

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202714Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

To: NDA 202-714 Seq. 0027
From: Josephine Jee, CMC-DP Reviewer, ONDQA
Date: 27-JUN-2012
Drug: Carfilzomib for Injection
Route of administration: Intravenous injection
Strength: 60 mg per vial
Subject: **Revised Container and Carton labels and** [redacted] (b) (4)
[redacted] Label

Introduction

This review covers NDA 202-714, Sequence 0027 submitted by ONYX Pharm. on 22-MAY-2012 to provide for revised container and carton labels in response to the FDA Information Request sent on 18-MAY-2012. In addition, it also covers ONYX request to review the [redacted] (b) (4) [redacted] Label. These issues were also reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and concluded the revised carton and container labels [redacted] (b) (4) to be acceptable.

The review from a CMC perspective also found the revised carton and container labels [redacted] (b) (4) to be acceptable; see attached labels.

Recommendation: The application is recommended for “**Approval**” from a CMC perspective

Revised Container Label:

[redacted] (b) (4)

Revised Carton Label:

[redacted] (b) (4)

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/s/

JOSEPHINE M JEE
06/28/2012

JANICE T BROWN
06/29/2012

ONDQA Division Director's Memo
NDA 202-714, Kyprolis (carfilzomib) for Injection, 60 mg/vial
Date: 07-JUN-2012

Introduction

Kyprolis (carfilzomib) for Injection is formulated as a sterile white to off-white lyophilized cake or powder intended for reconstitution with Water for Injection (29 mL) and subsequent intravenous injection. The commercial marketing configuration is a (b)(4) vial containing 60 mg of carfilzomib. All excipients are commonly used in injectable dosage forms.

The drug product is administered intravenously at 20/27 mg/m² (20 mg/m² in Cycle 1, escalating to 27 mg/m² in Cycle 2) over two (2) to ten (10) minutes, twice weekly on consecutive days for 3 weeks (Days 1,2, 8, 9,15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered one treatment cycle. The proposed indication is for the treatment of patients with relapsed and refractory multiple myeloma who has received at least two prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent.

All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding review deficiencies that would preclude a recommendation of approval from a CMC standpoint. An overall acceptable recommendation from the Office of Compliance was issued on 24-MAY-2012.

All CMC review issues have been resolved, and ONDQA recommends approval of this NDA.

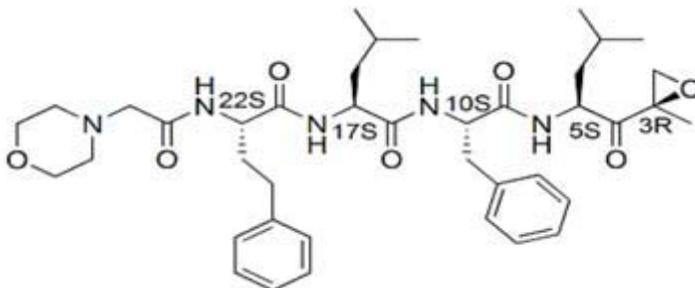
Administrative

The original submission of this 505(b)(1) NDA was received on 27-SEP-2011 from Onyx Pharmaceuticals, Inc. Several solicited CMC amendments were also reviewed during the review cycle. The comprehensive CMC assessment is captured in the following reviews, respectively: Chemistry Review #1 (for the Drug Substance, 25-MAY-2012, W. Adams), Chemistry Review #1 (for the Drug Product, 14-MAY-2012, J. Jee) and the Biopharmaceutics Review (24-MAY-2012, Dr. H. Mahayni).

The NDA is supported by IND 71,057 and four (4) drug master files (DMFs). All DMFs were assessed for adequacy in the respective chemistry reviews.

Drug Substance (carfilzomib)

Chemical Name: (αS)-α-[(4-morpholinylacetyl)amino]benzenebutanoyl-L-leucyl-N-[(1S)-3-methyl-1-[[[(2R)-2-methyloxiranyl]carbonyl]butyl]-L-phenylalaninamide



Molecular Formula C₄₀H₅₇N₅O₇
Molecular Weight 719.9 amu

Carfilzomib is a new molecular entity. It is a single enantiomer, small molecule with five (5) asymmetric centers and no counter ion. Bulk carfilzomib is a crystalline, non-hygroscopic solid (b) (4). It is insoluble in water at pH >1, and soluble in most alcohols and many organic solvents.

