

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207155Orig1s000

207155Orig2s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 207155 / Original -1 Original-2	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: EVOMELA™ (Captisol®-enabled melphalan HCl) for Injection Established/Proper Name: Melphalan HCl Dosage Form: Powder Strengths: 50 mg (free base)/vial		
Applicant: Spectrum Pharmaceuticals, Inc.		
Date of Receipt: 12/23/14		
PDUFA Goal Date: Cycle 1: 10/23/15 Cycle 2: 05/09/16		Action Goal Date (if different): 03/10/16
RPM: Rachel McMullen		
Proposed Indication(s): Original 1: high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma. Original 2: Palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
<i>Example: published literature</i>	<i>Nonclinical toxicology</i>
Published Literature	Bridging pharmacokinetic study in rats, a bioequivalence study (CDX-353-001) comparing EVOMELA to Alkeran, a literature review of the high-dose IV Melphalan regimen in the proposed indication, and a safety and efficacy study of EVOMELA used as a myeloablative conditioning regimen for autologous stem cell transplantation for patients with MM (CDX-353-002).
Alkeran (NDA 20207)	Various sections of labeling

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The applicant bridged the proposed product to the listed drug by means of a Phase IIa, open-label, randomized, cross-over study of CE-Melphalan HCl for injection ('test') and Alkeran for injection (reference).

Bridge from Literature to Bioequivalence Study

The melphalan formulation used in the Key Literature Studies that were reviewed for this literature summary was not always specified in the original publications. Alkeran for Injection (Melphalan HCl) was the only commercially available formulation of melphalan until 2009. The applicant concludes all studies conducted prior to 2009 used the Alkeran for Injection formulation. The Alkeran for Injection (Melphalan HCl) formulation that is available in the United States is also the same composition as the Alkeran for Injection formulation marketed and sold in other countries. The application includes direct confirmation the following studies were conducted with Alkeran (Melphalan HCl).

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

List of Studies:

Literature Reference
Barlogie, 1997 Advances in therapy of multiple myeloma: lessons from acute leukemia. Clin Cancer Res. 1997;3(12 Pt 2):2605-13.
Barlogie, 1999 Barlogie B, Jagannath S, Desikan KR, Mattox S, Vesole D, Siegel D, et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood. 1999;93(1):55-65.
Vesole, 1999 Vesole DH, Crowley JJ, Catchatourian R, Stiff PJ, Johnson DB, Cromer J, et al. High-dose melphalan with autotransplantation for refractory multiple myeloma: results of a Southwest Oncology Group phase II trial. J Clin Oncol. 1999;17(7):2173-9.
Tricot, 1996b Tricot G, Alberts DS, Johnson C, Roe DJ, Dorr RT, Bracy D, et al. Safety of autotransplants with high-dose melphalan in renal failure: a pharmacokinetic and toxicity study. Clin Cancer Res. 1996;2(6):947-52.

The Biopharmaceutics review explains why there is no concern about the “lack of a bridge. Our wording in the review was that there was “inadequate bridging” in the strict conventional sense. The information we relied on, which provided alternative grounds for developing confidence that the use of the (b) (4) scale batch formulation during the comparative BE study would pose no risk to patient safety when taking formulations manufactured using the proposed commercial scale blend, was:



These reasons served as the surrogate ‘bridge’.

RELIANCE ON PUBLISHED LITERATURE

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Alkeran	020207	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

- The sponsor added a new indication “*high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myelom.*” (Original-1).
- The formulation is different. This submission provides for a new injectable melphalan HCl formulation that incorporates Captisol.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): N

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If “**NO**”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES NO
If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES NO
If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of

approval

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/s/

RACHEL S MCMULLEN
03/10/2016

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

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

Memorandum

Date: March 1, 2016

To: Rachel McMullen, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Davis, Team Leader, OPDP

Subject: Comments on draft labeling for EVOMELA (Melphalan
hydrochloride) for injection, for intravenous use
NDA 207155

OPDP previously reviewed the first cycle draft labeling (Package Insert, Carton/Container Labeling) prior to the CR action for EVOMELA (melphalan hydrochloride) for injection, for intravenous use (Evomela) and provided comments to DHP on September 22, 2015, based on a consult request dated March 17, 2015. OPDP acknowledges there were no label updates to review during the review cycle for this Class 2 resubmission.

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/s/

WENDY R LUBARSKY
03/01/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: February 25, 2016

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Patient Labeling Review: Patient Package Insert (PPI)

Drug Name (established name): EVOMELA (melphalan)

Dosage Form and Route: for injection, for intravenous use
Application: NDA 207155
Type/Number:

Applicant: Spectrum Pharmaceuticals, Inc.

1 INTRODUCTION

On December 23, 2014, Spectrum Pharmaceuticals, Inc. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 207155 for EVOMELA (melphalan) for injection. On September 24, 2015, the Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP) completed a review of the Patient Package Insert (PPI) for EVOMELA (melphalan) for injection.

Due to outstanding product quality and facility deficiencies, a Complete Response (CR) letter was issued on October 22, 2015. On November 9, 2015, Spectrum Pharmaceuticals, Inc. submitted a complete class 2 response to the CR letter.

2 MATERIAL REVIEWED

- Patient Labeling Review of EVOMELA (melphalan) for injection PPI dated September 24, 2015.

3 CONCLUSIONS

This memorandum documents that DMPP has no further comments for the Patient Package Insert (PPI) for EVOMELA (melphalan) for injection.

4 RECOMMENDATIONS

Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

NATHAN P CAULK
02/25/2016

BARBARA A FULLER
02/25/2016

LASHAWN M GRIFFITHS
02/26/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: January 29, 2016
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 207155
Product Name and Strength: Evomela (melphan HCl) for Injection,
50 mg (free base)
Submission Date: October 8, 2015
Applicant/Sponsor Name: Spectrum Pharmaceuticals
OSE RCM #: 2015-3-1
DMEPA Primary Reviewer: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

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

2 CONCLUSION

The revised container label and carton labeling are acceptable from a medication error perspective. However, the Prescribing Information needs further revisions from a medication error perspective. We identified the following areas of vulnerability to error in the revised Prescribing Information:

¹ Rutledge, M. Label and Labeling Review for Evomela (NDA 207155). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 AUG 25. 16 p. OSE RCM No.: 2015-3.

- The Dosing and Administration Section includes the use of error-prone symbols such as the use of the IV abbreviation.

3 RECOMMENDATIONS

3.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert”². As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:
 - a. Revise the abbreviation “IV” to read “intravenous”.

