the Biopharmaceutics review dated February 17, 2015).

- PK studies – N/A
- IVIVC – N/A

E. Novel Approaches: None

F. Any Special Product Quality Labeling Recommendations



QUALITY ASSESSMENT
NDA 205004 Bortezomib for Injection
Fresenius Kabi USA, LLC



The drug product is light sensitive and should be stored in the original carton.

G. Life Cycle Knowledge Information (see Attachment A): Not applicable for a resubmission.

**OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE
SUMMARY**

Application Technical Lead Signature:

I recommend approval (tentative) of this NDA submission

Janice T. Brown, M.S.

10/23/2015

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ou=People, 0.9.2342.19200300.100.1.1=1300101685,
cn=Janice T. Brown -A

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QUALITY ASSESSMENT
NDA 205004 Bortezomib for Injection
Fresenius Kabi USA, LLC



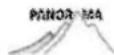
Director (Acting)
Division of New Drug API

II. List of Deficiencies To Be Communicated: None

III. Attachments

- A. Lifecycle Knowledge Management: Not applicable since the implementation of this review template occurred after the NDA was reviewed; therefore, it was not completed by the primary reviewer in review #1.

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NDA 205004-Orig1-Resubmission/Class 2(17) » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Task Summary **Task Details** Issues Updates More

Overview **Facility Inspection - Overall Application Recommendation**

Edit Custom Form

Custom Form
Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation
Approve

Navigation Links

Form Link
http://panorama.fda.gov/task/view?ID=556018eb00260d4a62fb9f04e39e8010&activeTab=content-dashboard__5418eab10003b6cd5f0c5f929c4fa823

Edit Task | Task Actions

Assigned To



OPF Reviewer



Zhong Li



IM - OPF Reviewer

Edit Assignment

This was done on
Oct 7, 2015
(40 days ago)

Status
Complete

Requested by



DARRTS Integration

This task is waiting on
Facilities

Last Update	Submitted On
Oct 7, 2015	May 23, 2015

Reference Number
4734822

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/s/

MARY GRACE LUBAO
11/23/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 23 September 2015

TO: Rabiya Laiq
Regulatory Health Project Manager
CDER/OPQ/OPRO/DRBPMI/RBPMBI

FROM: Erika Pfeiler, Ph.D.
Microbiologist
CDER/OPQ/OPF/Division of Microbiology Assessment
(301) 796-0642

THROUGH: John Arigo, Ph.D.
Quality Assessment Lead (Acting)
CDER/OPQ/OPF/Division of Microbiology Assessment

SUBJECT: NDA: 205004
Submission Date: 22 May 2015
Drug Product: Bortezomib Injection
Applicant: Fresenius Kabi USA, LLC

This NDA was previously recommended for approval during the first review cycle (See Microbiology Review 1 of NDA 205004, 08 April 2013). This application received a complete response on 03 October 2013. In the first resubmission, a memo was generated assessing the resubmission and proposed hold time information in product labeling. The application continued to be recommended for approval at this time (07 November 2014). This resubmission received a complete response on 02 April 2015 for items unrelated to the quality microbiology review.

The application was resubmitted a second time on 22 May 2015. Information relevant to a quality microbiology review was limited to a proposed master batch record that was updated to address deficiencies that arose as a result of a facility inspection. The master batch record was reviewed, and the information contained in it is in agreement with previously submitted documentation. The information contained in the master batch record includes descriptions of the container closure system, (b) (4)

All were within agreement with information previously submitted.

This application continues to be recommended for approval on the basis of product quality microbiology.

END

MEMORANDUM

Erika A.
Pfeiler -S

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ou=HHS, ou=FDA, ou=People,
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Date: 2015.09.23 07:56:06 -04'00'

John T.
Arigo -S

Digitally signed by John T. Arigo
-S
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ou=HHS, ou=FDA, ou=People,
cn=John T. Arigo -S,
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Memorandum

Date: April 20, 2013
To: Administrative File, NDA 205004
From: Timothy J. Pohlhaus, Ph.D., CDER/OC/OMPQ
Endorsement: David Doleski, Division Director, CDER/OC/OMPQ/DGMPA
Subject: Drug Product Facility and Process Review - NDA 205004
Applicant: Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300E
Schamburg, IL 60173
Product and Dosage Form: Bortezomib for Injection, 3.5 mg/vial, sterile, lyophilized
Indication: For treatment of patients with myeloma or mantle cell lymphoma who have received at least one prior therapy
PDUFA Date: October 3, 2013
NDA: 205004

Overall Reviewer Assessment

Approval of this product is not recommended at present time for the following reasons:

- drug product manufacturing process deficiencies
- the unacceptable compliance status of Fresenius Kabi, Grand Island, New York - the drug product manufacturing facility

(b) (4)

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/s/

TIMOTHY J POHLHAUS
05/01/2013

JOSEPH D DOLESKI
05/01/2013



Memorandum

Date April 1, 2015

From Zhong Li, Chemist, CDER/OPQ/OPF/DIA/IABI

Subject Concurrence with New York District Office (NYK-DO) Withhold Recommendation for NDA 205004, Resubmission, Bortezomib for Injection, 3.5 mg/vial, Sterile Lyophilized

Thru Mahesh Ramanadham, Branch Chief, CDER/OPQ/OPF/DIA/IABII

To Janice Brown, Application Technical Lead, CDER/OPQ/ONDP/DNDPI/NDPBII

Applicant: FRESENIUS KABI USA LLC
3 Corporate Drive
Lake Zurich, Illinois 60047

Establishment: FRESENIUS KABI USA LLC
3159 STALEY RD
GRAND ISLAND, NY US 14072
FEI: 3001833549

The Division of Inspectional Assessment (DIA) of Office of Process and Facility (OPF), CDER, has completed a review of an establishment inspection report (EIR) covering a pre-approval inspection (PAI) by New York District Office (NYK-DO) investigators from 2/24/2015-3/6/2015 at a Fresenius Kabi USA LLC (FK USA) facility in Grand Island, NY. OPF has also provided an initial review of the firm's 3/27/2015 written response to the FDA Form-483 observations. This inspection was initiated by NYK-DO to provide pre-approval coverage of NDA 205004, Resubmission (Bortezomib for Injection, 3.5 mg/vial, Sterile Lyophilized). FK USA is named in the NDA as the site for manufacturing, release and stability testing of the subject drug product.

DIA concurs with New York District Office's withhold recommendation for NDA 205004. OPF DIA has performed an initial review of the response received by OPF on 3/30/15 to provide a recommendation in support of 4/3/15 PDUFA date. NYK-DO recommended withholding approval of this application due to product specific deficiencies related to Batch Yield and Production Environmental Monitoring. The following deficiencies specific to the approved NDA-205004 were observed.

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CDER/OPQ/OPF/DIA Recommendation:

Based on the above assessment of the inspection findings and the firm's response to Form 483 observations, OPF concurs with the NYK-DO's recommendation to withhold approval of NDA 200504 (Bortezomib for Injection, 3.5 mg/vial, Sterile Lyophilized) until the significant (b) (4) issues uncovered during the inspection are further assessed and resolved.

If you have any questions, please contact me at (301) 796-1798 or by email at zhong.li@fda.hhs.gov.

Zhong Li
Chemist
CDER/OPQ/OPF/DIA/IABI

Zhong Li -S

Digitally signed by Zhong Li -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Zhong Li -S,
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Date: 2015.04.01 14:02:12 -04'00'

Mahesh R. Ramanadham -S

Digitally signed by Mahesh R. Ramanadham -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2000618629, cn=Mahesh R. Ramanadham -S
Date: 2015.04.01 14:25:40 -04'00'

cc:

HFR-NE1510 New York District Pre-Approval Manager (PAM), Matthew Spataro
CMS case #: 83162

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Memorandum

Date: April 1, 2015
To: Administrative File, NDA 205004
From: Zhong Li, Chemist, CDER/OPQ/OPF/DIA/Branch I
Endorsement: Mahesh Ramanadham, Branch Chief, CDER/OPQ/OPF/DIA/Branch II
Subject: Facility Review - NDA 205004 (resubmission)
Applicant: Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300E, Schamburg, IL 60173
Product/Dosage Form: Bortezomib for Injection, 3.5 mg/vial, sterile, lyophilized
Indication: For treatment of patients with myeloma or mantle cell lymphoma who have received at least one prior therapy
PDUFA Date: April 3, 2015
NDA: 205004

Overall Reviewer Assessment

Approval of NDA 205004 is not recommended until the [REDACTED] (b) (4) issues uncovered during the pre-approval inspection are resolved.

Fresenius Kabi USA, LLC – Drug Product Manufacturer

3159 Staley Road
Grand Island, NY
FEI: 3001833549

Responsibilities:

- Drug Product Manufacturer
- Drug Product In-Process Testing [REDACTED] (b) (4)
- Drug Product Release Testing (Chemistry/Analytical, Sterility and Bacterial Endotoxin, Container/Closure Integrity)
- Drug Product Stability Testing (Chemistry/Analytical)
- Drug Substance Testing (Chemistry/Analytical, Bacterial Endotoxin and Microbial Bioburden)

Drug Manufacturing and Testing Profile(s): SVL and CTL

Fresenius Kabi USA, Grand Island, NY was most recently inspected by FDA February 24 - March 6, 2015. This inspection of a sterile drug manufacturer was conducted pursuant to FACTS assignment #11505577 requesting a Pre-Approval Inspection for the manufacture of Bortezomib for Injection submitted under new drug application NDA #205004. This inspection was limited to a PAI which covered all six systems and the following Profile Classes: SVL and CTX. At the conclusion of the inspection, an FDA-483, Inspectional Observations, with two observations was issued. The observations included [REDACTED] (b) (4)

are not determined at the conclusion of each appropriate phase of manufacturing of the drug product and [REDACTED] (b) (4)

[REDACTED] Three conditions were observed during this inspection which warranted a verbal discussion with management. The conditions discussed with management were; Moisture (Water) Content test method and specification of the finished product, readiness to manufacture Bortezomib for Injection is not fully demonstrated, and the general approach of revalidation of equipment. The firm's 3.27.2015 responses to FDA's 483 Observations were found unacceptable. Approval of NDA 205004 was not recommended. Specifically, the firm has not provided adequate response to address the significant rate of [REDACTED] (b) (4)

[REDACTED] In addition, [REDACTED] (b) (4)
(See Memo, Concurrence with New York District Office (NYK-DO) Withhold Recommendation for NDA 205004, Resubmission, Bortezomib for Injection, 3.5 mg/vial, Sterile Lyophilized), dated 4.1.2015).

The previous establishment inspection of Fresenius Kabi USA, LLC was conducted on 10/20-10/24/2014 as a CGMP Surveillance inspection of a sterile drug manufacturer as part of the FY15 PG work plan, follow up to informant complaint, and a for-cause inspection per request of Office of Manufacturing and Product Quality (OMPQ) to verify the implementation of corrective actions in response to the February 2012 Warning Letter (NYK 2012-14). The inspection was classified VAI. A full inspection covering all six systems was conducted resulted in an issuance of an three-item FDA-483, Inspectional Observations, citing failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed, the number of containers to be sampled is not based upon appropriate criteria, and buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable construction to facilitate cleaning, maintenance, and proper operations.

Reviewer Assessment: This facility is currently considered unacceptable for the manufacture of bortezomib drug product due to ongoing product-specific GMP deficiencies.

[REDACTED] (b) (4) Drug Substance Manufacturer

[REDACTED] (b) (4)

[REDACTED] (b) (4) was most recently inspected by FDA [REDACTED] (b) (4)
The inspection, which was classified NAI (No Action Indicated), covered all six systems (quality, production, materials, facilities/equipment, packaging/labeling,

and laboratory control). An FDA-483 was not issued at the conclusion of the inspection, but two deficiencies were noted and discussed with management as described in the "Discussion with Management" section of the EIR. Management provided immediate corrective actions for these items during the inspection.

The previous FDA inspection of this site was conducted (b) (4)
The inspection, which was classified VAI (Voluntary Action Indicated), was initiated

(b) (4)

The Firm's Quality System was covered in depth, with limited coverage of the Laboratory and Production Systems. At the close of the inspection, the firm was issued a one-item FDA Form 483, citing failures to conduct adequate investigations. OMPQ/DIDQ found the firm's 483 response acceptable. Drug manufacturing profiles (b) (4) CSN (the relevant profile for this application), (b) (4) were updated as a result of this inspection and are considered acceptable.