(b) (4). During the review, the Applicant was asked to clarify analytical testing site responsibilities. The Applicant was also asked to provide additional details regarding the drug substance manufacturing process (including proposed raw and starting materials), analytical methodology and controls used for the testing of intermediates, and proposed specifications for the final drug substance. The Applicant's collective responses satisfactorily resolved these deficiencies.

Carfilzomib is relatively stable; no extraordinary storage precautions are required. The proposed re-test period of (b) (4) when stored in the recommended container closure system and under the proposed storage conditions (+2-8°C) is granted.

Drug Product (carfilzomib) for Injection, 60 mg/vial

Kyprolis (carfilzomib) for Injection is formulated as a sterile white to off-white lyophilized cake or powder for reconstitution and subsequent injection. Prior to use, each vial is reconstituted with 29 mL of sterile Water for Injection (not supplied) to provide up to a 60 mg deliverable dose as a 2 mg/mL carfilzomib solution for intravenous (IV) administration. Kyprolis (carfilzomib) for Injection contains 60 mg of carfilzomib, (b) (4) of sulfobutylether beta-cyclodextrin, and (b) (4) of anhydrous citric acid (b) (4).

The manufacturing process consists of (b) (4)

Sterility assurance was assessed in the Microbiology Review (08-MAY-2012, Dr. J. Metcalfe).

Identified review issues centered around the proposed drug product specifications and potential compatibility issues with the intended infusion set. As captured in the Chemistry Review, these deficiencies were resolved during the review clock. Acceptable container/carton labeling was received on 22-MAY-2012.

The Applicant proposed an **18 month expiry** for this product when stored in the commercial packaging at 5°C ± 3°C. Based on the stability data provided and in accordance with ICH Q1E, the Agency grants the proposed expiry. There is no need for additional confirmatory language in the action letter as there is no disagreement between the Applicant's proposed expiration dating period and that granted by the Agency.

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/s/

SARAH P MIKSINSKI
06/07/2012

NDA 202,714

KYPROLIS™ (carfilzomib) for Injection

Onyx Pharmaceuticals, Inc.

**William Adams (drug substance)
Office of New Drug Quality Assessment**

Division of Drug Hematology Products

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S.5 Reference Standards or Materials.....	Error! Bookmark not defined.
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Chemistry Review Data Sheet

1. **NDA 202-714**
2. **REVIEW #1**
3. **REVIEW DATE:** 25-MAY-2012
4. **REVIEWER:** William Adams (drug substance)
5. **PREVIOUS DOCUMENTS:** None
6. **SUBMISSION(S) BEING REVIEWED:**

<i>Submission</i>	<i>Date Received</i>	<i>Date Sent</i>
S-001 – original NDA w/CMC	27 Sep 2011	27 Sep 2011
S-008 – quality response to IR; MV package	20 Dec 2011	19 Dec 2011
S-023 – quality response to IR; API Information	27 Apr 2012	26 Apr 2012

7. NAME & ADDRESS OF APPLICANT:

Name: ONYX Pharmaceuticals, Inc.
Address: 249 E. Grand Avenue
S. San Francisco, CA 94080
Representative: John Bedard
Vice President, Regulatory Affairs
Telephone: (650) 266-1672

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: KYPROLIS™
 - b) Non-Proprietary Name (USAN): Carfilzomib
 - c) Code Name/# (ONDC only): PR-171
- c) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: Type 1 – New Molecular Entity
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)**10. PHARMACOL. CATEGORY:** Proteasome Inhibitor and Immunomodulatory**11. DOSAGE FORM:** Lyophilized Powder for Injection**12. STRENGTH/POTENCY:** 60 mg/vial (2 mg/mL after reconstitution)**13. ROUTE OF ADMINISTRATION:** Intravenously push

Executive Summary Section

14. Rx/OTC DISPENSED: Rx OTC

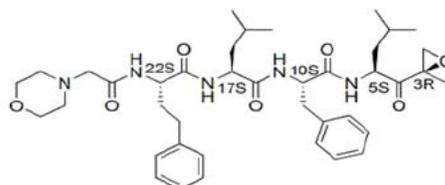
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Empirical Formula: C₄₀H₅₇N₅O₇

Molecular Weight: 719.9



17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
(b) (4)	III		(b) (4)	4	N/A		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 71,057	Onyx Pharm., Inc	PR-171	Active	18-JAN-2008	Designated as Orphan Drug for Mult. Myeloma
			(b) (4)		

