

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125388Orig1s000**

**OTHER REVIEW(S)**



Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

Office of Biotechnology Products  
Federal Research Center  
Silver Spring, MD  
Tel. 301-796-4242

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## Memorandum

### PROJECT MANAGER'S REVIEW

Application Number: STN 125388/0 and STN **125399/0**

Name of Drug: ADCETRIS™ (brentuximab vedotin)

Sponsor: Seattle Genetics

Material Reviewed: ADCETRIS™ (brentuximab vedotin)  
Carton and Container Labels

Submission Date: February 25, 2011 and August 9, 2011

### EXECUTIVE SUMMARY

The carton and container labels for ADCETRIS™ (brentuximab vedotin) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 8/1/11-12/1/11, USP 34/NF 29. Labeling deficiencies were identified and mitigated. The carton and container labels are acceptable. Please see comments in the conclusions section.

### Background

STN 125388/0 for brentuximab vedotin is an original Biologic License Application (BLA) indicated for the treatment of patients with relapsed or refractory Hodgkin lymphoma (STN 125388) or anaplastic large cell lymphoma (STN 125399). The product is available as a 50 mg lyophilized powder supplied in a vial.

### Labels Reviewed:

ADCETRIS™ (brentuximab vedotin) Container Labels  
Vial  
ADCETRIS™ (brentuximab vedotin) Carton Labels  
Carton

## Review

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Start of Sponsor Material

(b) (4)

End of Sponsor Material

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### I. Container

#### A. 21 CFR 610.60 Container Label

1. Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:
  - a. The proper name (established name), brentuximab vedotin is displayed along with the Trade name (proprietary name), ADCETRIS™. This conforms to the regulation.
  - b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. “Manufactured for: Seattle Genetics, Inc. Bothell, WA 98021, U.S. License No. XXX” is listed. This does not conform to the regulation. Change to “Manufactured by:” based on definition of manufacturer 21 CFR 600.3(t).

- c. The lot number or other lot identification – The lot number is located on the container label. This conforms to the regulation.
  - d. The expiration date – The expiration date is displayed on the container label. This conforms to the regulation.
  - e. The recommended individual dose, for multiple dose containers – This product is supplied in a single use vial. This regulation does not apply.
  - f. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on the label. This conforms to the regulation.
  - g. If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – A medication guide is not required. This regulation does not apply.
2. Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. – The container is enclosed in a package (carton). This regulation does not apply.
  3. Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. – the product bears a full label. This regulation does not apply.
  4. No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. – This container bears a label. This regulation does not apply.

5. Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – **This does not conform to the regulation. Information requested.**
  
- B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. Per 21 CFR 207.35, the last five digits of the NDC number represent the Product-Package Code configuration in either a 3-2 or 4-1 configuration. The NDC number appears as “NDC 51144-050-01”. This conforms to the regulation.
  
- C. 21 CFR 201.5 Drugs; adequate directions for use – A reference to the prescribing information is not stated on the container label. **This does not conform to the regulation. Recommend, “See Prescribing Information for dosage and dilution.”**
  
- D. 21 CFR 201.6 Drugs; misleading statements – The only names that appear on the label are the trade name (proprietary name), ADCETRIS™ and the proper name (established name), brentuximab vedotin. This conforms to the regulation.
  
- E. 21 CFR 201.10 Drugs; statement of ingredients – The proper name (established) is not printed in letters that are at least half as large as the letters comprising the proprietary name (trade name). **This does not conform to the regulation.**
  
- F. 21 CFR 201.15 Drugs; prominence of required label statements – This conforms to the applicable parts of the regulation.
  
- G. 21 CFR 201.17 Drugs; location of expiration date – The expiration date appears under the lot number. This conforms to 21 CFR 610.60 and 21 CFR 201.17.
  
- H. 21 CFR 201.25 Bar code label requirements –A bar code is displayed on the label. This conforms to the regulation.
  
- I. 21 CFR 201.50 Statement of identity – The proper name (established name), brentuximab vedotin is stated on the label with the trade name (proprietary name), ADCETRIS. This conforms to the regulation.
  
- J. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity is declared as, “50 mg”. This conforms to the regulation. **Recommend revising to “50 mg per vial”.**

- K. 21 CFR 201.55 Statement of dosage – No statement appears on the container label with a statement of dosage or a reference to a statement of dosage. A dosage statement is provided on the carton. This conforms to the regulation. Recommend, “See Prescribing Information for dosage and dilution.”
- L. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only” and other pertinent information. This conforms to the regulation.

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Start of Sponsor Material

### **Carton Labels**

(b) (4)



Revised label submitted August 9, 2011

(b) (4)

End of Sponsor Material

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## **II. Carton**

### **A. 21 CFR 610.61 Carton/Package Label –**

- a. The proper name (established name), brentuximab vedotin is displayed along with the Trade name (proprietary name), ADCETRIS™. This conforms to the regulation.
- b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. ‘(b) (4) Seattle Genetics, Inc. Bothell, WA 98021, U.S. License No.

XXX” is listed. This does not conform to the regulation. Change to “Manufactured by:” based on definition of manufacturer.

- c. The lot number or other lot identification – A section is identified on the carton for the lot number. This conforms to the regulation.
- d. The expiration date – A section is identified on the carton for the expiration date. This conforms to the regulation.
- e. The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative” –The statement “No Preservative” is not displayed on the carton. This does not conform to the regulation. Recommend adding the statement near the vial contents.
- f. The number of containers, if more than one –The product is supplied as listed as a single-use vial. This regulation does not apply.
- g. The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable – The amount of product is expressed as 50 mg. This conforms to the regulation. Recommend revising to 50 mg per vial.
- h. The recommended storage temperature – The statement “Recommended Storage: (b) (4) is displayed on the back panel of the carton. This does not conform to the regulation. Add storage temperature range and remove reconstituted temperatures from the carton.
- i. The words (b) (4)” or the equivalent, as well as other instructions, when indicated by the character of the product –This does not conform to the regulation. Revise the storage statement to “Store vial in carton to protect from light”.
- j. The recommended individual dose if the enclosed container(s) is a multiple-dose container –The product is

supplied in a single -use vial. This regulation does not apply.

- k. The route of administration recommended, or reference to such directions in and enclosed circular – The route of presented as, “For intravenous use only”. This conforms to the regulation.
- l. Known sensitizing substances, or reference to enclosed circular containing appropriate information –none listed. This conforms to the regulation.
- m. The type and calculated amount of antibiotics added during manufacture – none listed. This conforms to the regulation.
- n. The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information. The inactive ingredients are not listed on the carton and a reference to the enclosed prescribing information is unclear. **This does not conform to the regulation. Revise statement, “Recommended Dosage: [REDACTED] (b) (4) [REDACTED]” to “See Prescribing Information.”**
- o. The adjuvant, if present –none listed. This conforms to the regulation.
- p. The source of the product when a factor in safe administration –The source of the product is not listed on the carton. This conforms to the regulation.
- q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information. – None applicable. This conforms to the regulation.
- r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency” – “No U.S. Standard of Potency” is not displayed on the carton. **This does not conform to the regulation.**
- s. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on the carton. This conforms to the regulation.

- t. If a Medication Guide is required under part 208 of this chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label –A medication guide is not required. This regulation does not apply.
- B. 21 CFR 610.62 Proper name; package label; legible type: This product is a “specified” biological product and is not subject to this regulation. This conforms to the regulation.
- C. 21 CFR 610.63 Divided manufacturing responsibility to be shown –This regulation does not apply.
- D. 21 CFR 610.64 Name and address of distributor  
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: “Manufactured for \_\_\_\_\_”. “Distributed by \_\_\_\_\_”, “Manufactured by \_\_\_\_\_ for \_\_\_\_\_”, “Manufactured for \_\_\_\_\_ by \_\_\_\_\_”, “Distributor: \_\_\_\_\_”, or “Marketed by \_\_\_\_\_”. The qualifying phrases may be abbreviated. This regulation does not apply.
- E. 21 CFR 610.65 Products for export – No foreign labels were included in the submission.
- F. 21 CFR 610.67 Bar code label requirements  
Biological products must comply with the bar code requirements at §201.25 of this chapter. – A bar code appears on the carton label. This conforms to the regulation.
- G. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located near the bottom of the primary panel and appears as, “NDC 51144-050-01”. **This does not conform to the regulation. The NDC number must be relocated to the top 1/3 of the panel.**
- H. 21 CFR 201.5 Drugs; adequate directions for use – The following statement appears on the carton, “Recommended Dosage: (b) (4).” This conforms to the regulation.  
**Recommend revising to “See Prescribing Information.”**

- I. 21 CFR 201.6 Drugs; misleading statements – The only names that appear on the label are the trade name (proprietary name), ADCETRIS and the proper name (established name), brentuximab vedotin . This conforms to the regulation.
- J. 21 CFR 201.10 Drugs; statement of ingredients – The prominence of the proper name is not at least ½ the size of the proprietary name taking into account typography, layout, contrast, and other printing features to ensure it has prominence commensurate with the proprietary name. This does not conform to the regulation.
- K. 21 CFR 201.15 Drugs; prominence of required label statements – This conforms to the regulation.
- L. 21 CFR 201.17 Drugs; location of expiration date – The expiration date appears with the lot number on the bottom of the label. This conforms to 21 CFR 610.61 and 21 CFR 201.17.
- M. 21 CFR 201.25 Bar code label requirements – A bar code appears on the carton label. This conforms to the regulation.
- N. 21 CFR 201.50 Statement of identity – The proper name (established name), brentuximab vedotin, is stated on the label with the trade name (proprietary name), ADCETRIS™. This conforms to the regulation.
- O. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity is declared as “50 mg”. This conforms to the regulation. **Recommend revising to “50 mg per vial”.**
- P. 21 CFR 201.55 Statement of dosage –The statement “Recommended Dosage: [REDACTED] (b) (4).” appears on the label. This conforms to the regulation. **Recommend revising the statement to “See Prescribing Information.”**
- Q. 21 CFR 201.100 Prescription drugs for human use – The label bears statements “Rx Only” and other pertinent information. This conforms to the regulation.

## Conclusions

- 1. Container
  - a. Please indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60. **Information provided and acceptable.**

- b. Remove the storage conditions for the reconstituted solution and provide the storage temperature range and conditions for the vial to prevent confusion. **Change made and acceptable.**
  - c. Add the statement, "See Prescribing Information for dosage and dilution." to comply with 21 CFR 201.5 and 21 CFR 201.55. The statement, "See Prescribing Information" was added. **Acceptable.**
2. Carton label
- a. Add the required statement, "No Preservative" to the side panel per 21 CFR 610.61(e) near the vial contents listing. **Statement added. Acceptable.**
  - b. Add the required statement, "No U.S. Standard of Potency" to panel per 21 CFR 610.61. **Statement added. Acceptable.**
  - c. Please add the statement, "Store vial at 2-8°C (36-46°F) in the original carton to protect from light." per 21 CFR 610.61(i). **Statement added. Acceptable.**
  - d. Relocate the NDC number from the bottom of the primary panel to the top 1/3 of the primary panel to comply with 21 CFR 201.2. **Change made and acceptable.**
  - e. Revise the recommended dosage statement to read, "See Prescribing Information." **Change made and acceptable.**
3. Carton and Container
- a. Revise the manufacturer listing per the definition of manufacturer per 21 CFR 600.3(t) from (b) (4) to "Manufactured by: ..." **Change made and acceptable.**
  - b. Revise the presentation of the proper name to at least ½ the size of the trade name taking into account typography, layout, contrast, and other printing features to ensure it has prominence commensurate with the trade name per 21 CFR 201.10(g)(2). **Change made and acceptable.**

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Kimberly Rains, Pharm.D  
Regulatory Project Manager  
CDER/OPS/OBP

Comment/Concurrence:

Marjorie Shapiro 8/18/11  
Marjorie Shapiro, Ph.D.  
Team Leader  
Division of Monoclonal Antibodies  
CDER/OPS/OBP

Kathleen Clouse, DMA DIR  
for P. Swann 08/18/2011  
Patrick Swann, Ph.D.  
Deputy Director  
Division of Monoclonal Antibodies  
CDER/OPS/OBP

# Internal Consult

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

To: Lara Akinsanya, M.S., RPM, Division of Hematology Products (DHP)

From: Adam George, Regulatory Reviewer Officer  
Division of Drug Marketing, Advertising, and Communications,  
(DDMAC) *Adam George 8/17/11*

CC: Karen Rulli, Professional Review Group II Leader, DDMAC

Date: August 17, 2011

Re: Comments on draft labeling (Package Insert) for ADCETRIS™  
(brentuximab vedotin) for Injection

BLA 125388 & 125399

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In response to your consult request dated March 30, 2011, we have reviewed the draft version of the Package Insert for ADCETRIS™ (brentuximab vedotin). DDMAC's concerns have been addressed during labeling meetings. We have no additional comments on the proposed draft version of the PI.

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medication Error Prevention and Risk Management**

Date: August 17, 2011

Application Type/Number: BLAs 125388 & 125399

To: Ann Farrell, MD, Director  
Division of Hematology Products

Through: Carlos Mena-Grillasca, RPh, Team Leader *CMena 8/17/11*  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Walter Fava, RPh, MSED, Safety Evaluator *Walter Fava 8-17-11*  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Memorandum

Drug Name and Strength: Adcetris (Brentuximab Vedotin) for **Injection**  
50 mg/vial

Applicant: Seattle Genetics Inc.

