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RESEARCH**

APPLICATION NUMBER:

205004Orig1s000

OTHER REVIEW(S)

**REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 205004

Application Type: New 505(b)(2) NDA

Drug Name(s)/Dosage Form(s): **BORTEZOMIB FOR INJECTION**

Applicant: **Fresenius Kabi (FK)**

Receipt Date: **May 22, 2015**

Goal Date: **November 22, 2015**

1. Regulatory History and Applicant's Main Proposals

On November 30, 2012 (received December 3, 2012), Fresenius Kabi USA (FK USA) submitted a 505(b)(2) application for bortezomib for injection with relies on the FDA's previous findings of safety and effectiveness for the reference listed drug (LD), VELCADE® (bortezomib). On October 3, 2013, the application received a Complete Response (CR) Action. The application was resubmitted and classified as Class 2 resubmission on October 3, 2014 and received another CR action on April 2, 2015. The application was resubmitted and classified as Class 2 resubmission on May 22, 2014. The applicant's name has been changed to Fresenius Kabi (FK) which is reflected in their April 30, 2013 submission.

FK's application proposes the same indications as currently approved for the LD; however, their product is only intended as an intravenous injection. Since the LD is also approved for the subcutaneous route of administration, information regarding the subcutaneous route of administration has been carved out of the proposed label.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format (submitted 10/16/2015) of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
- Comment:** The Applicant was notified that they should adjust formatting, as appropriate. Reference to 21 CFR 201.56(d) and 201.57(b) and Guidance for Industry: Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirement was provided.*
- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
- Comment:***
- NO** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).
- Comment:** The Applicant will be made notified that horizontal line must separate the HL for the TOC the solid line which includes the "see 17 for..." and Revision date.*
- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.
- Comment:***
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.
- Comment:***
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Selected Requirements of Prescribing Information

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, "**HIGHLIGHTS OF PRESCRIBING INFORMATION**" must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *The Applicant will need to be reminded that the approval year will need to be updated with the correct year.*

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- See 17 for **PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- YES** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

JANET G HIGGINS
11/02/2015

MARA B MILLER
11/02/2015



Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV Division of
Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric Labeling Review

From: Carolyn L. Yancey, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Pediatric Team Leader
DPMH

John J. Alexander, MD, MPH, Deputy Director
DPMH

NDA Number: 205004

Sponsor: Fresenius Kabi USA, LLC

Drug: Bortezomib Injectable

Therapeutic Class: Protease Inhibitor

**Dosage Form and
Route of Administration:** For [REDACTED] (b) (4) intravenous use, single-use vial contains 3.5 mg
of Bortezomib as lyophilized powder.

Reference Listed Drug: Velcade, NDA 021602 by Millennium Pharmaceuticals, Inc.
Approved Indications: For the treatment of patients with multiple myeloma
For the treatment of patients with mantle cell lymphoma

Consult Request: The Division of Hematology Products (DHP) requests
DPMH's input on the proposed labeling for 505(b)(2), NDA 205004
Bortezomib by Fresenius Kabi USA (consult dated September 19,
2017).

Background:

The labeling under review is Bortezomib for Injection, 3.5 mg/vial, new drug application (NDA) 205004, 505(b)(2), manufactured by Fresenius Kabi, USA, LLC (FK). The reference product for bortezomib is Velcade[®] (NDA 021602), manufactured by Millennium Pharmaceuticals, Inc. (Millennium). Velcade[®] was approved for the treatment of multiple myeloma on May 13, 2003 under Priority Review as a new molecular entity (NME) with orphan designation related to the

indication for the treatment of multiple myeloma. Velcade was also approved for the treatment of patients with second line and then first line mantle cell lymphoma on December 8, 2006 and on October 8, 2014, respectively. Velcade received orphan designation for the treatment of mantle cell lymphoma on May 30, 2012. Currently, Velcade has orphan drug exclusivity for the treatment of patients with mantle cell lymphoma who have not received at least 1 prior therapy. This orphan drug exclusivity expires on October 8, 2021 and the pediatric exclusivity extension expires on April 8, 2022.

Because bortezomib for the approved indications has orphan drug designation, the sponsor is exempt from the Pediatric Research Equity Act (PREA).