C. Related Documents: None

Executive Summary Section

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Statistical Analysis	31-JAN-2012	Y.Jeon	Statistical analysis of drug product stability data – acceptable for 18M.
EES	Site inspections	24 Mar 2012	OC	Overall Recommendation: Acceptable
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)	On-going	T. Palmby	Pending
Biopharm	Product equivalence	24 Mar 2012	H. Mahayni	Recommendation: frozen/lyophilized product and the (b) (4) sites are equivalent
ODS/DMEPA	Labeling consult	03-FEB-2012	K. Defronzo	Recommended revisions for carton & container labels, and PI AMD dated 03-FEB-2012 as Unacceptable.
Methods Validation	Validation of HPLC methods used for ID, Assay, and Related Substances	15-MAR-2012	C.M. Ruzicka, and L. Mecker	Recommendation: Acceptable
EA	N/A	08-MAY-2012	J.Jee	Applicant cites 21 CFR 25.31(b) as applicable - Acceptable
Microbiology	(b) (4)	08-MAY-2012	J. Metcalfe	Recommendation: Approval.

The Chemistry Review for NDA 202,714

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend APPROVAL with respect to the chemistry, manufacturing, and controls (CMC) for drug substance.

The method validation for carfilzomib and the identified degradants/impurities submitted on 17-OCT-2011 was found acceptable by the Division of Pharmaceutical Analysis, St. Louis, MO on 21-MAR-2012.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessment

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

This section of the application includes a summary of the developmental study findings, but does not claim quality by design elements (design spaces, normal operating ranges or proven acceptable ranges) for drug manufacture or control.

Carfilzomib is a single enantiomer, small molecule with 5 asymmetric centers and no counter ion. Bulk drug material is a crystalline, non-hygroscopic solid (b) (4)

It is insoluble in water at pH >1, and soluble in most alcohols and many organic solvents.

Drug manufacture is started at (b) (4)

Both sites have been found to meet current GMP requirements. Manufacture is by (b) (4)

Master batch records for the NDA registration batches are not provided. Acceptable ranges for critical and non-critical process parameters are described and justified. The critical quality attributes are stated to be those addressed by the release specification. (b) (4)

Sources of each starting material are qualified by manufacturing experience and an impurity profile defined by a specified synthesis process. Synthesis intermediates are well controlled for purity and residual solvents. Reagents and solvents are

Executive Summary Section

adequately controlled for identity and purity. Sources and mechanisms of formation for impurities in intermediates and finished drug substance are identified, and the process controls for limiting impurities in finished drug substance are justified. Bulk drug substance is stored and transported in

(b) (4)

Drug substance, manufactured by the proposed commercial process, is adequately characterized for molecular structure and physicochemical attributes, including the absolute configuration and (b) (4). Provided are profiles of impurities observed in batches manufactured during process development; in batches used in the clinical and non-clinical studies; and in the three NDA registration batches. Potential impurities from material obtained by the proposed commercial manufacturing process are identified and those actually observed have been qualified by non-clinical studies. Residual solvents from the synthesis process are controlled to below the ICH Q3C safety limits. Residual catalyst (b) (4) heavy metals and inorganics are addressed at batch release.

Release and stability testing are performed by

(b) (4)

All sites have been found to meet current GMP requirements.

The release specification includes testing for appearance; identity for absolute configuration (specific rotation) and (b) (4) assay of active ingredient (HPLC); related substances (HPLC); residual solvents (GC); water content (KF); residual (b) (4) (ICP-OES), inorganics (ROI) and heavy metals (USP); bioburden (USP); and bacterial endotoxin load (USP). All analytical methods are described in sufficient detail and appropriately validated for their intended use. The proposed criteria are adequately justified by batch analysis data, stability study results, and calculated safe exposure levels (b) (4) and bacterial endotoxins). The designated reference standard batches for drug substance and its major impurity have been adequately characterized for identity and purity.

Tabulated and graphically presented data from stability studies on the three NDA registration batches and a supportive batch performed at 2-8°C (long term), 25°C (accelerated), ICH light stress and forced degradation conditions show that bulk drug substance is stable for up to (b) (4) when stored in the appropriate container closure system. The studies also show that bulk drug is not light sensitive. (b) (4)

The post approval stability commitment indicates that the NDA registration studies will be completed through 48 months; and that three process validation batches and an annual batch thereafter will be placed on stability. The results from these studies will be submitted in the annual reports. The proposed protocols adequately address appearance, identity, assay, impurities and bioburden at appropriate intervals through 48 months at 2-8°C and 6 months at 25°C.

