

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205004Orig1s000**

**CLINICAL REVIEW(S)**

**FILE MEMORANDUM  
DIVISION OF HEMATOLOGY PRODUCTS  
CLINICAL REVIEW OF NDA 205004**

<b>Date:</b>	10/25/2017
<b>TO NDA:</b>	205004
<b>SDN / SN:</b>	NDA 205004/26
<b>Drug:</b>	Bortezomib for Injection
<b>Sponsor:</b>	FRESENIUS KABI USA, LLC
<b>Received Date:</b>	09/05/2017
<b>FROM:</b>	Saleh Ayache, MD, Medical Reviewer; DHP
<b>SUBJECT:</b>	REQUEST FOR FINAL APPROVAL
<b>Via:</b>	Kathy M. Robie-Suh, M.D., Ph.D., team leader, DHP
<b>PM:</b>	Wonme Chon, RPM, DHP

**BACKGROUND:**

This is a 505(b)(2) New Drug Application for bortezomib for injection for the treatment of patients with multiple myeloma and for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy, that was originally submitted on 11/30/2012 (received 12/03/2012). No clinical studies were conducted for the application. The application received a Complete Response (CR) on 10/3/2013 due to Chemistry Manufacturing and Control (CMC) and Biopharmaceutical deficiencies. It was resubmitted on 10/3/2014 and deficiencies from previous review were found to be resolved pending facility approval recommendation by the Office of Process and Facility (OPF) (See CDTC review by Janice Brown, 4/2/2015). The facility review by OPF found deficiencies at a Fresenius Kabi USA LLC (FK USA) facility in Grand Island NY and a withhold recommendation was made. The sponsor was issued a second CR on 4/2/2015. The application was again resubmitted on 5/22/2015 and the manufacturing facilities were founded acceptable. The NDA received a TENTATIVE APPROVAL on November 17, 2015 due to unexpired patent and exclusivity protection for the listed drug upon which this application relies.

The reference drug is bortezomib for injection manufactured by Millennium Pharmaceuticals and the proposed indication is for the treatment of patients with multiple myeloma and for patients with mantle cell lymphoma who have received at least one prior therapy.

This submission includes patent status update, chemistry, manufacturing and controls update, safety update and labeling update to reflect the reference listed drug update dated June 9, 2017.

**Submission Review:**

The Applicant did not conduct any clinical studies with Bortezomib for Injection. However, the Applicant provided summary of worldwide experience of the safety of bortezomib using literature search which was conducted on August 16, 2017 through PubMed web based portal. The Applicant stated that the verbatim title search term “bortezomib” was used. The date range was set between April 14, 2015 (latest article in previous safety update) and August 16, 2017 the day of the literature search. A species filter was applied (humans). Additional filters included case reports and clinical trials (phase 1,2, 3 or 4) were used. The Applicant provided a summary of 38 articles in Module 5. Based on the review of the safety data from the search articles no new safety signals have been identified.

The PDUFA action due date for this resubmission is November 5, 2017. As of that date the reference listed drug will have continuing exclusivity for first line treatment of mantle cell lymphoma (MCL) and for retreatment for multiple myeloma (MM). Also, the sponsor has removed the subcutaneous route of administration and removed pediatric information describing a clinical study in lymphoid malignancies from section 8.4 of the label. (See Deputy Division Director Summary Review (Edvardas Kaminskas 11/10/2015)).

**Recommendations:**

This 505 (b)(2) application can be approved for:

- Treatment of patients with MM
- Treatment of patients with MCL who have received at least 1 prior therapy

Labeling will be similar to that of the reference listed drug except that:

- Pediatric information in section 8.4 is replaced with a reference to information in the listed drug label.
- Subcutaneous administration route is deleted
- The indications for treatments of relapse MM and for first line treatment of MCL are deleted

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/s/  
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SALEH AYACHE  
10/31/2017

KATHY M ROBIE SUH  
10/31/2017

Exact final wording of labeling is being developed in discussion with entire review team and negotiation with sponsor.

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Edvardas Kaminskas, M.D.
<b>Subject</b>	Deputy Division Director Summary Review
<b>NDA/BLA #</b>	NDA 205004
<b>Supplement #</b>	SDN 17
<b>Applicant Name</b>	Fresenius Kabi USA, LLC
<b>Date of Submission</b>	May 22, 2015
<b>PDUFA Goal Date</b>	November 22, 2015
<b>Proprietary Name / Established (USAN) Name</b>	Bortezomib for Injection
<b>Dosage Forms / Strength</b>	Sterile lyophilized powder/3.5 mg/vial
<b>Proposed Indications</b>	Treatment of patients with multiple myeloma Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.
<b>Action:</b>	Tentative Approval

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	Saleh Ayache, M.D./Romeo A. De Claro, M.D.
Pharmacology Toxicology Review	Pedro L. Del Valle, Ph.D./Christopher Sheth, Ph.D.
OPQ/Drug Substance Review	Hari Sarker, Ph.D.
OPQ/Product Review	Zhong Li, Ph.D.
OPQ/Process review/facility review	Zhong Li, Ph.D.
OPQ/Biopharmaceutics review	Kelly M. Kitchens, Ph.D.
OPQ/Microbiology Review	Erika A. Pfeiler, Ph.D.
Clinical Pharmacology Review	Young J. Moon, Ph.D./Bahru Habtemariam, Pharm.D.
OSE/OMEPRM/DMEPA	Michelle Rutledge, Pharm.D./Yelena Maslov, Pharm.D.
CDTL Review	Janice T. Brown, M.S.