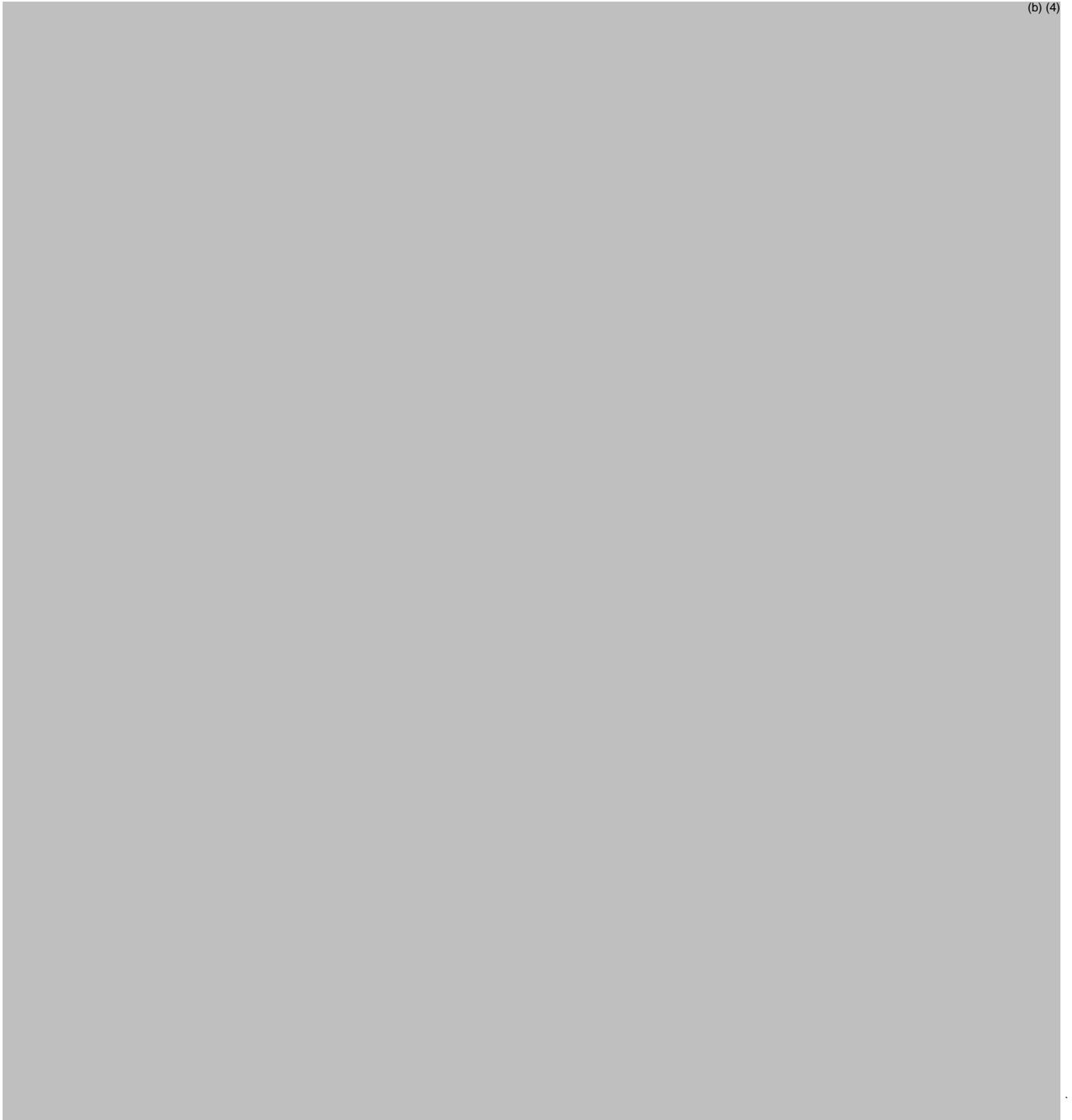
OSE RCM #: 2011-1053

This memorandum evaluates the revised container labels and carton labeling received on August 4, 2011 for Adcetris in response to a request from the Division of Drug Hematology Products (see Appendix A). DMEPA recommends including the strength statement on the side panels of the carton labeling following the presentation of the dosage form statement in the red band of the revised container labels and carton labeling. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Sponsor with regard to this memorandum. If you have further questions or need clarification, please contact OSE Regulatory Project Manager, Sean Bradley, at 301-796-1332.

**APPENDICES**

**Appendix A: Container Label and Carton Labeling**



(b) (4)

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: July 29, 2011

To: Ann Farrell, MD, Director  
Division of Hematology Products

Reviewer(s): Walter Fava, RPh, MSED, Safety Evaluator *Walter Fava 7-29-11*  
Division of Medication Error Prevention and Analysis

Team Leader Carlos Mena-Grillasca, RPh, Team Leader *C Mena 7/29/11*  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh, Director *Carol Holquist 7/29/11*  
Division of Medication Error Prevention and Analysis

Product Name/Strength: Adcetris (Brentuximab Vedotin) for Injection  
50 mg/vial

Application Type/Number: BLA 125388  
BLA 125399

Applicant/sponsor: Seattle Genetics, Inc.

OSE RCM #: 2011-1053

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1 INTRODUCTION

This review evaluates the proposed container labels and carton labeling for Adcetris (Brentuximab Vedotin) For Injection for BLA 125388 and BLA 125399. The review responds to a request from the Division of Hematology Products (DHP) to review the container labels and carton and insert labeling for these Applications. Review comments regarding the package insert were communicated to the Division during labeling meetings.

## 2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis<sup>1</sup>, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the product labels submitted on February 28, 2011 to identify vulnerabilities that may lead to medication errors. See Appendix A for samples of the draft container label and carton labeling.

## 3 CONCLUSIONS AND RECOMMENDATIONS

Our Label Risk Assessment indicates that the presentation of information on the labels and labeling introduces vulnerability to confusion that could lead to medication errors. The risks we have identified can be addressed and mitigated prior to drug approval, and thus we provide recommendations in section 3.2 be communicated to the Applicant prior to approval of these BLAs.

If you have further questions or need clarifications, please contact Sue Kang, Project Manager, at 301-796-4216.

### 3.1 COMMENTS TO THE APPLICANT

#### A. Container Label

1. Increase the prominence of the proper name to at least ½ the size of the proprietary name taking into account typography, layout, contrast, and other printing features to ensure it has prominence commensurate with the proprietary name per 21 CFR 201.10(g)(2).
2. Revise the presentation of the strength statement to read, '50 mg per vial' or '50 mg/vial'.
3. Revise the statement, (b) (4) to read, 'Single-use vial. Discard unused portion.' and relocate this statement to appear below the strength statement rather than appearing next to the strength statement.
4. Delete the vertical line on the principal display panel which appears between the strength statement, '50 mg' and the 'single-use vial' statement.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

**B. Carton Labeling**

1. See comments A1 through A4 and revise the carton labeling accordingly.
2. Relocate the NDC number to appear in the upper 1/3 portion of the principal display panel as required in 21 CFR 207.35(3)(i).
3. Revise the vial content statement on the side panel to omit the portion which reads, [REDACTED] (b) (4)
4. Revise the reconstitution statement on the side panel to read, 'After reconstitution...the concentration of Adcetris (brentuximab vedotin) is 5 mg/mL', instead of the current presentation of [REDACTED] (b) (4)
5. Revise the recommended dosage statement on the side panel to read, 'See Prescribing Information'.

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

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY**

DATE: July 25, 2011

TO: Lara Akinsaya, Regulatory Project Manager  
R. Angelo de Claro, Medical Officer  
Division of Hematology Products

FROM: Lauren Iacono-Connors, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance

THROUGH: Jean Mulinde, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance

SUBJECT: Evaluation of Clinical Inspections.

BLA: 125388

APPLICANT: Seattle Genetics

DRUG: Brentuximab Vedotin (SGN-35) for Injection

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of patients with relapsed or refractory Hodgkin lymphoma.

CONSULTATION REQUEST DATE: 4/5/2011

DIVISION ACTION GOAL DATE: 8/30/11

PDUFA DATE: 8/30/11

**I. BACKGROUND:**

Seattle Genetics Inc. (SG) seeks licensure to market Brentuximab vedotin for the treatment of relapsed or refractory Hodgkin Lymphoma (HL). Brentuximab vedotin is a CD30-directed

antibody-drug conjugate (ADC) consisting of 3 components; antibody cAC10 specific for human CD30, a potent antimicrotubule agent monomethyl auristatin E (MMAE), and a protease-cleavable linker that covalently attached MMAE to cAC10. The biological activity of Brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell.

The application is supported primarily by data from a pivotal study, Study SG035-0003, entitled, "A Pivotal Study of SGN-35 in Treatment of Patients with Relapsed or Refractory Hodgkin Lymphoma (HL)," sponsored by Seattle Genetics (SG). Planned enrollment was 100 subjects. The study enrolled 102 subjects at a total of 25 clinical sites; U.S. (19), France (3), Canada (2), and Italy (1). Eligible subjects had relapsed or refractory HL, had previously received an autologous stem cell transplant, and had histologically-documented CD30-positive disease by central review. This study was conducted under IND 71634.

Three clinical sites were inspected in accordance with the CDER Clinical Investigator Data Validation Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811); that of Dr. Robert Chen (site number 10008), Dr. Ajay Gopal (site number 10012), and Dr. Scott Smith (site number 10006). The study sponsor, SG, and a CRO, (b) (4) (Independent Review Facility), were also inspected, in accordance with the CDER Sponsor/Monitor/CRO Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.810).

The CI Sites were chosen for inspections based on high enrollment numbers and because they are significant drivers of positive efficacy result for study drug.

## II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
<b>CI#1:</b> Site #10008 – Robert (Yi-Jen) Chen, M.D. City of Hope National Medical Center 1500 E. Duarte Rd. Duarte, CA 91010	Protocol: SG035-0003  Site Number: 10008  Number of Subjects: 11	5/9/11- 6/1/11	Pending  Interim classification: VAI
<b>CI#2:</b> Site #10012 – Ajay Gopal, M.D. Seattle Cancer Care Alliance/ University of Washington Medical Center 825 Eastlake Avenue East E/MSG3-200 PO Box 19023 Seattle, WA 98109	Protocol: SG035-0003  Site Number: 10012  Number of Subjects: 7	4/26/11- 5/17/11	Pending  Interim classification: VAI

Name of CI or Sponsor/CRO, Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
<b>CI#3:</b> Site #10006 – Scott Smith, M.D. Cardinal Bernardin Cancer Center/Loyola University Medical Center 2160 S. First Ave. Bldg #112, room 245 Maywood, IL 60153	Protocol: SG035-0003  Site Number: 10006  Number of Subjects: 7	5/10/11- 6/3/11	Pending  Interim classification: VAI
<b>CRO:</b> (b) (4) (b) (4)	Protocol: SG035-0003 Site Numbers: 10008 10012 10006  Protocol: SG035-0004 Site Numbers: 10004 10012 10013	5/4/11- 5/11/11	Pending  Interim classification: NAI
<b>Sponsor:</b> Seattle Genetics POC : Clay Siegall 21823 30 <sup>th</sup> Drive SouthEast Bothell, WA 98021	Protocol: SG035-0003 Site Numbers: 10008 10012 10006  Protocol: SG035-0004 Site Numbers: 10004 10012 10013	6/29/11- 7/19/11	Pending  Interim classification: VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field and EIR has not been received from the field or complete review of EIR is pending and final classification letter has not issued.

**1. CI#1:** – Dr. Robert (Yi-Jen) Chen  
(Site Number 10008)  
City of Hope National Medical Center  
1500 E. Duarte Rd.  
Duarte, CA 91010

- a. What was inspected:** The site screened 12 subjects, 11 of those were treated. All 11 subjects completed the study. The study records of all subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed informed consent documents, and test article accountability.

**Note:** A complete review of the EIR was not available at the time this CIS was written. The general observations described below are based on preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Because the primary efficacy endpoint data were generated by an Independent Review Facility (IRF; [REDACTED] (b) (4)) the site did not have source records at the site to verify the primary efficacy endpoint reported in the application. However, the FDA field investigator verified that CT and PET scans were taken in accordance with the protocol for each subject, reviewed by the site and then sent for independent review to the IRF. The primary efficacy endpoint data for the subjects enrolled at this site were verified during the CRO inspection (see below). The FDA field investigator reviewed subject records, CRFs and source documents, assessed inclusion/exclusion criteria satisfaction and verified subject treatment regimens. There was no evidence of under-reporting of AEs. However, discrepancies were noted between source documents and CRFs for concomitant medications in 4 out of 11 subject records reviewed, and for one subject the source documents do not match the CRF for the one lot number of study drug administered. Finally, one subject received their cycle 1 dosage calculated based on their cycle 1 weight and not the protocol-specified baseline weight.

Consistent with the routine clinical investigator compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125388 were compared and verified. A Form FDA 483 was issued to the clinical investigator citing 2 inspectional observations.

**Observation 1:** Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, the source documents do not match the electronic CRF for concomitant medications in 4 out of 11 subjects.

- A. Subject 9011 was taking immune supplements and multivitamins but these were not recorded on the eCRF.
- B. Subject 9025 received the flu vaccine but this was not recorded on the eCRF.
- C. Subject 9031 received neupogen on [REDACTED] (b) (6), none of which were recorded on the eCRF.
- D. Subject 9051 was taking loperamide but this was not recorded on the eCRF.

Also, the source documents for Subject 9050 record that this subject received lot #SER011 on 3/22/10 for cycle 13 but the eCRF records that lot #SER010 was administered.

**OSI Reviewer's Note:** *This inspectional observation was unique for this site and all other drug accountability records matched that recorded in each subjects' eCRF. This*

*observation appears to be the result of a transcription error. The source records, study drug accountability records, show that Subject 9050 received study drug prepared from 18 vials of Lot# SER011 on 3/22/10. However, the eCRF for this subject records the Lot# SER010 was administered on 3/22/10. The FDA field investigator and the site personnel agreed that the discrepancy appeared to be the result of a typo in the eCRF. This explanation is plausible as the CRA transcribes the information from the drug accountability records into the eCRF via manual data entry.*

**Observation 2:** An investigation was not conducted in accordance with the investigational plan.

Specifically, the study drug dose for Subject 9022 was calculated using a weight of 61.6 kg for cycle 1 on 4/16/09; a dose of 110 mg of study drug was administered. However, the baseline weight for this subject was 62.5 kg and according to the protocol should have been used to calculate the study drug dose for cycle 1; the correct dose being 112.5 mg of study drug. It should be noted that this dose calculation error was isolated and subsequent treatment cycles used the subject's correct baseline weight for dose calculation of drug administered.

- c. Assessment of data integrity: While regulatory violations as noted above occurred at this site, they are unlikely to significantly impact primary efficacy and safety data, nor do they appear to have had a significant impact on the protection of subjects' rights or welfare.** Notwithstanding the regulatory violations noted above, the data for Dr. Chen's site, associated with Study SG035-0003 submitted to the Agency in support of BLA 125388, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary review of the EIR and communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon complete review of the final EIR.