Drug Product

To be provided in the CMC – Drug Product Review.

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B. Description of How the Drug Product is Intended to be Used

The drug product is administered intravenously at 20/27 mg/m² (20 mg/m² in Cycle 1, escalating to 27 mg/m² in Cycle 2) over two (2) to ten (10) minutes, twice weekly on consecutive days for 3 weeks (Days 1,2, 8, 9,15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered one treatment cycle. The proposed indication is for the treatment of patients with relapsed and refractory multiple myeloma who has received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation for APPROVAL is based on the submission of complete and acceptable CMC information for Drug Substance.

III. Administrative**A. Reviewer's Signature**

See electronic signatures in DARRTS.

B. Endorsement Block

See electronic signatures in DARRTS.

C. CC Block

See electronic signatures in DARRTS.

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/s/

WILLIAM M ADAMS
05/29/2012

SARAH P MIKSINSKI
05/29/2012

NDA 202,714

KYPROLIS™ (carfilzomib) for Injection

Onyx Pharmaceuticals, Inc.

Josephine Jee (Drug Product)

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II**

**For the Office of Hematology and Oncology Drug Products
Division of Drug Hematology Products**

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Chemistry Review Data Sheet

1. NDA 202-714, KYPROLIS™(carfilzomib) for Injection (Drug Product)
2. REVIEW #1
3. REVIEW DATE: 14-MAY-2012
4. REVIEWER: Josephine Jee (Drug Product)
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original NDA 202,714 Seq. 0000	31-JAN-2011
Original (CMC)	27-SEP-2011
Seq. 0008 – Response to Request for Method Validation Materials	19-DEC-2011
Seq. 0009 – Labeling Supplement	21-DEC-2011
Seq. 0024 – FDA Information Request	01-MAY-2012
Seq. 0025 – FDA Information Request (Carton & Container Lab.)	15-MAY-2012
Seq. 0026 – Response to FDA Comment – Container Labeling	22-MAY-2012

7. NAME & ADDRESS OF APPLICANT:

Name: ONYX Pharmaceuticals, Inc.
 Address: 249 E. Grand Avenue
 S. San Francisco, CA 94080
 Representative: John Bedard
 Vice President, Regulatory Affairs
 Telephone: (650) 266-0000

8. DRUG PRODUCT NAME/CODE/TYPE:

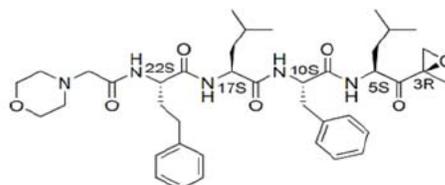
a) Proprietary Name: KYPROLIS™
 b) Non-Proprietary Name (USAN): Carfilzomib
 Code Name/# (ONDC only):
 c) Chem. Type/Submission Priority (ONDC only):
 • Chem. Type: Type 1 – New Molecular Entity
 • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1), Carfilzomib for Injection,

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10. PHARMACOL. CATEGORY: Proteasome Inhibitor and Immunomodulatory
 11. DOSAGE FORM: Lyophilized Powder
 12. STRENGTH/POTENCY: 60 mg/Vial (2 mg/mL after reconstitution)
13. ROUTE OF ADMINISTRATION: Intravenously
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
 (*αS*)-*α*-[(4-morpholinylacetyl)amino]benzenebutanoyl-L-leucyl-N-[(1*S*)-3-methyl-1-[[*(2R)*]-2-methyloxiranyl]carbonyl]butyl]-L-phenylalaninamide

Chemical Structure of Carfilzomib



Empirical Formula: C₄₀H₅₇N₅O₇

Molecular Weight: 719.9

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
(b) (4)	IV	Cydex Pharmaceutical	Captisol® (sulfobutylether β-cyclodextrin)	3	Adequate	25-SEP-2008	P. Shiromani
	V		(b) (4)	3	Adequate	11-SEP-2006	D.Lu
	III			3	Adequate	26-JUL-2010	J.S. Hathaway
	V			3	Adequate	06-SEP-2011	R.J. Mello
	III			3	Adequate	06-JUN-2011	J. Jee
	III			3	Adequate	14-MAR-2012	M. Stevens-Riley

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		(b) (4)				
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¹ Action codes for DMF Table:

- 1 – DMF Reviewed.
- Other codes indicate why the DMF was not reviewed, as follows:
- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 71,057	Onyx Pharm., Inc	PX-171	Active	18-JAN-2008	Designated as Orphan Drug for Mult. Myeloma

