CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205004Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205004	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: 5 *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Established/Proper Name: Bortezomib Dosage Form: Injection		Applicant: Fresenius Kabi Agent for Applicant (if applicable):
RPM: Janet G. Higgins		Division: Division of Hematology Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☒ New patent/exclusivity *(notify CDER OND IO)*
Date of check:10/15/2015

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is November 22, 2015	☐ AP ☒ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	CR 04/02/2015; CR 10/03/2013
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	n/a
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type: orphan, pediatric exclusivity; refer to the draft 505b2 assessment entered into DARRTS	☐ No ☒ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	11/17/2015 TA; 4/2/2015 CR; 10/3/2013 CR
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 11/13/2015
• Original applicant-proposed labeling	☒ Included 12/3/2013
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	n/a
• Original applicant-proposed labeling	n/a
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included 10/30/2015
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	n/a
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 11/02/2015; 03/05/2013 OPDP: ☒ 10/16/2015; 4/21/2015; 5/2/2013 DMEPA: ☒ 9/3/2015; 02/03/2015 DMPP/PLT (DRISK): ☒ None SEALD: ☒ None CSS: ☒ None Product Quality ☒ See PQ review dated 10/23/2015
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	01/29/2013 10/15/2015
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	n/a
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: This application does not trigger PREA.	n/a
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	10/22/2015; 10/15/2015; 10/15/2015; 10/07/2015; 10/07/2015; 07/21/2015; 06/25/2015; 03/12/2015; 03/03/2015; 02/27/2015; 04/30/2013; 04/08/2013; 04/05/2013; 03/18/2013; 03/15/2013; 03/07/2013; 02/13/2013; 02/13/2013; 02/01/2013; 01/24/2013; 01/23/2013; 01/22/2013; 12/10/2012; 12/05/2012
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	10/20/2015; 01/08/2014; 04/05/2013; 02/14/2013
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ no mtg
• Pre-NDA/BLA meeting *(date of mtg: 04/06/2010)*	05/03/2010
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	n/a

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	11/10/2015; 04/02/2015; 09/26/2013
Cross-Discipline Team Leader Review *(indicate date for each review)*	10/26/2015; 04/02/2015; 05/02/2013
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	04/30/2013
• Clinical review(s) *(indicate date for each review)*	10/21/2015; 03/17/2015; 04/08/2013
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	There was no clinical data submitted with the application, hence no financial disclosure.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Cosigned primary review 4/23/13
Clinical Pharmacology review(s) *(indicate date for each review)*	10/25/2015; 04/23/2014
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review Cosigned primary review 10/23/2015; 09/27/2013
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	10/23/3015; 03/13/2015; 09/27/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	10/23/2015; 4/1/2015; 3/12/2015; 3/10/2015 (2); 4/20/2013; 04/29/2013; 04/29/2013; 01/15/2013
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	09/23/2015; 2/17/2015; 11/7/2014; 04/22/2013;04/08/2013
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See review dated 4/29/2013, p. 89
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☐ Done

---

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

/s/

JANET G HIGGINS
11/17/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205004 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Bortezomib for injection Established/Proper Name: Bortezomib for injection Dosage Form: injection		Applicant: Fresenius Kabi USA, LLC Agent for Applicant (if applicable):
RPM: Katie Chon		Division: Division of Hematology Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: September 19, 2017 and October 15, 2015

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action: November 6, 2017 • User Fee Goal Date is November 5, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	CR 9/27/2013 CR 4/21/2015 TA 11/17/2015
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments: Class 1 Resubmission

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☐ No ☒ Yes Pediatric exclusivity-; label has been modified to remove pediatric data
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified 11/30/2012 submission ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)* (link)	☒ Included Also refer to 11/23/2015 DARRTS Action Package
Documentation of consent/non-consent by officers/employees (link)	☒ Included Also refer to 11/23/2015 DARRTS Action Package
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 11/6/2017 Tentative Approval 11/17/2015 Complete Response 4/2/2015; 10/3/2013
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included 9/5/2017
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included 11/3/2017 and 9/5/2017 10/30/15 Refer to 11/23/15 DARRTS Action Package
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 11/2/2015; 3/5/2013 (Refer to 11/23/2015 DARRTS Action Package) DMEPA: 10/20/17 and 9/3/2015; 2/3/2015 (Refer to 11/23/2015 DARRTS Action Package) DMPP/PLT (DRISK): ☒ None OPDP: 10/16/2015; 4/21/2015;

	5/2/2013 (Refer to 11/23/2015 DARRTS Action Package) SEALD: ☒ None CSS: ☒ None Product Quality: see Product Quality Review dated 10/23/2015 (Refer to 11/23/2015 DARRTS Action Package) Other: DPMH - 11/1/17
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing: 1/29/2013 (Refer to 11/23/2015 DARRTS Action Package) 505(b)(2) committee: 10/23/2017 and 10/15/2015 (Refer to 11/23/2015 DARRTS Action Package)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters*	11/2/2017; 11/1/2017 (2); 9/25/2017; 9/20/2017

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)	Refer to 11/23/2015 DARRTS Action Package for the following: 10/22/2015; 10/15/2015 (2); 10/7/2015 (2); 7/21/2015; 6/25/2015; 3/12/2015; 3/3/2015; 2/27/2015; 4/30/2013; 4/8/2013; 4/5/2013; 3/18/2013; 3/15/2013; 3/7/2013; 2/13/2013 (2); 2/1/2013; 1/24/2013; 1/23/2013; 1/22/2013; 12/10/2012; 12/5/2012
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Refer to 11/23/2015 DARRTS Action Package for the following: 10/20/2015; 1/8/2014; 4/5/2013; 2/14/2013
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	4/6/2010 Refer to 11/23/2015 DARRTS Action Package
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	Refer to 11/23/2015 DARRTS Action Package for the following: 11/10/2015; 4/2/2015; 9/26/2015
Cross-Discipline Team Leader Review *(indicate date for each review)*	11/3/2017 Refer to 11/23/2015 DARRTS Action Package for the following: 10/26/2015; 4/2/2015; 5/2/2013
PMR/PMC Development Templates *(indicate total number)*	☒ None

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Cosigned 10/31/2017 clinical review 4/30/2013 Refer to 11/23/2015 DARRTS Action Package
• Clinical review(s) *(indicate date for each review)*	10/31/2017 Refer to 11/23/2015 DARRTS Action Package for the following: 10/21/2015; 3/17/2015; 4/8/2013
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	No clinical data submitted with the application, therefore no financial disclosure needed.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ -No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Cosigned 11/3/2017 and 11/1/2017 clinical pharmacology review
Clinical Pharmacology review(s) *(indicate date for each review)*	11/3/2017; 11/1/2017 Refer to 11/23/2015 DARRTS Action Package for the following: 10/25/2015; 4/23/2013
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review Cosigned 11/6/2017 pharmtox review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	11/6/2017 Refer to 11/23/2017 DARRTS Action Package for the following: 10/23/2015; 3/13/2015; 9/27/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	IQA 10/23/2017 Refer to 11/23/2015 DARRTS Action Package for the following: 10/23/2015; 5/1/2015; 4/1/2015 (2); 3/16/2015; 3/12/2015; 3/10/2015 (2); 4/29/2013 (2); 4/20/2013; 1/15/2013
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	Refer to 11/23/2015 DARRTS Action Package for the following: 9/23/2015; 11/7/2014; 4/22/2013; 4/8/2013

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Refer to 11/23/2015 DARRTS Action Packing for the following: See previous review dated 4/29/2013 Product Quality Review, page 89
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable 10/7/2015 Refer to 11/23/2015 DARRTS Action Package ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	

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

/s/

WONME K CHON
11/13/2017
electronically signed by Katie Chon, PharmD, RPh

From:	Chon, Katie
To:	"Arabella Buesching"
Subject:	NDA 205004
Date:	Thursday, November 02, 2017 4:49:46 PM
Attachments:	NDA 205004_fkusa-fpl-pi-word_Nov__FDA TRACKED CHANGES_All changes accepted by FK USA_11-1-17_FDA Nov2.docx

Dear Arabella,

Reference is made to NDA 205004 for Bortezomib for Injection.
Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

Where you agree with the labeling revisions, "accept" the tracked changes.
Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please revised your carton and container labels to include the temperature excursion that is proposed in Section 16 of the USPI and provide it to us for review and comment.

Please provide your response by **10am ET on Friday, November 3, 2017**. The information can be sent by electronic mail to Katie Chon (katie.chon@fda.hhs.gov), followed by an official submission to the NDA.

Kindly confirm receipt.

Regards,
Katie

Katie Chon, PharmD, RPh
Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 3235
Silver Spring, MD 20993
Phone: 240-402-6578 | Email: katie.chon@fda.hhs.gov

Follow @FDAOncology on Twitter

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

/s/

WONME K CHON
11/02/2017
electronically signed by Katie Chon, PharmD, RPh

From: Chon, Katie
To: "Arabella Buesching"
Subject: RE: NDA 205004
Date: Wednesday, November 01, 2017 10:37:47 AM
Attachments: NDA 205004_fkusa-fpl-pi-word_FDA 01Nov.docx

Dear Arabella,

Thank you for your email below as I was out of the office.