OND=Office of New Drugs  
DDMAC=Division of Drug Marketing, Advertising and Communication  
OSE= Office of Surveillance and Epidemiology  
OMEPRM=Office of Medication Error Prevention and Analysis  
DMEPA=Division of Medication Error Prevention and Analysis  
CDTL=Cross-Discipline Team Leader

## Signatory Authority Review Template

### 1. Introduction

Bortezomib is a small molecule, antineoplastic agent approved for intravenous or subcutaneous injection for the treatment of patients with multiple myeloma and of patients with mantle cell lymphoma who have received at least one prior therapy. The current application for Bortezomib for Injection is a resubmission of a 505(b)(2) New Drug Application. The reference drug is Velcade (bortezomib) for Injection, manufactured by Millennium Pharmaceuticals, Inc. (NDA 21602), is a single-use vial containing 3.5 mg of bortezomib as a lyophilized powder.

### 2. Background

The NDA is for a new formulation of approved Bortezomb for Injection; it is supplied as a single dose vial containing 3.5 mg of bortezomib, 10.5 mg boric acid and 25 mg glycine as a sterile lyophilized powder. 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.

This is the third review cycle for this application. This 505 (b)(2) NDA was first submitted on November 30, 2012 (received December 3, 2012). On October 3, 2013 the Division issued a Complete Response letter to the applicant citing outstanding manufacturing and facility issues that remained to be resolved before the product can be approved. The second submission was on October 3, 2014. A Complete Response letter for the same reasons was issued on April 2, 2015. On May 22, 2015 the Applicant submitted a Class 2 Resubmission to address Complete Response issues.

### 3. CMC/Device

Drug Substance Review: The applicant cross-referenced the CMC information for bortezomib drug substance to DMF (b) (4). DMF (b) (4) was reviewed and found adequate. The API supplier had recently updated their DMF (b) (4)

The drug substance reviewer found the information adequate to support NDA 2005004.

Drug Product Review: (b) (4)

(b) (4)



Process Review – Drug Product: The Drug Process review was limited to an updated Master Batch Record. The changes were reviewed and found acceptable. The process reviewer recommended approval of the NDA.

Facility Review: The facility reviewer found no significant, outstanding manufacturing risks that prevent approval of this application. The manufacturing facilities are found to be acceptable.

Microbiology Review: The master batch record was reviewed, and the information is in agreement with previously submitted information. The microbiology review recommended approval of the NDA.

Biopharmaceutics – There is no new Biopharmaceutics information included in the current submission. The Division of Biopharmaceutics recommended approval of the application.

Note: OPQ reviews have been filed in Panorama; all other reviews in DARRTS.

“I concur with the conclusions reached by the CMC reviewers recommending approval of this NDA”.

## **4. Nonclinical Pharmacology/Toxicology**

The reviewer filed an updated memo indicating that there is no new nonclinical pharmacology and toxicology information in the resubmission and recommended approval of the NDA.

## **5. Clinical Pharmacology/Biopharmaceutics**

The reviewer filed an updated memo indicating that there is no new clinical pharmacology information in the resubmission and recommended approval of the NDA.

## **6. Clinical Microbiology**

N/A.

## **7. Clinical/Statistical-Efficacy**

The clinical reviewer filed an updated memo recommending approval of the NDA for the following indications:

1. Treatment of patients with multiple myeloma
2. Treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

There was no Statistical Review for this NDA.

## **8. Safety**

The Applicant did not conduct any clinical studies with Bortezomib for Injection. However, the Applicant provided a summary of worldwide experience of safety of bortezomib using a literature search of PubMed portal for the period between July 15, 2014 and April 13, 2015. A total of 28 articles were identified and summarized. In brief, no new safety signals were identified.

## **9. Advisory Committee Meeting**

There was no Advisory Committee meeting held for this application.

## **10. Pediatrics**

There was no Pediatric and Maternal Health Staff review for this NDA.

## **11. Other Relevant Regulatory Issues**

- Application Integrity Policy (AIP): There were no AIP issues raised during the pre-approval or follow-up inspections for this NDA.
- Exclusivity or patent issues of concern: This application cannot be granted final approval until all exclusivities expire. The final indications included in the labeling at the time of final approval of this application will depend upon existing exclusivities remaining. Table 1 lists the exclusivities for the listed drug, Velcade (bortezomib) for injection (from CDTL Review).

Table 1: Velcade (bortezomib) for injection\*

Exclusivity Code	Exclusivity Expiration
<a href="#">ODE</a> ORPHAN DRUG EXCLUSIVITY [First-line therapy of multiple myeloma.]	Jun 20, 2015
<a href="#">I - 695</a> REVISED INDICATION FOR BORTEZOMIB IN THE TREATMENT OF PATIENTS WITH MANTLE CELL LYMPHOMA	Oct 8, 2017
<a href="#">D - 142</a> DOSE MODIFICATION GUIDELINES FOR BORTEZOMIB WHEN GIVEN IN COMBINATION WITH RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE	Oct 8, 2017
<a href="#">D - 141</a> DOSING INFORMATION IN PREVIOUSLY UNTREATED MANTLE CELL LYMPHOMA	Oct 8, 2017
<a href="#">ODE</a> ORPHAN DRUG EXCLUSIVITY (I-695 indication)	Oct 8, 2021
<a href="#">M - 139</a> INFORMATION ADDED TO THE DOSING AND ADMINISTRATION SECTION OF THE PACKAGE INSERT REGARDING RETREATMENT WITH VELCADE FOR PATIENTS WITH MULTIPLE MYELOMA	Aug 8, 2017

\* Reproduced from email from Mary Ann Holovac on October 9, 2015

- Financial disclosures: N/A.
- Other GCP issues: None.
- DSI audits: N/A.
- Other discipline consults: None.
- Any other outstanding regulatory issues: None.

