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APPLICATION NUMBER:

205004Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	November 01, 2017
From	Anamitro Banerjee
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 205004
Type of Application	505(b)(2)
Applicant	Fresenius Kabi USA, LLC
Date of Submission	September 05, 2017
PDUFA Goal Date	November 05, 2017
Proprietary Name / Established (USAN) names	Bortezomib for Injection
Dosage forms / Strength	Lyophilized powder, 3.5 mg/vial
Proposed Indication(s)	<ul style="list-style-type: none">• Treatment of patients with multiple myeloma• Treatment of patients with mantle cell lymphoma who have received at least one prior therapy.
Recommended:	Approval

1. Introduction

Bortezomib is a small molecule, cytotoxic agent approved for intravenous or subcutaneous administration for:

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

The current application for Bortezomib for Injection 3.5 mg lyophilized powder is submitted as a 505(b)(2) NDA. The innovator product, Velcade® (bortezomib) for Injection from Millennium Pharmaceuticals, Inc. (NDA 021602) is a single dose vial containing 3.5 mg of bortezomib as a lyophilized powder.

2. Background

Bortezomib is a proteasome inhibitor that binds the catalytic site of the 26S proteasome, which is thought to prevent the degradation of proapoptotic proteins and permit the activation of programmed cell death. The listed drug Velcade® was approved on May 13, 2013 for the treatment of multiple myeloma and mantle cell lymphoma. Velcade® is available as a single-dose, 3.5 mg/vial lyophilized powder for intravenous and subcutaneous administration. The subject of the current NDA application is a new formulation of approved Bortezomib for Injection. This NDA was initially submitted on November 30, 2012 (received December 3, 2012) and received a Complete Response (CR) on October 03, 2013. This NDA was resubmitted on October 03, 2014 and again on May 22, 2015. This NDA was tentatively approved on November 17, 2015 due to unexpired patent and exclusivity protection of the listed drug. The current submission dated September 05, 2017 seeks final approval due to impending change in the patent status of the listed drug.

3. CMC

The DMF (b)(4) (DMF holder: (b)(4)) was updated since the Tentative Approval of this NDA. The amendments to the DMF were reviewed and were found acceptable. The applicant also updated the drug product specifications by widening the acceptance criteria for the reconstitution time based on additional data collected since the Tentative Approval. The proposed specifications were found acceptable. The applicant updated the master batch record (MBR) as per recommendations of the FDA inspection team.

No outstanding or additional CMC issues are identified during this review cycle. The OPQ review team recommends approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

No Nonclinical Review was conducted in this review cycle. The last Pharmacology/Toxicology review (Pedro Del Valle, Ph.D., final signature October 23, 2015) recommended approval of this NDA.

5. Clinical Pharmacology

The Clinical Pharmacology review (Yuhong Chen, MD, Ph.D., final signature November 11, 2017) indicated that the Office of Clinical Pharmacology will not be reviewing this application as no updates to clinical pharmacology information were provided in this submission.

6. Clinical/Statistical- Efficacy

There was no Statistical Review was done for this NDA. The applicant did not provide any clinical studies with Bortezomib for Injection, but provided a summary of worldwide experience of the safety of Bortezomib (literature search on August 16, 2017 through PubMed). The clinical review (Saleh Ayache, M.D., final signature October 31, 2017) did not identify any approvability issues for this application.

7. Safety

There was no Safety Review for this NDA.

8. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

9. Pediatrics

There is no Pediatric and Maternal Health Staff (PMHS) review for this NDA.

10. Other Relevant Regulatory Issues

None

11. Labeling

The labeling review was performed by DMEPA, CMC, and the DHP review team

CMC Recommendations:

The applicant was asked to add the excursion temperature range as per the USP controlled room temperature in the PI and the carton containers. The updated proposed labeling dated November 03, 2017 is acceptable.

DHP Recommendations:

The applicant accepted all the proposed FDA labeling recommendations on November 03, 2017

DMEPA Recommendations:

DMEPA found the proposed labeling acceptable

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

This product relies on the safety and efficacy of the listed product, Velcade®. The updates to the CMC information were found acceptable. No new clinical or nonclinical data were provided with this submission, as no other studies were conducted for this 505(b)(2) application. The cross disciplinary team lead recommends **approval** of this submission.