Please see the attached label for your review and comment.
Please review the changes/comments and do the following to the attached draft file:

- Accept any changes that you agree with including all format/minor editorial changes.
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed).
- Please address the comments directly to the document in tracked changes.
- Do NOT delete FDA comments.

Please provide your response by **10am ET on Thursday, November 2, 2017**. The information can be sent by electronic mail to Katie Chon (katie.chon@fda.hhs.gov), followed by an official submission to the NDA.

Kindly confirm receipt.

Regards,
Katie

Katie Chon, PharmD, RPh
Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 3235
Silver Spring, MD 20993
Phone: 240-402-6578 | Email: katie.chon@fda.hhs.gov

Follow @FDAOncology on Twitter

From: Arabella Buesching [mailto:Arabella.Buesching@fresenius-kabi.com]
Sent: Monday, October 30, 2017 2:42 PM
To: Chon, Katie <Wonme.Chon@fda.hhs.gov>
Subject: RE: NDA 205004

Hello Katie,

I wanted to follow-up with you regarding FK USA's NDA 205004 for Bortezomib for Injection. I just wanted to make sure we are still on track to meet the User Fee Goal Date of November 5, 2017 and

if you have any updates you can share.

I also wanted to ask if FK USA's [redacted] (b) (4) was also received on September 5, 2017. I was hoping to confirm the Agency also acknowledges this submission as well.

Thanks in advance for your help.

Kind Regards,
Arabella

Arabella Buesching
Regulatory Specialist, Regulatory Affairs

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, Illinois 60047
T: +1 847-550-2370
F: +1 847-550-7121
Arabella.Buesching@fresenius-kabi.com
www.fresenius-kabi.us

From: Arabella.Buesching@fresenius-kabi.com [mailto:Arabella.Buesching@fresenius-kabi.com]
Sent: Monday, October 30, 2017 1:25 PM
To: Arabella Buesching <Arabella.Buesching@fresenius-kabi.com>
Subject: Fw: NDA 205004

Arabella Buesching
Regulatory Specialist, Regulatory Affairs

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, Illinois 60047
T: +1 847-550-2370
F: +1 847-550-7121
Arabella.Buesching@fresenius-kabi.com
www.fresenius-kabi.us

----- Forwarded by Arabella Buesching/RA/LZ/US/HHC/Fresenius on 10/30/2017 01:25 PM -----

From: "EXTERN Chon, Katie" <Wonme.Chon@fda.hhs.gov>
To: "'arabella.buesching@fresenius-kabi.com'" <arabella.buesching@fresenius-kabi.com>
Date: 09/20/2017 11:48 AM
Subject: NDA 205004

Dear Arabella,

Reference is made to NDA 205004 for Bortezomib received on September 5, 2017.

1. Your 356h form that was included in the application has an error in Box 5 where your city is listed. Provide a corrected version in your application.
2. We also noticed FDA Form 3674 missing with your application. We believe the statutory requirements to submit a certification (Form 3674) applies to these types of submission. Provide the FDA Form 3674.
3. Provide the change of contact in module 1.3.1.2.

Attached is a courtesy copy of the letter which is also being mailed to you.
If you have any questions, kindly contact me; however, I will be out of the office and returning on Tuesday, Sep 26, 2017.

I look forward to working with you. Kindly confirm receipt of this email.

Regards,
Katie

Katie Chon, PharmD, RPh
Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 3235
Silver Spring, MD 20993
Phone: 240-402-6578 | Email: katie.chon@fda.hhs.gov

Follow @FDAOncology on Twitter
(See attached file: NDA 205004_Acknowledge Class 1 Resubmission_20170920.pdf)

33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

WONME K CHON
11/02/2017
electronically signed by Katie Chon, PharmD, RPh

Baird, Amy

From: Baird, Amy
Sent: Wednesday, November 01, 2017 3:31 PM
To: arabella.buesching@fresenius-kabi.com
Cc: Chon, Katie
Subject: NDA 205004 Bortezomib - Updated FDA Proposed Labeling

Good afternoon, Ms. Buesching:

I am sending this email on behalf of Katie Chon, Regulatory Project Manager.

Please refer to the electronic mail dated November 1, 2017, in which the Division of Hematology Products relayed draft proposed labeling for NDA 205004 Bortezomib. The FDA review team has since made additional edits to the labeling (Section 8.4 and Section 12.3).

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please provide your response and revisions by 10:00am EST Thursday, November 2, 2017, via email and follow-up with an official submission to your NDA.

Thank you,
Amy

Amy Baird
Chief, Project Management Staff
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 3220
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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

/s/

AMY C BAIRD
11/01/2017

Vora, Neil

From: Arabella.Buesching@fresenius-kabi.com
Sent: Monday, September 25, 2017 10:53 AM
To: Vora, Neil
Cc: arabella.buesching@fresenius-kabi.com
Subject: Re: NDA 205004

Hello Good Morning Neil,

FK USA will not be submitting a proprietary name. Please let me know if you need additional information.

Thanks and Kind Regards,
Arabella

Arabella Buesching
Regulatory Specialist, Regulatory Affairs

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, Illinois 60047
T: +1 847-550-2370
F: +1 847-550-7121
Arabella.Buesching@fresenius-kabi.com
www.fresenius-kabi.us

From: "EXTERN Vora, Neil" <Neil.Vora@fda.hhs.gov>
To: "arabella.buesching@fresenius-kabi.com" <arabella.buesching@fresenius-kabi.com>
Date: 09/25/2017 09:01 AM
Subject: NDA 205004

Hi good morning Ms. Buesching,

Reference is made to your September 5, 2017 resubmission for NDA 205004. Upon review of the submission, we note that Fresenius did not submit a request to review a proposed proprietary name. If Fresenius intends to submit a proprietary name, we request you submit the request as an amendment to the resubmission. However, if Fresenius does not submit a proprietary name, the Agency will review the NDA under the established name, bortezomib. Can you please let us know if a proprietary name will be submitted?

Thank you,
Neil

Neil Vora, PharmD, MBA, PMP
Safety Regulatory Project Manager (SRPM)

Center for Drug Evaluation and Research (CDER)
Office of Surveillance and Epidemiology (OSE)
U.S. Food and Drug Administration
Tel: 240-402-4845
Neil.Vora@fda.hhs.gov

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

/s/

NEIL VORA
09/25/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205004

ACKNOWLEDGE -
CLASS 1 COMPLETE RESPONSE

Fresenius Kabi USA, LLC
Attention: Arabella Buesching
Regulatory Specialist
Three Corporate Drive
Lake Zurich, IL 60047

Dear Ms. Buesching:

We acknowledge receipt on September 5, 2017, of your September 5, 2017, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for bortezomib for injection, 3.5 mg/vial.

We consider this a complete, class 1 response to our November 17, 2015, action letter. Therefore, the user fee goal date is November 5, 2017.

If you have any questions, contact me at katie.chon@fda.hhs.gov or (240) 402-6578.

Sincerely,

{See appended electronic signature page}
Katie Chon, PharmD, RPh
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

WONME K CHON
09/20/2017
electronically signed by Katie Chon, PharmD, RPh

From:	Higgins, Janet
To:	Bridget.Walsh@fresenius-kabi.com
Cc:	Higgins, Janet
Subject:	NDA 205004: bortezomib - Draft Package Insert with FDA revisions; Please respond by 10/26/2015
Date:	Thursday, October 22, 2015 3:03:01 PM
Attachments:	NDA205004_FDALabel10222015jh.docx

Dear Ms. Walsh,

Please refer to your New Drug Applications (NDA), submitted under section 505(b)2 of the Federal Food, Drug, and Cosmetic Act for bortezomib.

Please refer to the attached copy of proposed revisions to the label.

Please reply to our drafts and be sure to send me a courtesy copy via email of your edits in a WORD document that you also submit officially. Please review the changes/comments in the attached draft and do the following to the same draft.

- Use tracked changes to show YOUR edits.
- ACCEPT all of the tracked changes in our document with which you agree.
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed).
- You may provide annotation to justify your position within the PI, or, if extensive, in a separate document.

After you have made the changes, please send me the revised tracked change version before you make your official submission electronically. However, please submit officially to the NDA.

Please respond by **Monday, October 26, 2015, 10 AM EST** (in track change version). Please confirm receipt.

Thank you.

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

35 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

JANET G HIGGINS
11/05/2015

From:	Higgins, Janet
To:	Bridget.Walsh@fresenius-kabi.com
Cc:	Higgins, Janet
Subject:	Information Request for NDA205004: bortezomib injection
Date:	Thursday, October 15, 2015 10:27:10 AM

Dear Ms. Walsh:

Please refer to your submission dated May 22, 2015, to NDA 205004 Bortezomib Injection, which provides a Complete Response to the FDA CR letter dated April 2, 2015.