**2. CI#2:** Dr. Ajay Gopal  
(Site Number 10012)  
Seattle Cancer Care Alliance/  
University of Washington Medical Center  
825 Eastlake Avenue East  
E/MSG3-200  
PO Box 19023  
Seattle, WA 98109

- a. What was inspected:** The site screened 9 subjects, 7 of those were treated, and 6 completed the study. The study records of all subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, and reporting of AEs in accordance with the protocol. The FDA field

investigator also assessed informed consent documents, IRB correspondence, test article accountability, monitoring reports and safety reports, and financial disclosure documentation.

**Note:** A complete review of the EIR was not available at the time this CIS was written. The general observations described below are based on preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Because the primary efficacy endpoint data were generated by an IRF (CRO, [REDACTED] (b)(4)) the site did not have source records at the site to verify the primary efficacy endpoint reported in the application. However, the FDA field investigator verified that CT and PET scans were taken in accordance with the protocol for each subject, reviewed by the site and then sent for independent review to the IRF. The primary efficacy endpoint data for the subjects enrolled at this site were verified during the CRO inspection (see below). The FDA field investigator reviewed subject records, CRFs and source documents, assessed inclusion/exclusion criteria satisfaction and verified subject treatment regimens. There was no evidence of under-reporting of AEs. However, there were several inspectional observations that were discussed with the site related to protocol deviations and record keeping violations.

Briefly, the site could not demonstrate that all plasma samples for PK analysis were processed and stored at or below -20°C within 1 hour of collection, as required by the protocol. In some cases the records showed that the date and time of sample collection and processing were properly recorded. In other cases the records show the date and time of sample collection, but only the date of sample processing without the corresponding time. In a number of cases the records show the date and time of the sample drawn, but the date or time recorded for sample processing was not recorded.

There was one serious adverse event (Subject 0078 was hospitalized from [REDACTED] (b)(6) [REDACTED]) that was not reported to the sponsor within 24 hours of the site becoming aware of the event, as required by the protocol. However, the SAE was eventually reported to the sponsor on 11/11/09.

For each subjects' treatment cycle/Day 1 post-infusion samples were to be collected 10 (±5) minutes after the end of infusion. There were 18 out of 88 "Day 1" post-infusion samples that were collected outside (from 2 to 41 minutes) of the protocol specified time frame of 10 (±5) minutes. All 7 subjects treated at this site had at least one of their post-infusion PK samples drawn out of window. All but 3 of those 18 out-of-window post-infusion PK samples were drawn within 10 minutes of the required collection timeframe; however, 10 of those samples were taken too early, less than 5 minutes post-infusion.

The FDA field investigator also noted that there were several spurious and limited protocol deviations related to study-specified procedures not conducted according to the protocol, there was a record keeping error noted for one lot of study drug in the Study Drug Accountability Log, and the site's Serum and Plasma Freezer Storage Log was incomplete.

***OSI Reviewer's Note:** The review division may consider the impact of these out-of-window post-infusion PK samples on overall PK data analysis. Please note that these PK sampling protocol deviations noted by the FDA field investigator were all included in the data listings submitted in the BLA. The 7 subjects treated at this site had at least one PK sample taken out-of-window, and 3 study subjects had more than one sample out-of-window. As stated above all samples taken out-of-window were within 41 minutes of the protocol-specified time frame. OSI reviewer Lauren Iacono-Connors and review division medical Officer R. Angelo De claro discussed the PK sample collection time protocol deviations on July 21, 2011. Dr. De claro informed that these observations should not impact study endpoint outcomes and that the Clinical Pharmacology reviewers should have adjusted their analysis to account for these deviations. Dr. De claro stated that he would follow up with the Clinical Pharmacology reviewers on this issue to confirm. The remaining inspectional observations summarized above should not importantly impact data reliability for this site as it relates to primary and secondary endpoints.*

Consistent with the routine clinical investigator compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125388 were compared and verified. A Form FDA 483 was issued to the clinical investigator citing 2 inspectional observations.

**Observation 1:** An investigation was not conducted in accordance with the investigational plan.

**Observation 2:** Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

- c. **Assessment of data integrity:** While regulatory violations as noted above occurred at this site, they are unlikely to significantly impact primary efficacy and safety data, nor do they appear to have had a significant impact on the protection of subjects' rights or welfare. Notwithstanding the observations noted above, the data for Dr. Gopal's site, associated with Study SG035-0003 submitted to the Agency in support of BLA 125388, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary review of the EIR and communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon complete review of the final EIR.

**3. CI#3: Dr. Scott Smith**  
(Site Number 10006)  
Cardinal Bernardin Cancer Center/Loyola University Medical Center  
2160 S. First Ave.  
Bldg #112, room 245  
Maywood, IL 60153

- a. What was inspected:** The site screened 7 subjects, 7 of those were treated, and 7 completed the study. The study records of all subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed informed consent documents, IRB correspondence, test article accountability, monitoring reports and safety reports.

**Note:** The EIR was not available at the time this CIS was written. The general observations described below are based on preliminary communications from the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Because the primary efficacy endpoint data were generated by an IRF (CRO/ (b)(4) ) the site did not have source records at the site to verify the primary efficacy endpoint reported in the application. However, the FDA field investigator verified that CT and PET scans were taken in accordance with the protocol for each subject reviewed by the site and then sent for independent review to the IRF, with only one exception. The primary efficacy endpoint data for the subjects enrolled at this site were verified during the CRO inspection (see below). The FDA field investigator reviewed subject records, CRFs and source documents, assessed inclusion/exclusion criteria satisfaction and verified subject treatment regimens. There was no evidence of under-reporting of AEs. However, there were several inspectional observations that were discussed with the site related to protocol deviations, record keeping violations, IRB reporting requirements, and obtaining informed consent.

Consistent with the routine clinical investigator compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125388 were compared and verified. A Form FDA 483 was issued to the clinical investigator citing 4 inspectional observations. The inspectional observations are listed below with noteworthy observations provided in detail.

**Observation 1:** Failure to report promptly to the IRB all anticipated problems involving risk to human subjects or others.

Specifically,

- a. Subject 0057 experienced an SAE reported to the site on 8/3/09; Stevens-Johnson Syndrome. This SAE was not reported to the local IRB until 3/30/11 when the oversight was found during a monitoring visit.
- b. Subject 0035 experienced 5 SAEs during the course of study treatment that were not reported to the IRB in a timely manner.
- c. The Investigator's Brochure v.6, dated 2/10/10, (with summary of changes) was received via email on 2/18/10 but not submitted to the IRB until 3/28/11.

**Observation 2:** Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration.

Specifically, the site failed to provide an updated informed consent form that included important safety updates to their IRB in a timely manner. As a result, Subjects 0002 and 0047 were not provided the change of risk information available to the site while still on study drug.

**Observation 3:** An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

- a. Six subjects did not have vital signs taken after study drug infusion, in accordance with the protocol on at least one occasion. One subject did not have vital signs taken before a study drug infusion.
- b. For 5 subjects pre- and post-infusion study drug PK samples were either not drawn, or drawn outside of the protocol-specified timeframe of 10 ( $\pm$ 5) minutes. For 4 of these 5 subjects this occurred on more than one infusion event.

**OSI Reviewer's Note:** *Based on available information, 5 post infusion samples were drawn greater than approximately 30 minutes post-infusion, but were drawn on the same day and within 3 hours of the infusion event. Eleven pre-infusion samples were drawn on the same day, but from approximately 3 hours to 9 hours prior to the start of the infusions. Dr. Smith noted in his response to the Form FDA 483, dated June 23, 2011, that the site did contact the sponsor to discuss and request guidance as this protocol-specified blood sampling was found to be logistically difficult by the site. He also indicated that a note to file was generated that states the following, "Although this PK/PD immunogenicity window was included as part of our protocol, the intent is to obtain a trough level before initiation of the next infusion. Because the half-life of the analytes of interest is approximately 4 to 6 days and the time between infusions is 21 days, the difference of a few hours will not meaningfully change the pre-dose blood levels. In addition, the actual time of collection is used in the PK calculations so that differences from the specified nominal time are taken into account. Future protocols will incorporate a wider acceptable window prior to initiation of infusion."*

*Therefore, while this inspectional observation remains a protocol violation, the insights from the review division medical officer, Dr. De claro, discussed above, and the response from the inspected entity, Dr. Smith, OSI concludes that these out-of-window pre- and post-infusion study drug PK samples should not impact study endpoints.*

- c. Subject 0057 did not have the EOT central labs or PET scan performed.

**Observation 4:** Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

- a. Subject 0002 had discrepancies between the source documents and CRF for ECOG evaluations as follows:
- Baseline source supports (Nursing Karnofsky score of 90%) an ECOG score of 0, but the recorded CRF ECOG is 1.
  - C2D1 progress notes shows a "Performance Status" of 1, which is equivalent to an ECOG of 1, yet a Karnofsky score of 90% supports an ECOG of 0. The CRF ECOG is 0.
  - Both C4D1 and C7D1 progress notes show no documentation of ECOG or PS score, but a Karnofsky score of 90% supporting an ECOG of 0; however, the recorded ECOG is 1 in the CRF for those study visits.
- b. Subject 0004 had the following record discrepancies:
- History of cancer therapies was not clearly documented in that outside source documents indicate that this subject received at least 2 doses of lenalidomide, the last one being received on either 2/12/09 or 2/19/09, but the records were conflicting and unclear. The site enrolled this subject on 3/19/09.
  - For the EOT (visit date was 8/19/09) ECG the CRF indicated "not done": however, an ECG was found in the source records dated 9/2/09.
  - Two source documents indicate a prior treatment with "ICE" and one source document indicates prior treatment with "RICE". The CRF indicates prior treatment with "RICE". The prior treatment discrepancy was not clarified in the source documents.
- c. Subject 0018 was in a study of galixumab just prior to entering the SGN trial, yet this was not recorded in the CRF for prior cancer related systemic therapies.
- d. The research coordinator's notes for Subject 0057, taken 6/23/09, document that the subject "continues with itching and night sweats", and the physician's progress notes dated 6/25/09, state, "night sweats continue". However, the baseline visit on 6/24/09 has B symptoms marked "no" and the C1D1 visit on 6/25/09 as "yes". B symptom (fever, night sweats, or weight loss of >10%) resolution rate was not listed in the protocol as a primary or secondary endpoint, but was listed as an "additional endpoint" for this study (defined as the proportion of patients with B symptoms at baseline who achieve resolution of all B symptoms at any time during the treatment period).
- e. Subject 0035's source documents show administration of cyclophosphamide/mesna and etoposide from [REDACTED] <sup>(b) (6)</sup>; however, this was not recorded in the CRF as a prior therapy for this subject. The subject was enrolled on 5/26/09.

- f. Inclusion criteria 5 states that, "At least ONE of the following as evidence of relapsed or refractory HL"... must be satisfied. The source records for the following subjects do not match the criteria checked in the CRF:
- Subject 0018: entry criteria 5a and 5b were marked "yes", but should have been marked "no". However, criteria 5e was marked "no", but should have been marked "yes."
  - Subject 0057: entry criteria 5a-5c were marked "no" but should have been marked "yes".

***OSI Reviewer's Note:** Regarding observation 4.b.i., Dr. Smith indicated in his response to the Form FDA 483 that the outside records were unclear but based on the subject's own accounting the stop date for the drug lenalidomide was 2/12/09. According to Dr. Smith, the errors in the record were likely due to user error in manipulating the electronic medical records. Regarding observation 4.a., 4.b.ii., 4.b.iii., 4.c., 4.e., and 4.f. these would not affect these subjects' eligibility for the study, nor the study endpoints. Regarding observation 4.d., B symptom resolution rate was not listed as a primary or secondary endpoint, but was listed as an "additional endpoint" for this study, defined as the proportion of patients with B symptoms at baseline who achieve resolution of all B symptoms at any time during the treatment period. Therefore, the review division may consider the impact of this isolated observation on the additional endpoint of B symptom resolution.*

- c. **Assessment of data integrity:** While regulatory violations as noted above occurred at this site, they are unlikely to significantly impact primary efficacy and safety data. Notwithstanding the observations noted above, the data for Dr. Smith's site, associated with Study SG035-0003 submitted to the Agency in support of BLA 125388, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

4. **CRO:**

(b) (4)

(b) (4)

- a. **What was inspected:** The CRO was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection included a review of the firm's organization and personnel, training and qualification records, transfer of responsibilities, "Independent Radiology Review Charters," financial disclosures, subject records and source documents, practices for training clinical sites, media (imaging) receipts, image qualifications and reading, handling and transferring data to the sponsor, and data assessment and validation for primary efficacy endpoint. All of the primary efficacy endpoints were reviewed for all applicable subjects at each of the 3 clinical sites listed above for the identified study.

**Note:** The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to OSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** Records and procedures were clear, and generally well organized. The primary efficacy endpoint data submitted to BLA 125388 and BLA 125399 were verifiable at the CRO site for the 6 FDA audited clinical sites, 3 clinical sites per study, respectively.

(b)(4) has performed multiple system analyses in an effort to implement corrective actions initiated in response to observations listed on a previously received Form FDA 483. The analyses encompassed assessments of the blinding, storing, and reading of radiographic image activities, and audit trail assessments. Read results appeared complete and accurate. Impact analyses and validation implementation was reviewed and appeared adequate. A new tool for blinding has been implemented where a combination of blinding tape and blinding pens mask the information that requires blinding. In addition, a copy is then made after blinding marks to further ensure blinding is fully effective.

Training records, qualifications and certificates of completion of required training processes prior to performing independent reads were reviewed and maintained for all radiologists involved in the studies reviewed. CVs and financial disclosures were also current and available.