Millennium Pharmaceuticals, Inc., submitted an efficacy supplement (NDA 21602/Suppl-042) on March 25, 2015 for study (AALL07P1) entitled, “*A Phase II Pilot Trial of Bortezomib in Combination with Intensive Re-Induction Therapy for Children with Relapsed Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma*”, to fulfill a pediatric Written Request (WR) for Velcade issued on April 27, 2010.¹ A total of 140 pediatric and young adult patients (1 year to 26 years of age) with lymphoid malignancies (ALL or LL) failed to achieve an acceptable complete remission (CR) rate when compared to a historical control set of patients who received the identical chemotherapy backbone therapy without Velcade. No new safety concerns were observed when Velcade was added to a chemotherapy backbone regimen as compared with a historical control group without Velcade.² A determination of pediatric exclusivity was made under the Best Pharmaceuticals for Children Act (BPCA) and exclusivity was granted on August 14, 2015. This pediatric efficacy supplement was approved on September 14, 2015 and received 3 years of Hatch-Waxman exclusivity (expires September 14, 2018) as well as an additional 6 months of pediatric exclusivity (expires March 14, 2019).

The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) provided additional authority to permit the approval of drugs under 505(j) when pediatric information protected by exclusivity [three-year new clinical studies exclusivity (Hatch-Waxman)] had been added to the labeling and could not be safely “carved out”. It also expressly authorized FDA to include a disclaimer in ANDA labeling when such labeling was carved out. These provisions did not include retention of protected pediatric safety information from 505(b)(2) drug labeling or the inclusion of a disclaimer when protected pediatric information is carved out. The Food and Drug Administration (FDA) Reauthorization Act (FDARA) enacted on August 18, 2017, extended the provisions set forth under FDASIA of 2012 to NDA 505(b)(2) drug labeling.

(b) (4)
505(b)(2), NDA 209191
Bortezomib injection, 2.5 mg/vial, by Hospira (b) (4)
(b) (4)⁴

In this DPMH review, proposed labeling for 505(b)(2), NDA 205004 Bortezomib Injection by Fresenius Kabi USA, Section 8.4 Pediatric Use includes the statement, (b) (4)

¹ DPMH Consult from DHP (dated June 2015), NDA 21602 Velcade (bortezomib) Injection labeling review based on pediatric WR study report, written by Ethan Hausman (dated August 4, 2015).

² NDA 021602 Velcade (bortezomib) Injection, Section 8.4 extracted "from labeling approved on September 14, 2015 based on a pediatric efficacy supplement.

⁴ As of this review, Hospira Bortezomib injection, NDA 209191, has a Tentative Approval (TA).

(b) (4) and the pediatric study information is “carved out” as there is not a concern for safe use conditions without this information.

Fresenius Kabi USA NDA 205004, 505(b)(2) for Bortezomib received a tentative approval (TA) from FDA on November 17, 2015. On September 5, 2017, the sponsor submitted a complete, Class I response (request for approval) that includes proposed labeling and packaging that excludes the protected pediatric study results [performed to fulfill the pediatric Written Request (WR) under NDA 021602 Velcade (bortezomib) by Millennium issued on April 27, 2010] reported in Section 8.4 of Velcade® labeling.²

DPMH Pediatric Labeling Recommendations

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

The reference product, NDA 021602 Velcade (bortezomib) Injection by Millennium, most recent FDA-approved labeling is dated June 9, 2017 (Supplement 043) with updates to Section 6.2, Post-marketing Experience to add Steven Johnson Syndrome, and to Sections 5, 8, 13, and 17 per the Pregnancy and Lactation Labeling Rule (PLLR). Our recommendations for 505(b)(2) NDA 205004 Bortezomib Injection by Fresenius Kabi USA reflect labeling provided to the DHP on October 13, 2017. DPMH notes that the sponsor’s proposed bortezomib labeling omits description of the protected pediatric study in Section 8.4 Pediatric Use. (b) (4)

(b) (4) We believe that the Fresenius 505(b)(2) application can be approved with the information about the protected pediatric study omitted. (b) (4)

(b) (4) FDA has, as described above, been given new authority to add disclaimers and to retain pediatric information necessary for safe use for 505(b)(2) applications. Accordingly, we have determined that it is not appropriate to (b) (4)

(b) (4) In light of FDA’s new authority under FDARA, DPMH recommends revisions to add a disclaimer in Section 8.4. DPMH recommended information to be added to labeling is underlined. Information to be deleted has a ~~strike through~~. Comments and rationale for DPMH’s recommendations to the labeling are in *italics*.

