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*APPLICATION NUMBER:*

**205004Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

# Office of Clinical Pharmacology Review Memo

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<b>NDA</b>	205004
<b>Submission Date</b>	11/30/2012
<b>Submission Type</b>	Original, 505(b)(2)
<b>Brand Name</b>	Bortezomib Injection, (b)(4) mg/mL
<b>Generic Name</b>	Bortezomib
<b>Dosage Form and Strength</b>	1.3 mg/m <sup>2</sup> administered as a 3 to 5 second bolus intravenous injection
<b>Route of Administration</b>	Intravenous Injection
<b>Proposed Indication</b>	For treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy
<b>Applicant</b>	Fresenius Kabi USA
<b>OCP Review Team</b>	Guoxiang Shen, Ph.D.
<b>OCP Final Signatory</b>	Brian Booth, Ph.D.

## Addendum

In support of a waiver of in vivo bioequivalence (BE), the applicant conducted an in vitro bridging study to compare the proteasome inhibition activity between FK's product and the RLD with clinically relevant concentrations. The study suggests that the in vitro proteasome inhibitory activity of FK's product and Millennium's RLD product are comparable. In other words, the study indicated that the excipients used in Fresenius's bortezomib for injection or Velcade did not contribute to the pharmacological activity of the drugs. Based on the evidence submitted, FDA determined, consistent with 21 CFR 320.24(b)(6), that Fresenius established comparable bioavailability between its product and Velcade. Therefore, an acceptable in vitro bridge between FK's product and Millennium's RLD product was established.

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/s/  
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GUOXIANG SHEN  
11/03/2017

BRIAN P BOOTH  
11/03/2017

# Office of Clinical Pharmacology Memo

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<b>NDA or BLA Number</b>	NDA 205004
<b>Link to EDR</b>	\\CDSESUB1\evsprod\NDA205004\0025
<b>Applicant</b>	Fresenius Kabi USA
<b>Submission Date</b>	09/05/17
<b>Submission Type</b>	Resubmission/Class 1
<b>Brand Name</b>	Bortezomib for injection
<b>Generic Name</b>	Bortezomib
<b>Dosage Form and Strength</b>	1.3 mg/m <sup>2</sup> administered either as a 3 to 5 second bolus injection or subcutaneous injection; 3.5 mg/vial
<b>Route of Administration</b>	Intravenous injection
<b>Indication</b>	<ul style="list-style-type: none"><li>• Treatment of patients with multiple myeloma</li><li>• Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy</li></ul>
<b>OCP Review Team</b>	Yuhong Chen, MD & Ph.D.; Stacy Shord, Pharm.D.
<b>OCP Final Signatory</b>	Stacy Shord, Ph.D. Team Leader Division of Clinical Pharmacology V

Bortezomib for injection (Bortezomib) was tentatively approved for the treatment of patients with multiple myeloma, and for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy on 11/22/2015. The recommended dose for bortezomib is 1.3 mg/m<sup>2</sup> administered either as a 3 to 5 second bolus injection (b) (4) with strength of 3.5 mg/vial. In the tentative approval letter, the Agency stated “To obtain final approval of this application, submit an amendment two or six months prior to the: 1.) expiration of the patent or 2.) date you believe that your NDA will be eligible for final approval, as appropriate.” The applicant submitted the request for final approval according to the Agency’s requirement. The labeling was revised to be consistent with the current labeling practices as outline in the Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format.

The Office of Clinical Pharmacology will not be reviewing this application as there is no updated clinical pharmacology information.

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/s/  
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YUHONG CHEN  
11/01/2017

BRIAN P BOOTH  
11/01/2017

**OFFICE OF CLINICAL PHARMACOLOGY  
MEMO**

<b>Application Number (SDN)</b>	NDA 205004 (17)
<b>Submission Number (Date)</b>	5/22/2015
<b>Compound</b>	Bortezomib for Injection
<b>Dosing regimen</b>	1.3 mg/m <sup>2</sup> administered as a 3 to 5 second bolus intravenous injection
<b>Clinical Division</b>	DHP
<b>Primary Reviewer</b>	Bahru A Habtemariam, Pharm.D.