We have the following comments and recommendations **:**

Revise the carton labeling to include the following:

1. Lot number per 21 CFR 201.18
2. Expiration date per 21 CFR 201.17
3. Replace (b) (4) with single-dose
4. Remove the statement "The (b) (4) is not made with natural rubber latex".
5. Replace: (b) (4)

   With: Single-dose vial contains 3.5 mg of bortezomib, 10.5 mg boric acid, 25 mg glycine as a sterile lyophilized powder
6. Replace: (b) (4)

   With: Retain in original package to protect from light.

Revise the immediate container labeling to include the following:

1. Replace (b) (4) with single-dose

Please submit a tracked-change version and clean version of the labeling. Please submit this in PDF and WORD format via email followed by an official submission to your pending NDA. Please provide the requested information **by 3 PM on Thursday, October 22, 2015.**

Please confirm receipt of this email.

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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

/s/

JANET G HIGGINS
10/16/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 20, 2015

Application Number: NDA 205004
Product Name: Bortezomib for Injection
Applicant Name: Fresenius Kabi USA
Subject: CMC inquiry sent via email on 10/6/2015

FDA Participants :
Janet G. Higgins, Regulatory Project Manager, DHP
Haripada Sarker, PhD, CMC Reviewer
Kasturi Srinivasachar, PhD, Acting Branch Chief, API Division
Ying Lin, PhD, CMC reviewer, Division of Lifecycle API, Office of Pharmaceutical Quality
Janice Brown, MS, CMC Lead

Applicant Participants :
Bridget Walsh, Regulatory Specialist
Brad Schmitt, Regulatory Affairs Manager
Molly Rapp, VP Regulatory Affairs

1.0 BACKGROUND:

Fresenius Kabi USA has a pending PAI commitment to manufacture a commercial-scale (b) (4) batch of Bortezomib for Injection at our Grand Island, NY site. The batch manufacture is planned to occur in a couple of weeks.

The purpose of the phone call is just to confirm that the revised calculations proposed in the IR Response (SEQ-0017) are acceptable to the FDA.

As described in SEQ-0017 (submitted 31 July 2015), their API supplier had updated their DMF (b) (4)

(b) (4) so the applicant would like to make sure the Agency concurs with the changes before they proceed to manufacture the (b) (4) batch.

2.0 DISCUSSION:

The FDA has looked over your batch records and they appear accurate. The Applicant was just verifying that there were no additional inquiries prior to starting production. There appear to be no lingering questions.

3.0 ACTION ITEMS:

No action items were identified.

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

/s/

JANET G HIGGINS
11/04/2015

From:	Laiq, Rabiya
To:	Bridget.Walsh@fresenius-kabi.com
Cc:	Cox, Toni-Ann; Higgins, Janet
Subject:	FDA Information Request for NDA 205004- Please Respond by October 20, 2015.
Date:	Thursday, October 15, 2015 3:24:13 PM
Attachments:	image003.png
Importance:	High

Hello Ms. Walsh,

I am contacting you regarding the resubmission of NDA 205004, Bortezomib. The CMC team would like you to respond to this information request below.

1. Please provide a commitment that Fresenius Kabi will not distribute the lots that did not meet the specification (high Assay results). Include in the commitment all the affected lot numbers.

Please respond by **October 20, 2015**

Kindly confirm receipt of this email. Please email me the response followed by a formal submission through the FDA gateway.

Thank you,
Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov

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

/s/

JANET G HIGGINS
10/16/2015

From:	Higgins, Janet
To:	Bridget.Walsh@fresenius-kabi.com
Cc:	Higgins, Janet
Subject:	Information Request for NDA205004: bortezomib injection
Date:	Thursday, October 15, 2015 10:27:10 AM

Dear Ms. Walsh:

Please refer to your submission dated May 22, 2015, to NDA 205004 Bortezomib Injection, which provides a Complete Response to the FDA CR letter dated April 2, 2015.

We have the following comments and recommendations :

Revise the carton labeling to include the following:

1. Lot number per 21 CFR 201.18
2. Expiration date per 21 CFR 201.17
3. Replace (b) (4) with single-dose
4. Remove the statement "The (b) (4) is not made with natural rubber latex".
5. Replace: (b) (4)

   With: Single-dose vial contains 3.5 mg of bortezomib, 10.5 mg boric acid, 25 mg glycine as a sterile lyophilized powder
6. Replace: (b) (4)

   With: Retain in original package to protect from light.

Revise the immediate container labeling to include the following:

1. Replace (b) (4) with single-dose

Please submit a tracked-change version and clean version of the labeling. Please submit this in PDF and WORD format via email followed by an official submission to your pending NDA. Please provide the requested information by 3 PM on Thursday, October 22, 2015.

Please confirm receipt of this email.

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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

/s/

JANET G HIGGINS
10/16/2015

From: Cox, Toni-Ann
To: Higgins, Janet
Subject: FW: FDA Information Request for NDA 205004- Please Respond by October 9, 2015.
Date: Wednesday, October 07, 2015 3:45:50 PM
Attachments: image003.png
Importance: High

Hi Janet,

FYI, please see below…

Thanks,
Toni

From: Laiq, Rabiya
Sent: Wednesday, October 07, 2015 3:41 PM
To: Bridget.Walsh@fresenius-kabi.com
Cc: Cox, Toni-Ann
Subject: FDA Information Request for NDA 205004- Please Respond by October 9, 2015.
Importance: High

Hello Ms. Walsh,

I am contacting you regarding the resubmission of NDA 205004, Bortezomib. The CMC team would like you to respond to this information request below.

1. A review of the stability data submitted on July 31, 2015, shows that batch R340-025 failed the 90-110.0% assay limit at the at the 9 month test station with a result of (b) (4) %. In addition, batch C340-013 did not meet the release limit for Assay or any of the subsequent time points on stability. Provide an explanation of these failures.

   (b) (4)
   .

Please respond by **October 9, 2015**

Kindly confirm receipt of this email. Please email me the response followed by a formal submission through the FDA gateway.

Thank you,
Rabiya

Rabiya Laiq, Pharm.D.

Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov

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

/s/

JANET G HIGGINS
10/16/2015

From:	Higgins, Janet
To:	Bridget.Walsh@fresenius-kabi.com
Cc:	Higgins, Janet
Subject:	Information Request for NDA205004: bortezomib injection
Date:	Thursday, October 15, 2015 10:27:10 AM

Dear Ms. Walsh:

Please refer to your submission dated May 22, 2015, to NDA 205004 Bortezomib Injection, which provides a Complete Response to the FDA CR letter dated April 2, 2015.

We have the following comments and recommendations **:**

Revise the carton labeling to include the following:

1. Lot number per 21 CFR 201.18
2. Expiration date per 21 CFR 201.17
3. Replace (b) (4) with single-dose
4. Remove the statement "The (b) (4) is not made with natural rubber latex".
5. Replace (b) (4)

   With: Single-dose vial contains 3.5 mg of bortezomib, 10.5 mg boric acid, 25 mg glycine as a sterile lyophilized powder
6. Replace: (b) (4)

   With: Retain in original package to protect from light.

Revise the immediate container labeling to include the following:

1. Replace (b) (4) with single-dose

Please submit a tracked-change version and clean version of the labeling. Please submit this in PDF and WORD format via email followed by an official submission to your pending NDA. Please provide the requested information **by 3 PM on Thursday, October 22, 2015.**

Please confirm receipt of this email.

Sincerely,

Janet

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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

/s/

JANET G HIGGINS
10/16/2015

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Tuesday, July 21, 2015 2:31 PM
To: 'bridget.walsh@fresenius-kabi.com'
Cc: Cox, Toni-Ann
Subject: FDA Information Request for NDA 205004- Please respond by August 21, 2015

Hello Ms. Walsh,

My name is Rabiya Laiq, CMC RBPM and I am managing this resubmission NDA 205004, Bortezomib. The CMC team would like you to respond to this information request below.

1. The drug product acceptance criterion for description does not capture the characteristics of the finish dosage form as described in ICH Q6A, section 3.2.2 (a). Revise the acceptance criterion for description to include color and appearance (e.g. white to off-white cake or powder) in the drug product specification.

Please respond by **August 21, 2015**

Kindly confirm receipt of this email.

Thank you,
Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205004

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

Fresenius Kabi USA, LLC
Attention: Bridget Walsh
Regulatory Specialist
Three Corporate Drive
Lake Zurich, IL 60047

Dear Ms. Walsh:

We acknowledge receipt on May 22, 2015, of your May 22, 2015, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bortezomib for Injection lyophilized powder, 3.5mg/vial.

We consider this a complete, class 2 response to our April 2, 2015 action letter. Therefore, the user fee goal date is November 22, 2015.

If you have any questions, call me at (240) 402-4775.

Sincerely,

{See appended electronic signature page}

Toni-Ann Cox
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

TONI-ANN S COX
06/25/2015

Cox, Toni-Ann

From: Cox, Toni-Ann
Sent: Thursday, March 12, 2015 10:44 AM
To: Bridget.Walsh@fresenius-kabi.com
Subject: NDA 205004 FDA Recommendations for Carton and Container Labels

Good Morning, Bridget.