- Risk Benefit Assessment

Please refer to NDA 021602.

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/s/

ANAMITRO BANERJEE
11/03/2017

Cross-Discipline Team Leader Review

Date	See electronic date stamp
From	Janice Brown, M.S.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 205004
Applicant	Fresenius Kabi USA, LLC
Date of Submission	May 22, 2015 (received May 22, 2015)
PDUFA Goal Date	November 22, 2015
Proprietary Name / Established (USAN) names	Bortezomib
Dosage forms / Strength	For injection (lyophilized powder) / 3.5 mg
Proposed Indication(s)	Treatment of patients with multiple myeloma Treatment of patients with mantle cell lymphoma who have received at least one prior therapy.
Recommended:	Tentative Approval

1. Introduction

Bortezomib is a small molecule, antineoplastic agent approved for intravenous or subcutaneous administration for the treatment of patients with multiple myeloma or mantle cell lymphoma. The current application for Bortezomib for Injection is submitted as a 505(b)(2) NDA. The innovator product, Velcade (bortezomib) for Injection from Millennium Pharmaceuticals, Inc. (NDA 21602) is a single-dose vial containing 3.5 mg of bortezomib as a lyophilized powder.

2. Background

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 subject of the current NDA submission is a new formulation of an approved Bortezomib for Injection. 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 third cycle for this application. See the Cross-Discipline Team Leader (CDTL) review dated April 02, 2015 and May 02, 2013 for details of the regulatory history prior to this NDA resubmission and reviews for a summary and details of the application review history prior to this cycle. On April 02, 2015, 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 May 22, 2015 to address complete response issues with the 505(b)(2) application.

3. CMC

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 (b) (4)

The API supplier had recently updated their DMF to (b) (4)
(b) (4)
(b) (4). All the drug substance changes were reviewed and found acceptable and the drug substance reviewer found the information adequate (b) (4)
(b) (4)

Drug Product Review: The applicant has updated the DMF to reflect (b) (4)

(b) (4)

The lack of sufficient drug product for initial marketing is not an issue since this NDA submission will be receiving a tentative approval.

The drug product acceptance criterion for Description was revised from (b) (4) (b) (4) to “white to off-white powder or cake in an amber glass vial.” During the facility inspection, investigators discovered that a significant number of vials with an abnormal appearance passed visual inspection. FDA investigators determined that the drug product Description acceptance criterion (b) (4) was not discriminating and as a consequence, the abnormal appearance of the lyophilized cake passed the acceptance criterion of a (b) (4) during visual examination. This issue was communicated to the drug product reviewer and an information request was sent to the applicant to revise the Description acceptance criterion from (b) (4) to “white to off-white powder or cake in an amber glass vial.” The applicant submitted the revised specification with the new Description acceptance criterion of white to off-white powder or cake in an amber glass vial. All the drug product changes were reviewed and found acceptable and the drug product reviewer recommended approval of the NDA (refer to the drug product section of the integrated quality assessment signed by Janice Brown).

Process Review – Drug Product: Information relevant to the Drug Product Process review was limited to an updated master batch record (MBR) that was revised to add additional specificity on the pages of the batch records for all (b) (4) lyophilized products and to include clarification of the theoretical versus actual yield calculations. The changes in the MBR have been reviewed and deemed acceptable from a process review perspective. All the drug

product process changes were reviewed and found acceptable and the process reviewer recommended approval of the NDA (refer to the process section of the integrated quality assessment signed by Zhong Li on October 8, 2015).

Facility Review: The facility reviewer found no significant, outstanding manufacturing risks that prevent approval of this application. Based on firm inspectional history and pre-approval inspection review, the manufacturing facilities as listed for NDA 205004 are found to be acceptable and recommended approval of the NDA (refer to the facility section of the integrated quality assessment signed by Zhong Li on October 8, 2015).