This submission was intended to address facility issues identified during inspection.  
This submission contains no new clinical pharmacology information for review.  
NDA 205004 is recommended for approval from the standpoint of clinical pharmacology

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/s/  
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BAHRU A HABTEMARIAM  
10/25/2015

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## Clinical Pharmacology Review

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<b>NDA</b>	<b>205-004</b>
<b>Submission Type</b>	Original, 505(b)(2)
<b>Submission Date</b>	30-Nov-2012
<b>Brand Name</b>	Bortezomib Injection, (b)(4) mg/mL
<b>Generic Name</b>	Bortezomib
<b>Indication</b>	For treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy
<b>Formulation</b>	Single use vial contains 3.5 mg of bortezomib as a lyophilized powder
<b>Dosing Regimen</b>	1.3 mg/m <sup>2</sup> administered as a 3 to 5 second bolus intravenous injection
<b>Applicant</b>	Fresenius Kabi USA
<b>OCP Reviewer</b>	Young Jin Moon, Ph.D.
<b>OCP Team Leader</b>	Julie Bullock, Pharm.D.
<b>OCP Division</b>	Division of Clinical Pharmacology 5
<b>OND Division</b>	Division of Hematology Products

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## 1 EXECUTIVE SUMMARY

This 505(b)(2) application submitted by Fresenius Kabi USA (FK) is for Bortezomib Injection, <sup>(b)(4)</sup> mg/mL in single-dose vials. The FK USA's Bortezomib Injection has the same <sup>(b)(4)</sup> indication, dosage form, strength, and route of administration (IV) as the innovator drug approved by the FDA under NDA 21-602 (Millennium pharmaceuticals, Inc.). The innovator's Velcade<sup>®</sup> is the reference listed drug (RLD) for this 505(b)(2) application. FK USA's product contains different excipients (glycine and boric acid) than Velcade<sup>®</sup> which contains mannitol. In addition, Velcade<sup>®</sup> Labeling is also approved for a subcutaneous route of administration, whereas FK USA's drug product is submitted only for the intravenous route of administration. Therefore, the subcutaneous route of administration has been carved out for FK USA's Bortezomib for Injection labeling. This carve out was based on the 11 April 2012 email communication from the FDA where it was stated that submitted drug product labeling will be addressed during NDA review.

In support of a waiver of *in vivo* bioequivalence (BE), the applicant conducted an *in vitro* bridging study to compare the proteasome inhibition activity between FK's product and the RLD with clinically relevant concentrations. The study suggests that the *in vitro* proteasome inhibitory activity of FK's product and Millennium's RLD product are comparable. Therefore, an acceptable *in vitro* bridge between FK's product and Millennium's RLD product was established. However, due to major deficiencies identified with respect to facility inspections, a Complete Response (CR) letter will be issued by the FDA.

### 1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 considers this NDA acceptable from a clinical pharmacology perspective.

### 1.2 PHASE 4 REQUIREMENT

None.

### 1.3 SIGNATURES

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Young Jin Moon, Ph.D.  
Reviewer  
Division of Clinical Pharmacology 5

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Julie Bullock, Pharm.D.  
Team Leader  
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - K Bengtson ; MTL - V Kwitkowski; MO - K McGinn  
DCP-5: Reviewers - Y Moon; TL - J Bullock; DDD - B Booth  
DD - A Rahman

#### 1.4 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. Velcade<sup>®</sup>, the RLD for this 505(b)(2) application, was approved by the FDA under NDA 21-602 (Millennium pharmaceuticals, Inc.) for the treatment of patients with multiple myeloma and patients with mantle cell lymphoma.

Each single dose vial of Velcade<sup>®</sup> contains 3.5 mg of bortezomib and 35 mg mannitol as a sterile lyophilized powder. Prior to use, the contents of each vial must be reconstituted with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection, USP.

FK's bortezomib product is also a sterile lyophilized powder to contain the same strength of bortezomib as Velcade<sup>®</sup>, but utilizing different excipients. In addition, Velcade<sup>®</sup> Labeling is also approved for a subcutaneous route of administration, whereas FK USA's drug product is submitted only for the intravenous route of administration. See Table 1 for the quantitative comparison between FK's product and Millennium's RLD product.

The applicant is seeking approval for all the RLD indications.