## 12. Labeling

The following information was carved out from the proposed labeling:

1. Efficacy, safety, and dosing information related to the indication for the first-line treatment of mantle cell lymphoma (MCL). The first-line mantle cell lymphoma indication (I-695) exclusivity expires October 8, 2017 but is extended to April 8, 2018 with the pediatric extension. This is the indication that was approved October 8, 2014. This same indication also has orphan exclusivity until October 8, 2021 and is extended with pediatric exclusivity until April 8, 2022.
2. Efficacy, safety, and dosing information for the retreatment for multiple myeloma (MM). This exclusivity expires on August 8, 2017 but is extended with pediatric exclusivity to February 8, 2018.

3. (b) (4) This information is described in section 8.4 Pediatric Use. There is no individual exclusivity for the pediatric information. The Agency did not object with Applicant's proposal to remove this information from the labeling.
4. The applicant removed the subcutaneous route of administration and all relevant information in the proposed label. Note that the exclusivity for the subcutaneous route of administration expired on January 23, 2015. The Agency did not object with the Applicant's proposal to remove this information from the labeling.

**Office of Prescription Drug Promotion (OPDP):** The OPDP labeling revisions to the Full Prescribing information was forwarded to the applicant.

**Division of Medication Error Prevention and Analysis (DMEPA):** The DMEPA review for the revised container label and carton labeling was found acceptable.

**Proprietary name:** There was no proprietary name proposed for this product.

**Issues not resolved at the time of CDTL memo completion:** Final labeling from the applicant.

**Patient labeling/Medication guide:** Not required for this product.

### 13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** Tentative Approval. Final approval cannot be granted until all exclusivities expire.
- Risk Benefit Assessment

The review of this NDA is based primarily on chemistry, manufacturing and controls data. The applicant has satisfactorily responded to the drug substance, DMF, and drug product deficiencies. The process, microbiology and biopharmaceutics review recommended approval of the NDA application. Pharmacology/Toxicology has no concerns with the excipients used for Fresenius Bortezomib for Injection at the defined levels. The applicant has satisfactorily responded to the Complete Response for the withhold recommendation from the Office of Process and Facilities. Therefore, there are no outstanding regulatory issues for this NDA; the cGMP status for all manufacturing sites is acceptable. This NDA is recommended for approval from a product quality standpoint.

- Recommendation for Postmarketing Risk Management Activities  
None.
- Recommendation for other Postmarketing Study Commitments  
None.

- Recommended Comments to Applicant  
Standard language for conveying a tentative approval will be inserted into the action letter.

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EDVARDAS KAMINSKAS  
11/10/2015

**FILE MEMORANDUM  
DIVISION OF HEMATOLOGY PRODUCTS  
CLINICAL REVIEW OF NDA 205004**

<b>Date:</b>	10/15/2015
<b>TO NDA:</b>	205004
<b>SDN / SN:</b>	NDA 205004/17
<b>Sponsor:</b>	FRESENIUS KABI
<b>Submission Date:</b>	05/22/2015
<b>Received Date:</b>	05/22/2015
<b>FROM:</b>	Saleh Ayache, MD, Medical Reviewer; DHP
<b>SUBJECT:</b>	Minor Amendment- Response to Complete Response Letter (SEQ-0016)
<b>Via:</b>	R. Angelo de Claro, MD, team leader, DHP
<b>PM:</b>	Janet Higgins, RPM, DHP

**BACKGROUND:**

This is a 505(b)(2) New Drug Application for bortezomib for injection was originally submitted on 12/03/2012 and a Complete Response Action Letter was sent to the applicant on October 3, 2013 to address issues related to quality specification, process and facilities. In this submission, Fresenius Kabi USA submitted a Minor Amendment -Response to Complete Response Letter (SEQ-0016) to address the items identified in the second Complete Response Letter dated April 2, 2015 citing deficiencies identified during inspection of Fresenius Kabi USA LLC manufacturing facility.

The reference drug is bortezomib for injection manufactured by Millennium Pharmaceuticals and the proposed indication is for the treatment of patients with multiple myeloma and for patients with mantle cell lymphoma who have received at least one prior therapy.

This submission includes revised labeling, updated labeling files, and clinical and non-clinical safety update literature-based with a cutoff of April 30, 2015.

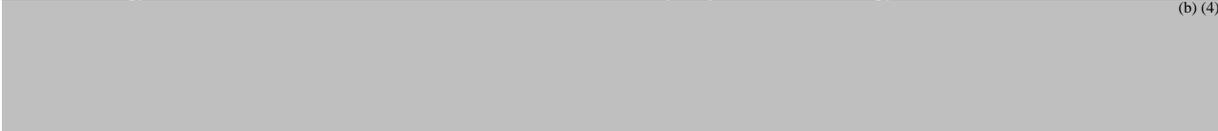
**Submission Review:**

The Applicant did not conduct any clinical studies with Bortezomib for Injection. However, the Applicant provided summary of worldwide experience of the safety of the bortezomib using literature search of PubMed portal between the periods of July 15, 2014 and April 13, 2015. A total of 28 articles were identified and summarized. The Applicant provided a summary of the

full article in Module 5. Based on the review of the safety data from the search articles no new safety signal has been identified.