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

² ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2016 January 28]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

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/s/

NICOLE B GARRISON
01/29/2016

YELENA L MASLOV
02/09/2016

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

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

Application: NDA 207155

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

Name of Drug/Dosage Form: EVOMELA™ (melphalan hydrochloride) for injection, powder).

Applicant: Spectrum Pharmaceuticals, Inc.

Receipt Date: December 23, 2014

Goal Date: October 23, 2015

1. Regulatory History and Applicant's Main Proposals

Spectrum Pharmaceuticals has submitted a 505(b)(2) NDA for a new injectable melphalan formulation (Captisol-enabled melphalan HCl, 50 mg(free base)/vial)). The reference listed drug (RLD) is Alkeran for Injection (NDA 20207). Spectrum's proposed drug is a new formulation of melphalan with two proposed indications: 1) a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma and 2) palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

The Applicant has orphan designation for the first indication above. The second indication (for palliative treatment) does not have orphan designation. The Applicant was notified that they would need to submit a pediatric plan because this product is a new formulation, which triggers PREA, and the second indication for palliative treatment does not have orphan designation. The application also includes a proprietary name, (EVOMELA), which will be reviewed by OSE.

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

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

All SRPI format deficiencies of the PI will be conveyed to the applicant in during labeling negotiations. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

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

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment: (*The Title WARNING: SEVERE BONE MARROW SUPPRESSION, HYPERSENSITIVITY, and LEUKEMOGENICITY is not bolded*)

- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

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

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

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

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

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

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- NO** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment: *The BW Warning does not appear at the beginning of the TOC.*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

N/A

Selected Requirements of Prescribing Information

34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- NO** 36. In the BW, all text should be **bolded**.

Comment: *All text in the BW in the FPI is not bolded*

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment: *The statement is not verbatim, but the modification is appropriate.*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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/s/

RACHEL S MCMULLEN
10/22/2015

MEMORANDUM

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

DATE: September 02, 2015

TO: Ann Farrell, M.D.
Director
Division of hematology Products (DHP)
Office of Hematology and Oncology Products
Office of New Drugs (OND)

FROM: Li-Hong Yeh, Ph.D.
Chemical Engineer
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR covering the clinical portion of NDA
207155 conducted at University of Kansas Medical
Center, Kansas City, and University of Kansas Cancer
Center and Medical Pavilion, Westwood, Kansas

Summary:

At the request of the Division of Hematology Products (DHP), the Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of the following study:

Study: CDX-353-001
Study Title: "A Phase IIa, Open-Label, Randomized, Pharmacokinetic Comparative, Cross-Over Study of Melphalan HCl for Injection (Propylene Glycol-Free) and Alkeran for Injection for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation"

Investigator: Omar S. Aljitawi, M.D.

Study period: 02/04/2010 - 06/08/2011(**Attachment 1**)

Clinical Sites:

The following clinical sites were inspected for study CDX-353-001:

- (1) University of Kansas Medical Center, Kansas City, Kansas
- (2) University of Kansas Cancer Center and Medical Pavilion, Westwood, Kansas

The inspection of the clinical portion of the above study was conducted by ORA Investigator Lori A. Gioia between June 24 - July 02, 2015. During the inspection, Investigator Gioia verified that during the study, the University of Kansas Medical Center Hospital was the site where all subjects received their stem cell transplants and the first three subjects also received their study drugs. All subsequent subjects received their study drugs at the University of Kansas Cancer Center's Westwood facility and follow up visits were conducted at the Westwood location as well.

The audit covered regulatory files and study records, including study monitoring procedures and activities, personnel training, specimen handling and integrity, study protocols, subjects' records, informed consent forms, communication records with IECs and sponsors, test article accountability, and record retention. 100% of the ICFs were verified. At least 50% of the subjects' CRFs were reviewed. All raw data matched the information in the study reports submitted to the Agency. No under-reporting of AEs was observed. All studies were approved by the IEC before the subjects were enrolled. Facilities appeared adequate to perform bioequivalence studies.

At the conclusion of the inspections, no significant deficiencies were observed at the University of Kansas Medical Center and Form FDA 483 was not issued. Form FDA 483 was issued to the University of Kansas Cancer Center and Medical Pavilion (Westwood facility) (**Attachment 2**). The University of Kansas Cancer Center and Medical Pavilion's response dated 07/31/2015 was received by OSIS on 07/31/2015 (**Attachment 3**). The Form FDA 483 observations, the firm's (Westwood facility) response, and our evaluation follow.

Inspection findings of study CDX-353-001 at University of Kansas Cancer Center and Medical Pavilion, Kansas

(1) Legally effective informed consent was not obtained from a subject or the subject's legally authorized representative, and the situation did not meet the criteria in 21 CFR 50.23 - 50.24 for exception.

Specifically, 23 of 24 subjects signed the informed consent form after study procedures had been performed for protocol CDX-353-001. These study procedures include screening tests such as infectious disease testing and full chemistry blood analysis used to determine subject eligibility.

Firm's Response: In their response, the University of Kansas Cancer Center acknowledged the observation and stated that the tests were standard procedures performed as part of the practice of medicine, independent of whether the subjects were enrolled in the study. They believed that these standards of care assessments for study inclusion, performed prior to consent, met the criteria provided in 'FDA Information Sheet- Screening Tests Prior to Study Enrollment' (Attachment 3).

The University of Kansas Cancer Center indicated that its Quality Assurance Unit will review all of Dr. Aljitawi's studies to ensure no further informed consent deviations occurred. All deviations will be reported in compliance with the protocol and IRB requirements. They intend to complete this review by 12/01/2015 and report the results to FDA by 12/04/2015. For future studies, no study-specific actions will be performed until after the study volunteer and clinical representative have signed the ICF. SOP # CT.005.001 (effective date 7/23/2015) was updated to reflect these changes.

OSIS Assessment: In my opinion, the above observation did not impact subject safety or the study outcome.

(2) An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically, for protocol CDX-353-001:

A) 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 anticancer drug (Cytoxan) within 21 days of their stem cell transplant (exclusion criteria 13).

Firm's Response: In their response, the University of Kansas Cancer Center acknowledged the observation and stated that Subject 001-020 was enrolled in a retrospective chart review study that did not involve treatment, procedures or interventions. Subject 001-010 was dosed with anticancer drug (Cytoxan) for one day, 20 days prior to their stem cell transplants. The Principal Investigator for the study felt that there was enough time for the drug to be eliminated from the systemic circulation given the half-life of the drug (3-12 hours). However, the Sponsor discovered the protocol deviation during their monitoring visit of the study and the deviation was reported to the IRB immediately. As a corrective action, the University of Kansas Cancer Center updated their procedures whereby the eligibility of subjects would be reviewed and verified by a second clinical staff member before the subject is included in a particular study.