Consistent with the routine Sponsor/Monitor/CRO data validation compliance program assessments for studies SG035-0003 and SG035-0004, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125388 and BLA 125399 were compared and verified. No deficiencies were noted. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data generated at this CRO, as it pertains to Studies SG035-0003 and SG035-0004 were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The data from this CRO submitted to the agency as part and in support of BLA 125388 and BLA 125399 appear reliable.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- 5. Sponsor:** Seattle Genetics, Inc.  
POC : Clay Siegall  
21823 30<sup>th</sup> Drive SouthEast  
Bothell, WA 98021

- a. **What was inspected:** The sponsor, Seattle Genetics, was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. Study, SG035-0003, was conducted at 25 Centers in the U.S., Europe, and Canada. Planned enrollment was 100 subjects, with 102 actually enrolled. Study, SG035-0004, was conducted at 22 Centers in the U.S., Europe, and Canada. Planned enrollment was 55 subjects, with 58 actually enrolled.

The FDA field investigators specifically audited subjects' records from 5 clinical study sites for each protocol. For each of the five sites for both protocols they reviewed documents associated with the IRB approvals, site and investigator qualifications, interim monitoring visits, number of patients enrolled at each site, shipping and receipt of the investigational drug, master drug label, drug accountability records, serious adverse events, protocol deviations and violations, and financial disclosure records and Form FDA 1572s.

For Study SG035-0003 the following sites were audited: Site 10004 (Dr. Anas Younes; 10 subjects), Site 10006 (Dr. Scott Smith; 7 subjects), Site 10008 (Dr. Robert Chen; 11 subjects), Site 10012 (Dr. Ajay Gopal; 7 Subjects), and Site 10015 (Dr. Joseph Rosenblatt; 6 subjects).

For Study SG035-0004 the following sites were audited: Site 10004 (Dr. Barbara Pro/Dr. Michelle Fanale; 8 subjects), Site 10005 (Dr. Nancy Bartlett; 4 subjects), Site 10012 (Dr. Andrei Shustov; 6 subjects), Site 10013 (Dr. Michael Link; 5 subjects), and Site 10018 (Dr. Radhakrishnan Ramchandren; 3 subjects).

**Note:** The EIR was not available at the time this CIS was written. The EIR will be submitted to OSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. **General observations/commentary:** Records and procedures were clear, and generally well organized. There was nothing to indicate under-reporting of AEs/SAEs. With some exceptions, overall site monitoring appeared adequate. There was no evidence of underreporting protocol violations. Written procedures for monitoring, data management and oversight of contractors were reviewed. All the U.S. and Canadian sites for both studies were monitored by either Seattle Genetics in-house CRAs or contract CRAs. For monitoring of foreign clinical sites, the Sponsor had business agreements with [REDACTED] <sup>(b) (4)</sup>. None of the sites (domestic or foreign) on either protocol was suspended or terminated. The Sponsor appeared to maintain adequate oversight on both studies. Monitoring notes indicated that efforts were made by the sponsor to ensure site compliance with the respective protocols. The monitors were timely in reminding sites to complete protocol related documentation and report adverse event information as required by the Sponsor and the IRB. There was no evidence of under-reporting of adverse events for both the

studies. The monitoring for both studies appeared to be generally adequate; however, there were a few issues related to monitoring of both studies that were identified and listed on the Form FDA 483 issued to the Applicant.

With respect to PK sampling during both protocols, the FDA field investigators inquired about whole blood stability and the effect of hemolysis on the analyte recovery in the event that blood samples are not processed and frozen within an hour, as specified in the protocol. The FDA field investigators were informed by the Sponsor that PK samples are stable for 24 hours at ambient temperature. This validation was performed by their vendor, (b) (4). Draft validation reports for the PK stability evaluation were available at the Sponsor site. Apparently, this PK stability data was not included with the BLAs, 125388 and 125399, submitted to the Agency.

Consistent with the sponsor compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125388 and BLA 125399 were compared and verified. At the conclusion of the inspection, a Form FDA 483 was issued, citing one inspectional observation, to management for deficiencies in monitoring and oversight of study conduct.

**Observation 1:** Failure to ensure proper monitoring of the study and ensure that study is conducted in accordance with the investigational plan.

Specifically, for studies SG035-0003 and SG035-0004, the study monitors failed to identify the following issues:

- a. For Study SG035-0004, Site 10012, the monitor failed to identify that an additional whole body PET scan was done for Subject 0019 on (b) (4) at Cycle 2, Day 15. According to the protocol, PET scans are to be done only at baseline, and Cycles 4 and 7. After the occurrence of this event, the monitor performed 13 monitoring visits between 11/23/09 and 6/14/11 at this site, but never discussed with the site personnel the potential risk to the subject of an additional PET scan or any corrective actions.
  - b. For Study SG035-0003, Site 10006, the monitor did not correct the failure of the site to promptly report all SAEs to the IRB.
  - c. For Studies SG035-0003 and SG035-0004, Site 10012, the monitor failed to verify that all serum and plasma samples collected for PK analysis were processed and stored at or below -20°C within 1 hour, as required by the protocol. For both the protocols, the Seattle Genetics "Serum and Plasma Freezer Storage Logs" were incomplete in that the "Verified by CRA" column, on these log sheets was never completed for any of the enrolled subjects.
- c. **Assessment of data integrity:** The data generated, as it pertains to Studies SG035-0003 and SG035-0004 were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. **While several regulatory violations were identified during the inspection, the violations are considered sporadic in nature**

**and unlikely to significantly impact primary efficacy and safety data, nor do they appear to have had a significant impact on the protection of subjects' rights or welfare.** Notwithstanding the inspectional observations noted above, the findings are that the data from this Sponsor submitted to the agency in support of BLA 125388 and BLA 125399 appear reliable.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigators. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Chen, Dr. Gopal, Dr. Smith, a study CRO (b)(4), the IRF), and study sponsor, Seattle Genetics, Inc., the study data collected appear reliable.

The 3 clinical sites inspected (Drs Chen, Gopal, and Smith) and the study sponsor, Seattle Genetics, were issued a Form FDA 483 citing inspectional observations and preliminary classifications for each of these inspections are Voluntary Action Indicated (VAI). The preliminary classification for the inspection of (b)(4), the CRO responsible for generation of primary efficacy endpoint data, is No Action Indicated (NAI).

During the inspection of Dr. Chen's site (Site 10008), minor discrepancies were noted between source documents and CRFs for concomitant medications for 4 subjects, Subject 9011 was taking immune supplements and a multivitamin, Subject 9025 received a flu vaccine, Subject 9031 received neupogen 3 times, and Subject 9051 was taking loperamide. For one subject the source documents do not match the CRF for the lot number of study drug administered at cycle 13. Finally, one subject (Subject 9022) received their cycle 1 dosage calculated based on their cycle 1 weight and not the protocol-specified baseline weight. Subject 9022 was given a dose of 110 mg of study drug which was based on cycle 1 weight. The subject's baseline weight of 62.5 kg should have been used to correctly administer 112.5 mg of study drug. This dose calculation error was isolated and subsequent treatment cycles used the subject's correct baseline weight for dose calculation of drug administered.

The inspection of Dr. Gopal's site (10012) found that the site could not demonstrate that all plasma samples for PK analysis were processed and stored at or below -20°C within 1 hour, as required by the protocol. The violation appeared to be one of record keeping and should not impact the reliability of PK analysis of samples collected by this site. The inspection also found one serious adverse event (Subject 0078 was hospitalized from (b)(6)) that was not reported to the sponsor within 24 hours of the site becoming aware of the event, as required by the protocol. However, the SAE was reported to the sponsor, albeit late, on 11/11/09. Finally, there were 18 out of 88 "Day 1" post-infusion samples that were collected outside (from 2 to 41 minutes) of the protocol

specified time frame of 10 ( $\pm$ 5) minutes after the end of infusion. All 7 subjects treated at this site had at least one of their post-infusion PK samples drawn out of window. OSI reviewer Lauren Iacono-Connors and review division medical Officer R. Angelo De claro discussed the PK sample collection time protocol deviations on July 21, 2011. Dr. De claro informed that these observations should not impact study endpoint outcomes.

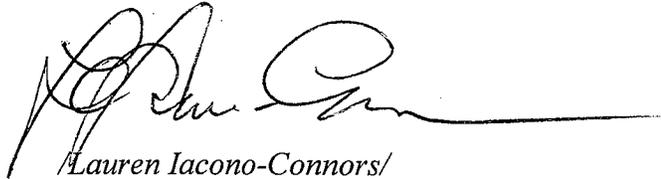
The inspection of Dr. Smith's site (10006) found that there were several inspectional observations related to protocol deviations, record keeping violations, IRB reporting requirements, and obtaining informed consent. Briefly, the site failed to provide an updated informed consent form that included important safety updates to their IRB in a timely manner. As a result, Subjects 0002 and 0047 were not provided the change of risk information available to the site while still on study drug. Further, subjects did not have vital signs taken on at least 6 occasions, as specified in the protocol, and 5 subjects pre- and post-infusion study drug PK samples were either not drawn, or drawn outside of the protocol-specified timeframe of 10 ( $\pm$ 5) minutes. While this latter inspectional observation remains a protocol violation, with the insights from the review division medical Officer, Dr. De claro, discussed above, and the response from the inspected entity, Dr. Smith, OSI concludes that these out-of-window pre- and post-infusion study drug PK samples should not impact study endpoints nor PK analyses. Also, Subject 0057 did not have the EOT central labs or PET scan performed. Finally, this site was found to have a number of discrepancies between source documents and CRFs. However, with only one exception, none of the discrepancies would have impacted subject eligibility or study endpoints. Briefly, Subject 0057 source records record that the subject reported "itching and night sweats" on 6/23/09, and on the physicians progress notes, dated 6/25/09 (C1D1), state, "night sweats continue". However, the baseline visit on 6/24/09 has B symptoms (fever, night sweats, or weight loss of  $>10\%$ ) marked "no" and the C1D1 visit on 6/25/09 as "yes". B symptom resolution rate was not listed as a primary or secondary endpoint, but was listed as an "additional endpoint" for this study; defined as the proportion of patients with B symptoms at baseline who achieve resolution of all B symptoms at any time during the treatment period. According to the data listing for B symptoms for Subject 0057, "night sweats" was reported at all study visits until the final EOT visit, on 8/20/09. Therefore, this B symptom never resolved and should have been reported as present at Baseline and unresolved while on study.

The inspection of the sponsor, Seattle Genetics Inc., revealed that the Sponsor appeared to maintain adequate oversight of both studies. The overall monitoring for both studies appeared to be adequate; however, there were a few sporadic issues related to monitoring of both studies that were identified and listed on a Form FDA 483. These monitoring deficiencies were minor and isolated; therefore, there was no systemic failure to adequately monitor the studies.

Although regulatory violations were noted as described above, for the 3 clinical investigator sites and the sponsor, Seattle Genetics Inc., they are unlikely to significantly impact safety and efficacy analyses. The overall data in support of this application may be considered reliable based on available information.

**Note:** Observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

**Follow-Up Actions:** OSI will generate an inspection summary addendum if the conclusions change significantly upon final review of the EIRs and supporting inspection evidence and exhibits.



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

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**Pediatric and Maternal Health Staff Labeling Review**

**Date:** July 13, 2011

**Date Consulted:** March 30, 2011

**From:** Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst  
Pediatric and Maternal Health Staff

**Through:** Hari Cheryl Sachs, MD, Team Leader – Pediatric Team  
Pediatric and Maternal Health Staff

Karen Feibus, MD, Team Leader – Maternal Health Team  
Pediatric and Maternal Health Staff

Lisa Mathis, M.D., OND Associate Director,  
Pediatric and Maternal Health Staff

**To:** Division of Hematology Products (DHP)

**Drug:** Adcetris (brentuximab vedotin) BLAs 125388 and 125399

**Subject:** Pregnancy, Nursing Mothers, and Pediatric Use Labeling

**Materials Reviewed:**

- Adcetris labeling, submitted March 25, 2011
- Draft Pharmacology/Toxicology Review, sent July 6, 2011

**Consult Question:** Please review the proposed Pregnancy, Nursing Mothers, and Pediatric Use subsections of Adcetris labeling.

*Jan Best 7/12/11*

*Jan Sachs 7/13/2011*

*Karen Feibus 7/13/2011*

*LLM 7/12/2011*

## **INTRODUCTION**

On February 25, 2011, Seattle Genetics submitted an original Biologics Licensing Application (BLA 125388) for Adcetris (brentuximab vedotin) for accelerated approval for the indications of relapsed or refractory Hodgkin lymphoma and relapsed of refractory systemic anaplastic large cell lymphoma (ALCL). The Division of Hematology Drug Products (DHP) administratively split the BLA and assigned BLA 125399 for the relapsed or refractory systemic ALCL indication.

DHP consulted both the Pediatric Team and Maternal Health Team of the Pediatric and Maternal Health Staff (PMHS) to review the proposed Pregnancy, Nursing Mothers, and Pediatric Use subsections of Adcetris labeling.

## **BACKGROUND**

### **Brentuximab Vedotin**

Brentuximab vedotin is a CD30-directed antibody drug conjugate (ADC) consisting of the antibody cAC10, specific for human CD30, the antimicrotubule agent MMAE and a protease-cleavable linker that covalently attaches MMAE to cAC10. Orphan designation was granted for both proposed brentuximab vedotin indications; Hodgkins lymphoma on January 30, 2007 and ALCL on October 23, 2008.

Clinical studies conducted to date include clinical pharmacology studies and Phase 2 open label clinical trials in patients with relapsed or refractory Hodgkin lymphoma and relapsed of refractory systemic ALCL. Phase 3 clinical trials are currently underway. The clinical trials have enrolled patients both internationally and in the U.S. The U.S. clinical trials have been open to enrollment for patients  $\geq 12$  years of age. The Phase 2 open label clinical trial for the indication of relapsed or refractory Hodgkin lymphoma included one patient between the ages of 12 and 18 years of age. The Phase 2 open label clinical trial for the indication of relapsed or refractory systemic ALCL did not enroll any patients between the ages of 12 and 18 years of age.

Embryofetal developmental studies with brentuximab vedotin were conducted in rats. Marked adverse events, including increased early resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, and fetal malformations (e.g., umbilical hernia and malrotated hind limbs), were seen in rats at doses equivalent to the recommended human dose. Fertility and early embryonic development studies and prenatal developmental studies were not conducted as these studies are not required for drugs to treat advanced cancer (see ICH S9 Guidance).