**Labeling Recommendations:**

The following information should be carved out of the proposed labeling:



In addition, we have no objections to the Applicant's proposal to carve out (a) the subcutaneous route of administration, or (b) pediatric information in Section 8.4.

Comment: The above labeling recommendations are based for a proposed action of tentative approval. The labeling will need to be re-assessed at the time of granting regular approval.

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SALEH AYACHE  
10/20/2015

ROMEO A DE CLARO  
10/21/2015

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Edvardas Kaminskas, M.D.
<b>Subject</b>	Deputy Division Director Summary Review
<b>NDA/BLA #</b>	NDA 205004
<b>Supplement #</b>	SDN 13
<b>Applicant Name</b>	Fresenius Kabi USA, LLC
<b>Date of Submission</b>	October 3, 2014
<b>PDUFA Goal Date</b>	April 3, 2015
<b>Proprietary Name / Established (USAN) Name</b>	Bortezomib for Injection
<b>Dosage Forms / Strength</b>	Sterile lyophilized/3.5 mg/vial
<b>Proposed Indications</b>	Bortezomib is a proteasome inhibitor indicated for treatment of patients with multiple myeloma and for treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.
<b>Action:</b>	Complete Response due to issues identified with the facility used to manufacture the Bortezomib for Injection drug product.

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	Karen McGinn, M.S.N./Romeo A. De Claro, M.D.
Pharmacology Toxicology Review	Pedro L. Del Valle, Ph.D
OPQ/Product Review	Zhe J. Tang, Ph.D./Ali H. Al Hakim, Ph.D.
OPQ/Process review/facility review	Donghao R. Lu, Ph.D./Zhong Li, Ph.D.
OPQ/Biopharmaceutics review	Kelly M. Kitchens, Ph.D./Angelica Dorantes, Ph.D.
OPQ/Microbiology Review	Erika A. Pfeiler, Ph.D./Stephen E. Langille, Ph.D.
Clinical Pharmacology Review	Young J. Moon, Ph.D./Bahru Habtemariam, Pharm.D.
OSE/OMEPRM/DMEPA	Michelle Rutledge, Pharm.D./Yelena Maslov, Pharm.D.
Office of Compliance	Timothy J. Pohlhaus, Ph.D./David D. Doleski, Ph.D.
CDTL Review	Janice T. Brown, M.S.

OND=Office of New Drugs  
DDMAC=Division of Drug Marketing, Advertising and Communication  
OSE= Office of Surveillance and Epidemiology  
OMEPRM=Office of Medication Error Prevention and Analysis  
DMEPA=Division of Medication Error Prevention and Analysis  
CDTL=Cross-Discipline Team Leader

## Signatory Authority Review Template

### 1. Introduction

Bortezomib is a small molecule, antineoplastic agent approved for intravenous or subcutaneous injection for the treatment of patients with multiple myeloma and of patients with mantle cell lymphoma who have received at least one prior therapy. The current application for Bortezomib for Injection is a resubmission of a 505(b)(2) New Drug Application, which had been submitted on December 3, 2012 and had received a Complete Response on October 3, 2013 due to multiple chemistry and manufacturing control issues that could not be corrected in time for the PDUFA due date. The reference drug is Velcade (bortezomib) for Injection, manufactured by Millennium Pharmaceuticals, Inc. (NDA 21602), is a single-use vial containing 3.5 mg of bortezomib as a lyophilized powder.

### 2. Background

The NDA is for a new formulation of approved Bortezomb for Injection. The route of administration, dosage form and strength of the proposed product are the same as for the listed drug, except that subcutaneous use is omitted from the proposed label. The applicant for this NDA is relying upon information in the public domain (labeling for approved bortezomib product and published studies and information about bortezomib) to support the safety and efficacy of the new product.

The applicant's Bortezomib for Injection is supplied as a single dose vial containing 3.5 mg of bortezomib, 10.5 mg boric acid and 25 mg glycine as a sterile lyophilized powder. 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.

This NDA was first submitted on November 30, 2012 (received December 3, 2012). This is the second review cycle for this application. On October 03, 2013 the Division issued a Complete Response letter to the applicant citing outstanding manufacturing and facility issues that remained to be resolved before the product can be approved. The Applicant submitted a Class 2 Resubmission on October 03, 2014 to address complete response issues with the 505(b)(2) application.

### 3. CMC/Device

Product Review – Drug Substance: The holder resubmitted DMF (b)(4) that included all submissions to the Agency in an eCTD format. This submission did not include any new drug substance information and the DMF review (Zhe J. Tang, Ph.D., final signature March 17, 2015) concluded that the DMF remained adequate to support NDA 205004.

Process Review – Drug Substance – The process reviewer previously found the process section in DMF (b)(4) acceptable. This submission did not include any new drug substance information and the drug substance review (Donghao (Robert) Lu, final signature March 10, 2015) concluded that the DMF remained adequate to support NDA 205004.