We are currently reviewing your NDA 205004 resubmission dated October 3, 2014, and have the following recommendations for the container and carton labels to improve important safety information.

Carton and Container Labeling Recommendations:

A. Carton and Container Labels
1. Revise the route of use statement on the principal display panel (PDP) to read, "FOR INTRAVENOUS USE ONLY" and delete the statement (b) (4) (b) (4)

B. Carton Label
1. Add reconstitution information to the Reconstitution section on the side panel of the Carton label to read, "Add 3.5 mL of **0.9% Sodium Chloride** to each 3.5 mg (b) (4) vial for the final concentration of 1 mg/mL".

Please confirm receipt of this email.

Best Regards,
Toni

Toni-Ann Cox
Regulatory Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|U.S. Food and Drug Administration
P: 240-402-4775|F: 301-796-9849|toni-ann.cox@fda.hhs.gov

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

/s/

TONI-ANN S COX
03/12/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205004

INFORMATION REQUEST

Fresenius Kabi USA, LLC
Attention: Bridget Walsh
Regulatory Specialist
Three Corporate Drive
Lake Zurich, IL 60047

Dear Mrs. Walsh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bortezomib for Injection.

We are requesting the following information. We request a prompt written response by March 4, 2015, in order to continue our evaluation of your NDA.

You have not provided sufficient data to support your product moisture content limit. Two significant issues remain:

1) You have not provided data demonstrating that your product has long-term stability when the moisture content exceeds (b) (4)%. You should provide stability data demonstrating that (b) (4)% residual moisture does not adversely affect product quality over the proposed shelf life. Alternatively, you should lower your limit to a value for which you have sufficient supporting stability data. Please provide data supporting any revised limit, keeping in mind that the data should demonstrate, with reasonable confidence, that a sufficient number of vials tested (on stability) for other product attributes are representative of your proposed limit.

(b) (4)

2) (b) (4)

3) The data that you have provided to support sufficient development of the lyophilization cycle used in your process qualification batches is insufficient and raises additional questions. It is unclear why, in response to Item #2 of our Complete Response Letter dated October 3, 2013, you did not provide the remainder of the data for process qualification batch #1, but instead submitted data from a lab-scale batch with only a single product temperature measurement. Furthermore, there appear to be significant product temperature differences between the lab-scale and process qualification batches, yet these cycles are reported to have been carried out under the same conditions. Similarly to what was provided in your response to Item #2 of our Complete Response letter, please provide all available cycle data for both of your process qualification batches and resubmit the data for the lab-scale cycle; however, please be sure to do the following:

- include temperature data for all product vials containing temperature probes
- submit the data for each of the three cycles so that it occupies a full page (landscape format)
- label the x-axis as hours, starting with t=0, covering the entire cycle
- keep the x and y axis domain and range the same for each of the three charts (with the x-axis being the longest of the three cycles if there were any differences) and the y-axis extending from -80 to 40 °C (unless you have a reason to submit data outside of that range).
- annotate the charts as you did in your response to Complete Response Item #2.

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

If you have any questions, call Teicher Agosto, Regulatory Business Process Manager, at (240) 402-3777.

Sincerely,

Ali Al Hakim, Ph.D.
Acting Division Director
Division of New Drug API
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Ali H. Al- Hakim -A

Cox, Toni-Ann

From: Cox, Toni-Ann
Sent: Friday, February 27, 2015 1:49 PM
To: Bridget.Walsh@fresenius-kabi.com
Cc: Brad.Schmitt@fresenius-kabi.com
Subject: NDA 205004 Bortezomib for Injection: Action Required by Mar 3

Importance: High

Good Afternoon, Bridget.

Thank you for sending draft labeling for the ND 205004 resubmission submitted and received on October 3, 2014. We are currently reviewing the resubmission and would like to request a redlined version of your proposed labeling that reflects recently approved changes made to the reference product label (you may omit references to the new indication). Please submit a redlined version of your proposed label **no later than 3:00 PM Tuesday March 3, 2015**.

Feel free to contact me should you have any questions or concerns.

Please confirm receipt of this email.

Best Regards,
Toni

Toni-Ann Cox
Regulatory Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|U.S. Food and Drug Administration
P: 240-402-4775|F: 301-796-9849|✉toni-ann.cox@fda.hhs.gov

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

/s/

TONI-ANN S COX
02/27/2015

MEMORANDUM

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

FDA INTERNAL MEMO

APPLICATION/DRUG: NDA 205004, Bortezomib for Injection

This memorandum documents certain facts concerning an application that relates to Millennium Pharmaceuticals, Inc.'s citizen petition dated August 12, 2013 (FDA-2013-P-0998).

As of January 8, 2014, the 505(b)(2) application for Bortezomib for Injection (NDA 205004) has not been approved. This application was submitted by Fresenius Kabi USA (Fresenius) on November 30, 2012 and received on December 3, 2012. This application received a complete response on October 3, 2013. Fresenius has not re-submitted their application for Bortezomib and therefore it would not be possible for an approval action of the application to occur when the petition response is due under 505(q) of the Federal Food, Drug, and Cosmetic Act.[1]

Ebla Ali Ibrahim, M.S.
Lead Regulatory Project Manager
The Division of Hematology Product
The Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

1 The completion of a review cycle and the issuance of a Complete Response or discipline review letter does not indicate that review of the application has been completed for purposes of determining whether it is appropriate to respond substantively to a petition governed by section 505(q) raising an issue that is directly applicable to the pending ANDA or 505(b)(2) application.

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

/s/

EBLA ALI IBRAHIM
01/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205004

ACKNOWLEDGE CORPORATE ADDRESS CHANGE

Fresenius Kabi USA, LLC
Attention: Aditi Dron
Manager, Regulatory Affairs
Three Corporate Drive
Lake Zurich, IL 60047

Dear Ms. Dron:

We acknowledge receipt on April 29, 2013, of your April 26, 2013 correspondence notifying the Food and Drug Administration (FDA) that the corporate address has been changed from

1501 East Woodfield Road
Suite 300
Schaumburg, IL 60173

to

Three Corporate Drive
Lake Zurich, IL 60047

for the following new drug application (NDA):

NDA 205004 for Bortezomib for Injection, 3.5 mg/vial.

We have revised our records to reflect this change.
Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, contact me at (301) 796-3338 or Karen.Bengtson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Karen Bengtson
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

KAREN E BENGTSON
04/30/2013

Bengtson, Karen

From: Aditi.Dron@fresenius-kabi.com
Sent: Monday, April 08, 2013 2:17 PM
To: Bengtson, Karen
Subject: RE: Bortezomib for Injection, NDA 205004 - patent complaint date

Hello Ms. Bengtson,

This is to confirm that Fresenius Kabi USA was notified of the complaint on March 22, 2013, the same date as the complaint filing date.

Sincerely,

Aditi Dron
Manager, Regulatory Affairs

Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300 East
Schaumburg, Illinois 60173
T: +1 (847) 330-3898
F: +1 (847) 413-8570
www.fresenius-kabi.us

From: "Bengtson, Karen" <Karen.Bengtson@fda.hhs.gov>
To: "Aditi.Dron@fresenius-kabi.com" <Aditi.Dron@fresenius-kabi.com>,
Date: 04/08/2013 12:15 PM
Subject: RE: Bortezomib for Injection, NDA 205004 - patent complaint

Hello Ms. Dron,

Can you please confirm if the date Fresenius was notified of the complaint was the same date as the attached complaint filing date (i.e., March 22, 2013)? If is was another date, please let me know that date.

Thank you,
Karen

Karen Bengtson
Regulatory Project Manager
DHP/OHOP/CDER/FDA

WO22, Room 2189
Phone: 301-796-3338
Fax: 301-796-9845
E-mail: karen.bengtson@fda.hhs.gov

From: Aditi.Dron@fresenius-kabi.com [mailto:Aditi.Dron@fresenius-kabi.com]
Sent: Friday, April 05, 2013 6:03 PM
To: Bengtson, Karen
Subject: RE: Bortezomib for Injection, NDA 205004 - patent complaint

Dear Ms. Bengtson,

A complaint has been filed against Fresenius Kabi USA for patent infringement for Bortezomib NDA 205004 on 3/22/13. The publicly available document is attached for your reference. We will submit an Amendment next week to update the NDA with this information.

Sincerely,

Aditi Dron
Manager, Regulatory Affairs

Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300 East
Schaumburg, Illinois 60173
T: +1 (847) 330-3898
F: +1 (847) 413-8570
www.fresenius-kabi.us

From: "Bengtson, Karen" <Karen.Bengtson@fda.hhs.gov>
To: "Aditi.Dron@fresenius-kabi.com" <Aditi.Dron@fresenius-kabi.com>,
Cc: "Bengtson, Karen" <Karen.Bengtson@fda.hhs.gov>
Date: 04/05/2013 11:02 AM
Subject: RE: Bortezomib for Injection, NDA 205004

Dear Ms. Dron,

Please provide me with the date of the notification that a complaint had been filed against the company for patent infringement.

