CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207155Orig1s000
207155Orig2s000

CHEMISTRY REVIEW(S)

Overall Manufacturing Inspection Recommendation

Edit Custom Form

Custom Form
Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation
Approve

Navigation Links

Form Link
http://panorama.fda.gov/task/view?ID=564ecdd4002b7f4263a86897fb677197&activeTab=content-dashboard__5418eab10003b6cd5f0c5f929c4fa823

Assigned To

OPF Reviewer

Donald Obenhuber

IM - OPF Reviewer

Edit Assignment

This was done on
Dec 22, 2015
(79 days ago)

Status
Complete

Requested by
DARRTS Integration

This task is waiting on
Facilities

Last Update
Jan 25, 2016

Submitted On
Nov 20, 2015

Reference Number
6152159

My Work Projects Reporting Requests Timesheet

NDA 207155-Orig1-New - Proprietary Name - Form 3674 - User Fee/NDA ... » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Edit Task | Task Actions

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Overview | **Facility Inspection - Overall Application Recommendation**

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Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation
Withhold

Navigation Links

Form Link
http://panorama.fda.gov/task/view?ID=549b9bcf000028dfbe06118ea668016b8activeTab=content-dashboard__5418eab10003b6cd5f0c5f929c4fa823

Assigned To

OPF Reviewer

Donald Obenhuber

IM - OPF Reviewer

Edit Assignment

This was done on
Oct 15, 2015
(147 days ago)

Status
Complete

Requested by

DARRTS Migration

This task is waiting on
2 Tasks

Last Update	Submitted On
Oct 16, 2015	Dec 25, 2014

Reference Number
3661857

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

/s/

ROBYN S JORDON
03/21/2016

Recommendation: NDA: Approval

NDA 207155
Review #2

Drug Name/Dosage Form	Evomela (melphalan HCl) for Injection
Strength	50 mg (free base) vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Spectrum Pharmaceuticals, Inc.
US agent, if applicable	Not Applicable

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Re-Submission	11/9/2015	CMC

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	OPQ/ONDP
Drug Product	Olen Stephens	OPQ/ONDP/DNDPI/NDPBII
Process	Steve Rhieu	OPQ/OLDP/DPMA1/BII
Microbiology	Vinayak Pawar	OPQ/OPF
Facility	Donald Obenhuber	OPQ/OPF/DIA
Biopharmaceutics	Maziar Kakhi	OPQ/ONDP/DB/BB1
Regulatory Process Manager	Rabiya Laiq	OPQ/OPRO/B1
Application Technical Lead	Olen Stephens	OPQ/ONDP/DNDPI/NDPBII
Environmental Assessment (EA)	Amit Mitra	OPQ/ONDP/DNDPI/NDPBII

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	05-Feb-2015	LoA provided DS mfg., testing and packaging.
	Type IV			Adequate	22-Jul-2015	LoA provided
	Type III			Not reviewed		Not proposed for commercial use
	Type III			Adequate	31-MAR-2014	See review by Dr. E. Jao, dated 31-MAR-2014
	Type V			Adequate	25-AUG-2015	See review by Dr. L.S. Shelton, dated 25-AUG-2015
	Type V			Adequate	11-SEP-2006	Dr. D.R.Lu, and Review by toxicologist BRENDA J GEHRKE, Ph.D of NDA 207155
	Type V			Adequate refer to comments	30-Oct-14	The product for NDA 207155 (b) (4) (b) (4) review of the DMF was not necessary

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Type A meeting minutes	NDA 207-155	Preparation for resubmission

2. CONSULTS: None

Executive Summary

Summary of Approvable recommendation:

In the original NDA submission, the NDA submission referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support the NDA and a nine

item deficiency letter was sent to the DMF holder on September 10, 2015. The drug product manufacturing facility, [redacted] received an overall not approval recommendation.

In the current resubmission of NDA 207-155, DMF [redacted] and [redacted] have been removed from the application. The only updates in Module 3 refer to the [redacted] drug product manufacturing site. There are no changes to the manufacturing process or specifications. A new reference is made to [redacted] Type V DMF [redacted] for [redacted] facility and processing information, but this DMF was not reviewed as the product for this NDA will use [redacted] described in the DMF. Refer to the microbiology review, which explains there is no additional information in the DMF that would change the status of the evaluation for DMF [redacted].

Action letter language, related to critical issues such as expiration date:
A shelf life of 36 months is granted for Evomela (melphalan HCl) for injection, when stored at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F), protected from light.

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

Spectrum will provide a toxicological risk assessment based on [redacted] for this compound to demonstrate the safety of any [redacted] in the final drug product. This report will be will be included in first NDA annual report. This is not a post-marketing commitment.

I. Summary of Quality Assessments

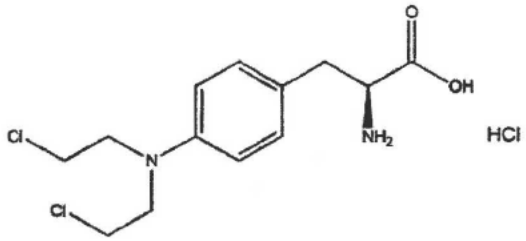
A. Drug Substance [melphalan] Quality Summary

The drug substance is melphalan HCl, a bifunctional DNA alkylating agent. Melphalan HCl is an L-phenylalanine derivative of nitrogen mustard [redacted]. The cytotoxicity of melphalan is related to the extent of its interstrand cross-linking with DNA, likely by binding at the N7 position of guanine. Like other bifunctional alkylating agents, melphalan is active against both resting and rapidly dividing tumor cells.

The applicant cross-referenced the CMC information for Melphalan HCl to DMF's [redacted] DMF [redacted] was reviewed and found adequate to support NDA 207155 (see review by Bapu Gaddam on 05-Feb-2015). DMF [redacted] was reviewed and found inadequate in the first review cycle and has been removed from the NDA in this resubmission.

1. Chemical Name or IUPAC Name/Structure

The chemical name of melphalan HCl is [redacted] (b) (4) {4-[bis(2-chloroethyl)amino]phenyl}propanoic acid and has the following structure.