Reviewer Assessment: (b) (4) *is acceptable for the manufacture of bortezomib API (profile: CSN) based on this firm's acceptable CGMP compliance status and recent inspectional coverage of the relevant manufacturing responsibility.*

Fresenius Kabi USA LLC - Testing Laboratory

8045 Lamon Ave.

Skokie, IL 60077

FEI: 3008604776

Responsibilities:

- Drug Substance (Alternate) Testing (Chemistry/Analytical)
- Drug Product Release Testing (Chemistry/Analytical, Sterility and Bacterial Endotoxin, Container/Closure Integrity)
- Drug Product Stability Testing (Chemistry/Analytical)

Profile: CTL

Fresenius Kabi (Skokie, Illinois) was most recently inspected June 17-18, 2013. The inspection was classified NAI (No Action Indicated), covered Quality and Laboratory Controls systems and Profile class CTL. No CGMP deficiencies were noted.

The previous inspection of this site, which was also classified NAI, was conducted September 4-7, 2012. The inspection, which was also classified NAI, covered the raw material, in process, release, and stability testing operations that support Fresenius Kabi's drug product manufacturing sites.

Reviewer Assessment: Freseniu Kabi (Skokie, IL) is acceptable for the above-listed bortezomib drug substance and drug product testing responsibilities on the basis of its currently acceptable CGMP compliance status and recent relevant inspectional coverage.

(b) (4) Testing Laboratory

(b) (4)

(b) (4) was most recently inspected by FDA (b) (4). The inspection, which was classified NAI, covered the quality and laboratory systems. No significant observations were noted. No FDA 483 was issued.

The facility was previously inspected by FDA (b) (4). The inspection, which was classified NAI, included pre-approval coverage as well as routine CGMP surveillance coverage. The firm functions solely as a control testing laboratory; therefore, the inspection covered the Quality and Laboratory systems. The inspection revealed no deficiencies. CGMP surveillance inspections of this firm were also conducted (b) (4). These inspections were classified VAI and NAI, respectively, and together resulted in a single CGMP deficiency observation.

Reviewer Assessment: (b) (4) is acceptable for bortezomib (b) (4), on the basis its currently acceptable CGMP compliance status and recent relevant inspectional coverage.

Zhong Li -S

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ou=FDA, ou=People, cn=Zhong Li -S,
0.9.2342.19200300.100.1.1=2000695751
Date: 2015.04.01 14:27:46 -04'00'

Mahesh R. Ramanadham -S

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-S
Date: 2015.04.01 15:22:15 -04'00'



NDA 205004

**Bortezomib for Injection
3.5 mg/Vial**

Fresenius Kabi USA, LLC

Z. Jean Tang, Ph.D
Division of New Drug Quality Assessment I
Branch II

For the Division of Drug Oncology Products (HFD-150)



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CMC Review Data Sheet

1. NDA 205-004
2. REVIEW #: 2
3. REVIEW DATE: 12-Mar-2015
4. REVIEWER: Z. Jean Tang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

Original PIND 107868 Meeting (Type B)
Pre-NDA Comments

05-APR-2010
27-SEP-2011

6. SUBMISSION(S) BEING REVIEWED (CMC):

Submission(s) Reviewed	Serial Number	DARRTS SD Number	Document Date	Stamp Date
Amendment	0016	0016	12-Mar-2015	12-Mar-2015

7. NAME & ADDRESS OF APPLICANT:

Name: Fresenius Kabi USA, LLC
Address: 1501 E. Woodfield Road, Suite 300 East
Schaumburg, IL 60173
Representative: Aditi Dron, Regulatory Affairs Manager
Telephone: (847)330-3898

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name: Bortezomib for Injection
- c) Code Name/# (ONDQA only): 761210
- d) Chem. Type/Submission Priority (ONDC only):

Chemistry Review Data Sheet

- Chem. 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: antineoplastic agent

11. DOSAGE FORM: Sterile lyophilized

12. STRENGTH/POTENCY: 3.5 mg/vial

13. ROUTE OF ADMINISTRATION: IV

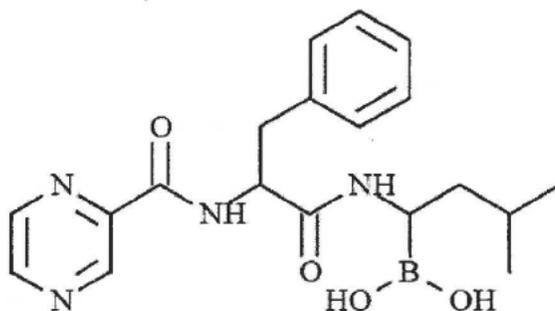
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical Name:

IUPAC: [(1R)-3-methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)propyl]amino] boronic acid
 USAN: bortezomib
 CAS Registry No.: 179324-69-7
 Molecular Formula: C₁₉H₂₅BN₄O₄
 Molecular Weight: 384.24 g/mol

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11-MAR-2015	N/A
	III			1	Adequate	28-DEC-2012	N/A
	III			1	Adequate	04-SEP-2012	N/A
	V			1	Adequate	13-DEC-2012	N/A
	III			1	Adequate	09-Apr-2013	N/A

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

N/A



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistic	N/A	N/A	N/A
EES	Pending	13-Mar-2015	N/A
Drug Substance	DMF Adequate	11-Mar-2015	Jean (Zhe) Tang
Drug Product	Approval pending acceptable facility recommendation	Up to the date	Jean (Zhe) Tang / Donghao (Robert) Lu
Pharm/Tox	Pending		Pedro Del Valle
Biopharm	Approval	05-Feb, 2015	Kelly Kitchens
LNC	N/A	N/A	N/A
Methods Validation	N/A, according to the current ONDQA policy	N/A	N/A
DMEPA*	N/A	N/A	N/A
EA	Satisfactory	29-Apr-2013	Jean Tang
Microbiology	Approval	07-Nov-2014	Erika Pfeiler

The Chemistry Review for NDA 205-004

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for approval from a CMC perspective pending acceptable facility recommendation.

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

II. Summary of Chemistry Assessments

A. Summary

The applicant submitted an updated drug product specification, SECTION 3.2.P.5.1 to be included in NDA #205004 as SEQ-0015 of the application.

Changes to the drug product specification in Section 3.2.P.5.1, shown in *italics*, include the revised water content limit of NMT (b) (4) % and the pH range of (b) (4) - (b) (4). The pH range is added here for completeness to correct a typographical error. FK USA agreed to include this pH range as response to information request (RFI#7) in SEQ-0008, but the update was inadvertently missed in the Section 3.2.P.5.1 document.

B. Description of How the Drug Product is Intended to be Used

Bortezomib for Injection is a selective inhibitor of the 26S mammalian proteasome, which is a large protein complex, consisting of 19S and 20S subunits that degrade ubiquitinated proteins. Bortezomib for Injection is an oncology product that is used for treatment of patients with multiple myeloma and patients with mantle cell lymphoma. The proposed clinical use for this submission will be consistent with current Velcade® labeling for the intravenous route of administration and carved out for the subcutaneous route of administration.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, approval of NDA 205004 is recommended pending an acceptable facility recommendation.



Executive Summary Section

III. Administrative

A. Reviewer's Signature

(See appended electronic signature page)

Z. Jean Tang, Ph.D.
CMC Reviewer
Branch III, Division I, ONDQA
CDER, FDA

Zhe
Tang -A

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ou=HHS, ou=FDA, ou=People,
cn=Zhe Tang -A,
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B. Endorsement Block

(See appended electronic signature page)

Janice Brown, M.S.
Team Leader
CDER, FDA

Janice T.
Brown -A

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Chemistry Assessment Section

Chemistry Assessment**I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:
Body Of Data****P.5 Control of Drug Product****P.5.1 Specification (Bortezomib for Injection, 3.5 mg/vial, Sterile Lyophilized)**

The applicant updated Bortezomib for Injection drug product specification to include the revised water content limit of NMT (b) (4)% and a pH range of (b) (4)

Regulatory Specifications for Bortezomib for Injection

Test	Acceptance Criteria	Test Method ¹
Description	Solid in an amber vial	Visual Examination
Identification:		
A HPLC	A. The retention time of the major peak in the chromatogram of the <i>Assay preparation</i> corresponds to that of the <i>Standard Preparation</i> . (b) (4)	A. 10-08-03-6530
B. Ultraviolet (UV) Spectrum using Photodiode Array Detector	B. The extracted spectra collected between (b) (4) (b) (4) at the apex of the Bortezomib peak in the <i>Standard Preparation</i> and the <i>Finished Product Assay Preparation</i> exhibit maxima at the same wavelength \pm (b) (4).	B. 10-08-03-6530
Reconstitution Time	Reconstitute each vial with 3.5 mL of 0.9% Sodium Chloride Injection, USP NMT (b) (4) minutes	10-08-05-6005
Constituted Solution		
1. Completeness	1 The solid dissolves completely leaving no visible residue as undissolved matter	10-08-05-6005 USP<1>
2. Clarity	2. The constituted solution is not significantly less clear than an equal volume of Sterile Water for Injection contained in a similar vial and examined similarly.	
3. Particulate Matter	3. The constituted solution is essentially free from particles of foreign matter that can be observed on visual inspection.	
4. Visual Color	4. Colorless	10-08-05-6005
Water Content	NMT (b) (4)%	10-08-03-6581 USP <921> Method 1c
Uniformity of Dosage Units	Meets USP requirements	USP<905>



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

Regulatory Specifications for Bortezomib for Injection (cont'd)

Test	Acceptance Criteria	Test Method ¹
Constituted Solution (cont.)		
pH	(b) (4)	10-08-05-6001 USP <791>
(b) (4)	NMT (b) (4)	USP (b) (4) (b) (4)
Container/Closure Integrity ²	The differential pressure of all sample vials being tested for each lot must be below the two bracketing Self Tests	10-08-00-6031 10-08-00-6032
Bortezomib Assay Label Claim 3.5 mg/vial	(b) (4) % of Label Claim	10-08-03-6530
Impurities ³		
1. (b) (4)	1. NMT (b) (4) %	10-08-03-6530
2. (b) (4)	2. NMT (b) (4) %	
3. Any Other Individual Impurity	3. NMT (b) (4) %	
4. Total Impurities	4. NMT (b) (4) %	
(b) (4)	NMT (b) (4) ppm	10-08-03-6537
Particulate Matter in Injections	1. For particles $\geq 10\mu\text{m}$: NMT (b) (4) per container 2. For particles $\geq 25\mu\text{m}$: NMT (b) (4) per container	USP <788>
Sterility ⁴	Sterile	USP <71>
Bacterial Endotoxins	NMT (b) (4) EU/mg	USP <85>
(b) (4)		

- References to compendia signify current compendia. If a compendial monograph or test changes, FK USA will implement the changes and report them via annual report.
- CCIT is performed only at annual stability interval
- Please refer to the TABLE 3.2.P.5.1- 1 above for the proposed limits and SECTION 3.2.P.5.6 for the justification of impurity limits.
The Certificates of Analysis (COAs) issued in support of this original 505(b)(2) application were generated for lots R340-025, R340-024, C340-013 and R342-032 that were manufactured on 08/02/2010, 08/23/2010, 09/03/2010 and 05/30/2012, respectively. FK USA has subsequently derived new limits for impurities (b) (4) any other individual impurity and total impurities based on the application of ICH recommendations for setting impurity limits. Therefore, the COA's presented in SECTION 3.2.P.5.4 do not reflect most current limits.
- Sterility test is performed only at release

Review Evaluation

Satisfactory



Memorandum

Date: March 12, 2015
To: Administrative File, NDA 205004
From: Timothy J. Pohlhaus, Ph.D., CDER/OC/OMQ
Zhong Li,¹ Ph.D., CDER/OPQ/OPF/DIA/Branch I
Endorsement: Zhihao Peter Qiu, Branch Chief, CDER/OPQ/OPF/DIA/Branch I
Mahesh Ramanadham, Acting Division Director, CDER/OPQ/OPF/DIA
Subject: Review of Response to Complete Response Letter - Drug Product Process
Review - NDA 205004 (resubmission mid-cycle memo)
Applicant: Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300E, Schamburg, IL 60173
Product/Dosage Form: Bortezomib for Injection, 3.5 mg/vial, sterile, lyophilized
Indication: For treatment of patients with myeloma or mantle cell lymphoma who have
received at least one prior therapy
PDUFA Date: April 3, 2015
NDA: 205004

Overall Reviewer Assessment

Approval of NDA 205004 is not recommended until:

- 1) Sufficient responses have been received addressing deficiencies communicated to FK through the IR process (see the Information Request section of this document for those items)
- 2) A pre-approval inspection (PAI) has been conducted at Fresenius Kabi's (FK's) Grand Island, NY bortezomib drug product manufacturing facility and significant concerns identified during the review process have been resolved. The PAI should cover, at a minimum:
 - FK's bortezomib lyophilization cycle, including supporting development work
 - understanding FK's (b) (4) proposed residual moisture limit
 - bortezomib stability testing, including a data integrity audit
 - the significant rate of lyophilization rejects observed in bortezomib exhibit and process qualification batches

Specific recommendations for bortezomib PAI coverage are provided in the Summary and Recommendations for Inspectional Coverage section of this memo.