Biopharmaceutics: There is no new Biopharmaceutics information included in the current submission. Therefore, the Division of Biopharmaceutics continues to recommend approval for this NDA (refer to the biopharmaceutics section of the integrated quality assessment signed see review by Kelly Kitchens, Ph.D., final signature October 06, 2015).

Microbiology Review: 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), sterilization parameters for stoppers, equipment, and lyophilizers, and vial depyrogenation parameters. All were within agreement with information previously submitted. The microbiology review recommend approval on the NDA (refer to the facility section of the integrated quality assessment signed by Erika Pfeiler, Ph.D., final signature October 05, 2015 and memo dated November 7, 2014).

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer filed an updated memo (Pedro Del Valle, Ph.D., signed October 23, 2015) indicating that there is no new nonclinical pharmacology and toxicology information in the resubmission and continues to recommend approval of the NDA.

5. Clinical Pharmacology

The clinical pharmacology reviewer filed an updated memo (Young Jin Moon, Ph.D., signed October 25, 2015) indicating that there is no new clinical pharmacology information in the resubmission and continues to recommend approval of the NDA.

6. Clinical Microbiology

There was no Clinical Microbiology review for this NDA.

7. Clinical/Statistical- Efficacy

No clinical studies were performed with the proposed drug product, Bortezomib for Injection.

There was no statistical review for this NDA.

8. Safety

The clinical review stated that 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.”

The clinical review removed the following (b) (4) from the proposed labeling:



The clinical reviewer (Saleh Ayache, Ph.D., final signature October 20, 2015) did not identify any new safety signals and recommended a tentative approval of the NDA.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

10. Pediatrics

There is no Pediatric and Maternal Health Staff (PMHS) 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 labeling at the time of final approval of this Fresenius application will depend upon existing exclusivities remaining. Table 1 lists the exclusivities for the listed drug, Velcade (bortezomib) for injection.

Table 1: Velcade (bortezomib) for injection*

Exclusivity Code	Exclusivity Expiration
<u>ODE</u> ORPHAN DRUG EXCLUSIVITY [First-line therapy of multiple myeloma.]	Jun 20, 2015
<u>I - 695</u> REVISED INDICATION FOR BORTEZOMIB IN THE TREATMENT OF PATIENTS WITH MANTLE CELL LYMPHOMA	Oct 8, 2017
<u>D - 142</u> DOSE MODIFICATION GUIDELINES FOR BORTEZOMIB WHEN GIVEN IN COMBINATION WITH RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE	Oct 8, 2017
<u>D - 141</u> DOSING INFORMATION IN PREVIOUSLY UNTREATED MANTLE CELL LYMPHOMA	Oct 8, 2017
<u>ODE</u> ORPHAN DRUG EXCLUSIVITY (I-695 indication)	Oct 8, 2021
<u>M - 139</u> 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:** Not applicable
- **Other GCP issues:** None
- **DSI audits:** Not applicable
- **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 firstline 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. Bortezomib in Combination with Intensive Re-Induction Therapy in Children with Relapsed Acute Lymphoblastic Lymphoma (ALL)". 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 (see review by Nisha Patel, final signature on October 16, 2015).

Division of Medication Error Prevention and Analysis (DMEPA): The DMEPA review for the revised container label and carton labeling was found acceptable (see review by Michelle Rutledge, PharmD, final signature on September 2, 2015).

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.

3. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Tentative Approval.

- 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 drug substance, DMF, and drug product deficiencies. The process, microbiology and biopharmaceutics review continue to recommended approval of the NDA application. Pharmacology/Toxicology has no concerns with the nonclinical findings and 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. Since there are existing exclusivities in effect for Velcade (bortezomib) for injection, the recommended regulatory action for this NDA submission is a tentative approval.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

None

- Recommended Comments to Applicant

Insert the standard language for conveying a tentative approval in into the action letter.