Full Prescribing Information

1 INDICATIONS AND USAGE

(b) (4)

Reviewer’s comment: Bortezomib is approved for the treatment of two oncology diagnoses

⁵ The prior version of the pediatric use section (8.4) stated: (b) (4)

(multiple myeloma and mantle cell lymphoma) that primarily occur in adults and that are extremely rare in pediatric patients.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

(b) (4)

Additional information describing a clinical study in which efficacy was not demonstrated in pediatric patients is approved for Millennium Pharmaceuticals, Inc. VELCADE (bortezomib) Injection. However, due to Millennium Pharmaceuticals, Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Reviewer's comments:

DPMH recommends that the statement,

(b) (4)

be deleted

(b) (4)

DPMH recommends adding a disclaimer to Section 8.4 to acknowledge omission of the protected pediatric information without inclusion of the diagnoses of the pediatric patients in the study report to not potentially describe or support an indication.

General comments

DPMH reviewed the sponsor's proposed labeling for bortezomib, a 505(b)(2) submission under NDA 205004 by Fresenius Kabi USA, and participated in internal meetings on October 13 and 18, 2017. Labeling recommendations were provided in track changes for DHP to revise the Bortezomib Injection labeling to conform to the *Guidance for industry and Review Staff on Pediatric Labeling*⁶ as well as to FDARA⁷. DPMH's input will be reflected in the final labeling and approval letter from DHP. Labeling negotiations are ongoing. Final labeling, which will be negotiated with the sponsor, may differ from the recommendations in this DPMH labeling review.

⁶ www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm341394.pdf

⁷ FDA Reauthorization Act of 2017 (FDARA), signed into law on August 18, 2017. SEC. 608 PEDAITRIC INFORMATION ADDED TO LABELING. Under Section 505A(o) of the FDCA (21 U.S.C. 355a(o)) is amended.

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/s/

CAROLYN L YANCEY

11/01/2017

505(b)(2) NDA 205004 Bortezomib Injection DPMH Labeling Review

HARI C SACHS

11/01/2017

I agree with these recommendations.

JOHN J ALEXANDER

11/01/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: October 19, 2017
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 205004
Product Name and Strength: Bortezomib for Injection, 3.5 mg vial
Applicant/Sponsor Name: Fresenius Kabi
Submission Date: September 5, 2017
OSE RCM #: 2017-1836
DMEPA Safety Evaluator: Leeza Rahimi, PharmD
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the proposed container label, carton labeling, and Prescribing Information (PI) for Bortezomib for injection (NDA 205004) for areas of vulnerability that may lead to medication errors (Appendix A). DHP requested this review as a part of their evaluation of the 505(b)(2) NDA class I resubmission for Bortezomib for injection. DMEPA had made recommendations during previous label and labeling reviews.^{a,b}

1.1 REGULATORY HISTORY

Fresenius Kabi submitted Bortezomib for Injection (NDA 205004) on October 03, 2014. The application received a Tentative Approval letter on November 17, 2015 due to patent protection of the listed drug, Velcade (NDA 021602) upon which the application relies. Fresenius Kabi submitted a request for final approval of Bortezomib for Injection (NDA 205004) on September 5, 2017.

^a Rutledge M. Label and Labeling Review for Bortezomib (NDA 205004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 FEB 03. RCM No.: 2014-2237.

^b Rutledge, M. Label and Labeling Review for Bortezomib Memo (NDA 205004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 02. RCM No.: 2014-2238.

2 CONCLUSION

We conclude the proposed container label, carton labeling, and Prescribing Information are acceptable from a medication error perspective. We have no further recommendations at this time.