DHP granted a priority review for both of the brentuximab vedotin BLAs and the applications will be discussed at an Oncology Drug Advisory Committee meeting scheduled to be held on July 13 and 14, 2011.

## **PROPOSED SPONSOR LABELING (submitted March 25, 2011)**

### **HIGHLIGHTS OF PRESCRIBING INFORMATION**

#### **Warnings and Precautions**

##### **Use in Pregnancy**

*Reviewer Comments:*

- 1. The heading for this warning should reflect the issue that required the warning, which in this case is embryofetal toxicity.*
- 2. The pregnancy category is not needed in WARNINGS AND PRECAUTIONS.*

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

*Reviewer Comments:*

1. *The pregnancy subsection is to provide clinically relevant information for the use of a drug during pregnancy. Information regarding females or males of reproductive potential belong in other sections/subsections if needed.*
2. *There is no need to provide a cross-reference back to WARNINGS AND PRECAUTIONS from the Pregnancy subsection. All of the information is contained in the Pregnancy subsection.*
3. *The following language is the required regulatory language for a pregnancy category D drug: "If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus."*

### **8.3 Nursing Mothers**

It is not known whether brentuximab vedotin (b) (4) excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ADCETRIS a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of (b) (4) to the mother.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.4 Pediatric Use**

## **PROPOSED PHARMACOLOGY/TOXICOLOGY REVISIONS FOR PREGNANCY LABELING**

### **HIGHLIGHTS OF PRESCRIBING INFORMATION**

#### **USE IN SPECIFIC POPULATIONS**

## **5 WARNINGS AND PRECAUTIONS**

### **5.6**

(b) (4)  
There are no adequate and well-controlled studies of ADCETRIS in pregnant women. However, based on its mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Brentuximab vedotin caused embryo-fetal toxicities, including (b) (4) and malformations, in animals at maternal exposures that were similar to human exposures at the recommended doses for patients with HL and ALCL. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. [see Use in Specific Populations (8.1)].

*Reviewer Comments:*

1. *The heading for this warning should reflect the issue that required the warning, which in this case is embryofetal toxicity.*

### **8.1 Pregnancy**

Pregnancy Category D [See 'Warnings and Precautions (5.6)].

There are no adequate and well-controlled studies of ADCETRIS in pregnant women. Brentuximab vedotin caused embryo-fetal toxicities in animals at maternal exposures that were similar to human exposures at the recommended doses for patients with HL and ALCL. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus.

In an embryo-fetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1, 3, and 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 6 and 13). Drug-induced embryofetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption ( $\geq 99\%$ ), pre-implantation and post-implantation loss ( $\geq 99\%$ ), decreased numbers of live fetuses, and fetal malformations (e.g., umbilical hernia and malrotated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same as exposure in HL and ALCL patients who received the recommended dose of 1.8 mg/kg every three weeks.

## **DISCUSSION AND CONCLUSIONS**

### **Pregnancy**

No human data is available on the use in brentuximab vedotin in pregnant women. Based on the drug's mechanism of action, as well as data from embryofetal development studies in rats, brentuximab vedotin is expected to cause fetal harm in a pregnant woman. A pregnancy category D classification is the appropriate pregnancy category for this product based on the benefit/risk analysis.

### **Nursing Mothers**

No human or animal data is available on the excretion of brentuximab vedotin in human or animal milk. However, because of the drug's mechanism of action and adverse event profile, human milk-feeding should not occur during brentuximab vedotin treatment.

### **Pregnancy and Nursing Mothers Labeling**

The Pregnancy and Nursing Mothers subsections of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the benefits of treating the patient with the potential risks to the mother, fetus and/or infant. PMHS- maternal health labeling recommendations comply with current regulations but incorporate "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women when available, and outcomes of studies conducted in animals, as well as the required regulatory language for the designated

pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management.

### **Pediatric Use**

The clinical trial U.S. enrollment for brentuximab vedotin have been open to pediatric patients  $\geq$  12 years of age; however, the phase 2 trial for the indication of relapsed or refractory Hodgkin lymphoma included one patient between the ages of 12 and 18 years of age and the Phase 2 open label clinical trial for the indication of relapsed or refractory systemic ALCL did not enroll any patients between the ages of 12 and 18 years of age. Both relapsed and refractory Hodgkins Lymphoma and ALCL are less common in the pediatric population than in adult patients. The Pediatric Research Equity Act PREA (21 U.S.C. 355c) requires that all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Required pediatric studies under the PREA are not applicable for either brentuximab vedotin BLAs, as orphan designation was granted for both the Hodgkins lymphoma and ALCL indications. FDA will review any pediatric studies that are conducted with brentuximab vedotin; however, will not require that any pediatric studies be initiated unless a new BLA is submitted that triggers PREA.

### **Pediatric Use Labeling**

The Pediatric Use subsection should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted.

### **PMHS LABELING RECOMMENDATIONS**

Provided below are the PMHS recommended Pediatric Use labeling for Adcetris (brentuximab vedotin). A tracked-changes version of labeling with these PMHS recommended labeling revisions can be found in Appendix A of this review.

#### **HIGHLIGHTS OF PRESCRIBING INFORMATION**

##### **Warnings and Precautions**

- (b) (4)

##### **USE IN SPECIFIC POPULATIONS**

- (b) (4)

### **5 WARNINGS AND PRECAUTIONS**

(b) (4)  
There are no adequate and well-controlled studies of ADCETRIS in pregnant women. However, based on its mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Brentuximab vedotin caused embryo-fetal toxicities, including (b) (4) and malformations, in animals at maternal exposures that

were similar to human exposures at the recommended doses for patients with HL and ALCL. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Category D

There are no adequate and well-controlled studies of ADCETRIS in pregnant women. However, based on its mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Brentuximab vedotin caused embryo-fetal toxicities, (b) (4) in animals at maternal exposures that were similar to human exposures at the recommended doses for patients with HL and ALCL. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus.

In an embryo-fetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1, 3, and 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 6 and 13). Drug-induced embryofetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption ( $\geq 99\%$ ) (b) (4) post-implantation loss ( $\geq 99\%$ ), decreased numbers of live fetuses, and fetal malformations (e.g., umbilical hernia and malrotated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same as exposure in HL and ALCL patients who received the recommended dose of 1.8 mg/kg every three weeks.

### 8.3 Nursing Mothers

It is not known whether (b) (4) is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ADCETRIS a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

The safety and effectiveness of ADCETRIS have not been established in the pediatric population (b) (4)

(b) (4)

## APPENDIX A – PMHS Tracked-Changes Labeling Revisions

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

Date: June 8, 2011

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.   
Division Director  
Division of Cardiovascular and Renal Products /CDER

To: Lara Akinsanya  
Regulatory Project Manager  
Division of Hematology Products

Subject: QT-IRT Consult to BLA 125388 and BLA 125399

**Interdisciplinary Review Team for QT Studies Consultation:  
Thorough QT Study Review**

<b>BLA</b>	125388
<b>Brand Name</b>	Adcetris
<b>Generic Name</b>	Brentuximab Vedotin
<b>Sponsor</b>	Seattle Genetics
<b>Indication</b>	Relapsed or Refractory Hodgkin Lymphoma and Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma
<b>Dosage Form</b>	IV infusion
<b>Drug Class</b>	CD30-Directed Antibody-Drug Conjugate
<b>Therapeutic Dosing Regimen</b>	1.8 mg/kg Every 21 Days
<b>Duration of Therapeutic Use</b>	Till DLT or Disease Progression
<b>Maximum Tolerated Dose</b>	1.8 mg/kg Every 21 Days
<b>Submission Number and Date</b>	February 25, 2011
<b>Review Division</b>	OODP / HFD 150

**1 SUMMARY**

**1.1 OVERALL SUMMARY OF FINDINGS**

No large changes (i.e., >20 ms) in QTc interval were detected following brentuximab vedotin 1.8 mg/kg i.v. infusion in patients with CD30-positive malignancies. The largest upper bound of the 2-sided 90% CI for the mean change from baseline was 2.9 ms, observed at one hour post-dose on Day 1 of Cycle 1. In addition, within the range of concentrations observed in this study, no apparent concentration-QT relationship was

identified. However, small increases in QTc interval (i.e., <10 ms) with the use of brentuximab vedotin cannot be excluded due to study design limitations.

In this non-randomized, open-label study 46 patients with CD30-positive malignancies received 1.8 mg/kg brentuximab vedotin as a 30-minute i.v. infusion every 3 weeks. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Brentuximab Vedotin (1.8 mg/kg) (FDA Analysis)**

Treatment	Day, Time (hour)	$\Delta$ QTcI (ms)	90% CI (ms)
Brentuximab Vedotin 1.8 mg/kg	Day 1, 1 hour	1.3	(-0.3; 2.9)

The tested dose of 1.8 mg/kg is the maximum tolerated dose in patients and is therefore adequate for QT evaluation. The current expected high clinical exposure scenario is a 25% increase in  $C_{max}$  with concomitant strong CYP3A4 inhibitors.

## 2 PROPOSED LABEL

### 2.1 THE SPONSOR PROPOSED LABEL

*The sponsor proposed the following language in the package insert.*

#### PHARMACODYNAMICS

##### Cardiac Electrophysiology

(b) (4)

*Reviewer's comments: A total of 52 patients were enrolled in the QT study. Among them, 46 patients were considered as evaluable.*

### 2.2 QT-IRT PROPOSED LABEL

*We have the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.*

#### Section 12.2 Pharmacodynamics:

*The effect of brentuximab vedotin (1.8 mg/kg) on QTc interval was evaluated in an open-label, single-arm study in 46 evaluable patients with CD30-expressing hematologic*

### 3 BACKGROUND

#### 3.1 PRODUCT INFORMATION

SGN-35 (brentuximab vedotin) is a CD30-directed antibody-drug conjugate (ADC) consisting of three components: 1) the antibody cAC10, specific for human CD30, 2) the antimicrotubule agent MMAE, and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. Brentuximab vedotin has an approximate molecular weight of 153 kDa. Approximately 4 molecules of MMAE are attached to each antibody molecule. SGN-35 is proposed for the treatment of patients with relapsed or refractory Hodgkin lymphoma (HL) and relapsed or refractory systemic anaplastic large cell lymphoma (ALCL).

#### 3.2 MARKET APPROVAL STATUS

Brentuximab is not approved for marketing in any country.

#### 3.3 PRECLINICAL INFORMATION

Source: *Pharmacology written Summary, eCTD 2.6.2,*

##### "hERG Assay

The effect of MMAE on hERG K<sup>+</sup> channels, heterologously expressed in Human Embryonic Kidney (HEK) 293 cells, was evaluated using the conventional whole cell voltage clamp technique (m2.6.3.1 Pharmacology Overview, Study Number: 129-09-001). The effects on hERG K<sup>+</sup> currents were examined by measuring peak hERG tail current before and during test and control article exposure at 35±1°C. MMAE effects at 10 and 100 µM were compared to the negative control (extracellular saline). Cisapride hydrate (25 nM) was used as a positive control. MMAE at 100 µM produced a fractional block of peak hERG tail current of 0.237±0.056 that was significantly different than the effect of the negative control (mean fractional rundown of 0.063±0.023, mean±SEM), whereas MMAE at 10 µM produced a fractional block of 0.103±0.030 that was not significantly different from the effect of the negative control. Even at the 100 µM high dose of MMAE the effect on the hERG K<sup>+</sup> channel was insufficient to calculate an IC<sub>50</sub>, but is estimated to be greater than 100 µM. At the human clinical dose level of 1.8 mg/kg brentuximab vedotin, the mean C<sub>max</sub> plasma concentration of MMAE was 6.92 nM (CSR SG035-0001). MMAE at 10 µM (approximately 1,000-fold greater than MMAE C<sub>max</sub> in patients) did not have a meaningful biologic effect on the hERG channel. Therefore, it is unlikely that MMAE derived from brentuximab vedotin would block hERG K<sup>+</sup> channels.

"There were no effects of brentuximab vedotin within 4 days following a single 1-hour intravenous infusion to cynomolgus monkeys at doses up to 3 mg/kg. Parameters evaluated in this study included measures of the cardiovascular system

(ECGs, heart rate, blood pressure), the respiratory system (respiration rate and blood gasses), and nervous system (neurological evaluations and body temperature), as well as clinical observations, body weights, and clinical pathology indices.”

### 3.4 PREVIOUS CLINICAL EXPERIENCE

Source: *Summary of Clinical Safety, eCTD 2.7.4*

A total of 357 patients have received at least 1 dose of brentuximab vedotin, 160 of whom comprise the Phase 2 Population and 249 of whom comprise the Phase 1/Phase 2 Population.

The 9 patients who died within 30 days of the last dose of brentuximab vedotin across the 6 clinical studies are listed as follows in the SCS:

**Table 17 Patient deaths within 30 days of last dose**

Study Number	Patient Number	Date of Death (Study Day)	Primary Cause of Death (Preferred Term/Verbatim Term from Fatal AE)	Related to Study Treatment?
SG035-0001	001-0010	15	Febrile Neutropenia/Febrile neutropenia	Y
			Septic Shock/Sepsis/Sepsis/septic shock	Y
SG035-0002	045-0015	84	Pneumonia Influenza/ Influenza a pneumonia (presumed H1N1)	N
SG035-0003	-	-	No deaths within 30 days of last dose	-
SG035-0004	10004-0057	38	Renal failure acute/ Acute renal failure	N
			Acute myocardial infarction/ Non st segment mi	N
	10012-0034	40	Anaplastic large cell lymphoma t-and null-cell types recurrent/ Systemic disease progression (alcl)	N
	10013-0053	74	Respiratory failure/ Respiratory failure secondary to progressive disease	N
	10016-0013	93	Anaplastic large cell lymphoma t-and null-cell types recurrent/ Progressive ALCL	N
	33001-0015	24	Anaplastic large cell lymphoma t-and null-cell types recurrent/ ALCL disease progression	N
	33001-0020	138	Sudden death/ Sudden death	N
SGN35-007	-	-	No deaths during Cycle 1	-
SGN35-008A	10010-0022	21	Haemorrhage intracranial/ Intracranial hemorrhage	Y
		21	Cytomegalovirus infection/ cmv reactivation	Y
		21	Pancytopenia/ Cytopenias	Y

Source: Listing 7.3.1; CSR SGN35-008A, Listing 16.2.7.2 and Listing 16.2.7.3

There is a report of sudden death at home in a 56 year old female with ALCL. This patient also experienced SAEs of tracheal disorder (tracheal compression due to adenopathy) arrhythmia supraventricular, superinfection bacterial, and rash papular. The investigator reported that the cause of death may have been attributed to tracheal obstruction from the patient's tracheal prosthesis.