**Table 1. Formulation Comparison Between FK's Bortezomib Injection and RLD Velcade<sup>®</sup>**

Ingredients	Velcade <sup>®</sup>	Bortezomib for Injection
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)	N/A	(b) (4)
	(b) (4)	

In support of a waiver of *in vivo* BE, the applicant conducted an *in vitro* bridge study (Study No. PD11-NB/F-016) to compare the proteasome inhibition activity between FK's product and the RLD with clinically relevant concentrations. The study results indicate that the solutions of bortezomib drug substance, FK USA's Bortezomib for Injection and Velcade<sup>®</sup> have equivalent *in vitro* proteasome inhibitory activity as a fit probability of greater than (b) (4) meeting acceptance criteria for curve fitting and a Chi Square ( $\chi^2$ ) probability of greater than (b) (4) meeting acceptance criteria for parallelism. The presence of different excipients showed no effect on the *in vitro* proteasome inhibitory activity of each product. Therefore, an acceptable *in vitro* bridge between FK's product and Millennium's RLD product was established.

## 2 QUESTION BASED REVIEW

Refer to Velcade<sup>®</sup> original NDA 21-602 (Approval Date: 13-May-2003) and the May 12, 2003, OCP review by Dr. Safaa Burns for the Clinical Pharmacology related issues. For brevity only QBR questions related to the current NDA submission are addressed below.

### 2.1 GENERAL ATTRIBUTITES

#### 2.1.1 What are the proposed dosage and route of administration?

The recommended dose of FK's bortezomib for injection is 1.3 mg/m<sup>2</sup> administered as a 3 to 5 second bolus intravenous injection.

#### 2.1.2 What are the proposed mechanisms of action and therapeutic indications?

The proposed indications are for the treatment of patients with multiple myeloma and patients with mantle cell lymphoma, (b) (4)

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Bortezomib binds the proteasome via the boronic acid moiety, and therefore, the presence of this moiety is necessary to achieve proteasome inhibition (Pekol T *et al.*, 2005).

The innovator has described the active ingredient in Velcade<sup>®</sup> as a mannitol boronic ester (Bortezomib-Mannitol) which, in reconstitution form, consists of the mannitol ester (Bortezomib-Mannitol) in equilibrium with its hydrolysis product, the monomeric boronic acid (Bortezomib). The applicant has evaluated the stability of Bortezomib-Mannitol in Velcade<sup>®</sup> and concluded that upon reconstitution for intravenous administration, Bortezomib-Mannitol does not significantly exist and the presence of mannitol in Velcade<sup>®</sup> should have no effect on pharmacokinetic and pharmacological activity of Bortezomib.

An *in vitro* proteasome inhibitory study (see Section 2.5.2) was proposed for generating additional evidence to demonstrate the absence of Bortezomib-Mannitol in aqueous solution. If Bortezomib-Mannitol in the RLD is sufficiently stable and significantly exists when reconstituted into an aqueous solution, the pharmacologically active boronic head group of the drug in the solution would likely be blocked by mannitol and the *in vitro* proteasome inhibitory activity of Velcade<sup>®</sup> would be significantly different from Bortezomib drug substance and from FK's Bortezomib for Injection. If there is no significant difference in proteasome inhibitory activity between the two products and the drug substance, it can be concluded that other drug forms (i.e., Bortezomib-Mannitol ester) besides Bortezomib do not significantly exist in the solution.

### 2.5 GENERAL BIOPHARMACEUTICS

#### 2.5.1 What is the composition of the to-be-marketed formulation?

The composition of the formulation and the function of each component are presented in Table 2.

**Table 2. Composition per Unit Dose**

<b>Bortezomib for Injection</b>	<b>Content (per mL)</b>	<b>Function</b>
Bortezomib	(b) (4)	Active ingredient
Boric Acid, NF	(b) (4)	(b) (4)
Boric Acid, NF		
Glycine, USP		

FK USA’s product contains different excipients (glycine and boric acid) than Velcade® which contains mannitol. Refer to Section 1.4 for the quantitative and qualitative comparisons between FK’s to-be-marketed product and the RLD. The FK USA product has the same active ingredient, dosage form, strength, and route of administration (IV) as the RLD.

**2.5.2 What data support or do not support a waiver of in vivo BE data?**

In support of the waiver of *in vivo* BE, FK conducted an *in vitro* study (Study No. PD11-NB/F-016) to compare the proteasome inhibition activity between FK’s product and the RLD based on the clinical relevance of proteasome inhibition of bortezomib.

The *in vitro* proteasome inhibitory study was conducted at 0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, and 5.0 ng/well in the 96-well plate to cover a range of 0-100% proteasome inhibition. Bortezomib drug substance, Velcade®, and FK’s Bortezomib for Injection were tested and statistical analysis was performed to determine equivalence or any significant difference in proteasome inhibitory activity between the two products and the drug substance.