(B) The following tests were not performed between all subjects as required in the protocol for the duration of the study: Approximately 18 ECGs, 14 urinalysis, 26 lactic acid, 22 serum osmolality, 19 total bilirubin, 10 alkaline phosphatase, 10 AST, 10 ALT, 1 full chemistry testing, 1 full hematology testing, 9 Uric Acid, 9 LDH, and 6 Creatinine clearance, were not performed across all 24 subjects throughout the study.

Firm's response: In their response, the University of Kansas Cancer Center acknowledged the observation and stated that the protocol deviations were noted by the sponsor during the study conduct and reported to the IRB. As a corrective action, they indicated that source documentation would be verified prior to subject discharge. The subsequent review would take place by a second clinical staff member to ensure all protocol required assessments were completed and recorded. SOP # CT.006.001 was updated to include the new procedures.

C) Subject 001-005 had both PK Day (-2) 2 hour post infusion labs and 4 hour post infusion labs drawn two hours too late. The 2 hour post infusion labs should have been drawn on 05/25/2010 at 11:25 am and were drawn at 1:35 pm. The 4 hour post infusion labs should have been drawn on 05/25/2010 at 1:25 pm and were drawn at 3:32 pm.

D) 2 hour post infusion and 4 hour post infusion chemistry tests for PK Day (-2) and Day (-3) were missed for Subject 001-021 as required in the protocol. Day (-3) PK labs should have been drawn for 2 hour and 4 hour post infusion on 03/21/2011 at 12:24 pm and again at 2:24 pm. Day (-2) PK labs should have been drawn for 2 hour and 4 hour post infusion on 03/22/2011 at 12:33 pm and 2:33 pm.

Firm's response: In their response, the University of Kansas Cancer Center acknowledged the observation and stated that they undertook a root-cause analysis to address missed and late pharmacokinetic (PK) safety assessments. The above protocol deviations were noted by the sponsor and reported to the IRB. As a corrective action, they updated their procedures to require PK safety sample collection by one clinical staff member and verification of the same according to the protocol by a second clinical staff member. SOP # SOP CT.006.001 titled "Creation and Use of Source Documents" was updated to reflect these changes.

OSIS Assessment:

The protocol deviations cited in observations 2A, 2B, 2C and 2D were reported to the IRB or FDA . In my opinion, observation 2A did not impact subject safety or the study outcome. With regards to Observations 2C and 2D, although safety assessments were not conducted per protocol for subjects 001-005 and 001-21, both subjects completed the study without reported adverse events. Therefore, it is unlikely that observations 2A, 2B, 2C, and 2D impacted subject safety or the study outcome.

(3) Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, approximately six adverse events and one concomitant medication were not recorded in the case report forms for subjects 001-011 (hyperglycemia), 001-013 (anemia and hypomagnesemia), 001-014 (hyperglycemia and hyperbilirubinemia), 001-018 (hyperglycemia), and 001-021 (Zometa) under protocol CDX-353-001.

Firm's Response: The University of Kansas Cancer Center acknowledged the observation and stated that they have now notified the sponsor of the observed adverse events and concomitant medications that were not previously reported. To prevent future reoccurrence, the University of Kansas Cancer Center promised to have additional review and verification steps

such that all concomitant medications and adverse events will be recorded in case report forms from the source documents.

OSIS Assessment:

The DHP medical reviewer should evaluate the impact of the adverse events (subjects 001-011, 001-013, 001-014, 001-018) and use of concomitant medication (subject 001-018) on study outcome.

Recommendations:

Following review of the inspectional findings, I recommend 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.

NDA 207155

Study# **CDX-353-001**

Li-Hong Yeh, Ph.D.
DNDBE, OSIS

Final Classification:

Clinical

VAI:

(1) University of Kansas Medical Center, Kansas City, Kansas
(2) University of Kansas Cancer Center and Medical Pavilion, Westwood, Kansas

CC:

OTS/OSIS/Taylor/Bonapace/Haidar/Choi/Dasgupta/Skelly/Cho/Yeh
OTS/OSIS/Fenty-Stewart/Nkah/Dejernet/Johnson/Kadavil

Draft: PY 09/02/2015

Edit: AD 09/02/2015, CB 09/02/2015

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/University_of_Kansas_Medical_Center

OSI File #: BE 6861

FACTS: 11531023

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/s/

LI-HONG P YEH
09/25/2015

ARINDAM DASGUPTA
09/25/2015

CHARLES R BONAPACE
09/28/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: September 24, 2015

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Robert Kane, MD
Deputy Director for Safety
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Rachael Conklin, MS, RN
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): EVOMELA (melphalan hydrochloride)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: NDA 207155

Applicant: Spectrum Pharmaceuticals, Inc.

1 INTRODUCTION

On December 23, 2014, Spectrum Pharmaceuticals, Inc. submitted for the Agency's review 505(b)(2) New Drug Application (NDA) 207155 for EVOMELA (melphalan hydrochloride) for injection. The Reference Listed Drug (RLD) is ALKERAN (melphalan hydrochloride) for Injection (NDA 020207) originally approved on November 18, 1992. The Applicant proposed indication for EVOMELA (melphalan hydrochloride) for injection is for:

- use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.
- the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on July 14, 2015 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for EVOMELA (melphalan hydrochloride) for injection.

2 MATERIAL REVIEWED

- Draft EVOMELA (melphalan hydrochloride) for injection PPI received on December 23, 2014, and received by DMPP and OPDP on September 14, 2015.
- Draft EVOMELA (melphalan hydrochloride) for injection Prescribing Information (PI) received on December 23, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on September 14, 2015.
- Draft EVOMELA (melphalan hydrochloride) for injection Prescribing Information (PI) received on December 23, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on September 13, 2015.
- Approved ALKERAN (melphalan hydrochloride) comparator labeling dated June 9, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

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/s/

NATHAN P CAULK
09/24/2015

RACHAEL E CONKLIN
09/24/2015

BARBARA A FULLER
09/25/2015

LASHAWN M GRIFFITHS
09/25/2015

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

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

Memorandum

Date: 9/22/15

To: Rachel McMullen, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Kathleen Davis, Team Leader, OPDP

Subject: Comments on draft labeling (Package Insert, Carton/Container Labeling) for EVOMELA (melphalan hydrochloride) for injection, for intravenous use
NDA 207155

In response to your labeling consult request dated March 17, 2015, we have reviewed the draft Package Insert (PI), draft Carton labeling, and draft Container labeling for EVOMELA (melphalan hydrochloride) for injection, for intravenous use (Evomela). This review is based upon the version of the draft PI e-mailed to OPDP on September 13, 2015, and the versions of the draft Carton and Container labeling e-mailed to OPDP on September 15, 2015.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or Rachael.Conklin@fda.hhs.gov.