The sponsor reports that twenty patients (8%) in the Phase 1/Phase 2 Population had at least 1 treatment-emergent AE within the cardiac disorders SOC. Tachycardia (12 patients, 5%), bradycardia (3 patients), and atrial fibrillation (2 patients) were the only treatment-emergent AEs reported in more than 1 patient (Sponsor's Table 7.2.12.4, SCS).

Table 7.2.12.4: Incidence of treatment-emergent adverse events by system organ class and preferred term in the Phase 1/Phase 2 Population

System Organ Class Preferred Term	3501 (N=45) n (%)	3502 (N=44) n (%)	3503 HL (N=102) n (%)	3504 ALCL (N=58) n (%)	Total (N=249) n (%)
Cardiac disorders	5 (11)	5 (11)	5 (5)	5 (9)	20 (8)
Acute myocardial infarction	0	0	0	1 (2)	1 (0)
Atrioventricular supraventricular	0	0	0	1 (2)	1 (0)

Page 1 of 32

System Organ Class Preferred Term	3501 (N=45) n (%)	3502 (N=44) n (%)	3503 HL (N=102) n (%)	3504 ALCL (N=58) n (%)	Total (N=249) n (%)
Cardiac disorders (cont.)					
Atrial fibrillation	0	0	1 (1)	1 (2)	2 (1)
Atrioventricular block complete	0	0	0	1 (2)	1 (0)
Bradycardia	0	0	1 (1)	2 (3)	3 (1)
Cardiomegaly	1 (2)	0	0	0	1 (0)
Cyanosis	0	0	1 (1)	0	1 (0)
Myocardial ischemia	1 (2)	0	0	0	1 (0)
Palpitations	0	1 (2)	0	0	1 (0)
Sinus tachycardia	0	1 (2)	0	0	1 (0)
Tachycardia	5 (11)	3 (7)	2 (2)	2 (3)	12 (5)

Two patients had treatment-emergent AEs within the cardiac disorder SOC in Study SGN35- 008A: 1 patient with sinus tachycardia and 1 patient with atrial fibrillation. There are no reports of TdP or significant ventricular arrhythmias in the clinical program.

### 3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of brentuximab vedotin's clinical pharmacology.

## 4 SPONSOR'S SUBMISSION

### 4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the interim study report SGN35-007 for brentuximab, including electronic datasets and waveforms to the ECG warehouse. The database was initially locked on 30-Sep-2010 in order to complete an interim analysis that summarized ECG data collected from all patients from baseline through Cycle 1 Day 4. The interim CSR summarizes the Cycle 1 ECG data and also includes information for Cycle 2 Day 1 predose safety ECGs.

### 4.2 QT STUDY

#### 4.2.1 Title

An intensive QT/QTc study to investigate the effects of SGN-35 (brentuximab vedotin) on cardiac ventricular repolarization in patients with CD30-positive malignancies

#### **4.2.2 Protocol Number**

SGN35-007

#### **4.2.3 Study Dates**

Date first patient visit: 02-Feb-2010

Date last patient Cycle 2 Day 1 visit: 27-Jul-2010

#### **4.2.4 Objectives**

- To evaluate the effect of treatment with brentuximab vedotin on cardiac ventricular repolarization in patients with CD30-positive malignancies.

##### **Additional:**

- To evaluate the effect of treatment with brentuximab vedotin on other electrocardiogram (ECG) parameters, including heart rate (HR), RR interval, PR interval, QRS duration, and waveform composition.
- To investigate the relationship between corrected QT (QTc) interval and monomethyl auristatin E (MMAE) concentration.
- To investigate the relationship between QTc interval and proarrhythmic adverse events.
- To assess the safety of treatment with brentuximab vedotin.

#### **4.2.5 Study Description**

##### **4.2.5.1 Design**

This was a multicenter open-label study to evaluate the effect of brentuximab vedotin on the duration of cardiac ventricular repolarization. Patients with CD30-positive malignancies received 1.8 mg/kg brentuximab vedotin on Day 1 of each 21-day treatment cycle.

Intensive ECG monitoring was conducted during the first 4 days of Cycles 1 and 3. An ambulatory 12-lead Holter monitor was placed on Day 1, prior to the intravenous (IV) infusion of brentuximab vedotin. Postdose monitoring was conducted on Days 1, 2, 3, and 4 of Cycles 1 and 3. Qualitative safety ECG monitoring, consisting of a 12-lead Holter monitor applied for at least 2 minutes, was performed predose in Cycles 2 and 4.

Serum and plasma concentrations of MMAE, antibody drug conjugate (ADC), and total antibody (TAB) were obtained at each ECG monitoring period and QTc interval-MMAE concentration relationship was investigated. Adverse events were collected over the course of the study and reviewed to identify proarrhythmic events and any association with QTc interval.

##### **4.2.5.2 Controls**

The sponsor did not use either placebo or positive (moxifloxacin) controls.

##### **4.2.5.3 Blinding**

This is an open-label study.

## 4.2.6 Treatment Regimen

### 4.2.6.1 Treatment Arms

Patients with CD30-positive malignancies received 1.8 mg/kg brentuximab vedotin on Day 1 of each 21-day treatment cycle.

### 4.2.6.2 Sponsor's Justification for Doses

"The clinical safety data observed in the Phase 1 dose-escalation study of brentuximab vedotin administered once every 3 weeks (SG035-0001) supported the 1.8 mg/kg dose level chosen for this study. This was also the dose selected for the pivotal Phase 2 trial in patients with HL (SG035-0003)."

*Reviewer's Comment: The 1.8-mg/kg dose is the maximum tolerated dose and the intended therapeutic dose and is therefore acceptable. A supratherapeutic dose cannot be administered to patients or healthy volunteers because of toxicity concerns. The current expected high clinical exposure scenario is a 25% increase in  $C_{max}$  with concomitant strong CYP3A4 inhibitors.*

### 4.2.6.3 Instructions with Regard to Meals

There were no instructions with regards to meals.

*Reviewer's Comment: Brentuximab vedotin is administered by i.v. infusion so food effects are not anticipated.*

### 4.2.6.4 ECG and PK Assessments

A 12-lead Holter monitor was applied to patients approximately 2 hours and 15 minutes before the Day 1 dosing on Cycle 1. ECGs were extracted in quadruplicate at 30, 60, 90 and 120 minutes pre-dose and 30, 60, 90 and 120 minutes post-dose. On Days 2, 3 and 4 the 12-lead Holter was reapplied to the patient as close as possible to the start time of the pre-dose ECGs on Day 1. ECGs were extracted at 30, 60, 90 and 120 minutes after start of ECG monitoring.

Serum and plasma samples for PK were collected in Cycle 1 on Day 1 at 30 minutes post-dose. On Days 2, 3 and 4 samples were collected 120 minutes after start of ECG monitoring. Measurements for the antibody drug conjugate (ADC), total antibody (Tab) and the antimicrotubule agent monomethyl auristatin E (MMAE) were evaluated.

*Reviewer's Comment: The timing of the ECGs is reasonable to capture the QT at peak concentrations of MMAE ( $T_{max} \sim 2$  days), which is the most likely component of the antibody-drug conjugate to have potential to effect the QT interval. The timing of ECGs does not capture the peak concentrations of ADC or Tab ( $T_{max} \sim 2-3$  hours).*

### 4.2.6.5 Baseline

Pre-dose baseline was used.

#### 4.2.7 ECG Collection

Flashcards were sent to [REDACTED] <sup>(b) (4)</sup> for analysis. The flashcards were analyzed and 12-lead ECGs obtained from the Holter recording were extracted, in quadruplicate with approximately 1 to 2 minutes between ECGs, at the time points listed above.

ECGs from a single patient were read by a single, board-certified cardiologist who was responsible for annotating each ECG and conducting an arrhythmia analysis. Lead II was used for interval measurements; if unsuitable, a consistent approach to selecting an alternate lead was employed. Annotations were placed at the beginning of the P-wave, onset of the Q-wave, peak of the R-wave, and end of the T-wave. Specific arrhythmias such as Torsade de Pointes, ventricular tachycardia/fibrillation, atrial fibrillation/flutter, and supraventricular tachycardia were identified.

The cardiologist was blinded to ECG time and day, as well as patient identifier. The cardiologist read the ECGs from Cycle 1 for a single patient in a single sitting (batch reading). ECGs from Cycle 3 for a single patient were also batch read.

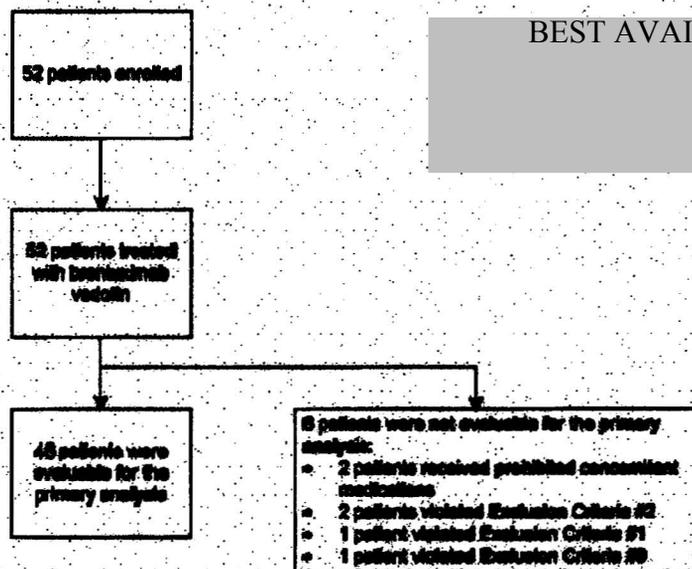
Quadruplicate ECGs were measured using semi-automated methods for the ECG intervals and overall ECG interpretation. For all ECGs, annotations were made on the Global Superimposed Median (GSM) beat. The Mortara eScribe software was used for the measurement.

#### 4.2.8 Sponsor's Results

##### 4.2.8.1 Study Subjects

52 patients with advanced CD-30 positive malignancies were enrolled. Patient disposition is as follows:

Figure 10-1: Patient disposition



(Source: Figure 10.1, CSR for SGN35-007)

## 4.2.8.2 Statistical Analyses

### 4.2.8.2.1 Primary Analysis

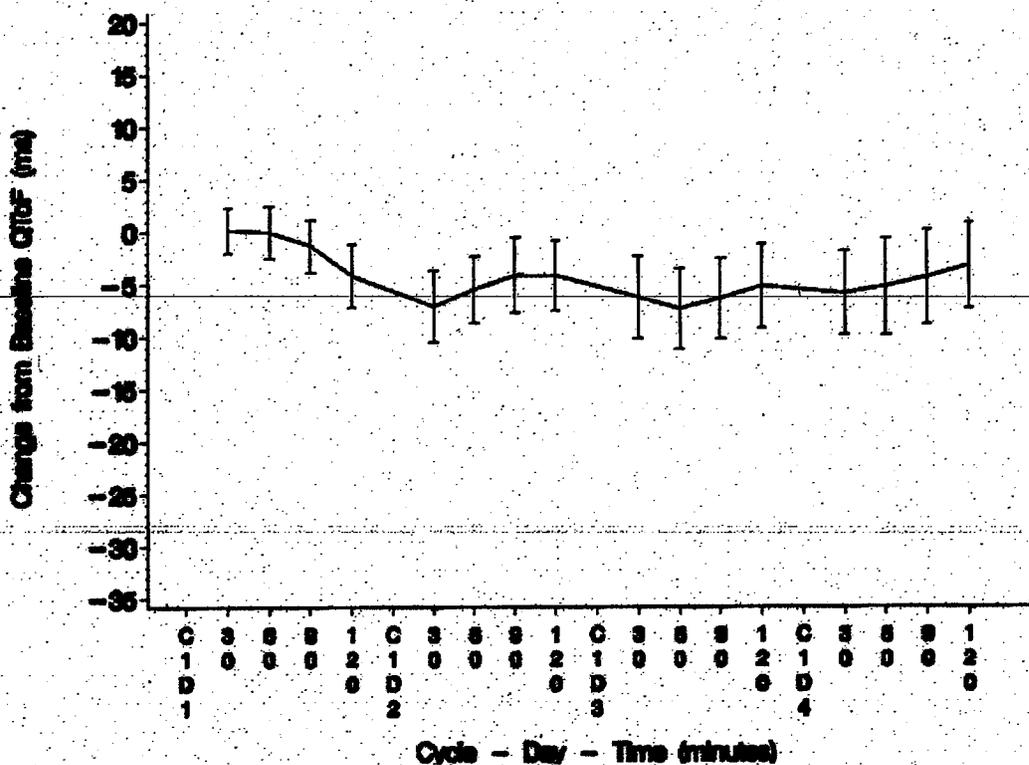
The sponsor's analysis of QTcF change from baseline in Cycle 1 is presented in Table 2 and displayed in Figure 1.