Background

During the previous (initial) bortezomib review cycle, several concerns that would have been most appropriately covered by a PAI were raised concerning the drug product manufacturing process. These concerns include inadequate development of the product lyophilization cycle, FK's (b) (4) proposed residual moisture limit, and significant rates of lyophilization rejects in the manufacture of exhibit and process qualification batches. Resolution of these concerns would have benefitted from Agency personnel engaging in active discussion with FK, while at

¹ Review written by Tim Pohlhaus; Information Request section amended by Zhong Li.



Furthermore, please provide all potency, residual moisture, pH and reconstitution time data for you PV lots and please indicate locations within the lyophilizer from which the vials were taken.

Zhong Li -S

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Zhihao Qiu -S

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Mahesh R.
Ramanadham -S

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 10, 2015

FROM: Donghao (Robert) Lu, Ph.D.
Jean Tang, Ph.D.
Division I of Pre-Marketing Assessment
Office of New Drug Quality Assessment

TO: File NDA 205-004 (SEQ-0012 and -0014) and DMF (b) (4)

SUBJECT: Amendments (SEQ-0012 and -0014) to address the items identified in the Complete Response Letter

RECOMMENDATION: This NDA is recommended for APPROVAL from a CMC perspective, pending the overall recommendation for the facilities by the Office of Process and Facilities (CDER/OPQ/OPF).

REVIEW NOTE:

Fresenius Kabi USA, LLC's (FK USA) submitted an Amendment (SEQ-0012 and -0014) for NDA 205-004 to address the items identified in the Complete Response Letter dated October 3, 2013. Based on the supporting stability data, the applicant agreed to tighten the DP moisture content limit to NMT (b) (4)%. **Evaluation:** Acceptable.

The drug substance DMF (b) (4) cited in the NDA 205-004 has submitted an amendment with full CMC information in an electronic format for the DMF. This DMF (b) (4) submission consolidated all data submitted to FDA previously. There was no new information and the previous recommendation is still valid.

The CMC review for both process and product was complete and recommends approval of NDA 205-004, pending an overall approval recommendation for the facilities by the Office of Process and Facilities (CDER/OPQ/OPF).

Signed by:

Donghao (Robert) Lu

Donghao R.
Lu -A

Digitally signed by Donghao R. Lu -A
DN: cn=D, ou=People, c=US, email=Donghao.R.Lu@FDA, o=FDA, ou=People, cn=Donghao R. Lu -A
Date: 2015.03.10 15:24:15 -0400

Jean Tang

Zhe Tang -A

Digitally signed by Zhe Tang -A
DN: cn=Z, ou=People, c=US, email=Zhe.Tang@FDA, o=FDA, ou=People, cn=Zhe Tang -A
Date: 2015.03.10 15:24:15 -0400

Janice Brown

Janice T. Brown
-A

Digitally signed by Janice T. Brown -A
DN: cn=J, ou=US, Government, o=HHS,
ou=FDA, ou=People,
c=US, email=Janice.T.Brown@FDA,
ou=FDA, ou=People,
cn=Janice T. Brown -A
Date: 2015.03.10 15:24:15 -0400



Memorandum

Date: March 10, 2015
To: Administrative File, NDA 205004
From: Zhong Li, Ph.D., CDER/OPQ/OPF/DIA/Branch I
Endorsement: Zhihao Peter Qiu, Branch Chief, CDER/OPQ/OPF/DIA/Branch I
Subject: Drug Product Process - NDA 205004: Review of Fresenius Kabi's Responses to the March 3, 2015 Information Request

Applicant: Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300E, Schamburg, IL 60173

Product/Dosage Form: Bortezomib for Injection, 3.5 mg/vial, sterile, lyophilized
Indication: For treatment of patients with myeloma or mantle cell lymphoma who have received at least one prior therapy

PDUFA Date: April 3, 2015
NDA: 205004

Overall Reviewer Assessment

Approval of NDA 205004 is recommended pending an acceptable facility recommendation.

(b) (4)

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Reviewer Assessment: FK's response is acceptable.

Zhong Li -A

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Appendix V.

Long-term Stability Summary of Process Qualification Batches, Lot R342-032 and C343-001

Test	Long-term Stability Results – Lot R342-032														
	0	3 months		6 months		9 months		12 months		18mo.	24 months				
		I	I	I	I	I	I	U	I	I	I	U	I		
Moisture Content (%) NMT (b) (4)	(b) (4)														
Assay (%) (b) (4) 0%LC (b) (4)	97.6	96.7	98.5	98.8	99.1	100.2	98.2	98.5	97.7	(b) (4)					
AOII (%) NMT (b) (4)	(b) (4)														
Total Impurities (%) NMT (b) (4)	(b) (4)														
pH (b) (4)	(b) (4)														
Reconstitution Time (sec) NMT (b) (4)	15	30	60	15	45	45	15	30	30						
Test	Long-term Stability Results – C343-001														
	0	3 months		6 months		9 months		12 months		18mo.	24 months				
		I	U	I	U	I	U	I	U	I	U	I			
Moisture Content (%) NMT (b) (4)	(b) (4)														
Assay (%) (b) (4) %LC (b) (4)	100.6	99.3	99.1	99.4	100.3	100.2	99.9	NA ¹							
AOII (%) NM (b) (4)	(b) (4)														
Total Impurities (%) NMT (b) (4)	(b) (4)														
pH (b) (4) .2	5.7	5.8	5.8	5.8	5.8	5.8	6.0								
Reconstitution Time (sec) NMT (b) (4)	45	45	30	30	15	30	30								

¹Stability program is in progress.

BIOPHARMACEUTICS REVIEW Office of New Drug Products			
Application No.:	NDA 205004 Resubmission – Class 2	Primary Reviewer: Kelly M. Kitchens, Ph.D.	
Submission Date:	October 3, 2014		
Division:	Division of Hematology Products	Secondary Reviewer: Angelica Dorantes, Ph.D.	
Applicant:	Fresenius Kabi USA, LLC		
Trade Name:	None proposed	Date Assigned:	October 7, 2014
Established Name:	Bortezomib for Injection	Date of Review:	February 5, 2015
Indication:	Indicated for treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy.	Type of Submission: NDA 505(b)(2) Resubmission – Class 2 (Applicant’s responses to Complete Response Letter dated October 3, 2013)	
Formulation/ strengths	Sterile lyophilized/ 3.5 mg/vial		
Route of Administration	Intravenous		
Type of Review:	Biowaiver Request (addendum to Biopharmaceutics review dated April 22, 2013)		
<u>SUMMARY:</u>			
<p>Background: Bortezomib for Injection was developed as a sterile lyophilized solid (powder or cake) containing 3.5 mg bortezomib in a 10 mL vial, and is indicated for treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy. The reference listed drug (RLD) for Bortezomib for Injection is Velcade® (bortezomib) for Injection (NDA 021602), which has the same indication as Bortezomib for Injection. Velcade® (bortezomib) for Injection is approved for intravenous or subcutaneous route of administration at concentrations of 1 mg/mL or 2.5 mg/mL, respectively.¹ After reconstitution to 1.0 mg/mL with commercially available 0.9% Sodium Chloride Injection, USP, Bortezomib for Injection is intended for 3-5 second bolus intravenous route of administration.</p> <p>The original submission of NDA 205004 dated November 30, 2012, included the Applicant’s request of a waiver for the requirement to provide in-vivo bioavailability/bioequivalence studies as per 21 CFR § 320.22(d). However, the submission did not include sufficient evidence demonstrating that the differences in the composition of the formulations of Bortezomib for Injection compared to that of the RLD, Velcade®, does not have an effect on the physiological disposition of the proposed drug</p>			

¹ Drugs@FDA, http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021602s031s0321bl.pdf

product. Therefore, the bioavailability/bioequivalence waiver request was not granted, and the Biopharmaceutics team recommended a Complete Response action for this NDA. On October 3, 2013, the FDA issued a CR Letter for NDA 205004, listing several CMC and labeling deficiencies.

Current Submission: On October 3, 2014, Fresenius Kabi USA, resubmitted NDA 205004 for Bortezomib for Injection. The resubmission is addressing the deficiencies identified in the CR letter.

Biopharmaceutics Review: In this review of the resubmission of NDA 205004 for Bortezomib, the Division of Biopharmaceutics is revising its previous recommendation for the biowaiver request. It is noted that the original Biopharmaceutics review for NDA 205004 by Dr. Kelly Kitchens, dated April 22, 2013 is filed in DARRTS.

RECOMMENDATION:

The overall scientific information supports the approval of the bioavailability/bioequivalence waiver request for Bortezomib for Injection, 3.5 mg/vial and the biowaiver is granted.

From the Biopharmaceutics perspective, the Resubmission (Class 2) of NDA 205004 for Bortezomib for Injection, 3.5 mg/vial is recommended for approval.

Signature

Kelly M.
Kitchens -S

Digitally signed by Kelly M. Kitchens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000336574, cn=Kelly M. Kitchens -S
Date: 2015.02.17 15:29:29 -05'00'

Kelly M. Kitchens, Ph.D.
Biopharmaceutics Primary Reviewer
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Signature

Angelica
Dorantes -S

Digitally signed by Angelica Dorantes -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300070843, cn=Angelica Dorantes -S
Date: 2015.02.17 17:53:30 -05'00'

Angelica Dorantes, Ph.D.
Biopharmaceutics Secondary Reviewer
Division of Biopharmaceutics
Office of New Drug Products, OPQ

cc. PSeo.

BIOPHARMACEUTICS ASSESSMENT

In the original submission of NDA 205004, the Applicant submitted a biowaiver request for Bortezomib for Injection, 3.5 mg/vial, relying on the FDA's safety and efficacy findings for NDA 21602 for Velcade® (bortezomib) for Injection, 3.5 mg/vial. In the original Biopharmaceutics review dated April 22, 2013, the biowaiver request was NOT granted due to the lack of complete supportive information justifying the formulation differences between the proposed product and the reference product.

Ingredients	Velcade [®]	Bortezomib for Injection
	Millenium Pharmaceuticals	FK USA
Bortezomib	3.5 mg/vial	3.5 mg/vial
Mannitol	35 mg/vial	N/A
Boric Acid, NF	N/A	10.5 mg/vial
Glycine, USP	N/A	25 mg/vial
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4) removed		
(b) (4)		
(b) (4)		

¹ Please note that for the FK USA drug product water during the lyophilization process.

The following potential review issue was communicated to the Applicant in the 74-day letter issued on February 13, 2013:

Submit justification that in the absence of mannitol and inclusion of glycine, the physiological disposition of the proposed drug product is not different than that of the RLD product.

The Applicant responded that:

- *the amount of glycine administered (15.7 mg/day) in the maximum daily dose of the proposed drug product is negligible compared to the approximately 3 g glycine that is biosynthesized in humans per day; and,*
- *the removal of mannitol from the proposed drug product composition should not affect the physiological disposition of the drug since mannitol inclusion in the RLD composition does not affect the physiological disposition of the drug.*

Although the Applicant's response did not fully justify the formulation differences between the proposed product and the reference product, The Division of Biopharmaceutics considers that the following information (*previously submitted*) properly addresses the pending issues related to the differences in formulation:

- IND 107868 (SN 004, August 25, 2011) was submitted by APP Pharmaceuticals for Bortezomib for Injection. In this Amendment, the Sponsor reported that the

(b) (4)

The Office of Clinical Pharmacology (OCP) Reviewer for this IND, Dr. Jun Yang, found this information to be sufficient and applicable to APP's proposed drug product, and that no additional non-clinical studies were needed to support the proposed 505 (b)(2) NDA submission.