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
None			

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Statistical Analysis	31-JAN-2012	Y.Jeon/ Approval	Statistical analysis of drug product stability data – acceptable for 18 M.
EES	Site inspections	24-MAY-2012	OC/M.Stock	Overall Recommendation – Acceptable (see Attachment A)
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)	Ongoing	T. Palmby/ Pending	Pending
Biopharm		24-MAY-2012	H. Mahayni	Recommendation: Approval
ODS/DMEPA	Labeling consult	23-MAY-2012	K. Defronzo	Recommended revisions for Carton and container labels, and PI Acceptable on 23-MAY-2012 (see email dated 23-MAY-2012 - Attachment B).
Methods Validation	Method Validation for HPLC methods used for ID, Assay, and Related Substances	15-MAR-2012	C.M. Ruzicka, and L. Mecker/ Acceptable	Recommendation: Acceptable

Executive Summary Section

EA	N/A	08-MAY-2012	J.Jee/ Acceptable	Applicant cites 21 CFR 25.31(b) as applicable - Acceptable
Microbiology	(b) (4)	08-MAY-2012	J. Metcalfe/ Approval	Recommended approval.

The Chemistry Review for NDA 202,714

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Applicant has resolved all outstanding CMC issues, and this application is recommended for approval with respect to the chemistry, manufacturing, and controls (CMC). An overall acceptable recommendation was received from the Office of Compliance on 24-MAY-2012. The sterilization process for Carfilzomib for Injection was found acceptable on 08-MAY-2012. The acceptance criteria for the degradants/ impurities in Carfilzomib for Injection Specification are acceptable based on the safety data submitted and recommended by Pharmacology/ Toxicology on 10-APR-2012. The applicant and the Holders of Drug Master Files (DMFs) for the excipient, sulfobutylether β -cyclodextrin, and other DMFs submitted for container closure systems have provided adequate information. The method validation for carfilzomib and the identified degradants/impurities submitted on 17-OCT-2011 was found acceptable by the Division of Pharmaceutical Analysis, St. Louis, MO on 21-MAR-2012. All CMC and DMEPA comments related to the container and carton labels and packaging insert have been identified on 16-MAR-2012 and they were communicated to Onyx on 11-MAY-2012. ONYX satisfactorily responded on 15-MAY-2012. However, additional comments were identified by DMEPA on 15-MAY-2012. ONYX satisfactorily responded on 22-MAY-2012. Comments on the inclusion of osmolality test and analytical method in the drug product specification; the tightening of the acceptance criteria for related substances; and the compatibility of the drug product reconstituted solution in the recommended intravenous bags and administration sets were sent to Onyx on 27-APR-2012. Onyx satisfactorily responded on 01-MAY-2012.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessment

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

See W.Adams (CMC-API) Review.

Drug Product

Kyprolis (carfilzomib) for Injection is formulated as a sterile white to off-white lyophilized cake or powder for solution. Initial formulation was in the form of a sterile frozen solution. Upon reconstitution, the concentration of carfilzomib and the excipients in the reconstituted solution from Carfilzomib for Injection is the same as Carfilzomib Injection (frozen solution); therefore, by design, these two dosage forms are provided in single vials and provided the same composition upon administration to patients in clinical studies. The pivotal Phase 2 trial, most patients received Carfilzomib for Injection (lyophilized); of 266 patients, 236 received the lyophilized form and 22 patients received both lyophilized and frozen dosage forms. Carfilzomib for Injection (lyophilized),

Executive Summary Section

60 mg per vial, is the proposed commercial presentation. Prior to use, each vial is reconstituted with 29 mL of sterile Water for Injection (not supplied) to provide up to 60 mg of deliverable dose as a 2 mg/mL carfilzomib solution for intravenous (IV) administration. Kyprolis (carfilzomib) for Injection is not recommended to dilute in 0.9% Saline Solution. The proposed Kyprolis (carfilzomib) for Injection contains 60 mg of carfilzomib, (b) (4) of sulfobutylether beta-cyclodextrin, and (b) (4) of anhydrous citric acid (b) (4)

The proposed drug is manufactured by (b) (4)

(b) (4) Drug product (DP) lots used in the pivotal clinical study were manufactured at (b) (4) and the primary stability lots were manufactured at (b) (4), which is the proposed commercial manufacturing site. An assessment was performed to establish that the DP manufactured at either of the two sites is comparable based on the attributes of a) raw materials, b) product formulation, c) manufacturing process, equipment, and facility, d) container closure system, and e) product quality, including assessment of lot release results, stability results and lyophilized cake characteristics. The results of these studies concluded that DP manufactured at (b) (4) is comparable to DP manufactured at (b) (4)