Package Insert

<u>Section</u>	<u>Statement from Draft (if applicable)</u>	<u>OPDP Comment</u>
HIGHLIGHTS OF PRESCRIBING INFORMATION		Please ensure that the information and the order of the information presented in the Highlights and the Table of Contents corresponds to the order of information in the FPI.
HIGHLIGHTS OF PRESCRIBING	"Most common adverse (b) (4) are neutrophil count	The criteria used to determine inclusion (e.g., frequency cutoff rate) should be

<p>INFORMATION, ADVERSE REACTIONS:</p> <p>6.1, Clinical Trials Experience</p>	<p>decreased, white blood cell count decreased, lymphocyte count decreased, platelet count decreased, diarrhea, nausea, fatigue, hypokalemia, anemia, and vomiting.”</p> <p>“The most common adverse reactions observed in patients with multiple myeloma treated with Evomela were neutrophil count decreased, white blood cell count decreased, lymphocyte count decreased, platelet count decreased, diarrhea, nausea, fatigue, hypokalemia, anemia, and vomiting.”</p>	<p>included here in order to be consistent with the recommendation in the Guidance for Industry, <i>Labeling for Human Prescription Drug and Biological Products—Implementing the PLR Content and Format Requirements</i>, dated February 2013.</p> <p>For example: “most common adverse reactions observed in at least x% of patients treated with Evomela . . .”</p>
<p>HIGHLIGHTS OF PRESCRIBING INFORMATION: ADVERSE REACTIONS:</p>	<p>“Most common adverse (b) (4)”</p>	<p>Should (b) (4) be changed to “reactions” in order to be consistent with the rest of the label?</p>
<p>5.3 Hepatotoxicity</p>		<p>If the information is available, we recommend that the incidence rates for hepatic events after administration of IV melphalan be included here as prescribers would benefit from prevalence information.</p>
<p>6.1 Clinical Trials Experience</p>	<p>(b) (4)</p>	<p>This phrasing minimizes the risk of serious adverse reactions associated with this product. Please consider revising to remove the word (b) (4). For example: (b) (4)</p>
<p>8.5 Geriatric Use</p>	<p>“A greater incidence of engraftment syndrome was</p>	<p>If available, we recommend the rates of engraftment syndrome in older patients</p>

	observed in older patients.”	versus other patients be included here as this would be informative for prescribers.
14.1 Myeloablative Conditioning in Patients with Multiple Myeloma Undergoing ASCT	<p>“The overall response rate (partial response or better) improved from 79% (48 of 61) prior to the ASCT procedure to 95% (58 of 61) at 90 to 100 days post-transplant.”</p> <p>and</p> <p>(b) (4) myeloablation (b) (4) occurred on ASCT day 5 (range ASCT days -1 to 6). The median time to neutrophil engraftment was 12 days (range ASCT days 10 to 16). The median time to platelet engraftment was 13 days (range ASCT days 10 to 28).”</p>	Should the confidence intervals be included with the data in this section?
17, PATIENT COUNSELING INFORMATION		<p>OPDP recommends revising the formatting and ordering of this section of the PI to ensure consistency with the Guidance for Industry, Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products—Content and Format dated December 2014 and to improve flow and readability. In particular, the Guidance recommends that “information in the PATIENT COUNSELING INFORMATION section should be ordered by the relative clinical significance of the information, with the most important topics applicable to the patient appearing first” and that “the use of subheadings to organize and differentiate topics within the PATIENT COUNSELING INFORMATION section is recommended because they allow the reader to quickly identify the major concepts.”</p> <p>For example of suggested formatting of this section, please refer to the label for</p>

		Targretin.
17, PATIENT COUNSELING INFORMATION	“Advise females of reproductive potential to avoid pregnancy, which may include use of effective contraception during treatment with Evomela.”	Should the recommendation to use effective contraception “after” treatment be added to this section to be consistent with sections 5.6 and 8.3? For example: “Advise females of reproductive potential to avoid pregnancy, which may include use of effective contraception during and after treatment with Evomela.”
17, PATIENT COUNSELING INFORMATION		Consider adding counseling information to this section for males of reproductive potential. For example: “Advise males with female sexual partners of reproductive potential that they should use effective contraception during and after treatment with Evomela.”

Carton/Container Labeling:

OPDP acknowledges the August 25, 2015, review of the carton and container labeling by the Division of Medication Error Prevention and Analysis (DMEPA) and has no additional comments on the carton and container labeling.

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

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/s/

RACHAEL E CONKLIN
09/22/2015

MEMORANDUM

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

DATE: September 04, 2015

TO: Ann Farrell, M.D.
Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products
Office of New Drugs

FROM: Li-Hong Yeh, Ph.D.
Chemical Engineer
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR covering the clinical portion of NDA
207155 conducted at University of Kansas Medical
Center, Kansas City, and University of Kansas Cancer
Center and Medical Pavilion, Westwood, Kansas

Summary:

At the request of the Division of Hematology Products (DHP), the Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of the following study:

Study: CDX-353-001
Study Title: "A Phase IIa, Open-Label, Randomized, Pharmacokinetic Comparative, Cross-Over Study of Melphalan HCl for Injection (Propylene Glycol-Free) and Alkeran for Injection for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation"

Investigator: Omar S. Aljitawi, M.D.

Study period: 02/04/2010 - 06/08/2011(**Attachment 1**)

Clinical Sites:

The following clinical sites were inspected for study CDX-353-001:

- (1) University of Kansas Medical Center, Kansas City, Kansas
- (2) University of Kansas Cancer Center and Medical Pavilion, Westwood, Kansas

The inspection of the clinical portion of the above study was conducted by ORA Investigator Lori A. Gioia between June 24 - July 02, 2015. During the inspection, Investigator Gioia verified that during the study, the University of Kansas Medical Center Hospital was the site where all subjects received their stem cell transplants and the first three subjects also received their study drugs. All subsequent subjects received their study drugs at the University of Kansas Cancer Center's Westwood facility and follow up visits were conducted at the Westwood location as well.