- IND 107868/SN 004 also included the results of in vitro proteasome inhibitory study, which was conducted to compare the inhibition activity Velcade and Bortezomib for Injection. The Sponsor asserted that if the mannitol ester in Velcade is sufficiently stable in the reconstituted aqueous solution, the pharmacological activity of bortezomib would be blocked or reduced greatly. Based on the FAB MS, LC/MS/MS, and in vitro proteasome inhibitory study results, the Sponsor stated that an in vivo human bioavailability study will not be conducted per 21 CFR 320.25(a). The OCP Reviewer for this IND, Dr. Jun Yang, stated that a **clinical study** would not differentiate the difference between the bortezomib-mannitol ester and bortezomib boric acid given the instability of bortezomib-mannitol ester in solution.²
- In the current NDA, the Pharmacology/Toxicology and OCP reviewers, Dr. Pedro Del Valle and Dr. Sophia Abraham, respectively, concluded that the inhibition study showed similar inhibition activity between innovator product and proposed product, despite the differences in the composition of their formulations.
- While the in vitro inhibition study results indicate that Bortezomib for Injection has similar in vitro receptor binding activity as Velcade, these results do not provide information with respect to the safety of the proposed product. Therefore, the following information has been considered in addressing the safety concerns for this product:
 - The maximum daily dose of boric acid that a patient will receive in Bortezomib for Injection is ~ 6.6 mg (*based on the maximum daily dose of Bortezomib for Injection (2.2 mg)*) and the maximum amount of boric acid approved by the FDA for injectable products is 3.19 mg/mL in Sodium Thiosulfate, for which 75 ml is the maximum volume that can be administered giving a maximum dose of boric acid of 239.25 mg.
 - The amount of boric acid dosed in Bortezomib for Injection would be approximately 36 times lower than the amount of boric acid dosed in Sodium Thiosulfate.
 - Based on the above, a 6.6 mg maximum daily dose of boric acid in the proposed Bortezomib for Injection product poses no safety risks.
- Additionally, it should be noted that the OCP review for the original NDA 21602 for Velcade® (bortezomib) for Injection shows that free Bortezomib was the

² DARRTS: IND 107868, YANG, JUN, Submit/Final Date: 10/31/2011, REV-CLINPHARM-01(General Review)

analyte measured in the in vivo PK studies, indicating that free Bortezomib is the active entity and not the Bortezomib-mannitol ester complex.³

Based on the overall scientific information described above indicating that the bioavailability, safety and effectiveness of the proposed Bortezomib for Injection product would not be different than that of the reference product, the Division of Biopharmaceutics considers that there is adequate information to support the approval of the biowaiver request.

RECOMMENDATION:

The overall scientific information supports the approval of the bioavailability/bioequivalence waiver request for Bortezomib for Injection, 3.5 mg/vial and the biowaiver is granted.

From the Biopharmaceutics perspective, the Resubmission (Class 2) of NDA 205004 for Bortezomib for Injection, 3.5 mg/vial is recommended for approval.

³ "Quantitation of PS-341 in Human Plasma Using LC/MS/MS", report no. RPT-0000 reviewed in Office of Clinical Pharmacology Review, see DARRTS: NDA 021602, BURNS, SAFAA, Submit/Final Date: 05/12/2003, REV-CLINPHARM-01(General Review)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 07 November 2014

TO: Teicher Agosto
Regulatory Health Project Manager
CDER/OPS/ONDQA

FROM: Erika Pfeiler, Ph.D.
Microbiologist
CDER/OPS/New Drug Microbiology Staff
(301) 796-0642

THROUGH: Stephen Langille, Ph.D.
Senior Review Microbiologist
CDER/OPS/New Drug Microbiology Staff

SUBJECT: NDA: 205004
Submission Date: 03 October 2014
Drug Product: Bortezomib Injection
Applicant: Fresenius Kabi USA LLC

There are no changes in this NDA resubmission that require a quality microbiology review. The 8-hour post-reconstitution hold time at room temperature that is listed in the package insert is acceptable, based on microbiology information provided prior to the resubmission.

A complete response was previously issued for this application (03 October 2013) for issues not pertaining to quality microbiology. Prior to the issuance of the complete response, the applicant submitted information (11 September 2013) to support a post-reconstitution hold time with the drug product. This information was not incorporated into the quality microbiology review (DARRTS Date 08 April 2013). The current package insert proposes an 8-hour post-reconstitution hold time at room temperature.

The applicant performed a post-reconstitution hold study by inoculating 9 vials of reconstituted (0.9% sodium chloride, 1 mg/mL) drug product with approximately 10-100 CFU *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Aspergillus brasiliensis*, and *Candida albicans* (63 total vials) and held for 24 hours at 20-25°C. Following the holding period, samples were taken by membrane filtration onto media cassettes and incubated. Results demonstrate that no microorganism increased > 0.5 log over the incubation period. The applicant's proposal of an 8-hour post-

MEMORANDUM

reconstitution hold time at room temperature is acceptable.

No other changes in the resubmission require a quality microbiology review. This application continues to be recommended for approval on the basis of product quality microbiology.

END

Erika A. Pfeiler -S

Digitally signed by Erika A. Pfeiler -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2000396533, cn=Erika A. Pfeiler -S
Date: 2014.11.07 08:02:09 -05'00'

Stephen E.
Langille -A

Digitally signed by Stephen E. Langille -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People,
0.9.2342.19200300.100.1.1=1300151320,
cn=Stephen E. Langille -A
Date: 2014.11.07 08:17:40 -05'00'

NDA 205004

**Bortezomib for Injection
3.5 mg/Vial**

Fresenius Kabi USA, LLC

Z. Jean Tang, Ph.D
Division of New Drug Quality Assessment I
Branch II

CMC REVIEW OF NDA 202324 DRUG SUBSTANCE
For the Division of Drug Oncology Products (HFD-150)

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CMC Review Data Sheet

1. NDA 205-004
2. REVIEW #: 1
3. REVIEW DATE: 07-Mar-2013
4. REVIEWER: Z. Jean Tang, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Original PIND 107868 Meeting (Type B)
Pre-NDA Comments

Document Date

05-APR-2010
27-SEP-2011

6. SUBMISSION(S) BEING REVIEWED (CMC):

Submission(s) Reviewed	Serial Number	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	0000	001	30-Nov-2012	03-Dec-2012
Amendment	0004	005	05-Feb-2013	05-Feb-2013
Amendment	0006	007	21-Mar-2013	05-Feb-2013
Amendment	0008	009	29-Mar-2013	21-Mar-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Fresenius Kabi USA, LLC
Address: 1501 E. Woodfield Road, Suite 300 East
Schaumburg, IL 60173
Representative: Aditi Dron, Regulatory Affairs Manager
Telephone: (847)330-3898

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name: Bortezomib for Injection
- c) Code Name/# (ONDQA only): 761210
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Selective inhibitor of the 26S mammalian proteasome, which is a large protein complex, consisting of 19S and 20S subunits that degrade ubiquitinated proteins

11. DOSAGE FORM: Sterile lyophilized

12. STRENGTH/POTENCY: 3.5 mg/vial

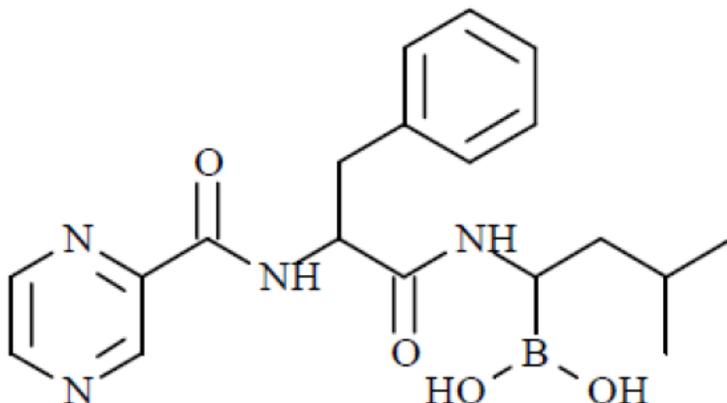
13. ROUTE OF ADMINISTRATION: IV

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemistry Review Data Sheet

Chemical Name:

IUPAC: [(1R)-3-methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)propyl]amino] boronic acid

USAN: Bortezomib

CAS Registry No.: 179324-69-7

Molecular Formula: C₁₉H₂₅BN₄O₄

Molecular Weight: 384.24 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	26-Apr-2013	N/A
	III			1	Adequate	28-DEC-2012	N/A
	III			1	Adequate	04-SEP-2012	N/A
	V			1	Adequate	13-DEC-2012	N/A
	III			1	Adequate	25-Apr-2013	N/A

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)**B. Other Documents:**

N/A

Chemistry Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistic	N/A	N/A	N/A
EES	Withhold	18-Jan-2013	N/A
Drug Substance	DMF Inadequate	Up to the date	Jean (Zhe) Tang
Drug Product	Complete response	Up to the date	Jean (Zhe) Tang / Donghao (Robert) LU
Pharm/Tox	Satisfactory	08-Apr-2013	Pedro Del Valle
Biopharm	Complete Response	22-Apr-2013	Kelly Kitchens
LNC	N/A	N/A	N/A
Methods Validation	N/A, according to the current ONDQA policy	N/A	N/A
DMEPA*	N/A	N/A	N/A
EA	Satisfactory	Up to the date	Jean Tang
Microbiology	Satisfactory	08-Apr-2013	Erika Pfeiler

The Chemistry Review for NDA 205-004

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is not recommended for APPROVAL from a CMC perspective due to the unsolved deficiencies described on page 90. Additionally, the manufacturing and testing facilities for the drug substance and drug product have an unacceptable overall recommendation from the Office of Compliance (Attachment II)

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCE

The drug substance is Bortezomib. The chemical name is [(1R)-3-methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) propyl]amino] boronic acid. It has a molecular formula of $C_{19}H_{25}BN_4O_4$ and its molecular weight is 384.24. All the related CMC information were referenced to DMF (b)(4) (type II). The NDA contains a letter of authorization, dated October 30, 2012, to the above DMF (b)(4). (b)(4) is the DMF holder; DMF (b)(4) was reviewed by OGD (Dr. Mike Dari) on June 02, 2010. There was no concern on the process section. However, there were two deficiencies related to residual solvent and potency. The DMF holder provided responses to these deficiencies which were reviewed and found acceptable by Dr. Jean Tang, concurrently with this NDA. Based on the stability data provided, the drug substance was granted a retest period of (b)(4) months.

DRUG PRODUCT

The drug product is Bortezomib for Injection, 3.5 mg/mL, Sterile Lyophilized. Bortezomib for Injection is an oncology drug product that is used for treatment of patients with multiple myeloma and patients with mantle cell lymphoma. The proposed clinical use for this submission will be consistent with current Velcade® (listed drug) labeling for the intravenous route of administration and carved out for the subcutaneous route of administration.

Executive Summary Section

Bortezomib for injection is filled in amber, (b) (4), Type I USP glass vials. The amber glass (b) (4) vials are closed with gray (b) (4) rubber, (b) (4) stoppers and capped with aluminum crimped flip-off seals. (b) (4)

Each single use vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. Inactive ingredients include 10.5 mg boric acid and 25 mg glycine. The manufacturing process for bortezomib for injection consists of (b) (4)

Specifications for the drug product include description, identification, assay, impurity, reconstitution time, constituted solution, water content, uniformity of dosage units, (b) (4) color, container/closure integrity, (b) (4), particulate matter in injections, sterility, bacterial endotoxins and statement of compliance to USP<467>. Based on the submitted stability data, expiry date of 24 months for drug product is granted.

B. Description of How the Drug Product is Intended to be Used

Bortezomib for Injection is a selective inhibitor of the 26S mammalian proteasome, which is a large protein complex, consisting of 19S and 20S subunits that degrade ubiquitinated proteins. Bortezomib for Injection is an oncology product that is used for treatment of patients with multiple myeloma and patients with mantle cell lymphoma. The proposed clinical use for this submission will be consistent with current Velcade® labeling for the intravenous route of administration and carved out for the subcutaneous route of administration.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, there were several CMC concerns (information request) that were sent to the sponsor on March 15, 2013. Fresenius Kabi USA, LLC has submitted responses to these CMC issues. However, there are still outstanding CMC concerns which were addressed adequately by the sponsor.. This NDA is thus not recommended for APPROVAL from a CMC perspective due to the unsolved deficiencies listed on page 92. The sponsor's responses and the CMC evaluations for these responses are described at the end of this document.