The sponsor's formulation development efforts indicated that (b) (4)

Degradation products from the Carfilzomib for Injection manufacturing process are primarily related to (b) (4)

The product is packaged in (b) (4)

(b) (4) Appropriate analytical tests and specifications have been developed and appropriately validated. The adequacy of the method validation was also confirmed by the Division of Pharmaceutical Analysis, CDER, FDA, St. Louis, MO. The sponsor studied the stability of eleven lots (three primary stability lots and 8 supportive stability lots) of the DP vials. The applicant provided 36 months of stability data from two supportive lots manufactured by (b) (4), and 24 months stability data from 6 supportive lots manufactured by (b) (4). Based on the satisfactory stability data provided and the statistical analysis in accordance with ICH Q1E, the sponsor's proposed shelf life of 18 months for the drug product is justified. The recommended storage conditions are presented in the labeling statements: "Unopened vials should be stored refrigerated (2°C to 8°C; 36°F to 46°F). Retain in original package to protect from light."

The stability data appears to provide adequate support for the proposed shelf-life of 18 months or expiration date and the labeling statements for the drug product storage conditions.

Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

The drug product is administered intravenously at 20/27 mg/m² (20 mg/m² in Cycle 1, escalating to 27 mg/m² in Cycle 2) over two (2) to ten (10) minutes, twice weekly on consecutive days for 3 weeks (Days 1,2, 8, 9,15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered one treatment cycle. The proposed indication is for the treatment of patients with relapsed and refractory multiple myeloma who has received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation for approval for NDA 202-714 is based on an acceptable CMC submission. This approval is pending on an acceptable recommendation from the Office of Compliance and the resolution of acceptable carton and container labels and package insert labeling.

III. Administrative

This NDA was submitted in electronic as a 505(b)(1) application. A Quality Overall Summary is included in the application.

A. Reviewer's Signature

See electronic signatures in DARRTS.

B. Endorsement Block

See electronic signatures in DARRTS.

C. CC Block

See electronic signatures in DARRTS.

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/s/

JOSEPHINE M JEE
05/25/2012

SARAH P MIKSINSKI
05/25/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Josephine Jee, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Josephine.Jee@fda.hhs.gov
Phone: (301)-796-1652
Fax: (301)-

FROM: FDA
Division of Pharmaceutical Analysis
James Allgire, Team Leader
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3813

Through: Benjamin J. Westenberger, Deputy Director
Phone: (314) 539-3869

SUBJECT: Methods Validation Report Summary

Application Number: NDA 202714

Name of Product: Carfilzomib for Injection

Applicant: Onyx Pharmaceuticals, Inc.

Applicant's Contact Person: Sheldon Mullins, Senior Director, Regulatory Affairs

Address: 249 E. Grand Avenue, South San Francisco, CA 94080

Telephone: 650-266-1033 Fax: 650-266-0491

Date Methods Validation Consult Request Form Received by DPA: 11/15/11

Date Methods Validation Package Received by DPA: 11/15/11

Date Samples Received by DPA: 12/21/11

Date Analytical Completed by DPA: 3/19/12

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments:

Cover memo and summary of results are attached.



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3897

Date: March 15, 2012
To: Josephine Jee, CMC Reviewer
Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis, (HFD-920)
From: Connie M. Ruzicka, Chemist (HFD-920)
Laura C. Mecker, Chemist (HFD-920)
Subject: Method Validation for NDA 202714
Carfilzomib Drug Substance and Carfilzomib for Injection Drug Product
Onyx Pharmaceuticals, Inc.

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. Determination of Purity, Identification and Assay of FP-101 (PR-171) and Impurities by HPLC (b) (4)
2. Determination of Identity, Assay and Impurities in Carfilzomib Drug Substance (DS) by HPLC (b) (4)
3. Determination of Identity, Assay, Uniformity of Dosage Units and Impurities in Carfilzomib for Injection DP by HPLC (b) (4)
4. Determination of Identity, Assay, Uniformity of Dosage Units and Impurities in Carfilzomib for Injection DP by HPLC (b) (4)
5. Determination of Identity of Carfilzomib for Injection Drug Product by PDA-UV HPLC (b) (4)

(b) (4)