**Table 2: Change from Baseline in QTcF at Cycle 1 Days 1, 2, 3 and 4**

QTcF Interval (ms)	Statistic	Evaluable Patients			
		30 Min (N=46)	60 Min (N=46)	90 Min (N=46)	120 Min (N=46)
Change: Cycle 1, Day 1 <sup>a</sup>	n	46	46	44	41
	Min	-17.3	-23.0	-27.0	-40.6
	Mean	0.2	0.0	-1.3	-4.2
	Median	-0.4	0.3	-0.7	-5.9
	Max	23.0	21.1	14.6	16.9
	Lower 90% CI <sup>b</sup>	-2.0	-2.5	-3.8	-7.2
	Upper 90% CI <sup>b</sup>	2.4	2.4	1.2	-1.1
Change: Cycle 1, Day 2 <sup>a</sup>	n	46	46	46	46
	Min	-48.1	-50.1	-38.4	-38.6
	Mean	-7.1	-5.5	-4.1	-4.2
	Median	-6.4	-5.2	-3.7	-2.3
	Max	17.0	19.0	33.0	24.3
	Lower 90% CI <sup>b</sup>	-10.5	-8.6	-7.7	-7.5
	Upper 90% CI <sup>b</sup>	-3.7	-2.3	-0.5	-0.8
Change: Cycle 1, Day 3 <sup>a</sup>	n	44	44	44	44
	Min	-30.9	-46.1	-46.1	-45.9
	Mean	-6.2	-7.3	-6.4	-5.2
	Median	-7.6	-7.6	-6.6	-6.9
	Max	40.3	42.0	47.3	40.5
	Lower 90% CI <sup>b</sup>	-10.1	-11.2	-10.3	-9.2
	Upper 90% CI <sup>b</sup>	-2.4	-3.5	-2.5	-1.2
Change: Cycle 1, Day 4 <sup>a</sup>	n	44	44	44	44
	Min	-45.1	-57.4	-49.4	-43.6
	Mean	-5.9	-5.2	-4.3	-3.3
	Median	-7.3	-4.7	-6.2	-3.6
	Max	30.8	43.0	47.8	48.0
	Lower 90% CI <sup>b</sup>	-9.8	-9.8	-8.8	-7.3
	Upper 90% CI <sup>b</sup>	-1.9	-0.6	0.1	0.8

Source: Study Report, Table 11-4, Page 51.

**Figure 1: Change from Baseline in QTcF over Time**



Source: Study Report, Figure 11-3, Page 52.

Reviewer's Comments: The reviewer's analysis is located in section 5.2.

**4.2.8.2.2 Categorical Analysis**

The categorical analysis is summarized in Table 3 and Table 4.

**Table 3: Maximum Categorical Change from Baseline in QTcF**

QTcF Interval (ms)	Statistic	Group
		Evaluable Patients (N=46)
Greatest increase from baseline to postdose	n	46
	no increase	6 (13%)
	1-29 ms	38 (83%)
	30-60 ms	2 (4%)
	>60 ms	0 (0%)

Source: Study Report, Table 11-5, Page 53.

**Table 4: Maximum Categorical Absolute QTcF**

QTcF Interval (ms)	Statistic	Group
		Evaluable Patients (N=46)
Any Event >450 ms <sup>a</sup>	n	46
	No - n %	42 (91%)
	Yes - n %	4 (9%)
Any Event >480 ms <sup>a</sup>	n	46
	No - n %	46 (100%)
	Yes - n %	0 (0%)
Any Event >500 ms <sup>a</sup>	n	46
	No - n %	46 (100%)
	Yes - n %	0 (0%)

Source: Study Report, Table 11-6, Page 54.

#### 4.2.8.3 Safety Analysis

No deaths occurred during Cycle 1 of this study.  
Serious AEs were as follows:

**Table 12.5: Serious adverse events during Cycle 1**

Patient Number	Preferred Term	CTC Grade	Onset Study Day	Event-related to study Relationship
10001-0001	Pyrexia	G1	Pre-study	Not related
	Pyrexia	G2	7	Not related
	Renal failure	G3	7	Not related
	Pyrexia	G1	9	Not related
	Cardio-respiratory arrest	G4	9	Not related
	Respiratory failure	G4	9	Not related
	Cytosanguivous vitreous	G1	28	Not related
10004-0003	Anaphylactic reaction	G3	22	Related
	Hypoxia	G3	29	Related
	Bradycardia	G1	29	Related
10005-0002	Radiation pneumonitis	G3	2	Not related
10006-0006	Nausea	G1	Pre-study	Not related
10006-0008	Pyrexia	G2	4	Related
	Hypoxia	G3	4	Related
	Hypoxia	G4	5	Related
	Rhinitis vasomotoria	G4	11	Related
	Rhinitis vasomotoria	G1	16	Related
Pyrexia	G2	28	Not related	

Source: Listing 16.17.3

Source table 12.5, CSR for study SGN35-007

The sponsor reports that no patients experienced Torsade de Pointes, death, ventricular tachycardia, ventricular fibrillation and/or flutter, syncope, or seizures during Cycle 1.

Patient 10001-0001 a 27-year-old female with Hodgkin lymphoma presented with Grade 1 palpitations at baseline which resolved post-baseline and was not considered to be clinically significant. This patient also experienced a Grade 4 treatment-emergent SAE of cardio-respiratory arrest during Cycle 1 that was considered by the investigator to be not related to brentuximab vedotin. The patient had a medical history of congestive heart failure. Prior echocardiogram (date not reported) showed an ejection fraction of 40-45 % with moderate pericardial effusion. At baseline, the patient came on study with an elevated blood creatinine level of 1.5 mg/dL on 26-Jan-2010. The patient had experienced worsening edema and mild renal insufficiency prior to treatment with SGN-35. On 03-Feb-2010, the day after receiving the first dose of SGN-35 (1.8 mg/kg), the patient's blood creatinine level worsened to a severity of Grade 2. The patient was admitted to the hospital on (b) (6) with an elevated creatinine (Cr) of 3.1 (units and reference ranges not available) and a fever of 102 degrees Fahrenheit. Upon admission, she was noted to be pancytopenic (values not available) and treatment with broadspectrum antibiotics, granulocyte colony stimulating factor (G-CSF) and intravenous fluid was initiated. Approximately 48 hours after hospital admission, on (b) (6), the patient experienced shortness of breath, became hypotensive and suffered a pulseless electrical activity (PEA) arrest punctuated by episodes of sinus tachycardia. She had no blood pressure and required cardiopulmonary resuscitation and Advanced Cardiac Life Support care with atropine and epinephrine, as well as intubation and pressors. The patient was found to have severe cardiomyopathy, likely ischemic and acute azotemia due to acute kidney injury. A renal consultation noted chronic kidney disease stage III. The patient was started on continuous renal replacement therapies (continuous venovenous hemodialysis). The sponsor reports that the serious adverse events of cardiopulmonary arrest, respiratory failure, renal insufficiency, CMV viremia, and pyrexia resolved.

The sponsor reports AEs of grade 1 or 2 dizziness, treatment related AEs of hypotension secondary to infusion reaction and chest discomfort with no QT prolongation associated with these events.

#### **4.2.8.4 Clinical Pharmacology**

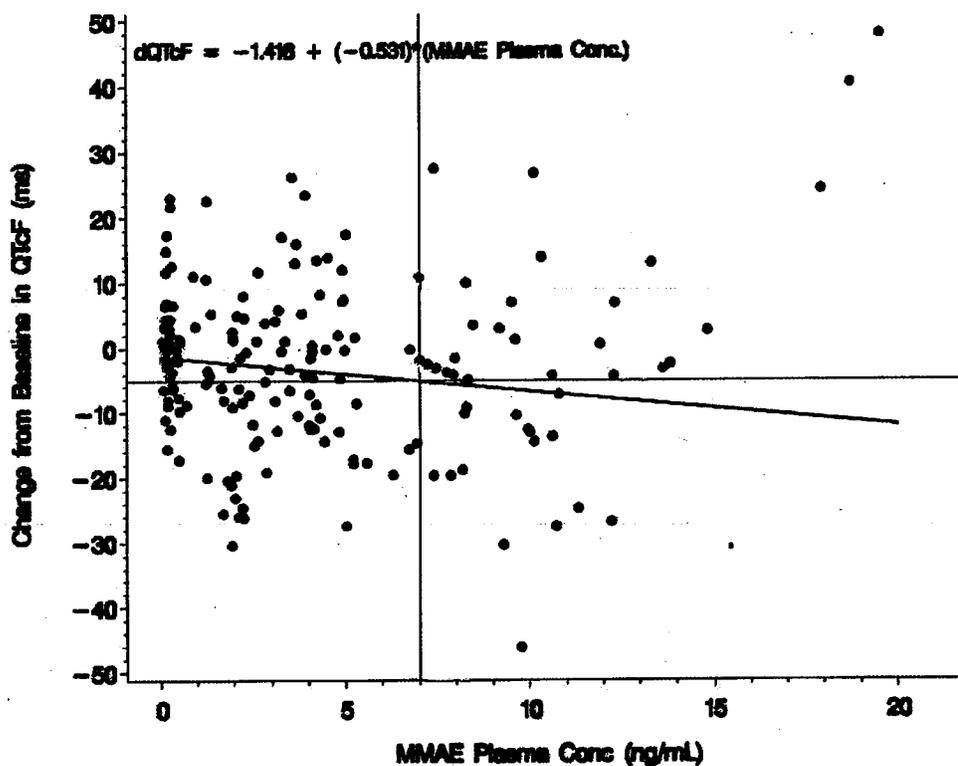
##### **4.2.8.4.1 Pharmacokinetic Analysis**

The sponsor reported the estimated  $C_{max}$  for MMAE to be 7.0 ng/mL.

*Reviewer's Analysis: Summaries of MMAE, ADC and Tab concentrations are provided in Table 10, Table 11 and Table 12, respectively.*

##### **4.2.8.4.2 Exposure-Response Analysis**

The sponsor examined the relationship between  $\Delta QTcF$  and plasma concentrations of MMAE and matched ECG Data from Cycle 1 Days 1, 2, 3 and 4 using a linear mixed effects model. The slope parameter was -0.5ms/ng/mL and the predicted  $\Delta QTcF$  at the estimated  $C_{max}$  (7.0 ng/mL) was -5 ms/ng/mL. A plot of the relationship is provided in Figure 2.

Figure 2: Sponsor's  $\Delta$ QTcF vs. MMAE Concentration

Source: Sponsor's Study Report, Figure 11-1, Page 48.

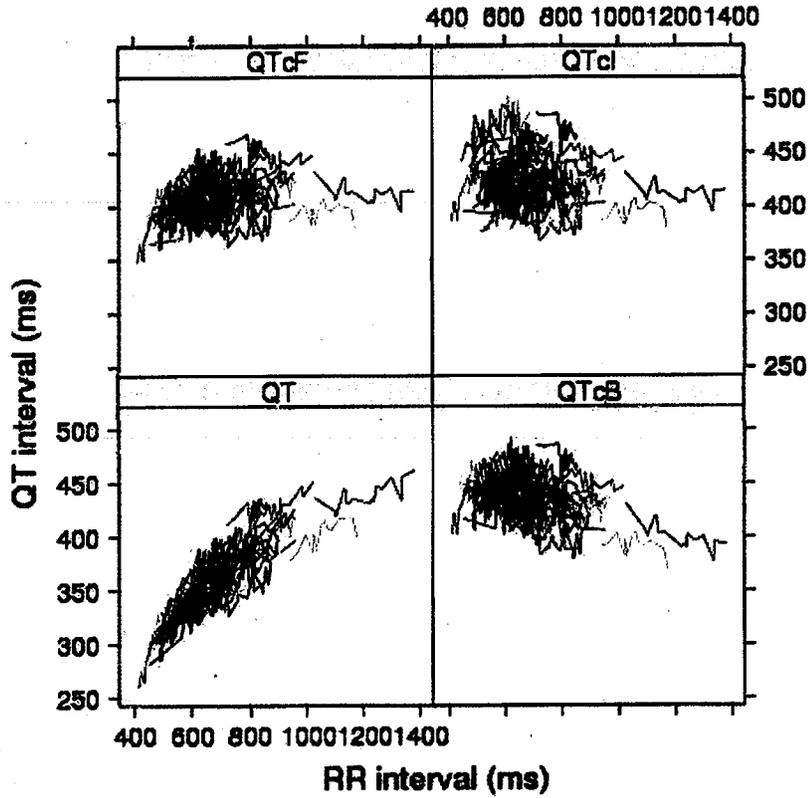
Reviewer's Analysis: Plots of  $\Delta$ QTc vs. MMAE, ADC and Tab concentrations are presented in Figure 4, Figure 5 and Figure 6, respectively.

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The relationship between different correction methods and RR is presented in Figure 3. QTcI appears to remove the heart rate effect and is therefore used in the reviewer's analysis.

**Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 Central Tendency Analysis

The mean and 90% CI of baseline-adjusted QTcI ( $\Delta$ QTcI) with time is shown in Table 5. The largest upper bound of the 90% CI was 2.88 ms.

**Table 5: Mean and 90% CI of  $\Delta$ QTcI**

Time (h)	Day	Mean $\Delta$ QTcI	Lower 90% CI	Upper 90% CI
0.5	1	1.09	-0.33	2.50
1	1	1.30	-0.27	2.88
1.5	1	-0.70	-1.96	0.55
2	1	-2.71	-4.59	-0.83
0.5	2	-6.76	-8.65	-4.87
1	2	-6.09	-7.81	-4.37
1.5	2	-4.83	-6.64	-3.02
2	2	-4.83	-6.44	-3.21
0.5	3	-5.50	-7.54	-3.46
1	3	-6.84	-8.82	-4.86
1.5	3	-6.89	-8.77	-5.01
2	3	-5.55	-7.46	-3.63
0.5	4	-5.34	-7.36	-3.32
1	4	-4.39	-6.69	-2.09
1.5	4	-4.32	-6.52	-2.12
2	4	-3.34	-5.30	-1.38

**5.2.1.2 Categorical Analysis**

Table 6 lists the number of subjects and the number of observations with QTcI values  $\geq 450$  ms, between 450 and 480 ms and  $>480$  ms.

**Table 6: Categorical Analysis of QTcI**

Treatment Group	Total N		Value $\leq 450$ ms		450 < Value $\leq 480$ ms		Value $> 480$ ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
1.8 mg/kg SGN-35	46	897	33 (71.7%)	741 (82.6%)	9 (19.6%)	128 (14.3%)	4 (8.7%)	28 (3.1%)

Table 7 lists the categorical analysis of  $\Delta$ QTcI.

**Table 7: Categorical Analysis of  $\Delta$ QTcI**

Treatment Group	Total N		Value $\leq 30$ ms		30 < Value $\leq 60$ ms		Value $> 60$ ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
1.8 mg/kg SGN-35	46	897	46 (100%)	897 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

## 5.2.2 PR and QRS Analyses

### 5.2.2.1 Categorical Analysis

Table 8 lists the number of subjects and the observations with PR measurements  $\leq 200$ ms and  $>200$  ms.