Properties/CQAs Relevant to Drug Product Quality

Melphalan HCl [redacted] (b) (4)
is a white to off-white powder and practically insoluble in water, [redacted] (b) (4) and freely soluble in 1 N HCl and methanol. [redacted] (b) (4)

[redacted] (b) (4)

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Application Technical Lead	Olen Stephens	Approval

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Evomela
Non Proprietary Name of the Drug Product	Melphalan hydrochloride for injection
Non Proprietary Name of the Drug Substance	Melphalan hydrochloride
Proposed Indication(s) including Intended Patient Population	1) Use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma. 2) The palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate
Duration of Treatment	For Conditioning Treatment: 2 days For Palliative Treatment: every 4 weeks until disease progression or unacceptable toxicity
Maximum Daily Dose	For Conditioning Treatment: 100 mg/m^2/day For Palliative Treatment: 16 mg/m^2
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

The Applicant's resubmission does not contain any new Biopharmaceutics information. Therefore the Division of Biopharmaceutics defers the approvability recommendation to the other review disciplines.

E. Novel Approaches: None

F. **Any Special Product Quality Labeling Recommendations:** Store in original carton.

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature: Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2016.01.25 19:04:51 -05'00'

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Previous inspection of this contract manufacturer conducted (b) (4) was classified NAI

(b) (4)

Facility approved: Approved based on District Recommendation.

(b) (4)

cGMP inspection of (b) (4) was classified NAI and covered the Quality and Laboratory systems.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Based on a review of the application and inspectional documents, there are no significant, outstanding manufacturing risks that prevent approval of this application

Donald C. Obenhuber, Ph.D., CDER/OPQ/OPF/DIA.

Supervisor Comments and Concurrence:
I concur with the facility reviewer's assessment

Zhihao Peter Qiu, Ph.D.
Branch Chief, OPQ/OPF/DIA/Branch 1

ASSESSMENT OF THE BIOPHARMACEUTICS

1. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

N/A. No biopharmaceutics data are included in the resubmission of this NDA.

2. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

N/A. No biopharmaceutics data are included in the resubmission of this NDA.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

The Division of Biopharmaceutics reviewed and recommended approval of the original NDA submission. The Applicant's resubmission does not contain any new Biopharmaceutics information. Therefore the Division of Biopharmaceutics defers the approvability recommendation of this resubmission to the other relevant review disciplines.

January 5, 2016.

Maziar Kakhi, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
ONDP/OPQ

Secondary Review Comments and Concurrence:

I concur with Dr. Kakhi's assessment and recommendation.

January 5, 2016.

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

3. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

Reviewer's Assessment: Yes. No change from the approved original submission.

2.3.P.7 Container/Closure System

4. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: Provided Method Validation Report No. 912383, dated August 2015 for Container Closure Integrity by Dye Immersion of Evomela (Melphalan HCl) for Injection.

Reviewer's Assessment: No change in the Container Closure System from the approved original submission. Method Validation Report 912383, dated August 2015 indicates that the Container Closure Integrity for Evomela was confirmed to be integral by the dye immersion Test. (b) (4)

vials passed the test.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

5. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: N/A

Reviewer's Assessment: There is no evidence of materials used from biological origin or derived from biological sources for the drug product.

6. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

Drug Product: Evomela [Captisol® enabled Melphalan HCl for Injection)

Resubmission Date: November 7, 2015 **Date Assigned:** December 22, 2015

Applicant: Spectrum Pharmaceuticals, Henderson, NY 89052

Representative: Anil Hiteshi, RAC, Vice Pres., Gobal RA, Tel No: 949-743-9228

Manufacturing Site: (b) (4) FEI (b) (4)

Dosage Form, Route of Administration & Strength/Potency: Sterile lyophilized (b) (4) for intravenous administration, 50 mg/vial.

Drug Product Composition: No change from the approved original submission.

Microbiological Attributes (Container Closure Integrity): See Section 2.3.P.7 above.

P.3.3. Description of Manufacturing Process:
Manufacturing Process remains the same as was used for exhibit/stability batches manufactured by (b) (4) for clinical studies [Three batches in 2009 and one in 2012]. The sponsor will (b) (4)

There are no changes to the approved (b) (4) (b) (4) from the original submission.

(b) (4)

assures that the manufacturing process for Evomela will be validated prior to commercialization and that process validation will be executed according to an approved validation protocol at the full commercial scale.

P.5 Control of Drug Product:
Specifications: No change from the approved original submission.
Analytical Procedures: No change from the approved original submission.

P.8 Stability:
Currently available data from (b) (4) is adequate from microbiology product quality standpoint. The Post-Approval Stability commitment remains unchanged.

END

Vinayak B. Pawar, Ph.D., Senior Review Microbiologist
January 7, 2016

Secondary Review Comments and Concurrence:

John Arigo, Ph.D., Branch Chief (Acting)
1/7/2015

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The applicant's claim of categorical exclusion from the requirement to submit an Environmental Assessment or Environmental Impact Statement has not changed since the original NDA submission. Refer to CMC Review #1.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

Refer to the labeling review in CMC Review #1.

II. List of Deficiencies To Be Communicated

None.

III. Attachments

A. Lifecycle Knowledge Management
Refer to the final risk assessment in CMC Review #1

QUALITY ASSESSMENT

Recommendation: Complete Response

NDA 207155
Review #1
September 18, 2015

Drug Name/Dosage Form	Evomela (melphalan HCl) for Injection
Strength	50 mg (free base) vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Spectrum Pharmaceuticals, Inc.
US agent, if applicable	Not Applicable

SUBMISSION(S) REVIEWED eCTD no. (SDN #), SD category	**Document Date**
000 (1), Original Submission	12/23/2014
0005 (6), Multiple Submissions	03/17/2015
0008 (9), Labeling	05/08/2015
0009 (10), Multiple Submissions	07/27/2015
0010 (11), Multiple Submissions	08/25/2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	OPQ/ONDP
Drug Product	Amit Mitra	OPQ/ONDP/DNDPI/NDPBII
Process	Lin Qi	OPQ/OLDP/DPMA1/BII
Microbiology	Vinayak Pawar	OPQ/OPF
Facility	Donald Obenhuber	OPQ/OPF/DIA
Biopharmaceutics	Maziar Kakhi	OPQ/ONDP/DB/BB1
Business Process Manager	Rabiya Laiq	OPQ/OPRO/B1
Application Technical Lead	Janice Brown	OPQ/ONDP/DNDPI/NDPBII
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	Amit Mitra	OPQ/ONDP/DNDPI/NDPBII

Table of Contents

Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION:** 505(b)(2)