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
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cn=Janice T. Brown -A
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Cross-Discipline Team Leader Review

Date	See electronic date stamp
From	Janice Brown
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 205004
Applicant	Fresenius Kabi USA, LLC
Date of Submission	November 30, 2012 (received December 3, 2012)
PDUFA Goal Date	September 12, 2013
Proprietary Name / Established (USAN) names	Bortezomib for Injection
Dosage forms / Strength	Lyophilized powder
Proposed Indication(s)	Indicated for treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy.
Recommended:	Complete Response

1. Introduction

Bortezomib is a small molecule, antineoplastic agent approved for intravenous or subcutaneous administration for the treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy. The current application for Bortezomib for Injection 3.5 mg lyophilized powder is submitted as a 505(b)(2) NDA. 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 CDTL memo serves to highlight the critical approvability issues for all review disciplines and recommends a “Complete Response” action for this application. All individual discipline reviews may be found in DARRTS. Due to the “Complete Response” recommendation, final labeling was not conveyed to the applicant during this review cycle.

2. Background

The subject of the current NDA application is a new formulation of approved Bortezomib for Injection. This NDA was submitted on November 30, 2012 (received December 3, 2012). The route of administration, dosage form and strength of the proposed drug product are the same as the listed drug. 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. A comparison of the listed drug and the proposed drug product is listed in table 1.

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

Name	Listed Drug	Proposed Drug Product
		Velcade® (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.

Name	Listed Drug	Proposed Drug Product
	Velcade® (bortezomib) for Injection	Bortezomib for Injection
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)	N/A	(b) (4)
		(b) (4)

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

This application is being reviewed under a pilot program for the new Office of Pharmaceutical Quality. The goal is to have a team review to accelerate the CMC review of an NDA. Under this pilot program the CMC review has been 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 reviewer
- Microbiology: One NDM reviewer
- Biopharmaceutics: One ONDQA biopharmaceutics reviewer

A total of five reviewers’ were assigned to this application with a goal to complete the NDA review in three months.

3. CMC

Product Review: Bortezomib drug substance is a small molecule drug consisting of a modified dipeptidyl boronic acid. All the related CMC drug substance information was referenced to DMF (b) (4). The DMF review (Zhe J. Tang, Ph.D., final signature April 26, 2013) concluded the DMF was adequate.

Bortezomib for Injection is supplied as a single use vial containing 3.5 mg of bortezomib, 10.5 mg boric acid and 25 mg glycine as a sterile lyophilized powder. The CMC product review (Zhe J. Tang, Ph.D., final signature April 29, 2013) did not have any outstanding deficiencies and did not recommend approval due to the outstanding deficiencies identified in the process review.

Process Review – The process reviewer found the process section in DMF (b) (4) acceptable. The manufacturing process for bortezomib for injection consists of (b) (4)

(b) (4). The CMC process review (Donghao Lu, Ph.D. final signature April 29, 2013) stated, “This NDA is not recommended for approval from a CMC perspective due to the unsolved deficiencies.” The CMC process and facility reviewer (Timothy J. Pohlhaus, Ph.D., final signature May 1, 2012) stated, “Approval of this product is not recommended at present time [due to] drug product manufacturing process deficiencies”. The significant CMC issue relates to the upper and lower moisture content of the drug product. The drug product has (b) (4) % moisture content limit which is unsupported by batch data. (b) (4). Other deficiencies relate to (b) (4), lyophilization cycle development and vial sampling.

Microbiology – Bortezomib for Injection is sterilized by (b) (4). The Microbiology review (Erika Pfeiler, Ph.D., final signature April 8, 2013) stated, “Recommend approval on the basis of product quality microbiology.” There are no outstanding microbiology issues related to the sterility assurance of the Bortezomib for injection product and the review recommended approval.

Biopharmaceutics – The biopharmaceutics review (Kelly Kitchens, Ph.D., final signature April 22, 2013) stated, “A complete response is recommended for NDA 205004 for Bortezomib for Injection at this time”. 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 was not adequately addressed. As a result of this deficiency, the waiver for in-vivo bioavailability/bioequivalence studies was not granted. The biopharmaceutics deficiency is included at the end of this review.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review (Pedro Del Valle, Ph.D., final signature April 5, 2013) stated, “From the Pharmacology/Toxicology perspective, Bortezomib for Injection may be approved for the proposed indications.” Pharmacology/Toxicology has no concerns with the nonclinical findings and the excipients used for the Bortezomib for Injection at the defined levels and the review recommends approval.