The audit covered regulatory files and study records, including study monitoring procedures and activities, personnel training, specimen handling and integrity, study protocols, subjects' records, informed consent forms, communication records with IECs and sponsors, test article accountability, and record retention. 100% of the ICFs were verified. At least 50% of the subjects' CRFs were reviewed. All raw data matched the information in the study reports submitted to the Agency. No under-reporting of AEs was observed. All studies were approved by the IEC before the subjects were enrolled. Facilities appeared adequate to perform bioequivalence studies.

At the conclusion of the inspections, no significant deficiencies were observed at the University of Kansas Medical Center and Form FDA 483 was not issued. Form FDA 483 was issued to the University of Kansas Cancer Center and Medical Pavilion (Westwood facility) (**Attachment 2**). The University of Kansas Cancer Center and Medical Pavilion's response dated 07/31/2015 was received by OSIS on 07/31/2015 (**Attachment 3**). The Form FDA 483 observations, the firm's (Westwood facility) response, and our evaluation follow.

Inspection findings of study CDX-353-001 at University of Kansas Cancer Center and Medical Pavilion, Kansas

(1) Legally effective informed consent was not obtained from a subject or the subject's legally authorized representative, and the situation did not meet the criteria in 21 CFR 50.23 - 50.24 for exception.

Specifically, 23 of 24 subjects signed the informed consent form after study procedures had been performed for protocol CDX-353-001. These study procedures include screening tests such as infectious disease testing and full chemistry blood analysis used to determine subject eligibility.

Firm's Response: In their response, the University of Kansas Cancer Center acknowledged the observation and stated that the tests were standard procedures performed as part of the practice of medicine, independent of whether the subjects were enrolled in the study. They believed that these standards of care assessments for study inclusion, performed prior to consent, met the criteria provided in 'FDA Information Sheet- Screening Tests Prior to Study Enrollment' (Attachment 3).

The University of Kansas Cancer Center indicated that its Quality Assurance Unit will review all of Dr. Aljitawi's studies to ensure no further informed consent deviations occurred. All deviations will be reported in compliance with the protocol and IRB requirements. They intend to complete this review by 12/01/2015 and report the results to FDA by 12/04/2015. For future studies, no study-specific actions will be performed until after the study volunteer and clinical representative have signed the ICF. SOP # CT.005.001 (effective date 7/23/2015) was updated to reflect these changes.

OSIS Assessment: In my opinion, the above observation did not impact subject safety or the study outcome.

(2) An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically, for protocol CDX-353-001:

A) 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 anticancer drug (Cytoxan) within 21 days of their stem cell transplant (exclusion criteria 13).

Firm's Response: In their response, the University of Kansas Cancer Center acknowledged the observation and stated that Subject 001-020 was enrolled in a retrospective chart review study that did not involve treatment, procedures or interventions. Subject 001-010 was dosed with anticancer drug (Cytoxan) for one day, 20 days prior to their stem cell transplants. The Principal Investigator for the study felt that there was enough time for the drug to be eliminated from the systemic circulation given the half-life of the drug (3-12 hours). However, the Sponsor discovered the protocol deviation during their monitoring visit of the study and the deviation was reported to the IRB immediately. As a corrective action, the University of Kansas Cancer Center updated their procedures whereby the eligibility of subjects would be reviewed and verified by a second clinical staff member before the subject is included in a particular study.

(B) The following tests were not performed between all subjects as required in the protocol for the duration of the study: Approximately 18 ECGs, 14 urinalysis, 26 lactic acid, 22 serum osmolality, 19 total bilirubin, 10 alkaline phosphatase, 10 AST, 10 ALT, 1 full chemistry testing, 1 full hematology testing, 9 Uric Acid, 9 LDH, and 6 Creatinine clearance, were not performed across all 24 subjects throughout the study.

Firm's response: In their response, the University of Kansas Cancer Center acknowledged the observation and stated that the protocol deviations were noted by the sponsor during the study conduct and reported to the IRB. As a corrective action, they indicated that source documentation would be verified prior to subject discharge. The subsequent review would take place by a second clinical staff member to ensure all protocol required assessments were completed and recorded. SOP # CT.006.001 was updated to include the new procedures.

C) Subject 001-005 had both PK Day (-2) 2 hour post infusion labs and 4 hour post infusion labs drawn two hours too late. The 2 hour post infusion labs should have been drawn on 05/25/2010 at 11:25 am and were drawn at 1:35 pm. The 4 hour post infusion labs should have been drawn on 05/25/2010 at 1:25 pm and were drawn at 3:32 pm.

D) 2 hour post infusion and 4 hour post infusion chemistry tests for PK Day (-2) and Day (-3) were missed for Subject 001-021 as required in the protocol. Day (-3) PK labs should have been drawn for 2 hour and 4 hour post infusion on 03/21/2011 at 12:24 pm and again at 2:24 pm. Day (-2) PK labs should have been drawn for 2 hour and 4 hour post infusion on 03/22/2011 at 12:33 pm and 2:33 pm.

Firm's response: In their response, the University of Kansas Cancer Center acknowledged the observation and stated that they undertook a root-cause analysis to address missed and late pharmacokinetic (PK) safety assessments. The above protocol deviations were noted by the sponsor and reported to the IRB. As a corrective action, they updated their procedures to require PK safety sample collection by one clinical staff member and verification of the same according to the protocol by a second clinical staff member. SOP # SOP CT.006.001 titled "Creation and Use of Source Documents" was updated to reflect these changes.

OSIS Assessment:

The protocol deviations cited in observations 2A, 2B, 2C and 2D were reported to the IRB or FDA. In my opinion, observation 2A did not impact subject safety or the study outcome. With regards to Observations 2C and 2D, although safety assessments were not conducted per protocol for subjects 001-005 and 001-21, both subjects completed the study without reported adverse events. Therefore, it is unlikely that observations 2A, 2B, 2C, and 2D impacted subject safety or the study outcome.

(3) Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, approximately six adverse events and one concomitant medication were not recorded in the case report forms for subjects 001-011 (hyperglycemia), 001-013 (anemia and hypomagnesemia), 001-014 (hyperglycemia and hyperbilirubinemia), 001-018 (hyperglycemia), and 001-021 (Zometa) under protocol CDX-353-001.

Firm's Response: The University of Kansas Cancer Center acknowledged the observation and stated that they have now notified the sponsor of the observed adverse events and concomitant medications that were not previously reported. To prevent future reoccurrence, the University of Kansas Cancer Center promised to have additional review and verification steps

such that all concomitant medications and adverse events will be recorded in case report forms from the source documents.

OSIS Assessment:

The DHP medical reviewer should evaluate the impact of the adverse events (subjects 001-011, 001-013, 001-014, 001-018) and use of concomitant medication (subject 001-018) on study outcome.

Recommendations:

Following review of the inspectional findings, I recommend 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.

ANDA 207155

Study# **CDX-353-001**

Li-Hong Yeh, Ph.D.
DNDBE, OSIS

Final Classification:

Clinical

VAI:

(1) University of Kansas Medical Center, Kansas City, Kansas
(2) University of Kansas Cancer Center and Medical Pavilion, Westwood, Kansas

CC:

OTS/OSIS/Taylor/Bonapace/Haidar/Choi/Dasgupta/Skelly/Cho/Yeh
OTS/OSIS/Fenty-Stewart/Nkah/Dejernet/Johnson/Kadavil

Draft: PY 09/02/2015

Edit: AD 09/02/2015, CB 09/02/2015 AD 09/04/2015

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/University_of_Kansas_Medical_Center

OSI File #: BE 6861

FACTS: 11531023

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/s/

ARINDAM DASGUPTA

09/04/2015

Uploading EIR review on behalf of Primary author
Li-Hong Yeh

CHARLES R BONAPACE

09/04/2015

LABEL AND LABELING REVIEW

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

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

Date of This Review: August 25, 2015
Requesting Office or Division: Office of Hematology Products (DHP)
Application Type and Number: NDA 207155
Product Name and Strength: Evomela (melphalan HCL) for Injection,
50 mg (free base)
Product Type: Single
Rx or OTC: Rx
Applicant/Sponsor Name: Spectrum Pharmaceuticals
Submission Date: December 23, 2015
OSE RCM #: 2015-3
DMEPA Primary Reviewer: Michelle Rutledge, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review responds to a request from DHP to evaluate the proposed carton labeling, vial label, and prescribing information for Evomela for areas of vulnerability that could lead to medication errors. This product is a 505(b)(2) to reference listed drug Alkeran and is seeking approval for the injection formulation only. The reference listed drug, Alkeran (melphalan hydrochloride) for injection, was approved on November 18, 1992 under NDA 020207, and is marketed as 50 mg per vial. A tablet formulation of Alkeran is also approved under a separate NDA.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Spectrum Pharmaceuticals is submitting a 505(b)(2) to reference listed drug (RLD) Alkeran injection. Although, the proposed Evomela product will be similarly marketed as 50 mg per vial, there are differences in reconstitution methods between the proposed Evomela and reference listed drug, Alkeran. Alkeran is indicated to be used with the *supplied diluent which contains polyethylene glycol* in comparison to the proposed Evomela product which can be reconstituted with *normal saline* (0.9% NaCl). In addition, the proposed Evomela product once reconstituted also has an expanded stability window (*24 hours at refrigerated temperature or 1 hour at room temperature*) versus the reference listed drug Alkeran (*complete administration within 60 minutes of reconstitution*).

We considered the potential for medication error in case the diluent for Alkeran is used to reconstitute the proposed Evomela and vice-versa. In communications with the clinical team and Office of Pharmaceutical Quality (OPQ), we learned there is no information on what will

occur if Alkeran’s diluent, propylene glycol, will be used to prepare the proposed Evomela product. However, if normal saline were used to reconstitute Alkeran, the Alkeran would not go into solution. Therefore, it is important to ensure that labels and labeling contain warning statements regarding the appropriate diluent.

Additionally, we conducted a FAERS search to identify whether any medication errors occurred with the currently marketed reference listed drug Alkeran product. One reported medication error case relevant to this review described a wrong preparation technique error, where a patient received less than a full dose due to a calculation error involving concentration during preparation of Alkeran’s dose. We note although the prescribing information labeling for RLD Alkeran does include final concentration of the product after reconstitution, the carton labeling and container label does not provide the final concentration information. Thus, it appears important to ensure the final concentration appears on relevant labels and labeling of Evomela.

We evaluated the proposed prescribing information, label and labeling, and have identified areas of improvement to increase clarity of the preparation for Evomela, readability, and prominence of important information.

4 CONCLUSION & RECOMMENDATIONS

We reviewed the label and labeling and identified that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. The Dosing and Administration Section includes the use of error-prone symbols¹. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations¹ appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Therefore, please revise accordingly, for example, to read “intravenous” instead of the use of the (IV) abbreviation.
2. Update Dosage and Administration Section 2.4 – Reconstitution and Infusion Instructions for clarity and to allow flexibility in calculating individualized dosing, such as:

¹ ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 April 2]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

1. Use normal saline solution (0.9% Sodium Chloride Injection, USP) (8.6 mL as directed), to reconstitute Evomela and make a 50 mg/10 mL (5 mg/mL) nominal concentration of melphalan. The normal saline used to reconstitute each vial should appear to be assisted or pulled into the vial by the negative pressure (partial vacuum) present in the vial. Discard any vial (and replace with another vial) if there is no vacuum present when reconstituting the vial with normal saline.

The reconstituted Evomela drug product is stable for 24 hours at refrigerated temperature (5°C) without any precipitation due to the high solubility.

The reconstituted Evomela drug product is stable for 1 hour at room temperature.

2. Calculate the required volume of Evomela needed for a patient's dose and withdraw that volume from the vials(s).
3. Add the required volume of Evomela to (b) (4) of 0.9% Sodium Chloride Injection, USP to a final concentration not greater than 0.45 mg/mL.

The Evomela admixture solution is stable for 4 hours at room temperature in addition to the 1 hour following reconstitution.

4. Infuse over 30 minutes via an injection port or central venous catheter.

Evomela may cause local tissue damage should extravasation occur. Do not administer by direct injection into a peripheral vein. Administer Evomela by injecting slowly into a fast-running IV infusion via a central venous access line.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit

4.2 RECOMMENDATIONS FOR THE OFFICE OF PHARMACEUTICAL QUALITY (OPQ)

A. Established name versus Strength Expression

1. We note inconsistencies between the established name (*melphalan hydrochloride*) and how the strength is expressed for this product (50 mg *melphalan* free base). Each vial contains 50 mg melphalan (equivalent to 56 mg melphalan hydrochloride). We recommend OPQ considers labeling the product as follows to ensure the strength statement is clear and not confusing:

Evomela
(Melphalan) for Injection, 50 mg per vial*

*Each vial Melphalan for Injection contains 56 mg of Melphalan Hydrochloride

4.3. RECOMMENDATIONS FOR THE SPECTRUM PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA:

a. Carton Labeling


1. Reduce the size of graphic clock design next to the proprietary name because this reduces the readability of the proprietary name. In addition, the clock graphic image can look like a “c”, therefore the proprietary name can be misinterpreted as ‘Cevomela’².
2. Increase font size of established name to at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2) and unitalicize the established name to increase readability³.
3. Use (b) (4) for the proprietary name (i.e., Evomela). The proprietary name
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
4. We recommend changing the font color of the proprietary name to one color to increase readability of this important information. For example, using different colors for one name may make the proprietary name appear like two names².
5. If space allows, replace (b) (4) to “For Intravenous Infusion Only” to assist with the correct use of this product.
6. Unbold Sterile on the PDP to help ensure that the most important information such as proprietary and established names, and route of administration is the most prominent on the principal display panel (PDP).
7. Add statement “Discard Unused Portion” after the statement “Single-Use Vial”.

² DMEPA Guidance for Industry. Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 [cited 2015 Aug 17].

³ Labeling, 21 CFR 201.10(g)(2), 2015

8. Unitalicize the reconstitution information on the side panel and add the mg per mL strength information with the total mg/mL information such as, 50 mg/10 mL (5 mg/5 mL).

9.  (b) (4)

10. Remove the  (b) (4) statement from the PDP. This information adds clutter to the PDP and reduces prominence of important product information.

11. Reduce the size of the company name and logo on the PDP and back panel to assist with ensuring the most important information is the most prominent.

b. Container Vial Label

1. See a.1-10 above and revise container vial label accordingly.
2. Unbold and reduce the font size of the Rx Only statement to help ensure that the most important information such as proprietary and established name, and route of administration is the most prominent on the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Evomela that Spectrum Pharmaceuticals submitted on December 23, 2014, and the listed drug (LD).

Table 2. Relevant Product Information for Evomela and the Listed Drug		
Product Name	Evomela	Alkeran
Initial Approval Date	N/A	November 18, 1992
Active Ingredient	Melphalan hydrochloride	Melphalan hydrochloride
Indication	<ul style="list-style-type: none"> • use as a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma • the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate 	<ul style="list-style-type: none"> • the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate
Route of Administration	Intravenous	Intravenous
Dosage Form	lyophilized powder for injection	lyophilized powder for injection
Strength	50 mg per vial	50 mg per vial
Dose and Frequency	<p><i>Conditioning Treatment: 100 mg/m²/day administered over 30 minutes by intravenous (IV) infusion for 2 consecutive days (Day -3 and Day -2) prior to autologous stem cell transplantation (ASCT, Day 0).</i></p> <p><i>Palliative Treatment: 16 mg/m² administered as a single IV infusion over 15-20</i></p>	<p><i>Palliative Treatment: 16 mg/m² administered as a single IV infusion over 15-20 minutes at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals.</i></p>

	minutes at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals.	
How Supplied	For injection: 50 mg of melphalan free base, lyophilized powder in single-use vial for reconstitution.	For injection: 50 mg of melphalan free base, lyophilized powder in single-use vial for reconstitution.
Instructions for Reconstitution and Infusion	See Table A below	See Table B below
Storage	Store at room temperature 25°C (77°F). Temperature excursions are permitted between 15-30°C (59-86°F). Retain in original package until use. [see USP Controlled Room Temperature]	Store at room temperature 25°C (77°F). Temperature excursions are permitted between 15-30°C (59-86°F). Retain in original package until use. [see USP Controlled Room Temperature]

Table A: Instruction for Reconstitution and Infusion of Proposed Evomela

Evomela	Reconstitution and Infusion Instructions
---------	--

	<p>1. Normal saline solution (0.9% Sodium Chloride Injection, USP) (8.6 mL as directed), (b) (4) to reconstitute Evomela and make a 50 mg/10 mL nominal concentration of melphalan. The normal saline used to reconstitute each vial should appear to be assisted or pulled into the vial by the negative pressure (partial vacuum) present in the vial. Discard any vial (and replace with another vial) if there is no vacuum present when reconstituting the vial with normal saline.</p> <p>2. The reconstituted Evomela drug product is stable for 24 hours at refrigerated temperature (5oC) without any precipitation due to the high solubility.</p> <p>3. The reconstituted Evomela drug product is stable for 1 hour at room temperature.</p> <p>4. (b) (4) (b) (4) a final concentration of 0.45 mg/mL (b) (4)</p> <p>5. The Evomela admixture solution is stable for 4 hours at room temperature in addition to the 1 hour following reconstitution.</p> <p>6. Infuse over 30 minutes via an injection port or central venous catheter.</p>
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Table B: Instruction for Reconstitution and Infusion of reference listed drug, Alkeran

Alkeran	Reconstitution and Infusion Instructions
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1. ALKERAN for Injection must be reconstituted by rapidly injecting 10 mL of the **supplied diluent** directly into the vial of lyophilized powder using a sterile needle (20-gauge or larger needle diameter) and syringe. Immediately shake vial vigorously until a clear solution is obtained. This provides a 5-mg/mL solution of melphalan. Rapid addition of the diluent followed by immediate vigorous shaking is important for proper dissolution.
2. **Immediately** dilute the dose to be administered in 0.9% Sodium Chloride Injection, USP, to a concentration not greater than 0.45 mg/mL.
3. Administer the diluted product over a minimum of 15 minutes.
4. Complete administration within 60 minutes of reconstitution.

The time between reconstitution/dilution and administration of ALKERAN should be kept to a minimum because reconstituted and diluted solutions of ALKERAN are unstable. Over as short a time as 30 minutes, a citrate derivative of melphalan has been detected in reconstituted material from the reaction of ALKERAN with Sterile Diluent for ALKERAN. Upon further dilution with saline, nearly 1% label strength of melphalan hydrolyzes every 10 minutes. A precipitate forms if the reconstituted solution is stored at 5°C. **DO NOT REFRIGERATE THE RECONSTITUTED PRODUCT.**

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 30, 2015, we searched the L:drive using the terms, Evomela to identify label and labeling reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On July 30, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing, Canada, Pennsylvania
Search Strategy and Terms	Match Exact Word or Phrase: Evomela

D.2 Results

Our search located no ISMP articles.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on May 11, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling of the injectable formulation of reference listed drug, Alkeran. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.⁴

Table 3: FAERS Search Strategy	
Date Range	May 11, 2015
Product	Melphalan [active ingredient]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]

E.2 Results

Our search identified 7 cases, of which 3 described errors relevant for this review. One case described a wrong preparation technique error resulting in underdose. During drug preparation, a pharmacist recalled the incorrect final concentration of 10 mg/mL instead of 5 mg/mL for Alkeran after reconstitution, the incorrect calculation of 10 mg/mL was subsequently checked by a technician which did not detect the error, resulting in patient receiving approximately half of prescribed dose for one dose. The outcome for patient is unknown. Contributing factors of human error and that package labeling does not include information on the final concentration was provided.

⁴ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

We excluded four cases because they described occupational exposures and two cases due to inappropriate schedule of administration (i.e., . delayed administration to patient).

E.3 List of FAERS Case Numbers

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

Case No.	Manufacturer Control No.
3916099	Not provided
6861101	A0695882A
8301867	A0925662A

E.4 Description of FAERS

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

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

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

/s/

MICHELLE K RUTLEDGE
08/25/2015

YELENA L MASLOV
08/26/2015

MEMORANDUM

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

DATE: April 7, 2015

TO: Division of Hematology Products (DHP)

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 207155

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting the data without an on-site inspection. The rationale for this decision is noted below.

The site listed below was inspected within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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

/s/

SHILA S NKAH
04/07/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 207155 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: EVOMELA™ Established/Proper Name: Melphalan HCl Dosage Form: Powder Strengths: 50 mg (free base)/vial		
Applicant: Spectrum Pharmaceuticals Inc. Agent for Applicant (if applicable):		
Date of Application: 12/23/14 Date of Receipt: 12/23/14 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: October 23, 2015		Action Goal Date (if different):
Filing Date: 2/21/15		Date of Filing Meeting: 2/4/15
Chemical Classification (original NDAs only) :		
Proposed indication(s)/Proposed change(s): <ul style="list-style-type: none"> (Orphan): high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma. (Original 1) (Non- Orphan): Palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate (Original 2) 		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none">• A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)• The product is a Qualified Infectious Disease Product (QIDP)• A Tropical Disease Priority Review Voucher was submitted• A Pediatric Rare Disease Priority Review Voucher was submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation (orphan designation was granted for one indication but not for the other) <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 104925

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid- (for non-orphan indication) <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes, answer the bulleted questions below:	<input checked="" type="checkbox"/>	<input type="checkbox"/>																		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i> If yes, please list below:	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>																	

If yes, # years requested:				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>				
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>				
<i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ <i>If not, explain (e.g., waiver granted).</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

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

(NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<p><i>original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		<p>Since one of the proposed indications does not have orphan indication, PREA is triggered.</p> <p><u>Non- Orphan Indication:</u> “palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.”</p>
<p>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Based on the indication submitted the applicant will need to address PREA requirements for

2

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

Version: 12/09/2014

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				the second indication: “palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.” Sponsor to submit Pediatric Assessment by March 9, 2015
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, “Proprietary Name/Request for Review.”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

3

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

4

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

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consults are planned
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	PPI will be consulted to Patient Labeling.
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consults are planned
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 6/23/14 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 4, 2015

APPLICATION: NDA 207155

PROPRIETARY NAME: EVOMELA™

ESTABLISHED/PROPER NAME: Melphalan HCl for Injection

DOSAGE FORM/STRENGTH: Powder, 50 mg (free base) vial

APPLICANT: Spectrum Pharmaceuticals Inc.

PROPOSED INDICATION(S): a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with Multiple Myeloma and 2) for the palliative treatment of patients with Multiple Myeloma for whom oral therapy is not appropriate.

BACKGROUND:

Spectrum Pharmaceuticals has submitted a 505(b)(2) NDA for a new injectable melphalan formulation (Captisol-enabled melphalan HCl, 50 mg(free base)/vial). The reference listed drug (RLD) is Alkeran for Injection (NDA 20207). Spectrum states the proposed drug is a new formulation of Melphalan with two proposed indications: 1) a high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with Multiple Myeloma and 2) for the palliative treatment of patients with Multiple Myeloma for whom oral therapy is not appropriate.

The applicant has orphan designation for the first indication. The applicant has paid a user fee for the second indication (for palliative treatment) as this is not an orphan indication. The applicant was notified that they would need to submit a Pediatric Plan in keeping with PREA requirements for the non-orphan indication. The submission also includes a proprietary name (EVOMELA), which will be reviewed by OSE.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Rachel McMullen	Y
	CPMS/TL:	Theresa Carioti	Y
Cross-Discipline Team Leader (CDTL)	Albert Deisseroth, MD		Y
Division Director/Deputy	Edvardas Kaminskas, MD		Y

Clinical	Reviewer:	Patricia Dinndorf	N
	TL:	Albert Deisseroth	Y
Clinical Pharmacology	Reviewer:	Christy John	Y
	TL:	Gene Williams	Y
Biostatistics	Reviewer:	Yuan Li Shen	Y
	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Brenda Gehrke	Y
	TL:	Pedro DelValle (acting)	Y
Product Quality (CMC)	Reviewer:	Amit Mitra	Y
	TL:	Janice Brown	Y
Biopharmaceutics	Reviewer:	Maziar Kakhi	Y
	TL:	Elsbeth Chikhale	Y
Quality Microbiology	Reviewer:	Vinayak Pawar	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Donald Obenhuber	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Kevin Wright Michelle Rutledge Yelena Maslov Steven Bird Kira Leishear Shaily Arora Tracy Salaam Joyce Weaver	Y

		Naomi Redd.	
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:	Haripada Sarker (Drug Substance) Lin Qi (Process) Paul Perdue Jr. (ORA)	Y
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>The applicant has provided a scientific “bridge”, namely a bioequivalence study (CDX-353-001 Phase 2a Comparative Study) comparing EVOMELA to Alkeran.</p>
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English 	<input checked="" type="checkbox"/> YES

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

Comments:	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
IMMUNOGENICITY (protein/peptide products only)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
Comments:	
New Molecular Entity (NDAs only)	
<ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: Will be taken care of by ONDQA RPM</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: E. Kaminskas, MD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): May 12, 2015

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Review	Standard
Primary Reviews:	September 18, 2015
Secondary Reviews:	September 25, 2015
Mid-cycle Meeting	May 23, 2015
Wrap up Meeting	September 18, 2015
PDUFA Goal Date:	October 23, 2015

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter.

	<input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

RACHEL S MCMULLEN
03/05/2015

AMY C BAIRD
03/05/2015