2. **RELATED/SUPPORTING DOCUMENTS:**

   A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	05-Feb-2015	LoA provided DS mfg., testing and packaging.
	Type II			Inadequate	09-Sep-2015	LoA provided DS mfg., testing and packaging.
	Type IV			Adequate	22-Jul-2015	LoA provided
	Type V			Adequate	17-SEP-2015	See Microbiology review
	Type III			Not reviewed		Not proposed for commercial use
	Type III			Adequate	31-MAR-2014	See review by Dr. E. Jao, dated 31-MAR-2014
	Type III			(b) (4)	23-MAY-2011	(b) (4) reviewed earlier. As an example, review by Dr. J. M. Jee, dated 23-MAY-2011
	Type V			Adequate	25-AUG-2015	See review by Dr. L.S. Shelton, dated 25-AUG-2015
	Type V			Adequate	11-SEP-2006	Dr. D.R.Lu, and Review by toxicologist BRENDA J GEHRKE, Ph.D of NDA 207155

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
000 (1)	NDA 20207	Listed drug: ALKERAN (melphalan hydrochloride) for Injection

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Nonclinical	Conducted separate review	Approve	24-AUG-2014	Brenda Gehrke, Ph.D.
CDRH				
Clinical				
Other				

Executive Summary

I. Recommendations

A COMPLETE RESPONSE is recommended for NDA 207155 from a product quality standpoint.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues

- The NDA submission referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support your submission and a nine item deficiency letter was sent to the DMF holder on September 10, 2015.

- The drug product manufacturing facility, (b) (4) received an overall not approval recommendation.

2. Action letter language, related to critical issues such as expiration date

- Your application referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on September 10, 2015. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

- During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

- Submit a toxicological risk assessment (b) (4) leachable (b) (4) (Note: This issue was going to be a post-marketing agreement; however, since this is a Complete Response action, this item will be included in the letter.)

3. Benefit/Risk Considerations

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

II. Summary of Quality Assessments

A. Drug Substance [melphalan] Quality Summary

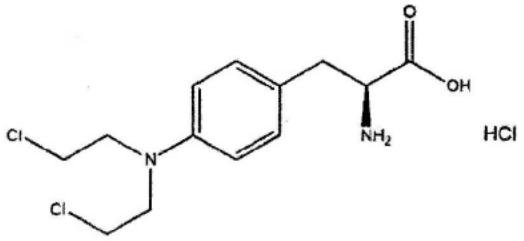
Background

The drug substance is melphalan HCl, a bifunctional DNA alkylating agent. Melphalan HCl is an L-phenylalanine derivative of nitrogen mustard (b) (4)). The cytotoxicity of melphalan is related to the extent of its interstrand cross-linking with DNA, likely by binding at the N7 position of guanine. Like other bifunctional alkylating agents, melphalan is active against both resting and rapidly dividing tumor cells.

The applicant cross-referenced the CMC information for Melphalan HCl to DMF's (b) (4) and (b) (4) DMF (b) (4) was reviewed and found adequate to support NDA 207155 (see review by Bapu Gaddam on 05-Feb-2015). DMF (b) (4) was reviewed and found inadequate (see review by Ying Lin on 09-Sep-2015 and GDUFA DMF Complete Response letter on 10-Sep-2015).

1. Chemical Name or IUPAC Name/Structure

The chemical name of melphalan HCl is (b) (4) {4-[bis(2-chloroethyl)amino]phenyl}propanoic acid and has the following structure.



Properties/CQAs Relevant to Drug Product Quality

Melphalan HCl (b) (4) is a white to off-white powder and practically insoluble in water, (b) (4) and freely soluble in 1 N HCl and methanol. (b) (4)

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standpoint because of an initial OAI recommendation issued for the 5/21-29/2015 inspection of the (b) (4) manufacturing site.
Don Obenhuber, Facility Reviewer
DIA/OPF/OPQ

Supervisor Comments and Concurrence:
I concur with the facility reviewer's recommendation.

Zhihao Peter Qiu
Branch Chief, DIA/OPF/OPQ

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF BIOPHARMACEUTICS

1. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

NDA 207255 is a 505(b)(2) submission for Captisol-enabled Melphalan ('CE-Melphalan') HCl for Injection, 50 mg free base/vial. The drug product is proposed as a lyophilized powder to be reconstituted with 8.6 mL of 0.9% Sodium Chloride Injection, USP to make a 50 mg/10 mL nominal concentration of Melphalan. Prior to intravenous administration (infusion), (b) (4) of the reconstituted drug product (5 mg/mL) is admixed in (b) (4) 0.9% Sodium Chloride Injection, USP to a give final concentration of 0.45 mg/mL of Melphalan. The CE-Melphalan admixture is then infused over 30 minutes via an injection port or central venous catheter. Given the route of administration, the proposed drug product's Specifications table[1] does not include an *in vitro* release test.

Reviewer's Comments: The drug product is administered in the dissolved state, therefore an *in vitro* release test is not relevant.

Background

The Biopharmaceutics review of this NDA is primarily focused on the evaluation of the bioequivalence (BE) study (CDX-353-001) comparing CE-Melphalan (proposed drug product) and Alkeran for Injection (listed drug product, NDA 20207, approved

[1] \\cdsesub1\evsprod\nda207155\0000\m3\32-body-data\32p-drug-prod\ce-melphalan-hcl-powder-all-01\32p5-contr-drug-prod\32p51-spec\p51-specs.pdf

November 18, 1992) and bridging of the 'to-be-marketed' formulation to the drug product formulations used in the submitted clinical studies.

The Applicant states that Melphalan free base is marginally soluble in water, with a measured intrinsic aqueous solubility of 3.11 mg/mL according to the cited literature reference[2] in section 3.2.P.2 (Pharmaceutical Development). The Applicant is proposing CE-Melphalan because it enables the use of an aqueous diluent (normal saline) to reconstitute the (b) (4) drug product, instead of the propylene glycol (b) (4) (b) (4) diluent required for the reconstitution of Alkeran. The Applicant states in section 2.5 (Clinical Overview) that propylene glycol is believed to contribute to some of the side effects of treatment particularly at high doses, which can include unconsciousness, lactic acidosis, hyperosmolality, arrhythmias, and cardiac arrest. The Applicant also asserts that complexation with cyclodextrins (such as Captisol) provides for greater stability in solution as compared with (b) (4) Alkeran, resulting in an increase in the preparation/use time and/or infusion time by at least five-fold compared to the immediate use requirement (up to 60 minutes) for the listed drug.