III. Administrative**A. Reviewer's Signature**

(See appended electronic signature page)

Z. Jean Tang, Ph.D.
CMC Reviewer
Branch III, Division I, ONDQA

Executive Summary Section

CDER, FDA

B. Endorsement Block

(See appended electronic signature page)

Ali Al Hakim, Ph.D.

Branch Chief

Branch II, Division I, ONDQA

CDER, FDA

C. CC Block entered electronically in DARRTS

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

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

/s/

ZHE J TANG
04/29/2013

ALI H AL HAKIM
04/29/2013
I concur

NDA 205004

Bortezomib for Injection

3.5 mg/vial

Fresenius Kabi USA, LLC

Division of Oncology Drug Products

Donghao (Robert) Lu, Ph.D.
Division I of Pre-Marketing Assessment
Office of New Drug Quality Assessment

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Chemistry Review Data Sheet

1. **NDA 205-004**
2. **REVIEW NUMBER:** 1
3. **REVIEW DATE:** 24 April 2013
4. **REVIEWER:** Donghao (Robert) Lu, Ph.D.
5. **PREVIOUS DOCUMENTS:**

PREVIOUS DOCUMENTS	DOCUMENT DATE
--------------------	---------------

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

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 205-004	30-Nov-2012
NDA 205-004, Amendment 004	05-Feb-2013
NDA 205-004, Amendment 006	21-Mar-2013
NDA 205-004, Amendment 008	29-Mar-2013

7. **NAME & ADDRESS OF APPLICANT:**

NAME:	Fresenius Kabi USA, LLC
ADDRESS:	1501 E. Woodfield Road, Suite 300 East Schaumburg, IL 60173
REPRESENTATIVE:	Aditi Dron, Regulatory Affairs Manager
TELEPHONE:	(847)330-3898

Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	N/A
NON-PROPRIETARY NAME (USAN)	Bortezomib for Injection
CODE NAME/ NUMBER (ONDC ONLY)	761210
CHEMISTRY TYPE / SUBMISSION PRIORITY	3S

9. LEGAL BASIS FOR SUBMISSION: 505(b)2

10. PHARMACOL. CATEGORY: Selective inhibitor of the 26S mammalian proteasome, which is a large protein complex, consisting of 19S and 20S subunits that degrade ubiquitinated proteins

11. DOSAGE FORM: Sterile lyophilized

12. STRENGTH/POTENCY: 3.5 mg/vial

13. ROUTE OF ADMINISTRATION: IV

14. R_x/OTC DISPENSED: R_x OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name (USAN, INN): Bortezomib

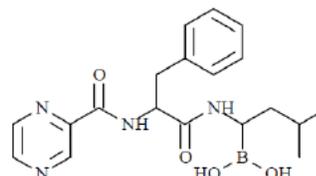
Name (IUPAC): [(1R)-3-methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) propyl]amino] boronic acid

CAS Registry No. 179324-69-7

Structural Formula:

Mol. Formula: C₁₉H₂₅BN₄O₄

Mol. Wt.: 384.24 g/mol



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs (see substance/product review by Dr. Jean Tang in DARRTS)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

See substance/product review by Dr. Jean Tang in DARRTS

The Chemistry Review for NDA 205-004

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is not recommended for APPROVAL from a CMC perspective due to the unsolved deficiencies. Additionally, the manufacturing and testing facilities for the drug substance and drug product have an unacceptable overall recommendation from the Office of Compliance.

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

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is Bortezomib. The chemical name is [(1R)-3-methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) propyl]amino] boronic acid. It has a molecular formula of $C_{19}H_{25}BN_4O_4$ and its molecular weight is 384.24. All the related CMC information were referenced to DMF (b)(4) (type II). The NDA contains a letter of authorization, dated October 30, 2012, to the above DMF (b)(4). (b)(4) is the DMF holder; DMF (b)(4) was reviewed by OGD (Dr. Mike Dari) on June 02, 2010. There was no concern on the process section. However, there were two deficiencies related to residual solvent and potency. The DMF holder provided responses to these deficiencies which were reviewed and found acceptable by Dr. Jean Tang, concurrently with this NDA. Based on the stability data provided, the drug substance was granted a retest period of (b)(4) months.

2. Drug Product

The drug product is Bortezomib for Injection, 3.5 mg/mL, Sterile Lyophilized. Bortezomib for Injection is an oncology drug product that is used for treatment of patients with multiple myeloma and patients with mantle cell lymphoma. The proposed clinical use for this submission will be consistent with current Velcade® (listed drug) labeling for the intravenous route of administration and carved out for the subcutaneous route of administration.

Chemistry Assessment Section

Bortezomib for injection is filled in amber, (b) (4) Type I USP glass vials. The amber glass (b) (4) vials are closed with gray (b) (4) rubber, (b) (4) stoppers and capped with aluminum crimped flip-off seals. (b) (4)

(b) (4) Each single use vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. Inactive ingredients include 10.5 mg boric acid and 25 mg glycine. The manufacturing process for bortezomib for injection consists of (b) (4)

(b) (4) Specifications for the drug product include description, identification, assay, impurity, reconstitution time, constituted solution, water content, uniformity of dosage units, (b) (4), container/closure integrity, (b) (4), particulate matter in injections, sterility, bacterial endotoxins and statement of compliance to USP<467>. Based on the submitted stability data, expiry date of 24 months for drug product is granted.

B. Description of How the Drug Product is Intended to be Used

Bortezomib for Injection is a selective inhibitor of the 26S mammalian proteasome, which is a large protein complex, consisting of 19S and 20S subunits that degrade ubiquitinated proteins. Bortezomib for Injection is an oncology product that is used for treatment of patients with multiple myeloma and patients with mantle cell lymphoma. The proposed clinical use for this submission will be consistent with current Velcade® labeling for the intravenous route of administration and carved out for the subcutaneous route of administration.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, there were several CMC concerns (information request) that were sent to the sponsor on March 15, 2013. Fresenius Kabi USA, LLC has submitted responses to these CMC issues. However, there are still outstanding CMC concerns which were not addressed adequately by the sponsor. This NDA is thus not recommended for APPROVAL from a CMC perspective due to the unsolved deficiencies. The sponsor's responses and the CMC evaluations for these responses are described at the end of this document.

Chemistry Assessment Section

III. Administrative**A. Reviewer's Signature**

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ali Al Hakim, Ph.D., Ph.D.

C. CC Block

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/s/

DONGHAO R LU
04/29/2013

ALI H AL HAKIM
04/29/2013
I concur

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205004	Reviewer: Kelly M. Kitchens, Ph.D.	
Submission Date:	November 30, 2012		
Division:	Division of Hematology Products	Team Lead: Angelica Dorantes, Ph.D.	
Applicant:	Fresenius Kabi USA, LLC	Acting Supervisor: Richard Lostritto, Ph.D.	
Trade Name:	None proposed	Date Assigned:	December 3, 2012
Established Name:	Bortezomib for Injection	Date of Review:	April 8, 2013
Indication:	Indicated for treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy.	Type of Submission: Original New Drug Application 505(b)(2)	
Formulation/ strengths	Sterile lyophilized/ 3.5 mg/vial		
Route of Administration	Intravenous		
Type of Review:	Biowaiver Request		
<u>SUMMARY:</u>			
<p>Background: Bortezomib for Injection is being developed as a sterile lyophilized solid (powder or cake) containing 3.5 mg bortezomib in a 10 mL vial, and is indicated for treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy. The reference listed drug (RLD) for Bortezomib for Injection is Velcade® (bortezomib) for Injection (NDA 021602), which has the same indication as Bortezomib for Injection. Velcade® (bortezomib) for Injection is approved for <u>intravenous or subcutaneous</u> route of administration at concentrations of 1 mg/mL or 2.5 mg/mL, respectively.¹ After reconstitution to 1.0 mg/mL with commercially available 0.9% Sodium Chloride Injection, USP, Bortezomib for Injection is intended for 3-5 second bolus <u>intravenous</u> route of administration.</p> <p>Submission: NDA 205-004 is a 505(b)(2) submission in which the Applicant is requesting a waiver for the requirement to provide in-vivo bioavailability/bioequivalence studies as per 21 CFR § 320.22(d).</p> <p>Review: The Biopharmaceutics review is focused on the evaluation and approvability of the information submitted to support the biowaiver request.</p>			

¹ Drugs@FDA, http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021602s031s032lbl.pdf

The proposed drug product formulation contains the same active ingredient in the same concentration as the RLD. However, boric acid and glycine were used as excipients in the proposed drug product formulation, instead of mannitol, which was used as the only excipient in the RLD. The Applicant submitted evidence to demonstrate that the physiological disposition of the proposed drug product does not differ from that of the RLD product in the absence of mannitol and inclusion of glycine. In addition, comparative osmolarity data was submitted for the proposed drug product and the RLD.

RECOMMENDATION:

The evidence that the different composition of Bortezomib for Injection compared to that of the RLD, Velcade®, does not affect the physiological disposition of the proposed drug product is lacking. Therefore, the waiver for in-vivo bioavailability/bioequivalence studies cannot be granted. To support the approval of the biowaiver, the Applicant should adequately address the following request:

- *You have not provided adequate supportive information demonstrating that the physiological disposition of your proposed drug product does not differ from that of the reference listed drug product in the absence of mannitol and inclusion of glycine. To support the approval of the biowaiver, submit a strong justification and evidence that the removal of mannitol and inclusion of glycine does not have any effect on the physiological disposition of your proposed drug product. You may include literature references to support your justification.*

From the Biopharmaceutics perspective, a **COMPLETE RESPONSE (CR)** is recommended for NDA 205004 for Bortezomib for Injection at this time. The above request should be included in the CR letter.

Signature

Kelly M. Kitchens, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. RLostritto.

BIOPHARMACEUTICS ASSESSMENT

The Applicant provided the following comparison table of the to-be-marketed drug product formulation to the RLD formulation:

Ingredients	Velcade®	Bortezomib for Injection
	Millenium Pharmaceuticals	FK USA
Bortezomib	3.5 mg/vial	3.5 mg/vial
Mannitol	35 mg/vial	N/A
Boric Acid, NF	N/A	10.5 mg/vial
Glycine, USP	N/A	25 mg/vial
(b) (4)		

¹ Please note that for the FK USA drug product water during the lyophilization process. (b) (4) removed (b) (4) (b) (4)

The above table indicates that proposed drug product formulation and the RLD formulation contain the same active ingredient in the same concentration. Boric acid and glycine were used as excipients in the proposed drug product formulation, instead of mannitol, which was used as the only excipient in the RLD. The applicant indicated that boric acid (b) (4)

A 74-day letter was issued to the Applicant on February 13, 2013, which identified potential review issues from the Biopharmaceutics perspective. The Applicant submitted responses to the potential review issues on March 21, 2013.

(The potential review issue #1 was issued and reviewed by the Product Quality Microbiology Reviewer, Dr. Erika Pfeiler).

Potential review issue #2: Submit justification that in the absence of mannitol and inclusion of glycine, the physiological disposition of the proposed drug product is not different than that of the RLD product.

Applicant's response to potential review issue #2:

Glycine is a non-essential amino acid that is biosynthesized in human body from serine in the reaction catalyzed by glycine hydroxymethyltransferase. Glycine is needed for the synthesis of porphyrins, purine base, glutathione and bile salts, detoxification of benzoic acid, and, especially, synthesis of collagen and other proteins. The composition of glycine in collagen is approximately one-third of the total amino acid residues present. An estimate of total glycine biosynthesis in humans at 3 g/day is reported in literature. See [MELENDEZ 2009](#).

The proposed drug product contains Bortezomib at 3.5 mg/vial and glycine at 25 mg/vial. Upon injection of the drug product for (b) (4) mg maximum bortezomib daily dose, a patient also receives from the proposed drug product the maximum amount of glycine at (b) (4) mg/day, which is only a small fraction ((b) (4) %) of the estimated daily glycine biosynthesis in humans at 3 g/day.

Based on the above information, it is very unlikely that glycine in the proposed drug product will have a significant influence on normal physiological condition to the extent that would affect the drug disposition any differently than that of the RLD.

In addition, cumulative evidence provided in the original submission, supporting bioequivalence between the two products, has shown that RLD in the reconstituted solution is present in the same form as that found in the reconstituted solution of the proposed drug product. The small dose of mannitol ((b) (4) mg) in the RLD is not enough to induce changes in physiological condition of human body (refer to Response #3 below on osmolality). Therefore, the presence or absence of mannitol should not have any significant effect on the physiological disposition of the drug.