Product Review – Drug Product: The previous drug product review (Zhe J. Tang, Ph.D., final signature April 29, 2013) did not identify any drug product issues but did not recommend approval due to the outstanding deficiencies identified in the drug product process review. In response to the moisture content issues identified in the process review, the resubmission included a revised drug product specification with a moisture content limit of NMT (b)(4)% and a correction to the pH range to (b)(4). The reviews (Zhe J. Tang, Ph.D., final signatures March 10, 2015, March 13, 2015) found the revised drug product specification acceptable and recommended approval of the NDA pending an approval facility recommendation by the Office of Process and Facilities.

Process Review – Drug Product: The previous CMC process and facility review by Timothy J. Pohlhaus, Ph.D. (final signature May 1, 2013) recommended a Complete Response due to deficiencies in the lyophilization process development including (b)(4) vial sampling, lyophilization cycle development and a withhold recommendation for the manufacturing facility in Grand Island, NY from the Office of Compliance.

The CMC information in the resubmission was reviewed by Timothy J. Pohlhaus, Ph.D. and Zhong Li, Ph.D. (reviews signed March 10, 2015 and March 12, 2015). There were multiple communications and amendments to the application to resolve the lyophilization deficiencies in the Complete Response letter. The review of the resubmission and amendments found that the applicant adequately addressed the lyophilization issues. Fresenius agreed to lower the drug product moisture content limit to (b)(4)%. The approval recommendation is located in the March 10, 2015 review. The review recommended approval of the NDA pending an acceptable facility recommendation.

Microbiology Process Review – Drug Product: The reviewer (Erika Pfeiler, Ph.D.) filed an updated memo dated November 7, 2014 (final signature November 7, 2014) indicating that there is no new product quality microbiology information in the resubmission and recommended approval of the NDA.

Facility Review: The Division of Inspectional Assessment (DIA) in the Office of Process and Facility (OPF) completed a review of an establishment inspection report (EIR) covering a preapproval inspection (PAI) by New York District Office (NYK-DO) investigators from March 9 - 10, 2015 at a Fresenius Kabi USA LLC (FK USA) facility in Grand Island, NY.

Based on the applicant's response to the two item 483, the Kansas City District Office's (KYKDP) recommend a withhold for NDA 205004 due to a product specific deficiencies related to batch yield and lyophilized cake appearance. **DIA concurs with the KYK-DO recommendation; a withhold recommendation was entered into Panorama on April 1, 2015.**

Biopharmaceutics – In this review cycle, the Division of Biopharmaceutics revised the previous recommendation that the biowaiver request not be granted. The review concluded that 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. The review (Kelly Kitchens, Ph.D., final signature February 17, 2015) recommended approval of the application.

Note: OPQ reviews have been filed in Panorama; all other reviews in DARRTS.

**I concur with the conclusions reached by the CMC reviewers, including a “Withhold recommendation for NDA 205004 due to product specific deficiencies”.**

#### **4. Nonclinical Pharmacology/Toxicology**

The reviewer filed an updated memo (Pedro Del Valle, Ph.D., signed March 13, 2015) indicating that there is no new nonclinical pharmacology and toxicology information in the resubmission and recommended approval of the NDA.

#### **5. Clinical Pharmacology/Biopharmaceutics**

The reviewer (Young Jin Moon, Ph.D.) filed an updated memo signed March 4, 2015 indicating that there is no new clinical pharmacology information in the resubmission and recommended approval of the NDA.

#### **6. Clinical Microbiology**

There was no Clinical Microbiology review for this NDA.

#### **7. Clinical/Statistical-Efficacy**

The previous clinical primary and secondary review (Karen McGinn, final signature April 8, 2013 and Romeo De Claro, M.D., final signature April 30, 2013, respectively) did not identify any approvability issues for this NDA application.

The clinical reviewer filed an updated memo (Karen McGinn, MSN, CRN, final signature March 17, 2015) recommending approval of the NDA for the following indications:

1. Treatment of patients with multiple myeloma
2. Treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

There was no Statistical Review for this NDA.

The listed drug, Velcade, is approved for a first line indication for mantle cell lymphoma and was granted exclusivity until October 8, 2017. See item 11 in this review for additional information on patents and exclusivity.

## **8. Safety**

There was no Safety Review for this NDA.

## **9. Advisory Committee Meeting**

There was no Advisory Committee meeting held for this application.

## **10. Pediatrics**

There was no Pediatric and Maternal Health Staff review for this NDA.

## **11. Other Relevant Regulatory Issues**

- Application Integrity Policy (AIP):

There were no AIP issues raised during the pre-approval or follow-up inspections for this NDA.

- Exclusivity or patent issues of concern:

In this application, the Applicant included the FDA Form 356h, which requested the Multiple Myeloma (MM) or Mantle Cell Lymphoma (MCL) who have received at least one prior therapy indications. Both the existing MM and MCL who have received at least one prior therapy indications for the Velcade NDA are protected by orphan drug exclusivity. The listed drug, Velcade, was recently approved for a first line indication for mantle cell lymphoma and was granted exclusivity until October 8, 2017. This application cannot be granted final approval until all exclusivities expire. The final indications included in labeling at the time of final approval of this Fresenius application, will depend upon existing exclusivities remaining.

Fresenius also submitted a Paragraph III and Paragraph IV patent certification for this application noting that there are unexpired patents and exclusivity for the reference listed drug (Velcade®).