Samples at each concentration were tested in three replicates per each test plate for a total of nine plates. Each test plate contained Negative Control Sample (Assay buffer containing proteasome without any inhibitors as a control sample to demonstrate 100% activity for suitability test on proteasome used in the study), Positive Control (Epoxomicin for 100% inhibitory activity (0% proteasome activity) for specificity test to confirm presence of chymotryptic subunit which is a specific inhibition site of bortezomib within the 20S proteasome subunit), Test Drug Samples (Drug substance, Velcade®, and FK’s Bortezomib for Injection), Diluent (0.9% Sodium Chloride Injection, USP for reconstitution and dilution of each test sample as a blank sample to correct fluorescence readings of the test samples), and Placebos (A placebo solution of each formulation at highest concentration corresponding to 5.0 ng/well of the drug was tested to confirm lack of effect from the excipients on the proteasome activity). Test drug samples were obtained by spiking serial dilutions of 3.91, 7.81, 15.63, 31.25, 62.5, 125, 250, and 500 ng/mL of the drug in normal saline solution into the proteasome test wells. Three individual sets of serial dilution of each test drug materials were prepared and each dilution set was tested in three different test

plates with each concentration tested in triplicates per plate, resulting in a total of 9 sets of data for each test material.

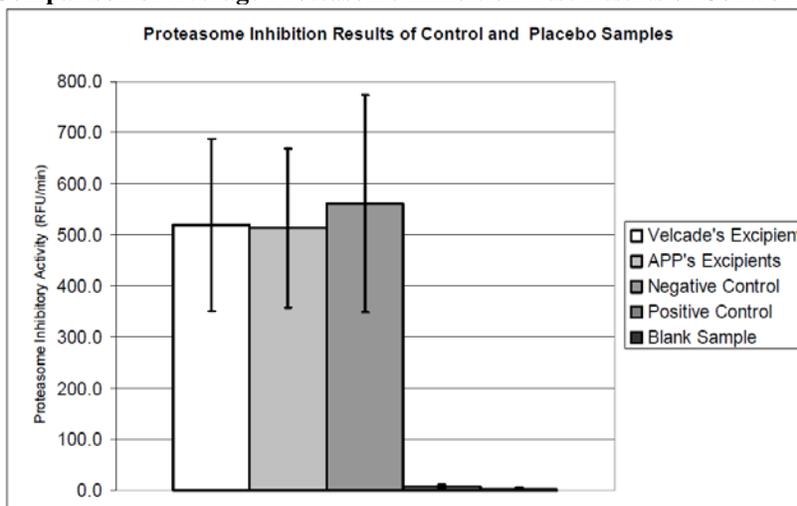
## Results

The actual drug concentrations of the spiking solutions were tested by HPLC. The results show some differences between the theoretical and the actual drug concentrations. However, the results among the replicates and among the test drug materials are similar.

### Proteasome Inhibition Test Results of Positive and Negative Controls, and placebo samples

The negative control, positive control, and blank samples are shown in Figure 1. Results of the negative control (containing proteasome with no inhibitor) confirm activity of proteasome used in the study. Results of the positive control (containing epoxomicin which is a selective show greatly diminished proteasome activity) confirm the presence of chymotryptic subunit which is a specific inhibition site of bortezomib within the 20S proteasome. The blank samples show no activity.

**Figure 1. Comparison of Average Proteasome Inhibition Test Results of Control and Placebo**

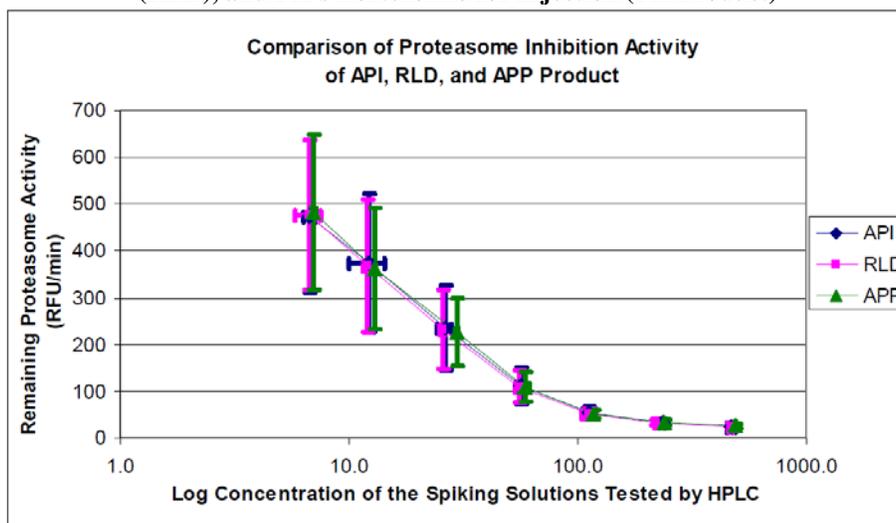


The results of placebo samples containing excipients in each drug product are similar among the negative control, Velcade<sup>®</sup>'s placebo, and FK's placebo (Figure 1). This indicates that the excipients in each drug product have no significant effect on proteasome activity.