Biopharmaceutics Reviewer comments:

- The Applicant indicated that the amount of glycine administered ((b) (4) mg/day) in the maximum daily dose of the proposed drug product is negligible compared to the approximately 3 g glycine that is biosynthesized in humans per day.
- The Applicant also suggests that the removal of mannitol from the proposed drug product composition should not affect the physiological disposition of the drug since mannitol inclusion in the RLD composition does not affect the physiological disposition of the drug.

Overall Assessment for Issue #2: Inadequate

The Applicant's response to potential review issue #2 is **not acceptable**. The Applicant will be requested to submit stronger justification that the removal of mannitol and inclusion of glycine does not affect the physiological disposition of the drug product.

Potential review issue #3: Submit comparative physicochemical property data, such as osmolarity of the proposed drug product and the RLD product. The comparative data for the proposed drug product and RLD product should be provided using at least 3 production lots, if available, of the proposed drug product, and 3 commercial lots of the RLD product. The measurements should be done in triplicate for each lot tested.

Applicant's response to potential review issue #3:

Since 0.9% Sodium Chloride Injection, USP is used for reconstitution of the drug products as recommended by the RLD (Velcade®) product insert, the resulting reconstituted solutions of each drug product are expected to be slightly hypertonic.

FK USA results for testing done in triplicate for the proposed drug product and the RLD are summarized on page 5 in the following **TABLE I**: Comparison of Osmolality of Drug Product Reconstituted Solutions, Normal Saline Solution and Parenteral Hypertonic Saline Solutions.

Osmolality of the proposed drug product is 430-450 mOsmol/kg and of the RLD is 332 – 343 mOsmol/kg. These results are slightly higher than a normal physiological osmolarity range of 280-310 mOsmol/L, but are lower than 600 mOsmol/L where potential vein damage might become a caution for concern. Please note that the results are much lower than results of 1,027 – 1711 mOsmol/L for hypertonic parenteral solutions of 3% and 5% Sodium Chloride Injection, USP, administered intravenously for fluid and electrolytes replenishment as reported in literature. Please see references **SODIUM CHLORIDE 3-5 PERCENT** and **DAILY MED – SODIUM CHLORIDE** and **HYPOTONIC SALINE INFO**.

In addition, the maximum IV bolus injection volume of the Bortezomib drug products (^(b)₍₄₎ mL for the maximum daily dose of ^(b)₍₄₎ mg) is much smaller than the infusion volume of 3% or 5% Sodium Chloride Injection, USP administered at 100 mL/hr (maximum 400 mL/day) to cause changes in physiological parameters in the body (e.g., cellular dehydration, sensitization of osmo receptors, stimulating secretion of the antidiuretic hormone, increasing retention of body fluid, etc.).

Based on the above information, it is very unlikely that the small ^(b)₍₄₎ mL IV bolus injection volume of the proposed drug product having relatively low osmotic pressure of 430-450 mOsmol/kg will significantly alter physiological parameters of the body in a different manner than the RLD which has similar osmotic pressure.

Other physicochemical properties (pH, viscosity, surface tension) are not expected to have a significant influence on the absolute bioavailability of either the proposed drug

product or the RLD. The pH results of the proposed drug product were provided and discussed in the original submission (pH (b)(4)) and are within the range of the RLD recommended diluent (pH (b)(4)). Neither the proposed drug product nor the RLD contain a viscosity imparting agent or a surfactant. The RLD contains mannitol and the proposed drug product contains glycine and boric acid. In addition, the total excipient content quantity is similar for the proposed drug product (35.5 mg/vial) and the RLD (35 mg/vial). Therefore, viscosity and surface tension of the proposed drug product and the RLD are not expected to be different or have significant effect on absolute bioavailability and the drug disposition in the body.

TABLE I: Comparison of Osmolality of Drug Product Reconstituted Solutions, Normal Saline Solution and Parenteral Hypertonic Saline Solutions

Product Name	Lot Number	Test Date	Osmolality Results of Reconstituted Solution (mOsmol/kg) ¹
Bortezomib for Injection (exhibit batches)	C340-013	Jan 2012	444
			439
			450
	R340-024	Jan 2012	435
			439
			430
	R340-025	Jan 2012	438
			432
			440
Velcade®	BGLSJ00 (expiry June 2014)	Mar 2013	340
			339
			332
	BGLSI01 (expiry June 2014)	Mar 2013	337
			340
			341
	BILSO00 (expiry August 2014)	Mar 2013	337
			340
			343
Osmolarity of Normal Physiological Range: 280 – 310 mOsmol/L			
Osmolarity of 0.9% Sodium Chloride Injection, USP: 308 mOsmol/L			
Osmolarity of 3% Sodium Chloride Injection, USP: 1027 mOsmol/L			
Osmolarity of 5% Sodium Chloride Injection, USP: 1711 mOsmol/L			

¹Test results are measured as Osmolality (mOsmol per kilogram of solution).

Biopharmaceutics Reviewer comments:

- The mean osmolality of the proposed drug product (439 mOsmol/kg) is 29.5% greater than the mean osmolality of the RLD (339 mOsmol/kg). These results do not demonstrate that the proposed drug product has comparable osmolality to the RLD.

- The Applicant provided references that report the osmolarity of 3% and 5% Sodium Chloride Injection, USP, as between 1027 – 1711 mOsmol/L, which is much greater than the osmolarity of the proposed drug product.
- The Applicant also indicated that the volume of the proposed drug product administered is much smaller than that of 3% and 5% Sodium Chloride Injection, USP. The recommended starting dose of bortezomib is 1.3 mg/m², equivalent to approximately (b) (4) mL of bortezomib, and is administered twice weekly during cycles 1-4, and once a week during cycles 5-9. The recommended maximum daily dose of 3% and 5% Sodium Chloride Injection, USP is 400 mL/day.
- In addition, this reviewer consulted with the Division of Hematology Products Clinical Reviewer to inquire if the higher osmolarity of the proposed drug product presents any safety concerns. The Clinical Reviewer, Karen McGinn, MSN, CRNP, indicated that the proposed drug product is not expected to disrupt blood vessels since the osmolality results are less than 500 mOsmol/kg.
- The pH results for the proposed drug product at accelerated storage conditions (1, 2, 3, and 6 months at 40±2°C/75±5% RH) and long term storage conditions (3, 6, 9, 12, and 18 months at 25±2°C/60±5% RH) are 5.7 – 5.8 and 5.5 – 5.9. These pH values are within the pH range of the RLD in water (2.0 – 6.5) and the pH range of the reconstitution diluent, 0.9% Sodium Chloride Injection, USP (b) (4). The pH values of the proposed drug product are comparable to those of the RLD.

Overall Assessment for Issue #3: Satisfactory

The Applicant’s response to potential review issue #3 is adequate and acceptable.

RECOMMENDATION:

The evidence that the different composition of Bortezomib for Injection compared to that of Velcade® does not affect the physiological disposition of the proposed drug product is lacking. Therefore, the waiver for in-vivo bioavailability/bioequivalence studies cannot be granted. To support the approval of the biowaiver, the Applicant should adequately address the following request:

Your response to potential review issue #2 does not demonstrate that the physiological disposition of your proposed drug product does not differ from that of the reference listed drug product in the absence of mannitol and inclusion of glycine. Submit a strong justification and evidence that the removal of mannitol and inclusion of glycine does not affect the physiological disposition of the drug product. You may include literature references to support your justification.

From the Biopharmaceutics perspective, at this time a COMPLETE RESPONSE is recommended for NDA 205004 for Bortezomib for Injection. The above request should be conveyed to the Applicant in the Complete Response letter.

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/s/

KELLY M KITCHENS
04/22/2013

ANGELICA DORANTES
04/22/2013

Product Quality Microbiology Review

05 April 2013

NDA: 205004

Drug Product Name

Proprietary: None listed

Non-proprietary: Bortezomib for Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
30 NOV 2012	03 DEC 2012	07 DEC 2012	12 DEC 2012
21 MAR 2013	21 MAR 2013	N/A	N/A

Applicant/Sponsor

Name: Fresenius Kabi USA, LLC

Address: 1501 East Woodfield Road, Suite 300E, Schaumburg, IL
60173

Representative: Aditi Dron

Telephone: 847-330-3898

Name of Reviewer: Erika Pfeiler, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** 505(b)(2)
 - 2. SUBMISSION PROVIDES FOR:** Initial marketing of a sterile drug product
 - 3. MANUFACTURING SITE:**
Fresenius Kabi USA, LLC
3159 Staley Road
Grand Island, NY 14072
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
Sterile lyophilized powder in a 10 ml glass vial
3.5 mg/vial, diluted to 1 mg/ml with sterile 0.9% sodium chloride
 - 5. METHOD(S) OF STERILIZATION:** [REDACTED] (b) (4)
 - 6. PHARMACOLOGICAL CATEGORY:** treatment of patients with multiple myeloma or with mantle cell lymphoma
- B. SUPPORTING/RELATED DOCUMENTS:**
Microbiology Review 9 of DMF [REDACTED] (b) (4) (DARRTS Date 13 December 2011)
- C. REMARKS:** This application was submitted in the eCTD format.

filename: N205004R1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – Recommend approval on the basis of product quality microbiology.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – Product is sterilized (b) (4).
- B. Brief Description of Microbiology Deficiencies** – N/A
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A

III. Administrative

- A. Reviewer's Signature** _____
Erika Pfeiler, Ph.D.
- B. Endorsement Block** _____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer
- C. CC Block**
N/A

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/s/

ERIKA A PFEILER
04/05/2013

STEPHEN E LANGILLE
04/08/2013

**Initial Quality Assessment
Division of New Drug Quality Assessment I
Branch II**

OND Division: Division of Hematology Products
NDA: 205004
Applicant: Fresenius Kabi USA, LLC
Stamp Date: 03-Dec-2012
PDUFA Date: Standard 03-Oct-2013
Proprietary (Brand) Name of Drug Product: None
Established Name: Bortezomib for Injection
Dosage Form(s): Lyophilized powder
Strength(s): 3.5 mg/vial
Route of Administration: Intravenous
Proposed Indication(s): Indicated for treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy.
CMC Lead: Janice Brown, Branch II/DNDQA1/ONDQA
Chief, Branch II (Acting): Nallaperumal Chidambaram/DNDQA1/ONDQA
Review team recommendation: CMC reviewer: Zhe (Jean) Tang
 Biopharmaceutics reviewer: Kelly Kitchens

	Yes	No
ONDQA Fileability:	X	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	X

CONSULTS/ CMC RELATED REVIEWS

Consult	Comment
ONDQA Biopharmaceutics	Kelly Kitchens
CDRH	Not Applicable
EA	Categorical exclusion requested
EES	Inspection request was submitted on 13-Dec-2012
DMEPA	Labeling consult request will be sent as part of DHP request.
Methods Validation	Not required per IQP 5105
Microbiology	Erika Pfeiler
Pharm-Tox	Determined by primary reviewer

SUMMARY

This 505(b)(2) application relies on the FDA’s finding of safety and effectiveness of the reference listed drug, Velcade® (bortezomib) for Injection marketed by Millennium Pharmaceuticals, Inc. under NDA 21602. Reproduced in table 1 is a comparison of the Velcade for injection (listed drug) and the proposed drug product, Bortezomib for Injection, described in this NDA.

The recommended dose of Bortezomib for Injection is 1.3 mg/m² administered as a 3 to 5 second bolus intravenous injection after reconstitution. The subcutaneous route of administration and all relevant information in the RLD package insert has been carved out of the FK labeling since the proposed drug product is submitted only for the intravenous route of administration.