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/s/

LEEZA RAHIMI
10/19/2017

HINA S MEHTA
10/20/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 16, 2015

To: Janet Higgins, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Davis, Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for
Bortezomib for injection, for intravenous use
NDA 205004, 505(b)(2)

In response to your consult dated August 5, 2015, we have reviewed the draft Package Insert (PI) for Bortezomib for injection, for intravenous use (bortezomib) and offer the following comments. Please note that OPDP has made these comments using the version e-mailed to OPDP on October 15, 2015.

We have no comments on the draft PI at this time.

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/s/

NISHA PATEL
10/16/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: September 2, 2015
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 205004
Product Name and Strength: Bortezomib for Injection,
3.5 mg per vial
Submission Date: May 22, 2015
Applicant/Sponsor Name: Fresenius Kabi
OSE RCM #: 2014-2238
DMEPA Primary Reviewer: Michelle Rutledge, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised carton labeling and container label (Appendix A) to determine if it is acceptable from a medication error perspective after receiving a complete response. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised Carton labeling and Container labels are acceptable from a medication error perspective.

¹ Rutledge, Michelle. Label and Labeling Review for Bortezomib (NDA 205004). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 FEB 3. OSE RCM No.: 2014-2237.

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/s/

MICHELLE K RUTLEDGE
09/02/2015

YELENA L MASLOV
09/03/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: April 21, 2015

To: Toni-Ann Cox, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Davis, Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for
Bortezomib Injection
NDA 205004

OPDP acknowledges receipt of DHP's February 5, 2015, consult request to review the proposed package insert for Bortezomib Injection. Reference is made to the correspondence from DHP to the sponsor on April 2, 2015, which informed the sponsor that DHP will take a Complete Response action on this product. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DHP submit a new consult request during the subsequent review cycle.

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/s/

NISHA PATEL
04/21/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: February 3, 2015
Requesting Office or Division: Division of Hematology (DHP)
Application Type and Number: NDA 205004
Product Name and Strength: Bortezomib for Injection
3.5 mg per vial
Product Type: Single Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Fresenius Kabi
Submission Date: October 3, 2014
OSE RCM #: 2014-2237
DMEPA Primary Reviewer: Michelle Rutledge, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review responds to a request from DHP to evaluate the proposed carton labeling, vial label, and prescribing information for Bortezomib for areas of vulnerability that could lead to medication errors. This product is a 505(b)(2) to RLD Velcade re-submission after receiving a complete response and is seeking approval for the intravenous route of administration only. The reference listed drug, Velcade (Bortezomib) for injection, was approved on May 13, 2003 under NDA 021602, is marketed as 3.5 mg per vial, and is also approved for a subcutaneous route of administration.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D – N/A
ISMP Newsletters	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The proposed bortezomib for injection is an intravenous (IV) product that can be administered the same intravenous route as the reference drug Velcade for Injection. Unlike the reference drug Velcade for Injection which can also be administered via the subcutaneous route, this proposed bortezomib for injection product is seeking approval for the intravenous (IV) route only. Therefore, healthcare providers may assume this product can also be administered via the subcutaneous route, and use this product by the unapproved route of administration. However, this error may not potentially cause any harm since the product is at the same concentration as original Velcade. However, we still recommend that the approved route of administration be placed in sufficient prominence to ensure correct preparation and administration of the product. We reviewed the label and labeling, and identified the following areas of vulnerability to error:

- Readability of strength
- Prominence of cautionary statements
- Prominence of important product information

Therefore, we conclude that the important safety information on the proposed labels and labeling can be improved.

4 CONCLUSION & RECOMMENDATIONS

We recommend changes to the container label and carton labeling to improve important safety information.

RECOMMENDATIONS FOR THE APPLICANT

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 single-use vial for the final concentration of 1 mg/mL”.

If you have further questions or need clarifications, please contact Kevin Wright, OSE Project Manager, at 301-796-3621.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bortezomib that Fresenius Kabi submitted on October 3, 2014, and the listed drug (LD).