5. Clinical Pharmacology

The Clinical Pharmacology review (Young Jin Moon, Ph.D., final signature April 23, 2013) stated “The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 considers this NDA acceptable from a clinical pharmacology perspective. To support of a waiver of *in vivo* bioequivalence (BE), the applicant conducted an *in vitro* bridging study to compare the proteasome inhibition activity between Fresenius’s product and the listed drug 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.

6. Clinical Microbiology

There was no Clinical Microbiology review for this NDA.

7. Clinical/Statistical- Efficacy

There was no Statistical Review was done for this NDA. The clinical review (Romeo De Claro, M.D., final signature April 30, 2013) did not identify any approvability issues for this application.

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 is no Pediatric and Maternal Health Staff (PMHS) review for this NDA.

11. Other Relevant Regulatory Issues

Manufacturing Facilities: On January 18, 2013 the Office of Compliance issued an overall withhold recommendation for this application.

- Application Integrity Policy (AIP): Not applicable
- Exclusivity or patent issues of concern: Not applicable
- Financial disclosures: Not applicable
- Other GCP issues: None
- DSI audits: Not applicable
- Other discipline consults: None

12. Labeling

The proposed labeling for Fresenius's Bortezomib for Injection is essentially the same in content as that of the innovator LD 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 has been constructed to comply with the requirements of the Physician's Labeling Rule (PLR). Due to the "Complete Response" recommendation, labeling was not negotiated and/or conveyed to the applicant in the current review cycle.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval of this NDA is not recommended based on CMC and Biopharmaceutics deficiencies. The OC has given an overall withhold recommended for this NDA.

- Risk Benefit Assessment

There are substantial review deficiencies associated with this application. Therefore, 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: Since this application was reviewed under a pilot program, ONDQA management will draft a memorandum detailing the deficiencies that should be communicated in the action letter. The following deficiencies have been identified:

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 adequate supportive information demonstrating that the physiological disposition of your proposed drug product does not differ from that of the 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.
3. It has been reported that the stability data with (b) (4) water content up to (b) (4) % did not result in a concern in product stability. However, it is unknown whether water content between (b) (4) % impacts the quality of the product stability. Therefore, additional study should be conducted to address this concern.
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. You have not appropriately set your finished product moisture content limit (^{(b) (4)} %). Specifically, you have added a ^{(b) (4)} for water content without demonstrating that ^{(b) (4)}. Furthermore, you have not justified the approach you use to calculate your moisture limit in your March 29, 2013 response to item 18 of our March 15, 2013 letter. Specifically, you have not provided justification for calculating the limit based on ^{(b) (4)}.
6. 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)} the lyophilizer.
7. Your March 29, 2013 response to item 22 of our March 15, 2013 is insufficient. Because you have not stated that these additional reconstitution time data points are results from ^{(b) (4)}

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/s/

JANICE T BROWN
05/02/2013

ALI H AL HAKIM
05/02/2013

Cross-Discipline Team Leader Review

Date	See electronic date stamp
From	Janice Brown, M.S.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 205004
Applicant	Fresenius Kabi USA, LLC
Date of Submission	October 03, 2014 (received October 03, 2014)
PDUFA Goal Date	April 03, 2015
Proprietary Name / Established (USAN) names	Bortezomib for Injection
Dosage forms / Strength	Lyophilized powder
Proposed Indication(s)	Treatment of patients with multiple myeloma Treatment of patients with mantle cell lymphoma who have received at least one prior therapy.
Recommended:	Complete Response

1. Introduction

Bortezomib is a small molecule, antineoplastic agent approved for intravenous or subcutaneous administration for the treatment of patients with multiple myeloma or mantle cell lymphoma. The current application for Bortezomib for Injection is submitted as a 505(b)(2) NDA. The innovator product, Velcade (bortezomib) for Injection from Millennium Pharmaceuticals, Inc. (NDA 21602) is a single-dose vial containing 3.5 mg of bortezomib as a lyophilized powder.