Table 1: Comparison of the Listed Drug and Bortezomib for Injection

Name	Listed Drug	Proposed Drug Product
	Velcade® (bortezomib) for Injection	Bortezomib for Injection
Conditions of Use (Indications)	Velcade® (bortezomib) for Injection is indicated for treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy.	Bortezomib for Injection is indicated for treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy.
Dosage Form	White to off-white cake or powder	White to off-white cake or powder
Route of Administration	Intravenous Injection: After reconstitution to 1.0 mg/mL with commercially available 0.9% Sodium Chloride Injection, USP, the product is intended for 3-5 second bolus intravenous administration. Subcutaneous use: Velcade® may be administered subcutaneously at a concentration of 2.5 mg/mL. For additional information see package insert.	Intravenous Injection: After reconstitution to 1.0 mg/mL with commercially available 0.9% Sodium Chloride Injection, USP, the product is intended for 3-5 second bolus intravenous administration. Subcutaneous use: Not applicable for the proposed drug product for this submission.
Vial size	10 mL	10 mL
Active Ingredient	Bortezomib	Bortezomib
Strength	3.5 mg/vial	3.5 mg/vial
Excipients		
Mannitol	35 mg/vial	N/A
Boric Acid, NF	N/A	10.5 mg/vial
Glycine, USP	N/A	25 mg/vial

(b) (4)

DRUG SUBSTANCE

1. The applicant provided a letter of authorization from (b) (4) dated 30-Oct-2012 allowing the agency to review the confidential information in DMF No. (b) (4). DMF (b) (4) was reviewed by OGD and two remaining deficiencies need to be resolved before the DMF is deemed adequate. Only summary drug substance information can be included in this IQA since the CMC information for the drug substance is included in the DMF. The primary reviewer should review the holders response to the deficiencies identified in the OGD review.
2. A complete list of the Bortezomib drug substance manufacturing facilities is appended as attachment 1. Bortezomib is manufactured and controlled by:
(b) (4)
3. The DMF review has identified the following physicochemical characteristics of Bortezomib:
(b) (4)
4. **IMPURITIES** - DMF review #1 lists the drug substance impurities as the bortezomib (b) (4) impurities.
5. **DRUG SUBSTANCE SPECIFICATION** - The bortezomib drug substance specification is appended as attachment 3.
6. **BATCH DATA** - The applicant submitted the COA for three batches (Lot 0907791, 10020261 and 1114435) of Bortezomib drug substance. All batches met the proposed acceptance criteria.
7. **CONTAINER – CLOSURE** - Bortezomib is packaged in (b) (4)

8. STABILITY - Bortezomib drug substance [REDACTED] (b) (4)
 [REDACTED] A retest period for the drug substance is [REDACTED] (b) (4)
 [REDACTED] months [REDACTED] (b) (4)

DRUG PRODUCT

9. Bortezomib for Injection is supplied as a single dose sterile lyophilized solid (powder or cake) containing 3.5 mg bortezomib in a 10 mL vial. Each vial is reconstituted with 3.5mL 0.9% sodium chloride (not supplied) to produce a final bortezomib concentration of 1 mg/mL. Other diluents are not allowed.
10. Bortezomib for Injection is formulated with 10.5 mg boric acid and 25 mg glycine. A comparison of the composition between Bortezomib for Injection and the LD, Velcade, is reproduced in table 2.

Table 2: Bortezomib and Velcade (listed drug) formulation comparison

Ingredients	Velcade ®	Bortezomib for Injection	Function of Ingredients
	Amount	Amount	
Bortezomib	3.5 mg/vial	3.5 mg/vial	Active pharmaceutical ingredient
Mannitol	35 mg/vial	N/A	[REDACTED] (b) (4)
Boric Acid, NF	N/A	10.5 mg/vial	[REDACTED]
Glycine, USP	N/A	25 mg/vial	[REDACTED]

¹ Water [REDACTED] (b) (4)
 removed during lyophilization. [REDACTED] (b) (4)

11. The applicant, Fresenius Kabi USA, LLC. (FK USA) has requested a waiver for *in-vivo* bioavailability/bioequivalence requirements for Bortezomib for Injection. The biowaiver will be reviewed by Dr. Kitchens, the assigned ONDQA biopharm reviewer.
12. The pharmaceutical development section includes a study report (PD11-NB/F-016) titled, "An In-vitro study to compare proteasome inhibitory activity of APP's Bortezomib for Injection with Velcade". After discussion with Julie Bullock, Clinical Pharmacology Team Leader, the study will be reviewed by Young-Jin Moon the assigned Clinical Pharmacology reviewer.
13. [REDACTED] (b) (4)

(b) (4)



14. FK USA has identified two physical chemical characteristics of Bortezomib that affect the formulation:

(b) (4)



15. The Bortezomib for injection manufacturing flow diagram is reproduced in attachment 4.

(b) (4)



The acceptability of the sterile processing will be performed by OPS Microbiology reviewer.

16. The drug product specification is appended in attachment 5.

17. DRUG PRODUCT IMPURITIES – The applicant has identified 2 degradation products (b) (4) [Impurity A]) and two process related impurities from the bortezomib drug substance (b) (4). Included in table 3 is a summary of the proposed impurity limits along with impurity results from batches manufactured at the investigational and proposed commercial sites. The applicant’s proposed impurity limits are permissive when compared to batch data.

Table 3: Justification of Impurity Limits for the Drug Product

Impurity	Proposed Acceptance Criteria	Justification	Exhibit Batches at Long Term Storage RT			
			I inverted	U upright	FIO – For Information only	
			R340-024	R340-025	C340-013	R342-032
			18 mo I	18 mo I	18 mo I	3 mo U
(b) (4)	(b) (4)	(b) (4)	(b) (4)			
	Not required	Process impurity controlled in API				
	Not required	Process impurity controlled in API				
Largest Unspecified Impurity	(b) (4)	ICH Q3B identification threshold				

18. CLOSURE SYSTEM –Bortezomib for Injection will be filled into amber, (b) (4) Type I USP glass vials provided by either (b) (4). The amber glass (b) (4) vials are closed with (b) (4) gray (b) (4) rubber; (b) (4) stoppers provided by (b) (4) and capped with aluminum crimped flip-off seals provided by (b) (4).

19. DRUG PRODUCT STABILITY STUDIES

19.1 The applicant submitted 18 months of long term stability data 25°C ± 2°C/60% RH and 6 months of accelerated stability data (40°C ± 2°C/75% ± 5% RH) for three primary lots (batches # R340-024, R340-025, C340-013) of drug product produced at (b) (4) to support a 24 month expiry.

19.2 3 months of long term and accelerated stability data was submitted for one lot (batch # R342-032) of drug product manufactured at the proposed commercial

site, FK USA Production personnel, Grand Island, NY. See comments under “Critical Issues for Review” at the end of this IQA.

- 19.3 A stability commitment provides that the first three commercial production batches for Bortezomib for Injection will be placed on stability ($25 \pm 2^\circ\text{C}$, $60 \pm 5\%$ RH)
- 19.4 The stability results for all lots have met all acceptance criteria for the proposed specification at the long-term and accelerated storage conditions up to 18 months and 6 months, respectively. Included in table 3.2.P.8.1-1 is a summary of the stability batches.

Table 3.2.P.8.1- 1 Overview of Stability Batches Filled

Batch no.	Con-tainer size [mL]	Batch size [litre]	Pro-duction Date	Batch type	Start of Storage ¹	Orien-tation	Study type storage conditions
R340-024	10	(b) (4)	08/02/10	Exhibit	9/17/10	Upright, Inverted	long-term $25^\circ\text{C} \pm 2^\circ\text{C}/60\% \pm 5\%$ RH
R340-025	10		08/23/10	Exhibit	9/17/10		accelerated $40^\circ\text{C} \pm 2^\circ\text{C}/75\% \pm 5\%$ RH
C340-013	10		09/03/10	Exhibit	9/17/10		long-term $25^\circ\text{C} \pm 2^\circ\text{C}/60\% \pm 5\%$ RH
R342-032	10		05/30/12	Process Qualification	06/17/12		accelerated $40^\circ\text{C} \pm 2^\circ\text{C}/75\% \pm 5\%$ RH

¹ Date when samples were placed in the stability chamber.

19.5 PHOTOSTABILITY

19.5.1 [Redacted] (b) (4)

19.5.2 DRUG PRODUCT: [Redacted] (b) (4)

19.5.3 The applicant submitted in-use stability of reconstituted product tested after 8 hours storage at ambient conditions (see table 4). The maximum reconstitution time of 8 hours was evaluated in the original vial and in a syringe as indicated in the RLD package insert. Testing included Assay, Impurities, Clarity, Color, pH, and Particulate matter. All reconstituted

solution test results met the proposed specification. There is no test or limit for pH in the drug product specification which should be considered.

TABLE 4: Study Design for Reconstituted Solution Stability

Lot #	Strength (mg/vial)	Diluent	Target Bortezomib Concentration (mg/mL)	Duration of Storage at Room Temperature and Normal Indoor Lighting (25 ± 2°C, ~60 foot-candle)
R340-024	3.5	NS	1.0	8 hours in the original vial
				8 hours in a syringe

20. The drug product release and stability specifications are reproduced in attachments 5 and 6, respectively.

21. Supporting DMFs – Listed below are the DMFs for this submission.

DMF	TYPE	HOLDER	ITEM REFERENCED
(b) (4)	II		(b) (4)
	III		

22. Environmental Assessment: The applicant has submitted a claim for categorical exclusion under 21 CFR § 25.31(a), a categorical exclusion exists for Action on a NDA if the action does not increase the use of the active moiety.

23. Establishment Evaluation: A full list of facilities involved in the manufacture, packaging and testing of Bortezomib for injection is reproduced in attachment 1.

CRITICAL ISSUES FOR REVIEW

1. Developmental studies have shown that Bortezomib is extremely sensitive to light.

(b) (4)

(b) (4)

2. (b) (4)

3. (b) (4)

4.

5. The applicant submitted 18 months long term and 6 months accelerated for 3 batches produced at (b) (4). Only 3 months of stability data for one lot was submitted at their proposed commercial site FK USA in Grand Island, NY. According to Dr. Chidambaram, at a minimum release data from three validation batches from the proposed commercial site should be submitted.

Comments for 74-Day Letter: None.

ATTACHMENT 1: FACILITY INFORMATION – DRUG SUBSTANCE

Bortezomib Drug Substance Manufacturing and Testing Facilities

Facility Name	Contact Information	FEI/DUNS	Responsibilities
(b) (4)			Drug Substance Manufacturing, Release/Stability Testing, and Packaging
			Drug Substance Supplier
FK USA Innovation and Development Center and Quality Control Laboratories 8045 Lamon Ave., Suite 300, Skokie, IL 60077	Contact: David Bowman, VP of I & D Phone: (847) 983-7021 Fax: (847) 983-7054 Email: david.bowman@fresenius-kabi.com	FEI: 3008604776 DUNS: 033630841	Drug Substance Release Testing Chemistry/Analytical
FK USA 3159 Staley Road, Grand Island, NY 14072	Contact: Anne Huffman, Sr. Director of QA/QC Phone: (716) 774-3715 Fax: (716) 774-3762 Email: anne.huffman@fresenius-kabi.com	FEI: 3001833549 DUNS: 840771732	Drug Substance Release Testing Chemistry/Analytical Bacterial Endotoxins Microbial Bioburden
(b) (4)			

ATTACHMENT 2 – FACILITY INFORMATION DRUG PRODUCT

Drug Product Manufacturing and Testing Facilities

Facility Name	Contact Information	FEI/DUNS	Responsibilities
Fresenius Kabi USA, LLC (FK USA) 3159 Staley Road, Grand Island, NY 14072	Contact: Anne Huffman, Sr. Director of QA/QC Phone: (716) 773-3715 Fax: (716) 773-0840 Email: anne.huffman@fresenius-kabi.com	FEI: 3001833549 DUNS: 840771732	Drug product manufacturing, release/stability testing, and packaging
FK USA Innovation and Development Center and Quality Control Laboratories 8045 Lamon Ave., Suite 300, Skokie, IL 60077	Contact: David Bowman, VP of Product Development Phone: (847) 983-7021 Fax: (847) 983-7054 Email: david.bowman@fresenius-kabi.com	FEI: 3008603776 DUNS: 033630841	Alternate drug product release/stability testing
(b) (4)			