### Proteasome Inhibition Test Results of Test Drug Materials

The average proteasome inhibition was plotted against the average actual drug concentrations in Figure 2.

**Figure 2. Comparison on Proteasome Inhibition Results of Bortezomib Drug Substance (API), Velcade® (RLD), and FK's Bortezomib for Injection (FK Product)**



These curves confirm that the drug concentrations were appropriately selected for the study. Figure 2 also shows good similarity among the drug response curves of Bortezomib drug substance, Velcade®, and FK's Bortezomib for Injection.

Test results were submitted to (b) (4) for statistical analysis. The sponsor stated that as the kinetics of proteasome inhibition produces nonlinear curves, the statistical analysis was conducted using a validated statistical software, StatLIA®, for the weighted regression and parallelism comparison. The analysis results show a fit probability of greater than 0.01 meeting acceptance criteria for curve fitting and a Chi Square ( $\chi^2$ ) probability of greater than 0.01 meeting acceptance criteria for parallelism, indicating equivalence between the drug response curves of Velcade® (RLD) and FK's Bortezomib for Injection (FK FP). This data analysis confirms that Velcade® in solution contains the same active moiety as FK's Bortezomib for Injection.

The reviewer also analyzed the data using Phoenix (Build 6.2.1.51) and reported the PD results between FK's and the RLD at those concentrations tested (Table 3). It is confirmed that FK's product met the criteria ( $CI_{90}$  between 80 and 125) for the PD equivalence to the RLD.

**Table 3. Comparison of the proteasome inhibitory activity of FK's Product to RLD**

Conc (µg/mL)	Product		Ratio ( $CI_{90}$ )
	FK	RLD	
0.0391	541.9 (30.4)	547.6 (34.1)	99.0 (83.8-120.0)
0.0781	483.4 (34.2)	476.9 (33.7)	101.4 (83.1-123.3)
0.156	361.6 (35.6)	368.6 (38.5)	98.1 (80.2-122.9)
0.313	226.8 (32.1)	231.3 (36.4)	98.1 (82.6-119.4)
0.625	109.9 (28.5)	109.3 (32.2)	100.5 (86.9-118.8)
1.25	51.3 (20.5)	50.8 (23.9)	100.9 (90.9-113.6)
2.5	33.4 (16.3)	32.5 (17.6)	103.0 (94.7-112.5)
5	25.8 (20.1)	25.1 (20.3)	102.8 (92.7-113.9)

\*Geo-mean (CV%)

Therefore, it is confirmed that an acceptable *in vitro* bridge between FK's product and Millennium's RLD product was established.

## 2.6 ANALYTICAL SECTION

### 2.6.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

A validated high performance liquid chromatography (HPLC) (Study Protocol # PR-11-00219) was used for the determination of bortezomib in bortezomib raw material and Bortezomib for Injection. Validation Summary is presented in Table 4.

**Table 4. Validation Summary**

Validation Parameter	Limit	Result
System Suitability:	S/N of bortezomib peak in <i>Standard Solution Preparation</i> (5 ng/mL): NLT (b) (4)	In the range of (b) (4)
	The correlation coefficient (r) for the calibration curve:	
	1. 0.05 mg/mL to 1.0 mg/mL: NLT (b) (4) 2. 5 ng/mL to 550 ng/mL: NLT (b) (4)	1. (b) (4) 2. (b) (4)
Quantitation Limit (QL): Standard Preparation at 5 ng/mL	S/N of bortezomib peak in five replicate injections: NLT (b) (4)	In the range of (b) (4)
	Percent relative standard deviation (%RSD) (n = 5) for bortezomib peak: Not more than (NMT) (b) (4)%	(b) (4)
Linearity for Bortezomib:	The correlation coefficient (r) for <i>Standard Preparation</i> :	
	1. 0.05 mg/mL to 1.0 mg/mL: NLT (b) (4)	1. (b) (4)
	2. 5 ng/mL to 550 ng/mL: NLT (b) (4)	2. (b) (4)