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/s/

JAMES F ALLGIRE
03/21/2012

BENJAMIN J WESTENBERGER
03/21/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Josephine Jee, CMC Reviewer
William Mike Adams, CMC Reviewer
Houda Mahayni, Biopharmaceutics Reviewer
John Metcalf, Microbiology Reviewer
Janice Brown, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Josephine.Jee@fda.hhs.gov, William.Adams@fda.hhs.gov, Houda.Mahayni@fda.hhs.gov, and
Janice.brown@fda.hhs.gov
Phone: (301)-796-1652 Janice Brown

Fax.: (301)-796-2410

Through: Sarah Pope Miksinski, Chief Branch 2
Phone: (301)-796-1436
and
Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 202714

Name of Product: Carfilzomib for Injection

Applicant: Onyx Pharmaceuticals, Inc.

Applicant's Contact Person: Sheldon Mullins, Senior Director, Regulatory Affairs

Address: 249 E. Grand Avenue, South San Francisco, CA 94080

Telephone: (650) 266-1033 Fax: (650) 266-0491

Date NDA Received by CDER: **9/27/2011**

Submission Classification/Chemical Class: 0

Date of Amendment(s) containing the MVP:

Special Handling Required: Yes

DATE of Request: **November 10, 2011**

DEA Class: N/A

Requested Completion Date: **2/15/2012**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **7/27/2012**

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA # 202714
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1
Specifications/Methods for New Drug Substance(s)				3.2.S.4.1
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.1.
Supporting Data for Accuracy, Specificity, etc.				3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				
Other:				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
(b) (4)	Drug Substance - Assay	3.2.S.4.3	0	
	Drug Substance - Impurities	3.2.S.4.3	0	
	Drug Product Assay	3.2.P.5.3	0	
	Drug Product - Related Substances	3.2.P.5.3	0	
	Drug Product - Identity	3.2.P.5.3	0	

For a summary of the application, see Initial Quality Assessment in Dartrts by J. Brown.

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)

6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

JANICE T BROWN
11/10/2011

SARAH P MIKSINSKI
11/10/2011

JEANNIE C DAVID
11/15/2011
ONDQA Methods Validation Project Manager

**Initial Quality Assessment
Division of New Drug Quality Assessment I
Branch II**

OND Division: Division of Hematology Products
NDA: 202714
Applicant: Onyx Pharmaceuticals, Inc.
Stamp Date: 27-Sep-2001
PDUFA Date:
Proprietary (Brand) Name of Drug Product: Kyprolis (pending)
Established Name: Carfilzomib for Injection
Dosage Form(s): Lyophilized powder
Strength(s): 60 mg
Route of Administration: Intravenous
Proposed Indication(s): Treatment of patients with relapsed and refractory multiple myeloma who has received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent.
CMC Lead: Janice Brown, Branch II/DNDQA1/ONDQA
Chief, Branch II: Sarah Pope Miksinski/DNDQA1/ONDQA
Review team recommendation: Team review
 CMC reviewers: Josephine Jee and Mike Adams
 Biopharmaceutics reviewer: Houda Mahayni

	Yes	No
ONDQA Fileability:	X	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	X

CONSULTS/ CMC RELATED REVIEWS

Consult	Comment
ONDQA Biopharmaceutics	Assigned to Houda Mahayni.
CDRH	Not Applicable
EA	Categorical exclusion requested
EES	Inspection request was submitted on 11-Oct-2011
DMEPA	Labeling consult request will be sent as part of DHP request.
Methods Validation	See methods validation request in DARRTS
Microbiology	Assigned to John Metcalf who will review DMF's (b)(4) Requested a review of DMF on 16-Oct-2011
Pharm-Tox	Determined by primary reviewer. Requested a non-clinical reviewer to review the Captisol (sulfobutylether beta-cyclodextrin) safety studies submitted in DMF (b)(4). A LOA was provided by CyDex Pharmaceuticals, Inc.
Statistics	Request consult to review the data extrapolation to support the 18 month shelf life for the carfilzomib drug product from the 12 month data

SUMMARY

Carfilzomib for Injection is a new molecular entity indicated for the treatment of patients with relapsed and refractory multiple myeloma who has received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent. Carfilzomib is a tetrapeptide epoxyketone that is a selective, irreversible inhibitor of the chymotrypsin-like activity of the 20S proteasome. The mechanism of action of carfilzomib involves a nucleophilic attack of the γ -OH side chain of the N-terminal Thr residue on the epoxide carbonyl of carfilzomib followed by a second nucleophilic attack by the free $-\text{NH}_3$ group of Thr on the epoxide ring to form an irreversible, dual covalent morpholino adduct with the proteasome active site.