Proposed Indications for CE-Melphalan

The listed drug is indicated for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate. The usual IV dose is 16 mg/m^{2}at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals. In addition to this indication, the Applicant also proposes CE-Melphalan HCl for use as a high-dose conditioning treatment (100 mg/m^2/day) prior to hematopoietic autologous stem cell transplantation (ASCT) in patients with multiple myeloma as a 30 minute IV infusion for 2 consecutive days (Day -3 and Day -2) prior to ASCT (Day 0).

It should be noted that although Alkeran for Injection is not indicated for high-dose conditioning treatment prior to ASCT (i.e. per FDA approval), it has been routinely used off-label in clinical practice for a number of years.

Assessment of the Comparative Bioequivalence Study CDX-353-001[3]

The Applicant has submitted a report pertaining to clinical study CDX-353-001 representing a comparative bioequivalence (BE) study to support NDA 207155. This represents a phase IIa, single-center, open-label, randomized, comparative, cross-over study of CE-Melphalan HCl for Injection (test formulation – proposed drug product) and Alkeran for Injection (reference formulation – listed drug product) for myeloablative conditioning in patients who had symptomatic multiple myeloma and qualified for ASCT.

[2] Ma et al. J. Pharm. Sci. 2000:89(2), 275-287.
[3] The report pertaining to clinical study CDX-353-001 dates back to August 29, 2012 and was submitted verbatim on October 28, 2013 under IND 104925. The Office of Clinical Pharmacology performed a summarized overview of this clinical study on January 6, 2014.

Overall Study Design and Plan

There were three distinct evaluation periods in this trial:

- The pretreatment period (day -30 to day -3) for the collection and recording of baseline assessments.
- The study period, during which patients were to be randomized to receive 100 mg/m^2 of either CE-Melphalan HCl for Injection or Alkeran for Injection on day -3 and the alternate drug product on day -2. Blood samples for pharmacokinetic evaluation were to be withdrawn through either an indwelling intravenous cannula or a central venous catheter each day of Melphalan dosing (day -3 and day -2). Following 1 day of rest after the myeloablative conditioning (day -1), patients were to receive an autologous graft (day 0).
- The follow-up period (day +1 to date of engraftment[4]) in which patients were to return for daily laboratory tests (basic chemistry and hematology panels) and be evaluated weekly by their physician until the date of engraftment, with the final end-of-study evaluation occurring up to 7 days after the date of engraftment.

Study Patients

A total of 40 patients were screened and 24 patients enrolled; all 24 patients received both formulations of Melphalan (Alkeran for injection and CE-Melphalan HCl for Injection), and no patients discontinued prematurely in this study. It should be noted that the bioequivalence study drug product batch (A48292A[5]) was manufactured by (b) (4) in April 2009[6] and is proposed to have a shelf-life of 36 months according to section 3.2.P.8.1 (Stability Summary and Conclusion). The first patient was enrolled on February 4, 2010, and the last patient completed the study on June 8, 2011.

Table 1 below summarizes the dose and duration of study drug by treatment group.

[4] Engraftment was defined as absolute neutrophil count (ANC) >0.5 × 109/L for 3 consecutive daily assessments. Date of engraftment was the first day the ANC >0.5 × 109/L.
[5] Listing of patients and specific batches administered can be found at: \\cdsesub1\evsprod\nda207155\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\cdx-353-001\cdx353001--list-patients-with-batches.pdf
[6] Refer to Table 3.2.P.5-1: \\cdsesub1\evsprod\nda207155\0000\m3\32-body-data\32p-drug-prod\ce-melphalan-hcl-powder-all-01\32p5-contr-drug-prod\32p54-batch-analys\p54-batch-ana.pdf

Table 1: Summary of Exposure to Study Drug

Parameter	Mean (SD)	
	Melphalan HCl (PG-Free) (N = 24)	Alkeran (N = 24)
Total Dose (mg)	185.9 (25.71)	185.9 (25.71)
Total Dose (mg/m^2)	100 (0.0)	100 (0.0)
Duration of Infusion (min)	32.1 (3.11)	32.6 (4.12)

PG = Propylene glycol.
SD = Standard deviation.
Data Source: *Table 14.3.1*.

Based on the dose administered, all patients received a 100 mg/m^2 dose according to their body surface area (BSA), which was calculated based on either actual body weight or ideal body weight if the actual body weight was >130% of the ideal body weight according to protocol specifications. Approximately one-half of the patients were dosed based on a BSA that was determined from their ideal body weight rather than their actual body weight.

Reviewer's Comments: In order to confirm the results of the BE analysis, this Reviewer performed the calculations taking into consideration the subject-specific dose amount (mg) and the duration of infusion, as detailed in Listing 16.2.5.1[7].

Randomization Scheme and Demographics

The random number generator in SAS Version 9.2 was used in two phases to assign subjects to a treatment sequence. The first phase was used to assign treatment order for the first five study subjects. After these subjects had completed the study and approval was given to proceed, the SAS random number generator was used again to assign treatment order for Subjects 06-24. The randomization table is listed in Appendix 16.1.7[8].

The study population consisted of 13 males (54%) and 11 females (46%). The majority of The patients (79%) were white, and 17% and 4% of patients were black and Asian, respectively. The mean (SD) age was 57.1 (4.74) years and the minimum and maximum age of study patients was 48 and 65 years, respectively. The mean (SD) weight and height of study patients was 87.9 (25.5) kg and 168 (11.0) cm, respectively. All enrolled patients had been diagnosed with either Stage II (37.5%) or Stage III (62.5%) multiple myeloma. The mean (SD) number of years since initial diagnosis was 1.6 (1.85) years.

Adverse Events

[7] \\cdsesub1\evsprod\nda207155\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\cdx-353-001\cdx353001--comply-drug-concentration.pdf.
[8] \\cdsesub1\evsprod\nda207155\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\cdx-353-001\cdx353001--randomisation-scheme.pdf.

No patients died during this study. No patients experienced an adverse event that led to study drug discontinuation. Table 2 summarizes the breakdown amongst patients by adverse event classification.

Table 2: Overall Summary of Adverse Events

Type of Adverse Event	n (%) of Patients Total (N = 24)
Patients With at Least 1 TEAE	24 (100%)
Patients With at Least 1 Treatment-Related TEAE	24 (100%)
Patients With at Least 1 Grade 3 to 4 TEAE	17 (71%)
Patients With at Least 1 Grade 3 to 4 Treatment-Related TEAE	16 (67%)
Patients With at Least 1 Serious TEAE	7 (29%)
Patients With at Least 1 Serious Treatment-Related TEAE	6 (25%)
Patients With a TEAE Leading to Discontinuation of Study Drug	0 (0%)

n = Number of patients with adverse events.
N = Number of patients studied.
TEAE = Treatment-emergent adverse event.
Data Source: *Table 14.3.2, Table 14.3.4, Table 14.3.6, Listing 16.2.7.1, Listing 16.2.7.4.*

Protocol Deviations

Table 3 below presents a summary of the protocol deviations. The table lists violations, deviations and exceptions, all of which are defined on page 72 of the clinical study report[9]. According to the Applicant's definitions, no protocol violations occurred during the study and thus, did not result in any patients being excluded from the pharmacokinetic, safety, or efficacy analyses.

[9] \\cdsesub1\evsprod\nda207155\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\cdx-353-001\cdx353001--study-report-body.pdf.

Table 3: Summary of Important Protocol Deviations

Category	Number of Violations	Number of Deviations	Number of Exceptions	Total	Comments
Exclusion Criteria	0	1	1	2	Patient 015 was enrolled and did not meet Exclusion Criterion 8 (no prior malignancies). This patient had a history of early-stage breast cancer followed by lumpectomy and radiation in (b) (6). This patient was cleared to enroll in the study per the Medical Monitor. Patient 022 did not meet Exclusion Criterion 13. This patient received anticancer therapy within 21 days of transplant.
Duration of Infusion	0	9	0	9	Four patients had infusion duration deviations >3 minutes: Patient 002 had an infusion deviation of 10 minutes; Patient 005 had infusion deviations of 3 and 8 minutes; Patient 007 had an infusion deviation of 12 minutes; and Patient 008 had an infusion deviation of ending 9 minutes early.
Incorrect Alkeran Formulation	1	0	0	1	Generic melphalan administered instead of Alkeran in Patient 002.
Pharmacokinetic Sampling from Central Venous Catheter	0	0	3	3	Protocol amendment changed the sampling procedures for pharmacokinetic sampling to allow sampling from central luman catheter.
Data Source: *Listing 16.2.2.1*, *Listing 16.2.2.2*, and *Listing 16.2.4.2*					

Reviewer's Comments: Patient/Subject 001-002 was excluded from the Reviewer's bioequivalence analysis because the administration of the generic form of Melphalan is not considered acceptable to support the conclusions of the study.

An inspectional report of the clinical site (located at 2330 Shawnee Mission Pkwy, Westwood, KS 66205-2005) and dated July 2, 2015 by field investigator Lori Gioia found:

Subjects 001-020 and 001-010 met exclusion criteria outlined in section 6.2 of the protocol and should not have been included in the study. Subject 001-020 was concurrently enrolled in another clinical trial (exclusion criteria 14) and subject 001-010 was on an anti-cancer drug (Cytoxan) within 21 days of their stem cell transplant (exclusion criteria 13).

As a result of this observation by the field inspector, subjects 001-020 and 001-010 were also excluded from the BE analysis reported in this review.

Bioequivalence Analysis

Blood samples were collected in blood collection tubes containing K_2EDTA as an anticoagulant. Immediately following collection, the blood specimen put on ice and centrifuged within 20 minutes of the collection time. All plasma samples were stored frozen (less than approximately -20 °C) until they were shipped to the analytical facility.

The plasma melphalan concentration-time plots for all subjects is shown in Figure 1 for both treatments.

Figure 1: Individual melphalan plasma concentration-time profiles sorted by treatment.

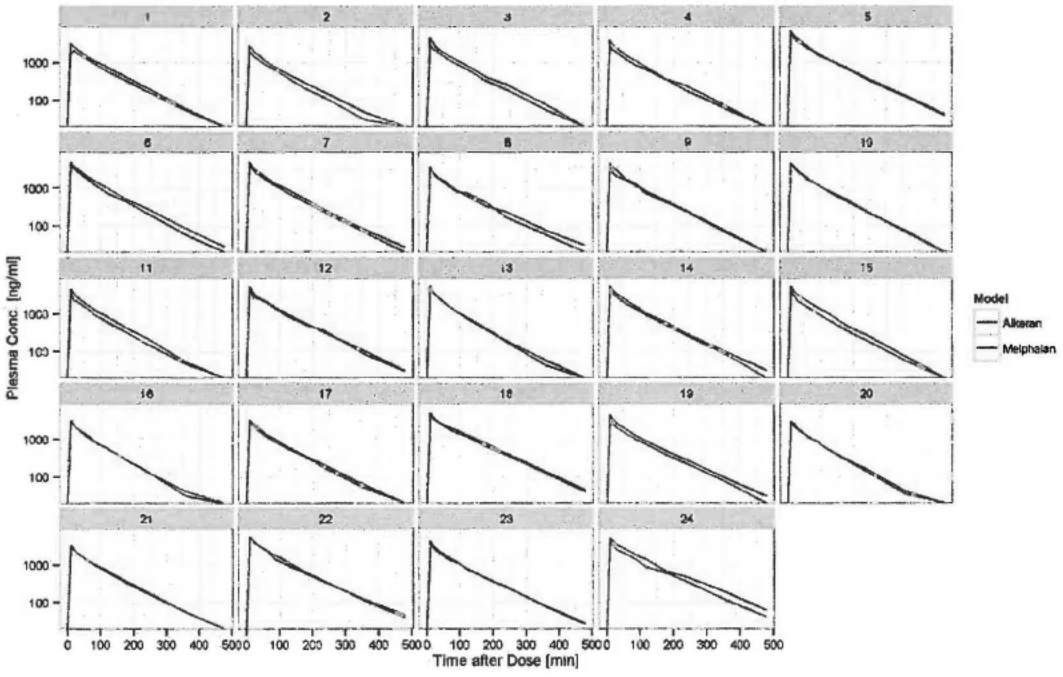
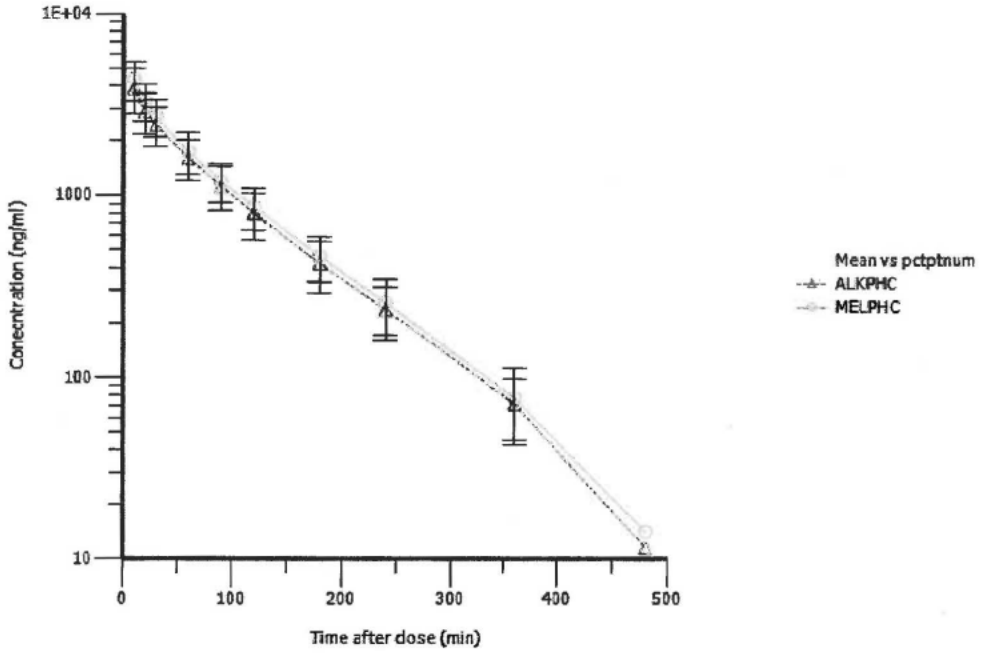


Figure 2 shows the averaged plasma concentration-time curves and error bars (expressed as standard deviation).

Figure 2: Average plasma concentration-time profile sorted by treatment



Reviewer's Comments: A bioequivalence analysis was performed using the study data set located at: Application 207155 - Sequence 0000 - CDX-353-001 PP. **Phoenix/WinNonlin (ver. 6.4.0.768) was used for the evaluation and the results are presented in Table 4.**

Table 4: Summary of bioequivalence analysis of PK parameters after IV administration of CE-Melphalan HCl and Alkeran for Injection

Parameter	All Patients		Without Patients #2, 10 & 20	
	Estimate	90% Confidence Interval	Estimate	90% Confidence Interval
C_{max}	112	105.58 - 118.8	111.1	104.35 - 118.25
AUC_{0-t}	110.9	105.13 - 116.98	110.2	104.01 - 116.67
$AUC_{0-\infty}$	110.77	105.08 - 116.78	110	103.93 - 116.39

Even with the exclusion of patients 2, 10 and 20 from the data pool, the 90% confidence intervals indicate that the test (CE-Melphalan HCl) and reference (Alkeran) drug products are bioequivalent.

Assessment of the Bioanalytical Study Report BCYDE0900P1

Report BCYDE0900P1[10] describes the analytical method using LC-MS/MS for the quantitation of Melphalan in K_2EDTA human plasma in conjunction with the comparative BE study CDX-353-001. The method involved the extraction of Melphalan and the added Melphalan-d8 (IS), using protein precipitation. This extract was then subjected to reverse phase high performance liquid chromatography on a C18 column and detection of the analytes by tandem mass spectroscopy using the Sciex API3000 LC-MS/MS.

Melphalan is reported to be stable in K_2EDTA human plasma for at least 603 days, when stored at -70°C. Human plasma samples were collected by (b) (4). A total of 528 original samples were received between (b) (4). They were delivered to (b) (4) by courier on dry ice. The samples were stored at or below the nominal temperature -70 °C at (b) (4). A total of 528 samples were analyzed at (b) (4), between (b) (4). The maximum period of storage stability duration for the samples of this study was 172 days.

Assessment of the Bioanalytical Method Report VCYDE9900P1

Bioanalytical method report VCYDE9900P1[11] details stability studies for Melphalan in human K_2EDTA plasma during blood collection and processing. Data are provided in this report to demonstrate that:

- Melphalan is stable during blood collection processing for up to one hour stored in an ice-water bath in polyethylene terephthalate containers.
- Hemolytic and lipemic plasma do not affect the accuracy or precision of the data.
- The analyte has been demonstrated to be stable in human K_2EDTA plasma over a period of 603 days when frozen at -70 °C in polypropylene tubes.
- The Melphalan primary solution and spiking solutions are stable over a period of 231 days and 141 days, respectively, when stored at -20 °C in glass and polypropylene containers, respectively.
- The calibration curve was constructed with eight different, non-zero standard concentrations ranging from 25.0 to 1200 ng/mL for original curve and 25.0 to 11200 ng/mL for extended curve in human plasma (K_2EDTA).
- The presence of Captisol does not affect the analysis of Melphalan in human plasma.
- Sensitivity: The LLOQ for this method was determined to be 25.0 ng/mL.
- Inter-assay (between batch) precision & accuracy and intra-assay (within batch) precision & accuracy were assessed in three batches by analyzing six (6)

[10] \\cdsesub1\evsprod\nda207155\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\ce-melphalan-ana-mths\m5314-bcyde0900p1-human-plasma.pdf.
[11] \\cdsesub1\evsprod\nda207155\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\ce-melphalan-ana-mths\m5314-vcyde9900p1-mel-assy-val-human-a3.pdf

replicates each of QCs fortified at four separate concentrations (LLOQ, low, mid, and high).

- The analyte was proven stable in human plasma over 3 cycles of freeze (at -70 °C) and thaw (ice-water bath).

Reviewer's Comments:
The Applicant has adequately demonstrated that the validation results presented in the bioanalytical study reports support a robust and reliable method for the measurement of Melphalan in human plasma with K_2EDTA as anticoagulant using LC/MS/MS in the concentration range of 25.0 - 11200 ng/mL.

Status of Inspections pertaining to Bioequivalence Study CDX-353-001

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommended on April 7, 2015 to accept the data from the bioanalytical facility at (b) (4)) without an on-site inspection. The justification for this recommendation was that the site was inspected within the last four years with No Action Indicated (NAI) as the outcome.

Field inspector Lori Gioia conducted an inspection of the clinical facility located at (b) (4) in the period (b) (4) . A 483 was issued. Specifically:

- Legally effective informed consent was not obtained from 23 of 24 subjects (or their legal, authorized representative) before the commencement of study procedures for protocol CDX-353-001.
- Subjects 001-020 and 001-010 met exclusion criteria outlined in section 6.2 of the protocol and should not have been included in the study.
- Numerous tests were not performed on all subjects as required in the protocol for the duration of the study.
- A number of post infusion labs were drawn several hours later than scheduled.
- Approximately six adverse events and one concomitant medication were not recorded in the case report forms for several subjects.

The EIR summary from ORA was reviewed by OSIS on September 4, 2015[12]. The OSIS review recommends that the clinical data for study CDX-353-001 be accepted for Agency review if the unreported adverse events and use of concomitant medication (Zometa) did not impact the study outcome.

Reviewer's Comments: The bioequivalence and bioanalytical study reports are acceptable from a Biopharmaceutics perspective.

[12] http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af803ad8ee

2. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

The Applicant states in the cover letter that the nonclinical and clinical studies conducted on CE-Melphalan were performed using drug substance sourced from (b) (4) and drug product manufactured by (b) (4) The proposed source of Melphalan HCl drug substance to be used in the commercial supply of CE-Melphalan will be manufactured by two companies: (b) (4) The Applicant asserts that the drug substance specifications for both manufacturers have been harmonized into a single specification. (b) (4) The proposed commercial supply of CE-Melphalan will be manufactured by (b) (4)

Table 5 below shows that the clinical study drug product batch (manufactured by (b) (4)) and the to-be-marketed commercial batch were/will be manufactured on significantly different scales ((b) (4)).

Table 5: (b) (4) clinical study to commercial batch

Ingredient	Reference to Quality Standard	Amount per mL (bulk solution)	Batch Size (b) (4)	Commercial Batch (b) (4)
Melphalan HCl	In-house	(b) (4)		
Captisol® [b] (Sulfobutylether-β–CD)	NF			
		(b) (4)		
				(b) (4)

Reviewer's Comments: The Applicant has not submitted information to adequately bridge the clinical study batch to the to-be-marketed formulation. However, Table 5 shows that the compositional amounts (b) (4) Consequently, given the nature of dosage form ((b) (4) powder), its route of administration (intravenous) & compositional consistency (b) (4) (dose proportional), the Division of Biopharmaceutics considers the risk to product quality resulting from the inadequate bridging to be very low and therefore has no further concerns in this respect.

Reviewer's Assessment:

In Vitro Dissolution Test: The drug product is administered in the dissolved state, therefore an *in vitro* release test is not relevant.

Bioequivalence Study CDX-353-001: Even with the exclusion of patients 2, 10 and 20 from the data pool, due to protocol violations, the 90% confidence intervals indicate that the test (CE-Melphalan HCl) and reference (Alkeran) drug products are bioequivalent. The result of the study supports the Applicant's assertion that (CE-Melphalan HCl and Alkeran for injection are bioequivalent.

Bioanalytical Method for Quantitation of Melphalan in Plasma: The Applicant has adequately demonstrated that the validation results presented in the bioanalytical study reports support a robust and reliable method for the measurement of Melphalan in human plasma with K_2EDTA as anticoagulant using LC/MS/MS in the concentration range of (b) (4) ng/mL.

Clinical and Bioanalytical facility Inspection: The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommended on April 7, 2015 to accept the data from the bioanalytical facility without an on-site inspection.

The clinical site inspection (in the period June 24 to July 2, 2015) resulted in the issuing of a 483 to the Applicant. The EIR summary from ORA was reviewed by OSIS on September 4, 2015. The OSIS review recommends that the clinical data for study CDX-353-001 be accepted for Agency review if the unreported adverse events and use of concomitant medication (Zometa) did not impact the study outcome.

The overall result of the bioequivalence study is adequate.

Bridging of the to-be-marketed product to clinical study Formulation: The Applicant has not submitted information to adequately bridge the clinical study batch to the to-be-marketed formulation. However, given the nature of dosage form ((b) (4) powder), its route of administration (intravenous) & compositional consistency (b) (4) (dose proportional), Biopharmaceutics considers the risk to product quality resulting from the inadequate bridging to be very low and therefore has no further concerns in this respect.

APPEARS THIS WAY ON ORIGINAL

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

The Division of Biopharmaceutics has reviewed the bioequivalence information/data provided in NDA 207155 and considers that this information supports the approval of the Application.

The Applicant did not submit data to adequately bridge the clinical study batch to the to-be-marketed formulation. However, given the nature of dosage form ((b) (4) powder), its route of administration (intravenous) & compositional consistency (b) (4) (dose proportional), Biopharmaceutics considers the risk to product quality resulting from the inadequate bridging to be very low.

The Division of Biopharmaceutics recommends APPROVAL of NDA 207155 for CE-Melphalan HCl for Injection, 50 mg free base/vial.

September 7, 2015

Maziar Kakhi, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
ONDP/OPQ

Supervisor Comments and Concurrence:

I concur with Dr. Kakhi's review and recommendation.

September 7, 2015

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

8. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: Microbial limits testing is not relevant (b) (4) Rather, sterility and bacterial endotoxins testing are performed on the Drug Product and these tests and the proposed acceptance criteria are adequate to assure microbial quality of this drug product.

2.3.P.6 Reference Standards or Materials

Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

The ability of the container closure system to maintain integrity was confirmed by performing a container closure integrity study using a dye intrusion test with blue methylene solution (b) (4)

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: The applicant's verification of container closure integrity is consistent with regulatory expectations for a pharmaceutical product.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

9. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: The sponsor assures that the drug product does not contain any ingredients which came either directly or indirectly from biological origin.

10. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
Currently Melphalan HCl is commercially available as Alkeran® for Injection. The new product is referred to as Captisol-enabled Melphalan HCl for Injection (CE-Melphalan HCl), and avoids reconstitution using the propylene glycol solution as required for Alkeran. (b) (4) has experience in manufacturing such oncology drug products and has provided adequate (b) (4) validation data and evidence of formal written procedures to support the manufacturing of the subject drug product as evidenced in the submission and DMF (b) (4).

QUALITY ASSESSMENT
NDA # 207155

Primary Reviewer: Vinayak B. Pawar, Ph.D. Sr. Review Microbiologist, OPQ/DMA

Supervisor Comments and Concurrence:

I concur with the primary reviewer's conclusion that NDA 207155 is recommended for approval from the standpoint of product quality microbiology.

Stephen e. Langille, Acting Branch Chief – DMA Branch 3

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Evomela Established Name: Melphalan (b) (4) for injection	Satisfactory IR sent to the applicant for revision of the established name to: Melphalan (b) (4) for injection. The applicant revised the established name via an amendment.
Dosage form, route of administration	Dosage: Injections (Powder for injection) Route: Intravenous infusion	Satisfactory
Controlled drug substance symbol (if applicable)	None	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	The drug product is a (b) (4) lyophilized (b) (4) containing 50 mg melphalan in a 20 ml glass vial. The drug product may be diluted with 0.9% NaCl solution to produce various concentrations of melphalan for intravenous infusion	Satisfactory

Conclusion:

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	For injection: 50 mg of melphalan free base, lyophilized powder in single use vial for reconstitution	Satisfactory
Strengths: in metric system	50 mg	Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	None	Dosage form is not a tablet. Therefore, identifying marks as recorded in the Item are not valid.

Conclusion:

#11: Description (21CFR 201.57(c)(12))

"(b) (4) Melphalan hydrochloride (b) (4)

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary name: Evomela. The reported established name is (b) (4) Melphalan (b) (4) for injection"	The proprietary name is Evomela. The applicant is recommended to include the proprietary name on the label and labelings. The established name (b) (4) Melphalan (b) (4) for injection" is not acceptable. The established name should be revised to "Melphalan (b) (4) for Injection". The applicant made the recommended change.
Dosage form and route of administration	Injections, Intravenous administration by infusion	Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	Active moiety is expressed as a concentration of the base (50 mg/vial). Equivalence statement for the salt was not provided.	Revise the sentence to read" ' (b) (4) equivalent to 56 mg melphalan hydrochloride). The equivalency statement is added during labeling changes.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Betadex Sulfobutyl Ether Sodium NF (2700 mg)	Satisfactory
Statement of being sterile (if applicable)	(b) (4)	Satisfactory
Pharmacological/ therapeutic class	Antineoplastic	Satisfactory
Chemical name, structural formula, molecular weight	Yes	Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Yes	Satisfactory

Conclusion:

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

(b) (4) is supplied in single (b) (4) carton (b) (4)

NDC 68152-109-00: Individual carton of (b) (4) 20 mL single-(b) (4) vial containing 50 mg Melphalan free base".

"Store [redacted] (b) (4) at room temperature 25°C (77°F). Temperature excursions are permitted between 15-30°C (59-86°F). [redacted] (b) (4) [see USP Controlled Room Temperature] [redacted] (b) (4) [redacted] *Note: Yellow highlights are additions of the reviewer.*

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	50 mg base per vial	Satisfactory
Available units (e.g., bottles of 100 tablets)	Single [redacted] (b) (4) vial in cartons	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC number is provided	Dosage form is not a tablet. Therefore, identifying marks as recorded in the Item are not valid.
Special handling (e.g., protect from light, do not freeze)	[redacted] (b) (4)	See addition in yellow.
Storage conditions	[redacted] (b) (4)	Not satisfactory. Revise the storage conditions to include the section heighted in yellow. The recommended changes were including in the label.

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured for: Spectrum Pharmaceuticals, Inc. Irvine, CA 92618	Satisfactory

Conclusion: Revised section is satisfactory (see revised labeling).

2. Labels

1) Immediate Container Label

(b) (4)

[redacted]

Reviewer's Assessment:

The applicant provided the following required items: Proprietary name, established name, dose strength, route of administration, single use sterile vial (b) (4) [redacted] prescription only, name and quantity of inactive ingredient, lot #, and expiration date. The immediate container label is satisfactory. DMEPA would comment on (b) (4) [redacted] statement.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Revision of immediate label made
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	None	Satisfactory
Net contents (21 CFR 201.51(a))	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
Storage (not required)	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	None	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Satisfactory (see revised label).

2) Cartons

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	DMEPA comments on font size and prominence. Established name should be changed from (b) (4) (b) (4)	Revision of the established name has been made.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	None	Satisfactory
Net contents (21 CFR 201.51(a))	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
Name of all inactive ingrédients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	None	**Satisfactory**
Sterility Information (if applicable)	None	**Satisfactory**
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
Storage Conditions	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	None	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
"See package insert for dosage information" (21 CFR 201.55)	None	Satisfactory
"Keep out of reach of children" (optional for Rx, required for OTC)	Revision recommended	**We recommend that you add a statement** "Keep out of reach of children". In an amendment, the applicant explained that the drug product would never reach the patient. Therefore, the requirement is waived.
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	None	Satisfactory.

Reviewer's comment: The revised labeling is satisfactory.

Environmental Assessment: The applicant stated that EIC is below 1 ppb (b) (4) and requested a categorical exclusion based according to 21CFR §25.31(b).

Conclusion: Approvable

II. List of Deficiencies To Be Communicated

A. Drug Substance
B. Drug Product
C. Process/Facility
D. Biopharmaceutics
E. Microbiology
F. Label/Labeling

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION

B. Lifecycle Knowledge Management

a) Drug Substance

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Initial Risk Ranking*	Justification	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments**
	H, M, or L			Acceptable or Not Acceptable	

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	H	(b) (4)	Acceptable to the microbiologist	Continue stability monitoring post approval
Endotoxin (b) (4)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M		Acceptable to the microbiologist	Continue stability monitoring post approval
Assay (API)	• Formulation • Container/closure • Process parameter • Scale/equipment	L		(b) (4)	Continue stability monitoring post approval

	• Site		(b) (4)		
Physical Stability (solid state)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	L		The drug product is reconstituted with normal saline leading to a solution	None
Uniformity of dose (Fill volume/deliverable volume)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M	Lyophilized drug product reconstituted with normal saline.		Fill volume is kept the same as that of the LD (see pharmaceutical development report)
Osmolality	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M	Lyophilized drug product reconstituted with normal saline	Bioequilvalence with LD, subject application site reactions were not monitored	Monitor post marketing safety report for unusual application site reaction in conjunction with the clinician
pH (high)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	L	(b) (4)		Monitor stability
pH (low)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	L			Monitor stability

Particulate matter	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M	Appearance specification change to include "essentially free of visible particles"		Monitor stability
Leachable Extractable	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	L	Post-approval commitment made to provide safety assessment data for (b) (4) extractables		Review of the supplement
Redispersibility/reconstitution time	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M	(b) (4)		
Moisture content	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	L			Monitor stability
Appearance (b) (4)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M			
Appearance(color/turbidity)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	L			Monitor stability

IV. Administrative

A. Reviewer's Signature: See discipline specific review sections for the primary and secondary signatures.

B. Endorsement Block

Reviewer Name/Date: See discipline specific review sections for the primary and secondary signatures.

Secondary Reviewer Name/Date: See discipline specific review sections for the primary and secondary signatures.

Project Manager Name/Date: Rabiya Laiq, 9/18/2015

Digitally signed by Janice T. Brown -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300101685, cn=Janice T. Brown -A
Date: 2015.09.18 18:53:20 -04'00'