Kind regards,

Karen

Karen Bengtson
Regulatory Project Manager
DHP/OHOP/CDER/FDA
WO22, Room 2189
Phone: 301-796-3338
Fax: 301-796-9845
E-mail: karen.bengtson@fda.hhs.gov

From: Aditi.Dron@fresenius-kabi.com [mailto:Aditi.Dron@fresenius-kabi.com]
Sent: Tuesday, March 26, 2013 10:58 AM
To: Bengtson, Karen
Cc: Grace.Burbulys@fresenius-kabi.com
Subject: Bortezomib for Injection, NDA 205004

Dear Ms. Bengtson,

In response to your voicemail message, I am writing to inform you that a complaint has been filed against Fresenius Kabi USA for patent infringement within 45 days of receipt of paragraph IV notice.

Please advise if this information needs to be included in an Amendment to the NDA.

Sincerely,

Aditi Dron
Manager, Regulatory Affairs

Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300 East
Schaumburg, Illinois 60173
T: +1 (847) 330-3898
F: +1 (847) 413-8570
www.fresenius-kabi.us

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

/s/

KAREN E BENGTSON
04/09/2013

MEMORANDUM

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

DATE: April 5, 2013

TO: NDA File

FROM: Karen Bengtson

SUBJECT: Complaint filed by RLD NDA owner and/or patent holder

APPLICATION/DRUG: 505(b)(2) NDA 205004 – Bortezomib for Injection

For NDA 205004, Fresenius Kabi USA (FK USA) submitted a Paragraph IV certification for two patents listed in the Orange Book for the reference listed drug (RLD) Velcade® (Bortezomib) for Injection – 6,713,446 and 6,958,319. On March 22, 2013, FK USA submitted documentation that the NDA owner and patent holders were notified that the 505(b)(2) application was filed by the Agency. In addition, the applicant provided documentation that the notifications were received on February 6, 2013.

Once notified, the RLD application owner/patent holders have 45 calendar days to file a patent infringement suit against FK USA. After Day 45 (March 23, 2013), FK USA was contacted to confirm whether they were or were not being sued for patient infringement. FK USA indicated via email (*see attached*) that "…a complaint has been filed against Fresenius Kabi USA for patent infringement within 45 days of receipt of paragraph IV notice."

Bengtson, Karen

From: Aditi.Dron@fresenius-kabi.com
Sent: Tuesday, March 26, 2013 10:58 AM
To: Bengtson, Karen
Cc: Grace.Burbulys@fresenius-kabi.com
Subject: Bortezomib for Injection, NDA 205004

Dear Ms. Bengtson,

In response to your voicemail message, I am writing to inform you that a complaint has been filed against Fresenius Kabi USA for patent infringement within 45 days of receipt of paragraph IV notice.

Please advise if this information needs to be included in an Amendment to the NDA.

Sincerely,

Aditi Dron
Manager, Regulatory Affairs

Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300 East
Schaumburg, Illinois 60173
T: +1 (847) 330-3898
F: +1 (847) 413-8570
www.fresenius-kabi.us

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

/s/

KAREN E BENGTSON
04/05/2013

Bengtson, Karen

From: Bengtson, Karen
Sent: Friday, April 05, 2013 12:02 PM
To: 'Aditi.Dron@fresenius-kabi.com'
Cc: Bengtson, Karen
Subject: RE: Bortezomib for Injection, NDA 205004
Importance: High

Dear Ms. Dron,

Please provide me with the date of the notification that a complaint had been filed against the company for patent infringement.

Kind regards,
Karen

KAREN BENGTSON
Regulatory Project Manager
DHP/OHOP/CDER/FDA
WO22, Room 2189
Phone: 301-796-3338
Fax: 301-796-9845
E-mail: karen.bengtson@fda.hhs.gov

From: Aditi.Dron@fresenius-kabi.com [mailto:Aditi.Dron@fresenius-kabi.com]
Sent: Tuesday, March 26, 2013 10:58 AM
To: Bengtson, Karen
Cc: Grace.Burbulys@fresenius-kabi.com
Subject: Bortezomib for Injection, NDA 205004

Dear Ms. Bengtson,

In response to your voicemail message, I am writing to inform you that a complaint has been filed against Fresenius Kabi USA for patent infringement within 45 days of receipt of paragraph IV notice.

Please advise if this information needs to be included in an Amendment to the NDA.

Sincerely,

Aditi Dron
Manager, Regulatory Affairs

Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300 East
Schaumburg, Illinois 60173

T: +1 (847) 330-3898
F: +1 (847) 413-8570
www.fresenius-kabi.us

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

/s/

KAREN E BENGTSON
04/09/2013

Bengtson, Karen

From: Bengtson, Karen
Sent: Monday, March 18, 2013 3:18 PM
To: 'Aditi.Dron@fresenius-kabi.com'
Subject: RE: Bortezomib NDA 205004 - Follow Up Regarding Paragraph IV Certification

Dear Ms. Dron,

Please submit to the NDA the signed certification stating that the NDA holder and patent owners were notified that this 505(b)(2) application was filed and provide the documentation showing the that the notifications were received on or before Friday, March 22, 2013.

Thank you,
Karen

KAREN BENGTSON
Regulatory Project Manager
DHP/OHOP/CDER/FDA
WO22, Room 2189
Phone: 301-796-3338
Fax: 301-796-9845
E-mail: karen.bengtson@fda.hhs.gov

From: Aditi.Dron@fresenius-kabi.com [mailto:Aditi.Dron@fresenius-kabi.com]
Sent: Wednesday, March 13, 2013 5:39 PM
To: Bengtson, Karen
Subject: RE: Bortezomib NDA 205004 - Follow Up Regarding Paragraph IV Certification

Dear Ms. Bengtson,

Yes, the NDA/patent holders were notified that our 505(b)(2) NDA for Bortezomib was filed. We will be submitting a Patent Amendment to the NDA to provide confirmation receipts soon.

Sincerely,

Aditi Dron
Manager, Regulatory Affairs

Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300 East
Schaumburg, Illinois 60173
T: +1 (847) 330-3898
F: +1 (847) 413-8570
www.fresenius-kabi.us

From: "Bengtson, Karen" <Karen.Bengtson@fda.hhs.gov>
To: "Aditi.Dron@fresenius-kabi.com" <Aditi.Dron@fresenius-kabi.com>,
Date: 03/13/2013 07:49 AM
Subject: RE: Bortezomib NDA 205004 - Follow Up Regarding Paragraph IV Certification

Dear Ms. Dron,

I wanted to follow up with you to confirm that the NDA holder/patent owners were notified that your 505(b)(2) application for Bortezomib for Injection was filed and that you received confirmation of their receipt of your notification.

Thank you,
Karen.

Karen Bengtson
Regulatory Project Manager
DHP/OHOP/CDER/FDA
WO22, Room 2189
Phone: 301-796-3338
Fax: 301-796-9845
E-mail: karen.bengtson@fda.hhs.gov

From: Aditi.Dron@fresenius-kabi.com [mailto:Aditi.Dron@fresenius-kabi.com]
Sent: Friday, February 01, 2013 4:16 PM
To: Kallungal, Beatrice
Cc: Bengtson, Karen
Subject: RE: Bortezomib NDA 205004 - Filing Date Inquiry

Dear Ms. Kallungal,

I thank you for responding to the Bortezomib NDA filing date request.

Sincerely,

Aditi Dron
Manager, Regulatory Affairs

Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300 East
Schaumburg, Illinois 60173

T: +1 (847) 330-3898
F: +1 (847) 413-8570
www.fresenius-kabi.us

From: "Kallungal, Beatrice" <Beatrice.Kallungal@fda.hhs.gov>
To: "'Aditi.Dron@fresenius-kabi.com'" <Aditi.Dron@fresenius-kabi.com>,
Cc: "Bengtson, Karen" <Karen.Bengtson@fda.hhs.gov>, "Kallungal, Beatrice" <Beatrice.Kallungal@fda.hhs.gov>
Date: 02/01/2013 03:01 PM
Subject: RE: Bortezomib NDA 205004 - Filing Date Inquiry

Hi Ms. Dron,
Per the NDA acknowledgement letter we sent you, “Unless we notify you within 60 days of the receipt date that the application is not sufficiently
complete to permit a substantive review, we will file the application on February 1, 2013, in accordance with 21 CFR 314.101(a).” Therefore, you can consider the application filed.

If you have any questions, please let me know.

Regards,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 6187
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

From: Aditi.Dron@fresenius-kabi.com [mailto:Aditi.Dron@fresenius-kabi.com]
Sent: Friday, February 01, 2013 11:25 AM
To: Kallungal, Beatrice
Subject: Fw: Bortezomib NDA 205004 - Filing Date Inquiry

Dear Ms. Kallungal,

I am forwarding this request regarding Bortezomib NDA 205004 to you based on Ms. Karen Bengtson's out of office message. Can you provide confirmation if our NDA 205004 has been filed. The 60-day filing date falls today, 2/1/13. It is critical due to the paragraph IV patent certification associated with this NDA.