- Financial disclosures: Not applicable
- Other GCP issues: None
- DSI audits: Not applicable
- Other discipline consults: None

## 12. Labeling

The proposed labeling for the Fresenius Bortezomib for Injection is essentially the same in content as that of the innovator listed drug product. 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.

The DMEPA review for the revised container label, carton labeling and Prescribing Information labeling included comments that were not conveyed to the applicant due to the pending complete response action. All container/carton and PI labeling will need to be re-evaluated for acceptability by all disciplines during any subsequent review cycle.

## 13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** Complete Response due to issues identified with the facility used to manufacture the Bortezomib for Injection drug product.
- Risk Benefit Assessment

The review of this NDA is based primarily on chemistry, manufacturing and controls and clinical pharmacology/biopharmaceutics data. The applicant has satisfactorily responded to the lyophilization deficiencies in the Complete Response letter. A Complete Response action is recommended for this NDA based on the withhold recommendation from the Office of Process and Facilities. Therefore, there are outstanding regulatory issues for this NDA, the cGMP status for all manufacturing sites is unacceptable, and the proposed manufacturing sites are not confirmed as suitable for producing drug product for the commercial market.

- Recommendation for Postmarketing Risk Management Activities  
None.

DD Summary Review  
NDA 205004 SDN 13

- Recommendation for other Postmarketing Study Commitments  
None.
- Recommended Comments to Applicant  
Standard language for conveying an unacceptable facility recommendation will be inserted into the action letter.

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/s/  
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EDVARDAS KAMINSKAS  
04/02/2015

**Resubmission of New Drug Application  
Division of Hematology Products**

**NDA/SDN:** 205004/13  
**Drug Name:** Bortezomib injection  
**Sponsor:** Fresenius Kabi  
**RPM:** Toni-Ann Cox  
**Resubmission Date:** October 3, 2014  
**PDUFA Date:** April 3, 2015  
**Completion Date:** March 17, 2015  
**Clinical Reviewer:** Karen McGinn, MSN, CRNP  
**Clinical Team Leader:** R. Angelo de Claro, MD

**BACKGROUND:**

The Applicant has resubmitted a 505(b)(2) New Drug Application for bortezomib for injection. The reference labeled drug (RLD) is bortezomib for injection manufactured by Millennium Pharmaceuticals, Inc. and is indicated for patients with multiple myeloma and for patients with mantle cell lymphoma who have received at least one prior therapy.

This application includes 41 references describing clinical trials of the reference drug used alone and in combination with other agents in patients with hematologic and non-hematologic malignancies.

The Sponsor submitted the original 505(b)(2) application December 3, 2012. The application received a Complete Response October 3, 2013 due to multiple chemistry and manufacturing control (CMC) issues that were not able to be corrected in time for the PDUFA due date. This submission is a resubmission in which the Sponsor claims to have corrected all of the CMC deficiencies. The CMC reviews are pending at this time.

Labeling meetings are ongoing. The United States Prescribing Information (USPI) for bortezomib for injection, will be identical to that of the reference drug with the following exceptions due to exclusivity:

- Bortezomib for injection will not be approved for the subcutaneous route of administration [REDACTED] (b) (4)
- Bortezomib for injection will not be approved for patients with newly diagnosed mantle cell lymphoma.

The consultants from Pediatric and Maternal Health have recommended changes to the label in Sections 8.1 (Pregnancy), 8.2 (lactation guidelines) and 8.3 (contraception guidelines). The Division of Hematology Products does not agree with making these changes to the label for the 505(b)(2) application before the changes have been made to the USPI of the RLD.

**REGULATORY RECOMMENDATION:**

The clinical review team recommends approval of this 505(b)(2) application for bortezomib injection for the treatment of patients with multiple myeloma and for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

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KAREN M MCGINN  
03/17/2015

ROMEO A DE CLARO  
03/17/2015

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Edvardas Kaminskas, M.D.
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	NDA 205004
<b>Supplement #</b>	
<b>Applicant Name</b>	Fresenius Kabi USA, LLC
<b>Date of Submission</b>	December 3, 2012
<b>PDUFA Goal Date</b>	October 3, 2013
<b>Proprietary Name / Established (USAN) Name</b>	Bortezomib for Injection
<b>Dosage Forms / Strength</b>	Sterile lyophilized/3.5 mg/vial
<b>Proposed Indications</b>	Bortezomib is a proteasome inhibitor indicated for treatment of patients with multiple myeloma and for treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.
<b>Action/Recommended Action for NME:</b>	Complete Response

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	Karen McGinn/Romeo A. De Claro
Pharmacology Toxicology Review	Pedro L. Del Valle/Haleh Saber
ONDQA/CMC Review	Zhe J. Tang/Donghao R. Lu/Ali H. Al Hakim
ONDQA/Biopharmaceutics	Kelly M. Kitchens/Angelica Dorantes
ONDQA/Microbiology Review	Erika A. Pfeiler/Stephen E. Langille
Clinical Pharmacology Review	Young J. Moon/Julie M. Bullock
Office of Compliance	Timothy J. Pohlhaus/David D. Doleski
CDTL Review	Janice T. Brown

OND=Office of New Drugs  
 ONDQA=Office of New Drug Quality Assessment  
 OBP=Office of Biotechnology Products  
 CDTL=Cross-Discipline Team Leader

# Signatory Authority Review Template

## 1. Introduction

Bortezomib is a small molecule, antineoplastic agent approved for intravenous or subcutaneous injection for the treatment of patients with multiple myeloma and of patients with mantle cell lymphoma who have received at least one prior therapy. The current application for Bortezomib for Injection is submitted as a 505(b)(2) New Drug Application. The reference drug is Velcade (bortezomib) for Injection, manufactured by Millennium Pharmaceuticals, Inc. (NDA 21602), is a single-use vial containing 3.5 mg of bortezomib as a lyophilized powder.