Table 2. Relevant Product Information for Proposed Bortezomib and Reference Listed Drug Velcade		
Product Name	<i>Bortezomib</i>	Velcade
Initial Approval Date	N/A	May 13, 2003
Active Ingredient	Bortezomib	Bortezomib
Indication	<ul style="list-style-type: none"> • Treatment of patients with multiple myeloma • Treatment with mantle cell lymphoma who have received at least one prior therapy 	<ul style="list-style-type: none"> • Treatment of patients with multiple myeloma • Treatment with mantle cell lymphoma who have received at least one prior therapy
Route of Administration	<i>Intravenous</i>	Intravenous and Subcutaneous
Dosage Form	Powder for Injection	Powder for Injection
Strength	3.5 mg per vial	3.5 mg per vial
Dose and Frequency	1.3 mg/m ² administered as a 3 to 5 second bolus intravenous injection.	1.3 mg/m ² is the recommended starting dose of VELCADE. VELCADE may be administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL. When administered intravenously, VELCADE is administered as a 3 to 5 second bolus intravenous injection.
How Supplied	3.5 mg single use vial	3.5 mg single use vial
Instructions for Reconstitution	See Table A below	See Table B below
Storage	Unopened vials may be stored at controlled room	Unopened vials may be stored at controlled room

	temperature 25°C (77°F); excursions permitted from 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Retain in original package to protect from light.	temperature 25°C (77°F); excursions permitted from 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Retain in original package to protect from light.
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Table A: Instruction for Reconstitution of Proposed Bortezomib

Route of Administration	Vial Size	Volume of Diluent (0.9% Sodium Chloride)	Final Concentration
Intravenous	3.5 mg	3.5 mL	1 mg/mL

Table B: Instruction for Reconstitution of reference listed drug, Velcade

Route of Administration	Vial Size	Volume of Diluent (0.9% Sodium Chloride)	Final Concentration
Intravenous	3.5 mg	3.5 mL	1 mg/mL
Subcutaneous	3.5 mg	1.4 mL	2.5 mg/mL

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on January 16, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter²

Table 3: FAERS Search Strategy	
Date Range	May 10, 2014 to January 16, 2015. The last FAERS search was May 8, 2014 for OSE review 2014-103 on Bortezomib, dated on June 18, 2014.
Product	Bortezomib[active ingredient] Bortezomib [product verbatim] Velcade [product name]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]

B.2 Results

Our search identified 5 cases, of which 1 described an error relevant for this review.

The following section describes the 1 case involving medication errors in detail:

Wrong Drug (n = 1)

- One case described a wrong drug, Velcade, being administered instead of Procrit (epotein alfa).

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

- The case did report potential contributing factors.

We do not believe the labels and labeling were contributing factors to this error because there are sufficient differences between the carton and container label, such as presentation of the information and dosage form. We will continue to monitor postmarketing data for this error.

We excluded 4 cases because they described concomitant medication not related to medication error (n=1), literature review described (n=1), and foreign case (n=2).

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control number for the case relevant for this review.

Table 4 below provides the reported characteristics of 1 case associated with a medication error due to wrong drug.

Table 4:

Case No.	Case version	Manufacturer Control No.	Summary Description of Medication Error
10226541	2	US-AMGEN INC.- USASP2014018745	Velcade administered instead of Procrit

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L drive on January 16, 2015 using the terms, Bortezomib to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified 1 previous review¹:

NDA 205004 Label and Labeling Memo dated ~May 8, 2013 (OSE Review# 2012-2862)

¹ Wright K. Label and Labeling Review Memo for Bortezomib (NDA 205004). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); ~2013 May 08. OSE RCM No.: 2012-2862.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on January 16, 2015 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care
Search Strategy and Terms	Match Exact Word or Phrase: Bortezomib

E.2 Results

Institute for Safe Medication Practices. Safety briefs: Bortezomib deaths due to misadministration. ISMP Med Saf Alert Acute Care. 2012;17(4).1-2

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/s/

MICHELLE K RUTLEDGE
02/03/2015

YELENA L MASLOV
02/03/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 2, 2013

To: Karen Bengston, Regulatory Project Manager
DHP

From: Kathleen Davis, Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: Comments on draft labeling (Package Insert and Carton/Container)
for Bortezomib Injection
NDA 205004

We acknowledge receipt of your January 18, 2013, consult request for the proposed product labeling (Package Insert (PI) and Carton/Container) for Bortezomib Injection, NDA 205004. OPDP notes the correspondence with DHP on May 2, 2013, during which it was conveyed that final labeling negotiations would not be initiated during the current review cycle. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DHP submit a new consult request during the subsequent review cycle.