I will greatly appreciate your help with this request.

Sincerely,

Aditi Dron
Manager, Regulatory Affairs

Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300 East
Schaumburg, Illinois 60173
T: +1 (847) 330-3898
F: +1 (847) 413-8570
www.fresenius-kabi.us

----- Forwarded by Aditi Dron/RA/SC/US/HHC/Fresenius on 02/01/2013 10:21 AM -----

From: Aditi Dron/RA/SC/US/HHC/Fresenius
To: karen.bengtson@fda.hhs.gov,
Date: 02/01/2013 10:20 AM
Subject: Bortezomib NDA 205004 - Filing Date Inquiry

Dear Ms. Bengtson,

This is to request confirmation regarding the filing of our Bortezomib NDA 205004 on February 1, 2013 (today), as indicated within the Agency's NDA Acknowledgement letter dated 12/5/12. Since this involves a paragraph IV patent certification, we would like to know the filing date as soon as possible, in order to proceed with the next step of providing notice to RLD/patent holder.

Agency's response will be greatly appreciated.

Sincerely,

Aditi Dron
Manager, Regulatory Affairs

Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300 East
Schaumburg, Illinois 60173
T: +1 (847) 330-3898
F: +1 (847) 413-8570
www.fresenius-kabi.us

THIS TRANSMISSION CONTAINS INFORMATION INTENDED FOR THE EXCLUSIVE USE OF THE INDIVIDUAL OR ENTITY TO WHOM IT IS ADDRESSED, AND MAY CONTAIN INFORMATION THAT IS PROPRIETARY, PRIVILEGED, CONFIDENTIAL, AND/OR OTHERWISE EXEMPT FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the intended recipient (or agent responsible for delivering this transmission to the intended recipient), you are hereby notified that any review, printing, copying, disclosure, distribution, transmission or use of this information (including any attachments) is strictly prohibited and may be subject to legal sanction. If you have received this transmission in error, please permanently delete it, and notify us immediately. Thank you.

Please consider our environment before printing this e-mail

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

/s/

KAREN E BENGTSON
03/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205004

INFORMATION REQUEST

Fresenius Kabi USA, LLC
Attention: Aditi Dron
Manager, Regulatory Affairs
1501 East Woodfield Road
Suite 300E
Schaumburg, IL 60173

Dear Ms. Dron:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bortezomib for Injection.

We also refer to your original NDA submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by March 29, 2013, in order to continue our evaluation of your NDA.

1. Method validation report (PR-09-00048) "Determination of Assay and Impurities in Bortezomib and Bortezomib for Injection and Identification of Bortezomib in Bortezomib for Injection by HPLC", submit the following:
   a. results from the accuracy recovery studies for bortezomib and impurities and include the acceptance criteria of RSDs.
   b. results of accuracy recovery study using the specified impurities reference standard.

2. (b) (4) .

3. The accuracy study was not performed in method verification report "Water Content Determination for Bortezomib Raw Material by (b) (4) by FK USA and by (b) (4)). Since the method is identical to the API supplier's method, provide the results of the accuracy

recovery study or a side-by-side comparison of the test results of water content performed by the API supplier and FK USA.

4. [redacted]

5. [redacted]

6. [redacted]

7. Revise your Bortezomib for Injection specification to include a test and limit for pH of the constituted solution.

8. The accuracy study was not performed in the method verification report for "Determination of Water Content of Bortezomib Finished Product (Bortezomib for Injection 3.5 mg/vial) by [redacted] Since the method is identical to the API supplier's method, please provide accuracy recovery studies or a side-by-side comparison of the test results performed by [redacted] and API supplier.

9. The purpose of the method verification report "Water Content Determination for Bortezomib for Injection, 3.5mg/vial, by [redacted] is to demonstrate the reproducibility of the Test Method between [redacted] and APP for the water content determination of Bortezomib for Injection, 3.5 mg/vial, by [redacted]. However, a side-by-side comparison of the test results of water content performed by [redacted] and APP is not provided. Submit either an accuracy recovery study or provide a side-by-side comparison of the test results performed by APP and [redacted].

10. Provide batch analysis results for four exhibit batches (R340-024, R340-025, C340-013 and R342-032) or specify the location in the NDA.

11. Revise your [redacted] limits listed in table 3.2.p.3.3-1. [redacted]

12 [redacted]

13. From the stability data, some of the impurities showed % increasing trend. Due to [redacted] water content [redacted]%) in your drug product and the lack of the statistical analysis, the shelf life will be based on real time stability data. Submit all stability updates to support your prosposed shelf life..

14 [redacted]

15. Provide a copy of your [redacted] Process Development Study (referred to in section 3.2.P.2 of your application).

16. It does not appear that you are filling your product to meet the overage requirement in USP <1>. Please comment.

17. You state that your product water content limit [redacted] is based, in part, [redacted], for which you provide a reference. Please provide data demonstrating that you have confirmed the

phenomenon of moisture stabilization for your product. This data should include comparative stability data for product below (b) (4) moisture content.

18. You have proposed a finished product water content limit of NMT (b) (4)% ((b) (4)%). (b) (4) Please revise your limit (b) (4) include data to support the revised limit.

19. Provide temperature mapping data for product vials that supports the development of your lyophilization cycle. Also, please state any criteria/requirements for minimum finished product water content you had when developing your lyophilization cycle.

20. Explain the "Lyophilization Rejects" reject rates in the Packaging Reconciliation Control Sheets provided (in section 3.2.P.3.3 1.7 of your application) for Batches R340-024 (b) (4)). Explain whether there were any process control issues during lyophilization that may have contributed to the reject rates.

21. Explain and justify the extensive handwritten lyophilization cycle changes made to the batch record for process qualification batch R342-032 (provided in section 3.2.R of your application).

22. Although you have a significant amount of stability data from exhibit batches demonstrating that your product meets your specification for reconstitution time, the limited amount of data provided from your Process Qualification Study (study PR-12-00262, provided in section 3.2.P.2 of your application) suggests that your process qualification batch may produce finished product with a high degree of variability in reconstitution times. In your Process Qualification study, you tested a single vial for reconstitution time from each of the top, middle, and bottom lyophilizer shelves. (b) (4) (b) (4) there may be a significant number of vials that would not meet your proposed NMT (b) (4) reconstitution time if a higher number of samples were tested. Provide additional data demonstrating that this lyophilization cycle produces, with high confidence, drug product that will meet your specification for reconstitution. Explain whether any variation in shelf temperature is correlated to differences in reconstitution times.

23. Explain why only 50 samples were inspected for the visual inspection AQL for batch R342-032 (your process qualification batch) whereas the batch record indicates that 200 vials should have been inspected. Also, explain why the lyophilization rejects listed in the Packaging Reconciliation Control Sheet for batch R342-032 ((b) (4)) are not accounted for in the 100% visual inspection reconciliation for this batch.

24. (b) (4)

25 (b) (4)

26

27 (b) (4)

28. Confirm that all future media fill simulations will be conducted to meet your requirement of a minimum of (b) (4) units filled.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

ALI H AL HAKIM
03/15/2013

Bengtson, Karen

From: Bengtson, Karen
Sent: Thursday, March 07, 2013 11:41 AM
To: 'Aditi.Dron@fresenius-kabi.com'
Subject: NDA 205004 Bortezomib for Injection - Filing Communication - Follow up to Voice Message

Importance: High

Dear Ms. Dron,

I am following up to your voice message regarding the filing communication. Please submit a response to item #1 listed under the potential review issues as soon as possible. We request that you respond to the other potential review issues and requests for information within the next two weeks (on or before March 21, 2013).

Please acknowledge receipt of this email.

If you need further information or clarification, please feel free to contact me.

Kind regards,
Karen

KAREN BENGTSON
Regulatory Project Manager
Division of Hematology Products
OHOP/CDER/FDA
WO22, Room 2189
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3338
Fax: 301-796-9845
E-mail: karen.bengtson@fda.hhs.gov

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

/s/

KAREN E BENGTSON
03/07/2013

MEMORANDUM OF TELECONFERENCE MEETING MINUTES

MEETING DATE: February 14, 2013
TIME: 3:30 – 4:00 PM
APPLICANT: Fresenius Kabi USA, LLC
APPLICATION: NDA 205004
DRUG NAME: Bortezomib for Injection
TYPE OF MEETING: Guidance

MEETING CHAIR: Julie Bullock, Pharm.D.