## 2. Background

The NDA is for a new formulation of approved Bortezomb for Injection. The route of administration, dosage form and strength of the proposed product are the same as for the listed drug, except that subcutaneous use is omitted from the proposed label. The application was reviewed under a pilot program of the new Office of Pharmaceutical Quality with the objective to accelerate the CMC review of an NDA. The goal is to complete the NDA review in 3 months. Under this pilot program the CMC review was divided as follows:

- product review (drug substance and drug product - one ONDQA chemistry reviewer),
- process/facility review (drug substance and drug product - one ONDQA chemistry reviewer and one OC [Office of Compliance]) reviewer,
- microbiology – one New Drug Microbiology reviewer, and
- biopharmaceutics – one ONDQA biopharmaceutics reviewer.

## 3. CMC

Product Review: Bortezomib for Injection is supplied as a single-use vial containing 3.5 mg bortezomib, 10.5 mg boric acid and 25 mg glycine as a sterile lyophilized powder. Velcade contains 3.5 mg bortezomib and 35 mg mannitol as excipient. The CMC product reviewer concluded that the DMF (b)(4) was adequate and the reviewer did not have any outstanding deficiencies.

Process Review: The process reviewer found the process section in DMF (b)(4) acceptable. The CMC process and facility reviewer found a number of drug product manufacturing deficiencies, including (b)(4) % moisture content of the drug product which is unsupported by batch data, absent data to support the (b)(4) lyophilization cycle development and vial sampling. The CMC process and facility reviewer stated “**Approval of this product is not recommended at the present time [due to] drug manufacturing process deficiencies.**”

Microbiology: Bortezomib for Injection is sterilized (b) (4). The Microbiology review stated that there are no outstanding microbiology issues and recommended approval from the standpoint of product quality microbiology.

Biopharmaceutics: The review found that the applicant did not provide evidence showing that the different composition of Bortezomib for Injection compared to that of RLD Velcade® does not affect the physiological disposition of the proposed drug product. Hence, the waiver for *in vivo* bioavailability/bioequivalence studies cannot be granted. **From the Biopharmaceutics perspective, a Complete Response is recommended for NDA 205004 for Bortezomib for Injection at this time. The Biopharmaceutics deficiency is included at the end of this review.**

I concur with the conclusions reached by the CMC reviewers.

## 4. Nonclinical Pharmacology/Toxicology

The Sponsor included in this NDA a study comparing the *in vitro* proteasome inhibition of bortezomib drug substance, the proposed Fresenius Kabi USA drug product Bortezomib for Injection and Velcade® using a proteasome inhibition assay. The results showed that the bortezomib drug substance, the proposed Fresenius Kabi USA drug product Bortezomib for Injection and Velcade® had similar *in vitro* proteasome inhibition and that the excipients in the formulation did not contribute to this inhibition. From pharmacology/toxicology perspective, Bortezomib for Injection may be approved for the proposed indications.

I concur with the conclusions reached by the Pharmacology/Toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

## 5. Clinical Pharmacology

The Clinical Pharmacology review stated “The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 5 considers this NDA acceptable from a clinical pharmacology perspective”. To support a waiver of *in vivo* bioequivalence, the applicant conducted an *in vitro* bridging study to compare the proteasome inhibition activity between the proposed Fresenius Kabi USA drug Bortezomib for Injection with the listed drug at clinically relevant concentrations. The study suggests that the *in vitro* proteasome inhibitory activities of the two products are comparable. Therefore, an acceptable *in vitro* bridge between the FK’s product and Millenium’s RLD product was established.

I concur with the conclusions reached by the Clinical Pharmacology/Biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

## 6. Clinical Microbiology

There was no Clinical Microbiology review for this NDA.

## **7. Clinical/Statistical-Efficacy**

This application includes 42 references describing clinical trials of the reference drug used in patients with follicular lymphoma, mantle cell lymphoma, multiple myeloma and Waldenstrom's macroglobulinemia. No clinical approvability issues were identified. There was no statistical review for this NDA.

I concur with the conclusions reached by the clinical reviewer that there are no outstanding efficacy issues that preclude approval.

## **8. Safety**

There was no Safety Review for this NDA.

## **9. Advisory Committee Meeting**

There was no Advisory Committee meeting held for this application.

## **10. Pediatrics**

There was no Pediatric and Maternal Health Staff review for this NDA.

## **11. Other Relevant Regulatory Issues**

Office of Compliance on Drug Product Facility and Process Review concluded on April 20, 2013: "Approval of this product is not recommended at present time for the following reasons: 1) drug product manufacturing process deficiencies, and 2) the unacceptable compliance status of Fresenius Kabi, Grand Island, New York – the drug product manufacturing facility". On January 18, 2013 the Office of Compliance had issued an **Overall Withhold** recommendation for this application.

## **12. Labeling**

The proposed labeling for Fresenius Kabi Bortezomib for Injection is essentially the same in content as that of the innovator listed drug product, except for the Dosage and Administration, Dosage Forms and Strength, Description and How Supplied sections of the labeling. The formatting of the applicant's proposed labeling was constructed to comply with the

requirements of the Physician Labeling Rule. Due to the Complete Response recommendation, labeling was not negotiated and/or conveyed to the applicant in the current review cycle.