Carfilzomib for Injection is supplied as an individually cartoned single-use vial containing a deliverable dose of 60 mg of carfilzomib as a white to off white lyophilized cake or powder. Each vial is reconstituted with 29 mL Sterile Water for Injection, USP (not supplied); other diluents such as 0.9% Sodium Chloride Injection, USP are not allowed. The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL. After reconstitution, the drug product is administered intravenously (IV) over 2 to 10 minutes, twice weekly on consecutive days for 3 weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered 1 treatment cycle.

Carfilzomib for injection was developed under the Fast Track program and has been granted orphan drug designation.

(b) (4)

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/s/

JANICE T BROWN
11/10/2011

SARAH P MIKSINSKI
11/10/2011

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number: 202714 **Supplement Number and Type:** Original NDA **Established/Proper Name:** Carfilzomib for Injection

Applicant: Onyx Pharmaceuticals, Inc. **Letter Date:** 26-Sep-2011 **Stamp Date:** 27-Sep-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	PARAMETER	YES	NO	COMMENT
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 		X	Facility information found under manufacturer's in the M3 module.

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

B. FACILITIES*				
	PARAMETER	YES	NO	COMMENT
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 		X	See #7
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 		X	See #7
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	
E. drug product (dp)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Expiry will be determined by primary reviewers in ONDQA
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			Defer to micro reviewer

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N.A.
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

{See appended electronic signature page}

Janice Brown
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Date: 10-Nov-2011

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch 2
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Date: 10-Nov-2011

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/s/

JANICE T BROWN
11/10/2011

SARAH P MIKSINSKI
11/10/2011

**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 202714/000	Sponsor:	ONYX PHARMS
Reg. Code:	161		249 EAST GRAND AVE
Facility ID:	1		SOUTH SAN FRANCISCO, CA 94080
Receipt Date:	27-SEP-2011	Brand Name:	Carfilzomib
DUFA Date:	27-JUL-2012	Estab. Name:	
Completion Goal:		Generic Name:	
District Goal:	27-JAN-2012	Product Number; Dosage Form; Ingredient; Strengths	

001; POWDER, FOR INJECTION SOLUTION, LYOPHILIZED;
CARFILZOMIB; 60MG

DA Contacts:	S. GOLDIE	Project Manager	(HFD-800)	3017962055
	J. JEE	Review Chemist		3017961375
	J. BROWN	Team Leader		3017961652

Overall Recommendation:	ACCEPTABLE	on 24-MAY-2012	by M. STOCK	(HFD-320)	3017964753
	PENDING	on 11-OCT-2011	by EES_PROD		
	PENDING	on 11-OCT-2011	by EES_PROD		

Establishment: **CFN:** **FEI:** (b) (4)
 (b) (4)

MF No: **AADA:**

Capabilities: DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Next Milestone: OC RECOMMENDATION

Milestone Date: 10-JAN-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA ORDER # [REDACTED]
**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

MF No: [REDACTED] (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER

Profile: [REDACTED] (b) (4) **OAI Status:** NONE

Next Milestone: OC RECOMMENDATION

Milestone Date: 18-OCT-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

MF No: [REDACTED] (b) (4) **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: SMALL VOLUME PARENTERAL, LYOPHILIZED **OAI Status:** NONE

Next Milestone: OC RECOMMENDATION

Milestone Date: 04-MAY-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

MF No: [REDACTED] (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Next Milestone: OC RECOMMENDATION

Milestone Date: 04-JAN-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA OVERVIEW
**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

MF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

1st Milestone: OC RECOMMENDATION

Milestone Date: 13-OCT-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

MF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

1st Milestone: OC RECOMMENDATION

Milestone Date: 18-OCT-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

MF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER

Profile: (b) (4) **OAI Status:** NONE

1st Milestone: OC RECOMMENDATION

Milestone Date: 18-OCT-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER LEO
**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

MF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Next Milestone: OC RECOMMENDATION

Milestone Date: 13-OCT-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

MF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Profile: SMALL VOLUME PARENTERAL, LYOPHILIZED **OAI Status:** NONE

Next Milestone: OC RECOMMENDATION

Milestone Date: 26-OCT-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

MF No: AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Next Milestone: OC RECOMMENDATION

Milestone Date: 28-DEC-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA OVERVIEW
**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

MF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-MAY-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION