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/s/

KATHLEEN T DAVIS
05/02/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 205004

Application Type: New 505(b)(2) NDA

Name of Drug: Bortezomib for Injection

Applicant: Fresenius Kabi USA, LLC (FK USA)

Submission Date: November 30, 2012

Receipt Date: December 3, 2012

1.0 Regulatory History and Applicant's Main Proposals

On November 30, 2012 (received December 3, 2012), FK USA submitted a 505(b)(2) application for bortezomib for injection which relies on the FDA's previous findings of safety and effectiveness for the reference listed drug (RLD), VELCADE[®] (bortezomib). VELCADE is marketed by Millennium Pharmaceuticals, Inc. under NDA 021602. FK USA's application proposes the same indications as currently approved for the RLD; however, their product is only intended as an intravenous injection. The RLD is also approved for the subcutaneous route of administration. Information regarding the subcutaneous route of administration has been carved out of FK USA's proposed labeling.

2.0 Review of the Prescribing Information (PI)

On December 10, 2012, the applicant was requested to submit an updated PI reflecting the most current approved RLD PI (approved October 26, 2012). On January 18, 2013, the updated PI was submitted to the NDA (SDN 3/eCTD 002).

This review is based on the applicant's Microsoft Word format of the PI submitted January 18, 2013. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. In the Highlights Limitation Statement, it is recommended that the name of the drug product be presented in upper case letters to improve its prominence.

RPM PLR Format Review of the Prescribing Information

2. All required elements of the product title in the Highlights (i.e., drug names, dosage form and route of administration) should be presented on a single line if space permits.
3. The Recent Major Changes (RMCs) from the RLD's PI are included in the Highlights and should be removed. The RMC section is not applicable to an application's original proposed labeling.
4. In the Full Prescribing Information (FPI), the font of the headings and subheadings (Arial) is not consistent with other text (Times New Roman).
5. The revision date at the end of Highlights replaces the "revision" or "issued" date at the end of the FPI and should not appear in both places.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant during labeling negotiations.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *The references are present and will be checked for accuracy.*

Selected Requirements of Prescribing Information (SRPI)

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment: *It is recommended that the name of the drug product be presented in upper case letters in the limitation to improve its prominence.*

Product Title

YES

10. Product title in HL must be **bolded**.

Comment: *All required elements for the product title in HL should be presented on a single line as space permits (e.g., dosage form, route of administration). However, the proposed labeling is consistent with the current RLD labeling.*

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Boxed Warning

- N/A** 12. All text must be **bolded**.

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

N/A Comment: *The proposed PI includes the (b) (4) from the RLD labeling. The applicant will be told to remove this section from the highlights.*

18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Selected Requirements of Prescribing Information (SRPI)

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment: *The font of the sections and subsections is not consistent with the rest of the labeling.*

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use

Selected Requirements of Prescribing Information (SRPI)

8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: See comment under 17.

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: A modification of this statement is included. The review team will determine if the modification is appropriate.

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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
03/05/2013

JANET K JAMISON
03/05/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205004 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Bortezomib for Injection Dosage Form: Lyophilized powder for Injection Strengths: 3.5 mg/vial		
Applicant: Fresenius Kabi USA, LLC Agent for Applicant (if applicable): N/A		
Date of Application: November 30, 2012 Date of Receipt: December 3, 2012 Date clock started after UN:		
PDUFA Goal Date: October 3, 2013	Action Goal Date (if different):	
Filing Date: February 1, 2013	Date of Filing Meeting: January 16, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 5		
Proposed indication(s)/Proposed change(s): Treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): 107868				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	√			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	√			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	√			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		√		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	√			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>√</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>√</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>√</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p>	<p>√</p>			<p>3-year exclusivity for the subcutaneous route of administration.</p>																
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>N021602</td> <td>Velcade</td> <td>NR</td> <td>January 23, 2015</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	N021602	Velcade	NR	January 23, 2015												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
N021602	Velcade	NR	January 23, 2015																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>		√		Velcade has orphan designation for both indications - multiple myeloma and mantle cell lymphoma. The Orphan exclusivity for Velcade expired on March 25, 2012.