### 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete Response. Approval of this NDA is not recommended based on CMC and Biopharmaceutics deficiencies. The Office of Compliance has given an overall withhold recommendation for this NDA.

- Risk Benefit Assessment

There are substantial review deficiencies associated with this application. This product is currently unsuitable for commercial production and marketing.

- Recommendation for Postmarketing Risk Management Activities  
Not discussed during the current review cycle.

- Recommendation for other Postmarketing Study Commitments  
Not discussed during the current review cycle.

- Recommended Comments to Applicant

Deficiencies:

#### QUALITY – SPECIFICATION, PROCESS, and FACILITIES

1. During a recent inspection of APP Pharmaceuticals, LLC, Grand Island NY, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.
2. You have not provided sufficient data to show that you have adequately developed your product lyophilization cycle. Your March 29, 2013 response to item 19 of our March 15, 2013 letter was incomplete and, therefore, is insufficient. Furthermore, you state in your response to item 17 of the same letter that you have been unable to produce a batch with moisture content below (b) (4). Provide evidence that you have fully developed each stage of the lyophilization cycle that you intend to validate in commercial-scale batches. State explicitly your criteria for determining advancement through each stage of the lyophilization cycle and provide data showing that the criteria have been met. Include temperature mapping (b) (4).
3. You have not appropriately set your finished product moisture content limit ( (b) (4) %). (b) (4)  
(b) (4)  
you have not justified the approach you

use to calculate your moisture limit. Specifically, you have not provided justification for calculating the limit (b) (4)

4. Your March 29, 2013 response to item 11 of our March 15, 2013 letter is inadequate because you did not revise your (b) (4)
5. Your March 29, 2013 response to item 22 of our March 15, 2013 letter is insufficient. Because you have not stated that these (b) (4)  
However, you have not (b) (4) statistically justified the use of (b) (4) to support your response.

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EDVARDAS KAMINSKAS  
09/26/2013

**Clinical Review  
New Drug Application  
Division of Hematology Products**

<b>NDA:</b>	205004
<b>Drug Name:</b>	Bortezomib injection
<b>Sponsor:</b>	Fresenius Kabi
<b>RPM:</b>	Karen Bengston
<b>Submission Date:</b>	December 3, 2012
<b>PDUFA Date:</b>	October 3, 2013
<b>Completion Date:</b>	March 18, 2013
<b>Clinical Reviewer:</b>	Karen McGinn, MSN, CRNP
<b>Clinical Team Leader:</b>	R. Angelo de Claro, MD
<b>Review Completion Date:</b>	April 30, 2013

**BACKGROUND:**

The Applicant has submitted a 505(b)(2) New Drug Application for bortezomib for injection. The reference drug is bortezomib for injection manufactured by Millennium Pharmaceuticals and indicated for patients with multiple myeloma and for patients with mantle cell lymphoma who have received at least one prior therapy.

This application includes 42 references describing clinical trials of the reference drug used in patients with follicular lymphoma, mantle cell lymphoma, multiple myeloma and Waldenstrom's macroglobulinemia.

During the mid-cycle meeting March 19, 2013, there was extensive discussion about multiple chemistry and manufacturing control (CMC) issues that have previously been identified and communicated to the Sponsor and cannot be corrected in time for the PDUFA due date. DHP has decided that this application will receive a complete response. All review teams are in agreement regarding due dates for primary and CDTL reviews, and a goal date for issuing a Complete Response (CR) letter has been established.

Labeling meetings have been scheduled; however, they will be postponed until the Sponsor corrects the manufacturing deficiencies and resubmits the application during the next review cycle.

**REGULATORY RECOMMENDATION:**

Due to outstanding chemistry manufacturing and control deficiencies, DHP plans to issue a Complete Response (CR) letter. Labeling meetings will be scheduled during the next review cycle after the Sponsor submits a satisfactory response to the CR letter.

**SECONDARY REVIEW (CLINICAL TEAM LEADER):** No clinical approvability issues identified during this review cycle. However, labeling negotiations have been deferred until the next review cycle due to Compete Response issues with product quality.

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ROMEO A DE CLARO  
04/30/2013

**Senior Clinical Analyst Review  
New Drug Application  
Division of Hematology Products**

<b>NDA:</b>	205004
<b>Drug Name:</b>	Bortezomib injection
<b>Sponsor:</b>	Fresenius Kabi
<b>RPM:</b>	Karen Bengston
<b>Submission Date:</b>	December 3, 2012
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<b>Clinical Team Leader:</b>	R. Angelo de Claro, MD
<b>Review Completion Date:</b>	March 19, 2013

**BACKGROUND:**

The Applicant has submitted a 505(b)(2) New Drug Application for bortezomib for injection. The reference drug is bortezomib for injection manufactured by Millennium Pharmaceuticals and indicated for patients with multiple myeloma and for patients with mantle cell lymphoma who have received at least one prior therapy.

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Labeling meetings have been scheduled; however, they will be postponed until the Sponsor corrects the manufacturing deficiencies and resubmits the application during the next review cycle.

**REGULATORY RECOMMENDATION:**

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KAREN M MCGINN  
04/08/2013

ROMEO A DE CLARO  
04/08/2013