MEETING RECORDER: Karen Bengtson

FDA ATTENDEES:

OFFICE OF NEW DRUGS/OFFICE OF HEMATOLOGY AND ONCOLOGY DRUG PRODUCTS/DIVISION OF HEMATOLOGY PRODUCTS

Julie Bullock – Clinical Pharmacology Team Leader
Young-Jin Moon – Clinical Pharmacology Reviewer
Karen Bengtson – Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

FRESENIUS KABI USA, LLC

David Bowman, Vice President, Innovation & Development
Arunya Usayapant, Manager, Formulation Development
Anton Stetsenko, Principal Scientist, Analytical Development
(b) (4)
Aditi Dron, Manager, Regulatory Affairs

BACKGROUND:

On November 30, 2013 (received December 3, 2013), FK USA submitted a 505(b)(2) application for Bortezomib for Injection. On February 12, 2013, the Agency sent an information request to FK USA asking for the applicant to submit SAS transport files (*.xpt) of the raw data used in study report PD11-NB/F-016 titled "An *in-vitro* Study to Compare Proteasome Inhibitory Activity of APP's Bortezomib for Injection with Velcade®." On February 14, 2013, FK USA requested a teleconference with the Agency because the study data was analyzed by proprietary software which is not a SAS database and they wanted to know how best to provide the requested data.

MEETING OBJECTIVES:

To clarify how best to provide the data requested to the Agency.

DISCUSSION POINTS:

The Agency clarified the type of data they were requesting and what format is acceptable. The sponsor clarified the details and explained the (b) (4) analysis.

The Sponsor will submit raw data from Table 4 to Table 7 (Page 24-27) in PD11-NB/F-016 Final Report in Excel file format. The agency agreed this was acceptable.

DECISIONS (AGREEMENTS) REACHED:

The raw data can be submitted in the Excel file format instead of the originally requested SAS transport files.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

The Sponsor will submit raw data from Table 4 to Table 7 (Page 24-27) in PD11-NB/F-016 Final Report in Excel file format.

ATTACHMENTS/HANDOUTS:

None

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

/s/

KAREN E BENGTSON
02/15/2013

JULIE M BULLOCK
02/19/2013

Bengtson, Karen

From: Bengtson, Karen
Sent: Wednesday, February 13, 2013 3:52 PM
To: 'Aditi.Dron@fresenius-kabi.com'
Cc: Grace.Burbulys@fresenius-kabi.com
Subject: NDA 205004 Bortezomib for Injection - Clinical Pharmacology Information Request

Dear Ms. Dron:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Bortezomib for Injection, 3.5 mg/vial.

We are reviewing your submission and have the following information request. We request that you submit your response by **close of business February 15, 2013.**

Clinical Pharmacology

- Provide all the raw data used in study report PD11-NB/F-016 (An in-vitro study to compare proteasome inhibitory activity of AAP's bortezomib for injection with Velcade) as SAS transport files (*.xpt).

Please acknowledge receipt of this email correspondence.

Kind regards,
Karen

KAREN BENGTSON
Regulatory Project Manager
Division of Hematology Products
OHOP/CDER/FDA
WO22, Room 2189
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3338
Fax: 301-796-9845
E-mail: karen.bengtson@fda.hhs.gov

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

/s/

KAREN E BENGTSON
02/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205004

FILING COMMUNICATION

Fresenius Kabi USA, LLC
Attention: Aditi Dron
Manager, Regulatory Affairs
1501 East Woodfield Road
Suite 300 E
Schaumburg, IL 60173

Dear Ms. Dron:

Please refer to your New Drug Application (NDA) dated November 30, 2012, received December 3, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Bortezomib for Injection, 3.5 mg/vial.

We also refer to your amendment(s) dated January 18, 2013 and January 29, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 3, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 5, 2013.

During our filing review of your application, we identified the following potential review issues:

1. Your application does not contain microbiological data to support an extended post-constitution hold period. Without this data, drug product labeling should recommend that the post-constitution storage period is not more than 4 hours at room temperature or 24 hours under refrigeration. If you desire a longer hold period, microbiological data should

be provided to demonstrate that the reconstituted product solution will not support microbial growth during the proposed storage period. Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. Generally, "no growth" is interpreted as not more than a 0.5 $\log_{10}$ increase from the initial count; however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3 times the label's recommended storage period, and use the label-recommended fluids inoculated with low numbers (≤100 CFU/mL) of challenge microbes. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.

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

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

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

(b) (4)

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, contact Karen Bengtson, Regulatory Project Manager, at (301) 796-3338 or Karen.Bengtson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

ANN T FARRELL
02/13/2013

From: Martin, Jewell
To: "Aditi.Dron@fresenius-kabi.com"
Subject: NDA 205004- Information Request
Date: Friday, February 01, 2013 9:58:00 AM

From: Martin, Jewell
Sent: Friday, February 01, 2013 9:47 AM
To: 'Aditi.Dron@fresenius-kabi.com'
Subject: NDA 205004- Information Request

Hello Ms. Dron,

This email is in reference NDA 205004. Please provide the following information by COB February 5, 2013:

Please confirm that the analytical method validation submitted in the NDA are identical to the method validation in DMF 22160 for the following:

Number of report	Title of the validation report
PR-09-00048 A1	Validation of the HPLC Method for the Determination and Identification of the Bortezomib and Impurities in Bortezomib Raw Material and Bortezomib for Injection. (Test Method 10-08-03-6530)
PR-09-00492	Verification of the Test Method for the Water Content Determination for Bortezomib Raw Material By (b) (4)
PR-09-00077	(b) (4)
NG-1137549	(b) (4) Final Report for the method verification for the r Content of Bortezomib Raw Material By (b) (4)) ((b) (4))
PR-10-00119	(b) (4))
Microbial Bioburden and Bacterial Endotoxins	Microbiological Method Validation Package

In addition to formally submitting this information to your NDA, please email me a courtesy copy of your response to this request. Thank you in advance.

Please confirm receipt of this email.

Best,

Jewell

Jewell D. Martin, MA, MBA, PMP
Product Quality Regulatory Project Manager
Office of New Drug Quality Assessment
Food and Drug Administration
White Oak Building 21, Rm 2625
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(301) 796-2072
jewell.martin@fda.hhs.gov


Please consider the environment before printing this e-mail

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

/s/

JEWELL D MARTIN
02/01/2013

Bengtson, Karen

From: Bengtson, Karen
Sent: Thursday, January 24, 2013 3:48 PM
To: 'Aditi.Dron@fresenius-kabi.com'
Cc: Grace.Burbulys@fresenius-kabi.com
Subject: NDA 205004 - Bortezomib for Injection - Debarment Certification

Importance: High

Dear Ms. Dron,

Please refer to the following FDA guidance:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080584.pdf

The FDA regards the following wording, taken from section 306(k)(1) of the Act, as the most acceptable form of the debarment certification:

[Name of the applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Please submit a revised debarment certification to your application by January 29, 2013.

Please confirm receipt of this e-mail correspondence

Kind regards,
Karen

KAREN BENGTSON
Regulatory Project Manager
Division of Hematology Products
OHOP/CDER/FDA
WO22, Room 2189
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3338
Fax: 301-796-9845
E-mail: karen.bengtson@fda.hhs.gov

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

/s/

KAREN E BENGTSON
01/24/2013

Bengtson, Karen

From: Bengtson, Karen
Sent: Wednesday, January 23, 2013 12:35 PM
To: 'Aditi.Dron@fresenius-kabi.com'
Cc: Grace.Burbulys@fresenius-kabi.com
Subject: RE: NDA 205004 Bortezomib for Injection - Information Request

Dear Ms. Dron,

Thank you for providing the location of the requested documents. No further action is needed in response to the information request.

Kind regards,
Karen

KAREN BENGTSON
Regulatory Project Manager
DHP/OHOP/CDER/FDA
WO22, Room 2189
Phone: 301-796-3338
Fax: 301-796-9845
E-mail: karen.bengtson@fda.hhs.gov

From: Aditi.Dron@fresenius-kabi.com [mailto:Aditi.Dron@fresenius-kabi.com]
Sent: Wednesday, January 23, 2013 12:13 PM
To: Bengtson, Karen
Cc: Grace.Burbulys@fresenius-kabi.com
Subject: Re: NDA 205004 Bortezomib for Injection - Information Request

Dear Ms. Bengtson,

I need to replace one of the attachments provided in my previous email sent at 11:03 AM with the current attachment included in this email.

The file titled 'Test Method 10-08-03-6670' contained other information in addition to the test method 10-08-03-6670. I am providing the Test Method 10-08-03-6670 again.

I apologize for this error.

Sincerely,

Aditi Dron
Manager, Regulatory Affairs

Fresenius Kabi USA, LLC

1501 East Woodfield Road, Suite 300 East
Schaumburg, Illinois 60173
T: +1 (847) 330-3898
F: +1 (847) 413-8570
www.fresenius-kabi.us

From: Aditi Dron/RA/SC/US/HHC/Fresenius
To: "Bengtson, Karen" <Karen.Bengtson@fda.hhs.gov>,
Cc: "Grace.Burbulys@fresenius-kabi.com" <Grace.Burbulys@fresenius-kabi.com>
Date: 01/23/2013 11:03 AM
Subject: Re: NDA 205004 Bortezomib for Injection - Information Request

---

Dear Ms. Bengtson,

This is in reference to the Agency's Clinical Pharmacology request for information received on 1/22/13 re-iterated below:

Clinical Pharmacology

- Submit attachment 2 'Proteasome Inhibitory Assay method' (test method 10-08-03-6670) and attachment 3 'Validation of the HPLC Method for the Determination of Bortezomib' (PR-11-00219 Final Report) mentioned in Study No. PD11-NB/F-016.