ATTACHMENT 3: DRUG SUBSTANCE SPECIFICATION

Regulatory Specification for Bortezomib

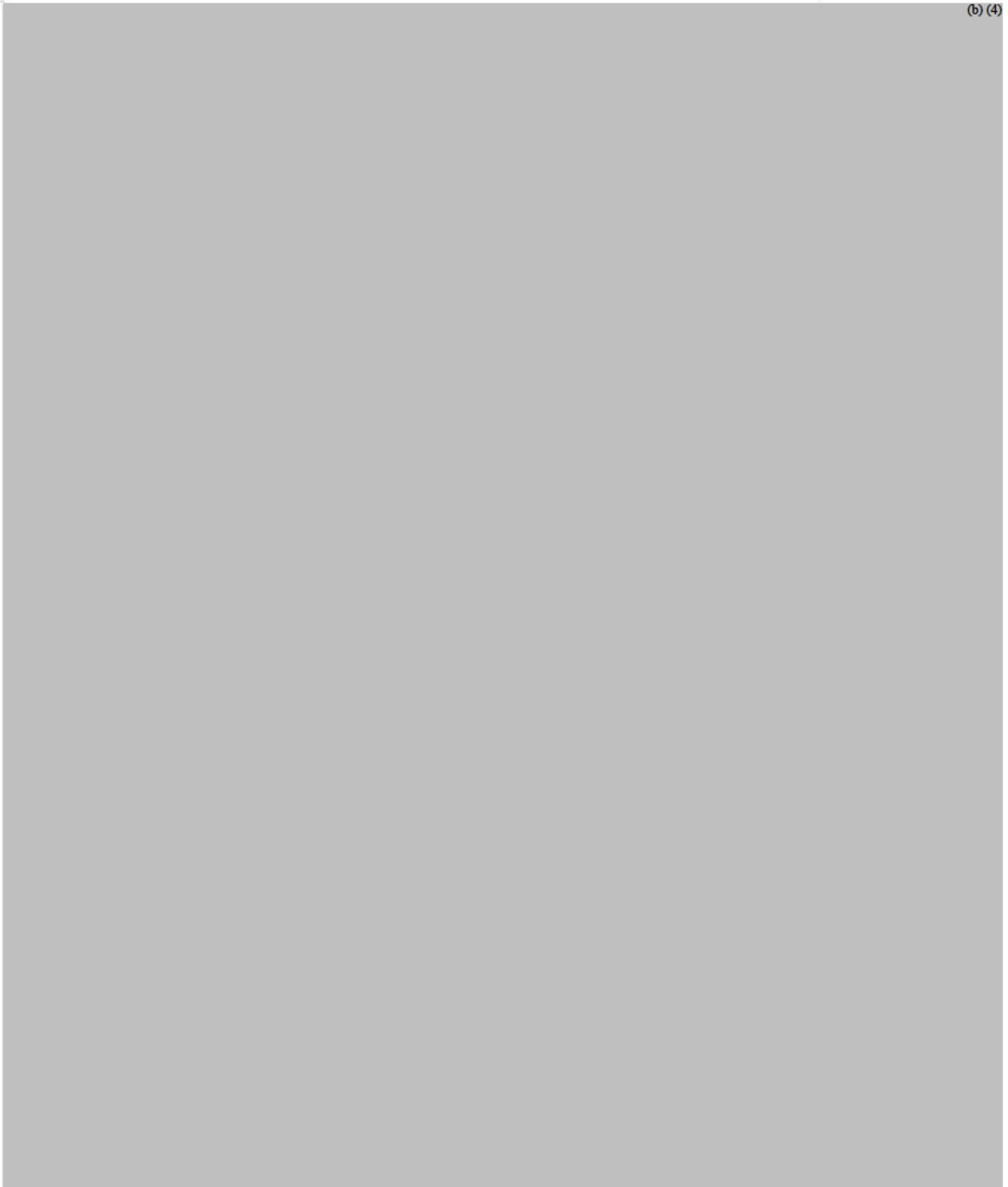
Test	Acceptance Criteria	Test Method ¹
Description	White to off-white solid or powder	Visual Examination
Identification:		
A. Infrared Absorption	A. The sample exhibits maximum absorption peaks at only the same wavelengths as a similar preparation of Bortezomib reference standard.	A. USP <197K>
B. HPLC	B. The retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the Assay. (b) (4)	B. 10-08-03-6530
Water	NMT (b) (4) %	USP <921> Method Ic
Heavy Metals	NMT (b) (4)	USP <231>, Method II
Chiral Purity Test	(b) (4) %	HPLC 10-08-01-6550
Assay	(b) (4) % (on anhydrous basis)	HPLC 10-08-03-6530
Chromatographic Purity (b) (4)	(b) (4)	
	A. NMT %	HPLC 10-08-03-6530
	B. NMT %	
	C. NMT %	
D. Any Other Individual Impurity	D. NMT %	
E. Total Impurities	E. NMT (b) (4) %	
Residual Solvents:	No other solvents, including those established as USP<467> Class 1, 2 or 3 solvents, are likely to be present in the raw material per manufacturer's certification other than those listed below.	USP <467>
A (b) (4)	A. NMT (b) (4) ppm5	GC 10-08-6337
B	B. NMT ppm5	
C	C. NMT ppm	
D	D. NMT (b) (4) ppm	
E	E. NMT (b) (4) ppm5	
Microbial Bioburden	Total Yeast and Mold Count NMT (b) (4) CFU/g	USP <61>, USP<1111>
	Total Aerobic Count NMT (b) (4) CFU/g	
Bacterial Endotoxin	NMT (b) (4) EU/mg	USP <85>

¹ References to compendia signify current compendia. If a compendial monograph or test changes, Fresenius Kabi USA, LLC will implement the changes and report them via annual report. (b) (4)

3 (b) (4)
 4
 5

ATTACHMENT 4: BORTIZOMIB FOR INJECTION DRUG PRODUCT
MANUFACTURING FLOW DIAGRAM

(b) (4)



ATTACHMENT 5: DRUG PRODUCT SPECIFICATION – 3.5 MG/ML

Table 3.2.P.5.1- 1 Regulatory Specifications for Bortezomib for Injection

Test	Acceptance Criteria	Test Method ¹
Description	Solid in an amber vial	Visual Examination
Identification:		
A. HPLC	A. The retention time of the major peak in the chromatogram of the <i>Assay preparation</i> corresponds to that of the <i>Standard Preparation</i> . (b) (4)	A. 10-08-03-6530
B. Ultraviolet (UV) Spectrum using Photodiode Array Detector	B. (b) (4) <i>Assay Preparation</i> exhibit maxima at the same wavelength (b) (4)	B. 10-08-03-6530
Reconstitution Time	Reconstitute each vial with 3.5 mL of 0.9% Sodium Chloride Injection, USP NMT (b) (4) minutes	10-08-05-6005
Constituted Solution		
1. Completeness	1. The solid dissolves completely leaving no visible residue as undissolved matter.	10-08-05-6005 USP-10
2. Clarity	2. The constituted solution is not significantly less clear than an equal volume of Sterile Water for Injection contained in a similar vial and examined similarly.	
3. Particulate Matter	3. The constituted solution is essentially free from particles of foreign matter that can be observed on visual inspection.	
4. Visual Color	4. Colorless	10-08-05-6005
Water Content	NMT (b) (4)%	10-08-03-6581 USP <921> Method 1c
Uniformity of Dosage Units	Meets USP requirements	USP <905>

Continued on next page.

ATTACHMENT 5: DRUG PRODUCT SPECIFICATION – 3.5 MG/ML - CONTINUED

Table 3.2.P.5.1-1 Regulatory Specifications for Bortezomib for Injection (cont.)

Test	Acceptance Criteria	Test Method ¹
Constituted Solution (cont.)		
(b) (4)		
Container Closure Integrity ²	The differential pressure of all sample vials being tested for each lot must be below the two bracketing Self Tests	10-08-00-6031 10-08-00-6032
Bortezomib Assay Label Claim 3.5 mg/vial	(b) (4) % of Label Claim	10-08-03-6530
Impurities ³		
(b) (4)	1. NMT (b) (4) %	10-08-03-6530
(b) (4)	2. NMT (b) (4) %	
3. Any Other Individual Impurity	3. NMT (b) (4) %	
4. Total Impurities	4. NMT (b) (4) %	
(b) (4)	(b) (4)	10-08-03-6537
Particulate Matter in Injections	1. For particles $\geq 10\mu\text{m}$: NMT (b) (4) per container 2. For particles $\geq 25\mu\text{m}$: NMT (b) (4) per container	USP <788>
Sterility ⁴	Sterile	USP <71>
Bacterial Endotoxins	NMT (b) (4) U/mg	USP <85>
(b) (4)		

¹ References to compendia signify current compendia. If a compendial monograph or test changes, FK USA will implement the changes and report them via annual report.

² CCT is performed only at annual stability interval

³ Please refer to the TABLE 3.2.P.5.1-1 above for the proposed limits and SECTION 3.2.P.5.6 for the justification of impurity limits.

The Certificates of Analysis (COAs) issued in support of this original 505(b)(2) application were generated for lots R340-025, R340-024, C340-013 and R342-032 that were manufactured on 08/02/2010, 08/23/2010, 09/03/2010 and 05/30/2012, respectively. FK USA has subsequently derived new limits for impurities (b) (4)

(b) (4) any other individual impurity and total impurities based on the application of ICH recommendations for setting impurity limits. Therefore, the COAs presented in SECTION 3.2.P.5.4 do not reflect most current limits.

⁴ Sterility test is performed only at release

ATTACHMENT 6: DRUG PRODUCT STABILITY SPECIFICATION

Bortezomib for Injection Stability Specification

Test	Acceptance Criteria	Test Method ¹
Description	Solid in an amber vial	Visual Examination
Identification ² :		
A. HPLC	A. The retention time of the major peak in the chromatogram of the <i>Assay preparation</i> corresponds to that of the <i>Standard Preparation</i> . (b) (4)	A. 10-08-03-6530
B. Ultraviolet (UV) Spectrum using Photoiodide Array Detector	B. (b) (4) <i>Assay Preparation</i> exhibit maxima at the same wavelength (b) (4)	B. 10-08-03-6530
Reconstitution Time	Reconstitute each vial with 3.5 mL of 0.9% Sodium Chloride Injection, USP NMT (b) (4) minutes	10-08-05-6005
Constituted Solution		
1. Completeness	1. The solid dissolves completely leaving no visible residue as undissolved matter	10-08-05-6005 USP<1>
2. Clarity	2. The constituted solution is not significantly less clear than an equal volume of Sterile Water for Injection contained in a similar vial and examined similarly.	
3. Particulate Matter	3. The constituted solution is essentially free from particles of foreign matter that can be observed on visual inspection.	
4. Visual Color	4. Colorless	10-08-05-6005
Water Content	NMT (b) (4)%	10-08-03-6581 USP <921> Method 1c

Continued on next page.

ATTACHMENT 6: DRUG PRODUCT STABILITY SPECIFICATION – CONTINUED

Bortezomib for Injection Stability Specification (cont.)

Test	Acceptance Criteria	Test Method ¹
Uniformity of Dosage Units ²	Meets USP requirements	USP<905>
(b) (4)		
Container/Closure Integrity	The differential pressure of all sample vials being tested for each lot must be below the two bracketing Self Tests	10-08-00-6031 10-08-00-6032
Bortezomib Assay Label Claim 3.5 mg/vial	(b) (4) of Label Claim	10-08-03-6530
Impurities		
(b) (4)	1. NMT (b) (4) %	10-08-03-6530
	2. NMT (b) (4) %	
3. Any Other Individual Impurity	3. NMT (b) (4) %	
4. Total Impurities	4. NMT (b) (4) %	
(b) (4)		
		10-08-03-6537
Particulate Matter in Injections	1. For particles $\geq 10\mu\text{m}$: NMT (b) (4) per container 2. For particles $\geq 25\mu\text{m}$: NMT (b) (4) per container	USP<788>
Sterility ²	Sterile	USP <71>
Bacterial Endotoxins	NMT (b) (4) EU/mg	USP <85>
(b) (4)		

¹ References to compendia signify current compendia. If a compendial monograph or test changes, FK USA will implement the changes and report them via annual report.

² Release test only

ATTACHMENT 7: SITE SPECIFIC DATA REQUIREMENTS

Brown, Janice

From: Chidambaram, Nallaperum
Sent: Wednesday, December 12, 2012 9:20 AM
To: Brown, Janice
Subject: RE: Stability Policy

Janice,

I am assuming there are no differences in the manufacturing process between (b) (4) and the proposed commercial site FK USA, Grand Island, NY. If that be the case, then we need at a minimum release data from three validation batches from the proposed commercial site.

Chid

From: Brown, Janice
Sent: Tuesday, December 11, 2012 3:33 PM
To: Chidambaram, Nallaperum
Subject: Stability Policy

Chid,

I am writing the IQA for NDA 205004. They included 18 month long term and 6 months accelerated for 3 batches produced at (b) (4). They submitted 3 months of stability data for one lot at their commercial site FK USA in Grand Island, NY. Since we had an issue with stability testing previously, could you confirm the amount of site specific stability data required for an NDA?

Janice

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

/s/

JANICE T BROWN
01/15/2013

ALI H AL HAKIM
01/15/2013