2. Background

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 subject of the current NDA application is a new formulation of approved Bortezomib for Injection. 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. See the Cross-Discipline Team Leader (CDTL) review dated May 02, 2013 for details of the regulatory history prior to this NDA resubmission and reviews for a summary and details of the application review history prior to this cycle. 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.

This CDTL memo serves to highlight the critical approvability issues and recommends a "Complete Response" action for this application. All individual discipline reviews may be found in DARRTS or Panorama. Final container/carton and Package Insert (PI) labeling is still pending due to the recommended "Complete Response" action. Any updated container/carton and/or PI labeling will need to be reviewed by all disciplines during subsequent review cycles.

3. CMC

This application is reviewed under a pilot program for the new Office of Pharmaceutical Quality. The goal is to have a team review to accelerate the CMC review of an NDA. Under this pilot program the CMC review has been divided as follows:

Review type	Section Reviewed	Reviewer Name
Product review	Drug substance and drug product	Zhe J. (Jean) Tang, Ph.D.
Process review/facility review	Drug substance and drug product	Donghao (Robert) Lu, Ph.D. Zhong Li, Ph.D.
Microbiology/facility review	Drug product sterility assurance and performed the facility inspection	Erica Pfeiler, Ph.D.
Bio pharmaceuticals:	Bioavailability/bioequivalence waiver	Kelly Kitchens, Ph.D.

Product Review – Drug Substance: All the related CMC drug substance information was referenced to DMF (b)(4). The previous DMF review (Zhe J. Tang, Ph.D., final signature April 26, 2013) concluded the DMF was adequate to support NDA 205004.

The holder resubmitted the DMF 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) t, 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 change the drug product moisture content limit from (b)(4)% which is consistent with level observed

in the stability batches. At my request, the previous communications and review of the deficiencies in the Complete Response letter were documented in the March 12, 2015 review. The approval recommendation for the process review is in the March 10, 2015 review. The review recommended approval of the NDA pending an acceptable facility recommendation.

Microbiology Process Review – Drug Product: The previous microbiology review (Erika Pfeiler, Ph.D., final signature April 8, 2013) recommend approval on the basis of product quality microbiology.

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 and a withhold recommendation was entered into Panorama on April 1, 2015.

Biopharmaceutics – The previous biopharmaceutics review (Kelly Kitchens, Ph.D., final signature April 22, 2013) did not grant the bioavailability/bioequivalence waiver request due to the lack of complete supportive information justifying the formulation differences between the proposed product and the reference product and recommended a complete response for the NDA.

In this cycle, the biopharmaceutics review of the resubmission, the Division of Biopharmaceutics revised the previous recommendation for the biowaiver request. 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.

4. Nonclinical Pharmacology/Toxicology

The previous Pharmacology/Toxicology review (Pedro Del Valle, Ph.D., final signature April 5, 2013) recommended approval of the NDA.

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

The previous Clinical Pharmacology review (Young Jin Moon, Ph.D., final signature April 23, 2013) recommended approval of the NDA.

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

There was no Statistical Review for this NDA. 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.

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 is no Pediatric and Maternal Health Staff (PMHS) 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
- **Any other outstanding regulatory issues:** 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.

OSE/DMEPA. The DMEPA review for the revised container label, carton labeling and Prescribing labeling included comments that were not conveyed to the applicant due to the pending complete response action (see review by Michelle Rutledge, PharmD, final signature on February 3, 2015).

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

Issues not resolved at the time of CDTL memo completion: All container/carton and PI labeling will need to be re-evaluated for acceptability by all disciplines during any subsequent review cycle.

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

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The CMC deficiencies in the Complete Response have been resolved. No pharmacology/toxicology or clinical pharmacology issues have been found to preclude approval. Clinical review finds the application adequate and recommends approval. The Office of Process and Facilities did not recommend approval of the NDA due to the 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. Pharmacology/Toxicology has no concerns with the nonclinical findings and the excipients used for Fresenius Bortezomib for Injection at the defined levels. 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

- Recommendation for other Postmarketing Study Commitments

None

- Recommended Comments to Applicant

Insert the standard language for conveying an unacceptable facility recommendation into the action letter.

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
04/02/2015