Fresenius Kabi USA's Response:

The requested documents were included within Module 1 of the original NDA (SEQ-0000). The location of these documents within SEQ-0000 are as follows:

- Attachment 2 'Proteasome Inhibitory Assay method' (test method 10-08-03-6670) is located in pages 151-161 of the following file in Module 1: fk-type-c-mtg-info-pkg-25aug2011
- Attachment 3 'Validation of the HPLC Method for the Determination of Bortezomib' (PR-11-00219 Final Report) is located in pages 163-208 of the following file in Module 1: fk-type-c-mtg-info-pkg-25aug2011

The two requested documents are also attached to this email for your convenience.

Please advise if this information provided via email will suffice as a response to this Request for Information.

Sincerely,

Aditi Dron
Manager, Regulatory Affairs

Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300 East
Schaumburg, Illinois 60173
T: +1 (847) 330-3898
F: +1 (847) 413-8570
www.fresenius-kabi.us

From: Aditi Dron/RA/SC/US/HHC/Fresenius
To: "Bengtson, Karen" <Karen.Bengtson@fda.hhs.gov>,
Cc: "Grace.Burbulys@fresenius-kabi.com" <Grace.Burbulys@fresenius-kabi.com>
Date: 01/22/2013 09:50 AM
Subject: Re: NDA 205004 Bortezomib for Injection - Information Request

---

Dear Ms. Bengtson,

We acknowledge the receipt of your email. We will get back to you soon.

Sincerely,

Aditi Dron
Manager, Regulatory Affairs

Fresenius Kabi USA, LLC
1501 East Woodfield Road, Suite 300 East
Schaumburg, Illinois 60173
T: +1 (847) 330-3898
F: +1 (847) 413-8570
www.fresenius-kabi.us

From: "Bengtson, Karen" <Karen.Bengtson@fda.hhs.gov>
To: "Aditi.Dron@fresenius-kabi.com" <Aditi.Dron@fresenius-kabi.com>,
Cc: "Grace.Burbulys@fresenius-kabi.com" <Grace.Burbulys@fresenius-kabi.com>
Date: 01/22/2013 09:28 AM
Subject: NDA 205004 Bortezom b for Injection - Information Request

Dear Ms. Dron:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Bortezomib for Injection, 3.5 mg/vial.

We are reviewing your submission and have the following information request. We request a written response by **close of business January 25, 2013** in order to continue our evaluation of your NDA.

Clinical Pharmacology

- Submit attachment 2 'Proteasome Inhibitory Assay method' (test method 10-08-03-6670) and attachment 3 'Validation of the HPLC Method for the Determination of Bortezomib' (PR-11-00219 Final Report) mentioned in Study No. PD11-NB/F-016.

  Please acknowledge receipt of this correspondence.

  Kind regards,
  Karen

Karen Bengtson
Regulatory Project Manager
Division of Hematology Products
OHOP/CDER/FDA
WO22, Room 2189
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3338
Fax: 301-796-9845
E-mail: karen.bengtson@fda.hhs.gov

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

/s/

KAREN E BENGTSON
01/24/2013

From: "Bengtson, Karen" <Karen.Bengtson@fda.hhs.gov>
To: "Aditi.Dron@fresenius-kabi.com" <Aditi.Dron@fresenius-kabi.com>,
Cc: "Grace.Burbulys@fresenius-kabi.com" <Grace.Burbulys@fresenius-kabi.com>
Date: 01/22/2013 09:28 AM
Subject: NDA 205004 Bortezomib for Injection - Information Request

Dear Ms. Dron:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Bortezomib for Injection, 3.5 mg/vial.

We are reviewing your submission and have the following information request. We request a written response by **close of business January 25, 2013** in order to continue our evaluation of your NDA.

Clinical Pharmacology

- Submit attachment 2 'Proteasome Inhibitory Assay method' (test method 10-08-03-6670) and attachment 3 'Validation of the HPLC Method for the Determination of Bortezomib' (PR-11-00219 Final Report) mentioned in Study No. PD11-NB/F-016.

Please acknowledge receipt of this correspondence.

Kind regards,
Karen

Karen Bengtson
Regulatory Project Manager
Division of Hematology Products
OHOP/CDER/FDA
WO22, Room 2189
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3338
Fax: 301-796-9845
E-mail: karen.bengtson@fda.hhs.gov

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

/s/

KAREN E BENGTSON
01/24/2013

Bengtson, Karen

From: Bengtson, Karen
Sent: Tuesday, January 22, 2013 10:28 AM
To: 'Aditi.Dron@fresenius-kabi.com'
Cc: Grace.Burbulys@fresenius-kabi.com
Subject: NDA 205004 Bortezomib for Injection - Information Request

Importance: High

Dear Ms. Dron:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Bortezomib for Injection, 3.5 mg/vial.

We are reviewing your submission and have the following information request. We request a written response by **close of business January 25, 2013** in order to continue our evaluation of your NDA.

Clinical Pharmacology

- Submit attachment 2 'Proteasome Inhibitory Assay method' (test method 10-08-03-6670) and attachment 3 'Validation of the HPLC Method for the Determination of Bortezomib' (PR-11-00219 Final Report) mentioned in Study No. PD11-NB/F-016.

Please acknowledge receipt of this correspondence.

Kind regards,
Karen

KAREN BENGTSON
Regulatory Project Manager
Division of Hematology Products
OHOP/CDER/FDA
WO22, Room 2189
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3338
Fax: 301-796-9845
E-mail: karen.bengtson@fda.hhs.gov

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

/s/

KAREN E BENGTSON
01/22/2013

From:	Bengtson, Karen
To:	"Aditi.Dron@fresenius-kabi.com"
Cc:	Grace.Burbulys@fresenius-kabi.com
Subject:	NDA 205004 Bortezomib for Injection - Information Request
Date:	Monday, December 10, 2012 11:46:00 AM

Dear Ms. Dron,

On October 26, 2012, a new version of the package insert was approved for the reference listed drug (RLD), VELCADE ® (bortezomib) for Injection. This version can be found at Drugs@FDA. Submit an updated draft package insert that reflects the most current RLD labeling to your 505(b)(2) NDA as soon as possible.

Please acknowledge receipt of the e-mail correspondence.

Kind regards,
Karen

KAREN BENGTSON
Regulatory Project Manager
Division of Hematology Products
OHOP/CDER/FDA
WO22, Room 2189
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3338
Fax: 301-796-9845
E-mail: karen.bengtson@fda.hhs.gov

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

/s/

KAREN E BENGTSON
12/10/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205004

NDA ACKNOWLEDGMENT

Fresenius Kabi USA, LLC
Attention: Aditi Dron
Manager, Regulatory Affairs
1501 East Woodfield Road
Suite 300 E
Schaumburg, IL 60173

Dear Ms. Dron:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Bortezomib for Injection

Date of Application: November 30, 2012

Date of Receipt: December 3, 2012

Our Reference Number: NDA 205004

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 1, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, contact me at (301) 796-3338 or Karen.Bengtson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Karen Bengtson
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

KAREN E BENGTSON
12/05/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES P

Food and Drug Administration
Silver Spring, MD 20993

preIND 107868 **MEETING MINUTES**

APP Pharmaceuticals
Attention: Dale Carlson
Director, Regulatory Affairs,
1501 East Woodfield Road
Suite 300 East
Schaumburg, IL 60173

Dear Mr. Carlson:

Please refer to your pre-Investigational New Drug Application (preIND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Bortezomib for Injection."

We also refer to the April 5, 2010, meeting between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Attachment: Meeting Minutes

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF MEETING MINUTES

MEETING DATE: **April 6, 2010**
APPLICATION: **preIND 107868**
SPONSOR: **APP Pharmaceuticals (APP)**
DRUG NAME: **Bortezomib for Injection**
INDICATION: **Treatment of multiple myeloma and mantle cell lymphoma**
TYPE OF MEETING: **Type B; preIND/preNDA**
MEETING RECORDER: **Sharon Sickafuse**

FDA ATTENDEES:
Office of Oncology Drug Products
Tamy Kim

Division of Biologic Oncology Products
Suzanne Demko,
Patricia Keegan, M.D.
Andrew McDougal, Ph.D.
Anne Pilaro, Ph.D.
Kamal Sharma, M.D.
Sharon Sickafuse, M.S.

Office of Clinical Pharmacology
Division 5
Bahru Habtemariam, Ph.D.

Office of New Drugs Quality Assurance
Division 3
Sarah Pope,
Haripada Sarker, Ph.D.

Biopharmaceutics
Angelica Dorantes, Ph.D.

Office of Regulatory Policy
Nancy Boocker

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-107868	GI-1	APP PHARMACEUTICALS	Bortezomib for Injection

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

/s/

SHARON K SICKAFUSE
05/03/2010