Validation Parameter	Limit	Result
Stability	<p>S/N = NLT (b) (4) for <i>Standard Preparation</i> at 5 ng/mL</p> <p>Time interval at which the change in response from time zero is:</p> <p>250 ng/mL: within ± (b) (4) %</p> <p>0.5 mg/mL: within ± (b) (4) %</p>	<p><b><u>Standard Preparation</u></b></p> <p><b>(5 ng/mL)</b> (b) (4) hours at 5 ± 3 °C when protected from light</p> <p><b>(250 ng/mL)</b> (b) (4) hours at 5 ± 3 °C when protected from light</p> <p><b>(0.5 mg/mL)</b> (b) (4) hours at 5 ± 3 °C when protected from light</p>
	<p align="center"><b>Raw Material, Finished Product (APP and RLD) Preparations</b></p> <p>Time interval at which the change in response from time zero is:</p> <p>250 ng/mL: Within ± (b) (4) %</p> <p>0.5 mg/mL: Within ± (b) (4) %</p>	<p><b><u>Raw Material</u></b></p> <p><b>(250 ng/mL)</b> (b) (4) hours at 5 ± 3 °C protected from light</p> <p><b>0.5 mg/mL</b> (b) (4) hours at 5 ± 3 °C protected from light</p> <p><b><u>APP Finished Product</u></b></p> <p><b>(250 ng/mL)</b> (b) (4) hours at 5 ± 3 °C protected from light</p> <p><b>0.5 mg/mL</b> (b) (4) hours at 5 ± 3 °C protected from light</p> <p><b><u>RLD Finished Product</u></b></p> <p><b>(250 ng/mL)</b> (b) (4) hours at 5 ± 3 °C protected from light</p> <p><b>0.5 mg/mL</b> (b) (4) hours at 5 ± 3 °C protected from light</p>
Range	(b) (4)	The method proved to be linear, accurate and precise within this region.

Validation Parameter	Limit	Result	
Accuracy	<b>Raw Material Assay</b>		
	Average recovery (n=3) of bortezomib	Concentration (b) (4)	
	<b>APP Finished Product Assay</b>		
	5 , 250, and 550 ng/mL:	In the range of 75.0 to 125.0%	5 ng/mL: 97.0%
			250 ng/mL: 98.9%
			550 ng/mL: 103.5%
	0.05, 0.5, and 1.0 mg/mL:		0.05 mg/mL: 101%
			250 mg/mL: 102%
			550 mg/mL: 101%
	<b>RLD Finished Product Assay</b>		
5 , 250, and 550 ng/mL:	In the range of 75.0 to 125.0%	5 ng/mL: 95.5%	
		250 ng/mL: 96.8%	
		550 ng/mL: 100.8%	
0.05, 0.5, and 1.0 mg/mL:		0.05 mg/mL: 102%	
		250 mg/mL: 102%	
		550 mg/mL: 101%	
Precision	<b>Raw Material %RSD (n=6)</b>		
	(b) (4)		
	<b>APP Finished Product %RSD (n=6)</b>		
	250 ng/mL	NMT (b) (4) %	1%
	0.5 mg/mL	NMT (b) (4) %	0.1%
	<b>RLD Finished Product %RSD (n=6)</b>		
	250 ng/mL	NMT (b) (4) %	1%
	0.5 mg/mL	NMT (b) (4) %	0.1%

Proteasome inhibitory test was conducted using 20S Proteasome Assay Kits for Drug Discovery (Cat # BML-AK740 from Enzo Life Sciences) and the inhibitory effect was detected by Molecular Devices FelixStation3. Briefly, purified proteasome from human erythrocytes, test solution, and buffer solution were mixed and incubated for 10 minutes at 30°C. A substrate was then added and the release of fluorophore was monitored by measuring fluorescence over time. The slope, indicating relative velocity of 20S proteasome subunit activity in the substrate cleavage kinetic, was calculated from ‘Relative Fluorescence Unit (RFU) versus Time’ profile. The slope (RFU/min) of each test sample was plotted against the sample drug concentration.

### 3 DETAILED LABELING RECOMMENDATIONS

No labeling recommendations were given since a Complete Response (CR) letter will be issued.

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/s/  
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YOUNG J MOON  
04/19/2013

JULIE M BULLOCK  
04/23/2013