If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			√	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		√		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		√		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			√	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	N/A

Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	√			
Index: Does the submission contain an accurate comprehensive index?	√			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	√			
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #			√	
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			√	
• If yes, were all of them submitted on time?			√	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			√	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			√	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	√			
Are all establishments and their registration numbers listed on the form/attached to the form?	√			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	√			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>		√		No clinical studies included with this application. Applicant has requested a waiver for <i>in vivo</i> bioequivalence/bioavailability studies.
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	√			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of 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." Applicant may not use wording such as, "To the best of my knowledge..."</i>	√			Applicant's original statement said "...debarred under subsections (a) and (b) of Section 335a..." A revised certification was requested and submitted on January 29, 2013.

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			√	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			√	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		√		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			√	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			√	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>			√	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<u>BPCA (NDAs/NDA efficacy supplements only):</u>				
Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		√		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		√		
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		√		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	√			
Is the PI submitted in PLR format? ⁴	√			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			√	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	√			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)			√	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	√			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	√			
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			√	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			√	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			√	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		√		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		√		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 6, 2010; September 27, 2011	√			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		√		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 16, 2012

BLA/NDA/Supp #: 205004

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: Bortezomib for Injection

DOSAGE FORM/STRENGTH: Lyophilized powder for injection, 3.5 mg/vial

APPLICANT: Fresenius Kabi USA, LLC (FK USA)

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of patients with multiple myeloma or with mantle cell lymphoma who have received at least one prior therapy

BACKGROUND:

On November 30, 2012, FK USA submitted a 505(b)(2) NDA for Bortezomib for Injection (received December 3, 2012). The application relies on the FDA's previous finding of safety and effectiveness for the reference listed drug (RLD), VELCADE® (bortezomib) for Injection. VELCADE is marketed by Millennium Pharmaceuticals, Inc. under NDA 021602. FK USA's drug product has the same active ingredient, indications, dosage form, strength, and route of administration (IV) as the RLD. The RLD is also approved for the subcutaneous route of administration; however, FK USA is only seeking the intravenous route of administration for their product. FK USA's drug product differs from the RLD because of the inactive ingredients used in their formulation. FK USA's product contains glycine and boric acid where VELCADE® contains mannitol.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Karen Bengtson	Y
	CPMS/TL:	Janet Jamison/ Ebla Ali Ibrahim	Y Y
Cross-Discipline Team Leader (CDTL)	Janice Brown		Y
Clinical	Reviewer:	Karen McGinn	Y
	TL:	R. Angelo de Claro	N
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Clinical Pharmacology	Reviewer:	Young-Jin Moon	N
	TL:	Julie Bullock	N
Biostatistics	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Pedro Del Valle	Y
	TL:	Haleh Saber	Y
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer:	Jean Tang	Y
	TL:	Janice Brown	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Erika Pfeiler	Y
	TL:	Stephen Langille	N
CMC Labeling Review	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Facility Review/Inspection	Reviewer:	Mahesh Ramanadham	N
	TL:	Tara Goen	N
OSE/DMEPA	Reviewer:	Kevin Wright	Y
	TL:	Yelena Maslov	Y

OSE/DRISK (REMS)	Reviewer:	NA	N/A
	TL:	NA	N/A
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	N/A
	TL:	NA	N/A
Bioresearch Monitoring (OSI)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers	Kelly Kitchens (Biopharmaceutics) Angelica Dorantes (TL)		Y N
Other attendees	Ann Farrell, Division , DHP Ed Kaminskas, Deputy Director, DHP Diane Leaman, Safety RPM, DHP Sue Kang, OSE Jewell Martin, ONDQA Natalie Simpson, DHOT Chris Sheth, DHOT		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: No clinical studies were performed. This application relies on the previous FDA findings of safety and efficacy for the RLD.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: Quality Microbiology has review issue for the day-74 letter.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Edvardas Kaminskas - Deputy Director, DHP</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): N/A</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments: N/A</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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 BENGTON
01/29/2013

JANET K JAMISON
01/29/2013