**Table 8: Categorical Analysis of PR**

Treatment Group	Total N	Total N	Value $\leq 200$ ms		Value $>200$ ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
1.8 mg/kg SGN-35	46	897	46 (100%)	897 (100%)	0 (0%)	0 (0%)

Treatment Group	Total N	Total N	Value $\leq 20$ ms		Value $>20$ ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
1.8 mg/kg SGN-35	46	713	43 (93.5%)	706 (99%)	3 (6.5%)	7 (1%)

Table 9: lists the categorical analysis of QRS measurements.

**Table 9: Categorical Analysis of QRS**

Treatment Group	Total N	Total N	Value $\leq 100$ ms		100 $<$ Value $\leq 110$ ms		Value $>110$ ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
1.8 mg/kg SGN-35	46	897	39 (84.8%)	855 (95.3%)	5 (10.9%)	23 (2.6%)	2 (4.3%)	19 (2.1%)

## 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The concentration-time profile on MMAE is flat, because of its long half-life.

Summaries of mean concentrations at the 4 sampling time points for MMAE, ADC and Tab are provided in Table 10, Table 11 and Table 12, respectively.

**Table 10: Summary of MMAE Concentrations**

Time (h)	Day	Mean	Lower 90% CI	Upper 90% CI
		Concentration (ug/L)		
0.5	1	0.28	-1.75	2.31
2	2	5.44	2.88	8.00
2	3	5.86	3.24	8.48
2	4	5.51	2.92	8.10

**Table 11: Summary of ADC Concentrations**

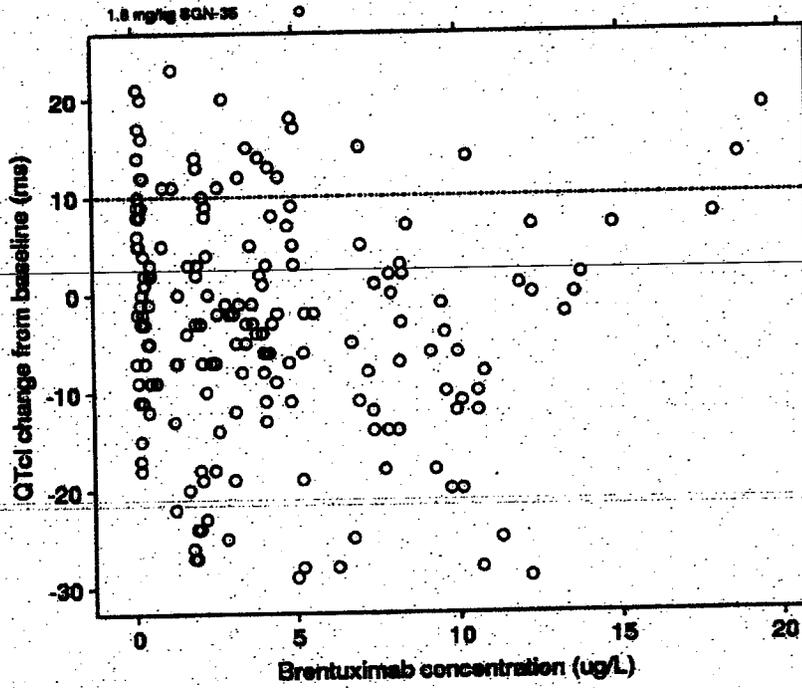
<b>Time (h)</b>	<b>Day</b>	<b>Mean Concentration (g/m<sup>3</sup>)</b>	<b>Lower 90% CI</b>	<b>Upper 90% CI</b>
0.5	1	36.54	33.21	39.87
2	2	12.69	10.11	15.28
2	3	7.83	5.46	10.20
2	4	5.60	3.31	7.89

**Table 12: Summary of Tab Concentrations**

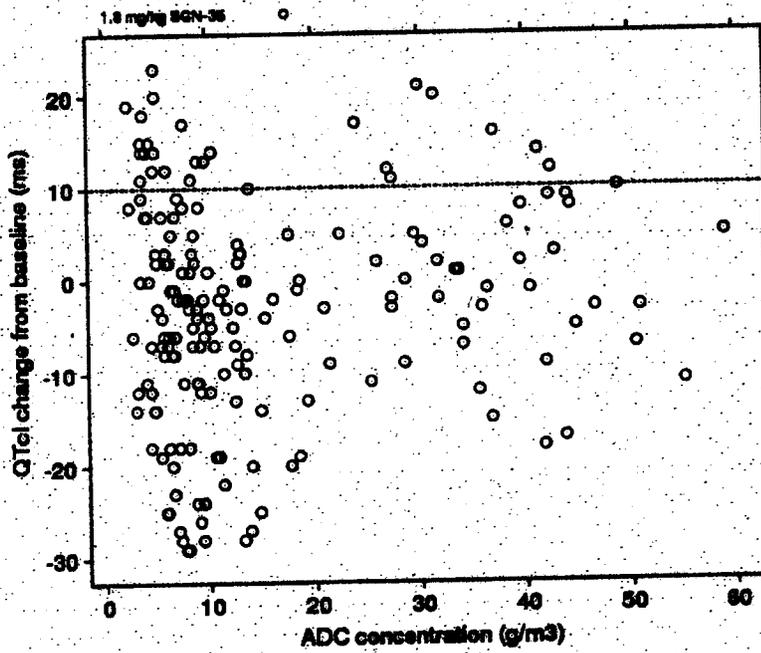
<b>Time (h)</b>	<b>Day</b>	<b>Mean Concentration (g/m<sup>3</sup>)</b>	<b>Lower 90% CI</b>	<b>Upper 90% CI</b>
0.5	1	39.51	35.95	43.06
2	2	24.67	21.44	27.90
2	3	17.91	15.01	20.81
2	4	13.80	11.06	16.54

The relationship between  $\Delta QTeI$  and MMAE, ADC and Tab concentrations is visualized in Figure 4, Figure 5 and Figure 6, respectively with no evident exposure-response relationship. A narrow range of MMAE concentrations was observed because only one dose was studied and samples were all taken close to  $T_{max}$ . Therefore, the existence of a relationship between concentrations and  $QTe$  cannot be ruled out.

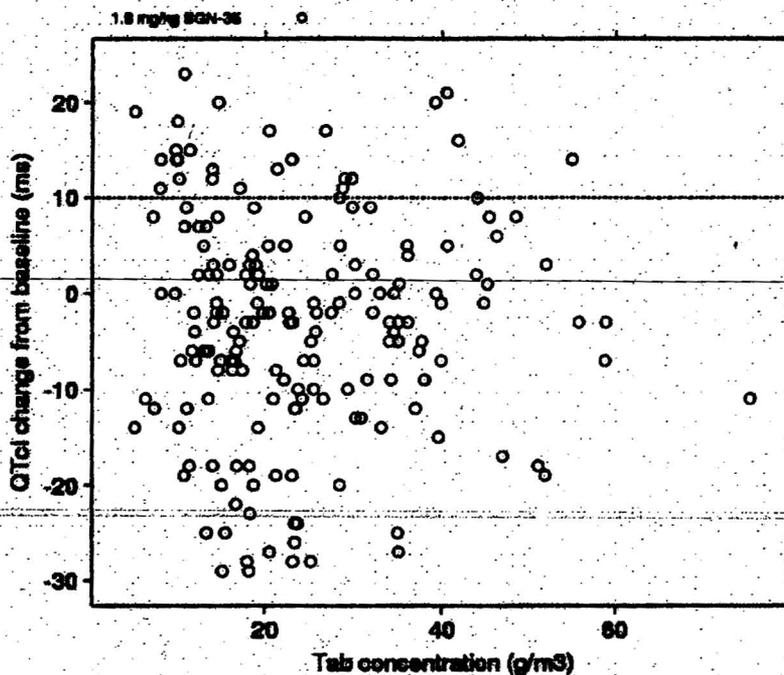
**Figure 4:  $\Delta$ QTcI vs. MMAE concentration**



**Figure 5:  $\Delta$ QTcI vs. ADC concentration**



**Figure 6:  $\Delta$ QTcI vs. Tab concentration**



## **5.4 CLINICAL ASSESSMENTS**

### **5.4.1 Safety assessments**

Events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death did not occur in this study and are discussed in sections 4.2.8.3.

### **5.4.2 ECG assessments**

Waveforms from the ECG warehouse were reviewed. The global median beat with 12-lead overlay was annotated. 1.84% of ECGs reported to have significant QT bias, according to the automated algorithm which is as expected for studies in patients. However the histogram of the distribution was narrow and symmetric, and on review of subsets of ECGs at random which were reported to have negative bias, the annotations seemed acceptable. Overall ECG acquisition and interpretation in this study appears acceptable.

### **5.4.3 PR and QRS Interval**

There were no clinically relevant effects on the PR and QRS intervals. No subject had a mean PR interval over 200 ms reported and subjects with a post-treatment QRS interval over 110 ms had a change from baseline that was less than 25%.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	1.8 mg/kg every 21 days																						
Maximum tolerated dose	1.8 mg/kg every 21 days																						
Principal adverse events	<p><b>Most common AEs</b></p> <p>The most common AEs (occurring in ≥ 20% of either Hodgkin lymphoma or systemic anaplastic large cell lymphoma patients) treatment emergent adverse events in the Phase 2 Population (SG035-0003 and SG035-0004) were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), URTI (28%), neutropenia (21%), and vomiting (20%).</p> <p><b>DLT AEs</b></p> <p>Dose limiting adverse events (SG035-0001) were</p> <ul style="list-style-type: none"> <li>• At the 1.8 mg/kg dose level: Grade 4 thrombocytopenia in 1 patient</li> <li>• At the 2.7 mg/kg dose level: Grade 3 renal failure acute, Grade 3 prostatitis and Grade 3 febrile neutropenia in the same patient, and Grade 3 hyperglycemia</li> <li>• At the 3.6 mg/kg dose level: Grade 5 febrile neutropenia and Grade 5 septic shock in the same patient</li> </ul>																						
Maximum dose tested	Single Dose	3.6 mg/kg																					
	Multiple Dose	2.7 mg/kg every 21 days																					
Exposures Achieved at Maximum Tested Dose	Single Dose	3.6 mg/kg (Study SG035-0001). A single patient was administered 3.6 mg/kg and was followed for 14 days until death.																					
	Geometric Mean (%CV)	<table border="0"> <tr> <td></td> <td>AUC<sub>0-∞</sub></td> <td>C<sub>max</sub></td> </tr> <tr> <td></td> <td>(day-μg/mL)</td> <td>(μg/mL)</td> </tr> <tr> <td>ADC</td> <td>190.71 (-)</td> <td>76.70 (-)</td> </tr> <tr> <td></td> <td>AUC<sub>0-24</sub></td> <td>C<sub>max</sub></td> </tr> <tr> <td></td> <td>(day-ng/mL)</td> <td>(ng/mL)</td> </tr> <tr> <td>MMAE</td> <td>NA (-)</td> <td>20.00 (-)</td> </tr> <tr> <td></td> <td colspan="2">NA = not available</td> </tr> </table>		AUC <sub>0-∞</sub>	C <sub>max</sub>		(day-μg/mL)	(μg/mL)	ADC	190.71 (-)	76.70 (-)		AUC <sub>0-24</sub>	C <sub>max</sub>		(day-ng/mL)	(ng/mL)	MMAE	NA (-)	20.00 (-)		NA = not available	
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<b>Range of linear PK</b>	0.1 – 3.6 mg/kg every 21 days (Study SG035-0001)																																											
<b>Accumulation at steady state</b>	Dose and regimen: 1.8 mg/kg every 21 days (Study SG035-0001)																																											
<b>Geo Mean Ratio (90% CI)</b>	<p style="text-align: center;">Accumulation Ratio</p> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 30%;"></th> <th style="width: 35%; text-align: center;">AUC<sub>0-24h</sub></th> <th style="width: 35%; text-align: center;">C<sub>max</sub></th> </tr> </thead> <tbody> <tr> <td>ADC</td> <td style="text-align: center;">0.93 (0.60, 1.43)</td> <td style="text-align: center;">0.73 (0.26, 2.01)</td> </tr> <tr> <td>MMAE</td> <td style="text-align: center;">0.69 (0.47, 1.00)</td> <td style="text-align: center;">0.54 (0.36, 0.80)</td> </tr> </tbody> </table>			AUC <sub>0-24h</sub>	C <sub>max</sub>	ADC	0.93 (0.60, 1.43)	0.73 (0.26, 2.01)	MMAE	0.69 (0.47, 1.00)	0.54 (0.36, 0.80)																																	
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ADC	0.93 (0.60, 1.43)	0.73 (0.26, 2.01)																																										
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<b>Metabolites</b>	<p>Urinary and fecal metabolite profiles suggest limited biotransformation of MMAE in patients following IV administration of brentuximab vedotin (SGN35-008). The following list contains all metabolites identified in vitro and/or in vivo for rat, monkey, and humans. The IC<sub>50</sub> was determined from a cytotoxicity assay using the human Karpas 299 cell line (Study TRN-1201-A)</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 20%;">Metabolite Designation</th> <th style="width: 50%;">Metabolic Pathway</th> <th style="width: 30%;">IC<sub>50</sub> (nM)</th> </tr> </thead> <tbody> <tr><td>C1</td><td>Oxidation</td><td>ND</td></tr> <tr><td>C2</td><td>Oxidation</td><td>ND</td></tr> <tr><td>C3<sup>a</sup></td><td>Oxidation</td><td>ND</td></tr> <tr><td>C4<sup>a</sup></td><td>O-demethylation</td><td>0.09</td></tr> <tr><td>C5<sup>a</sup></td><td>Amide hydrolysis</td><td>ND</td></tr> <tr><td>C6<sup>a</sup></td><td>Oxidation</td><td>ND</td></tr> <tr><td>C7<sup>a</sup></td><td>N-demethylation</td><td>31</td></tr> <tr><td>C8<sup>a</sup></td><td>Dehydrogenation</td><td>0.01</td></tr> <tr><td>C9<sup>a</sup></td><td>Oxidation</td><td>ND</td></tr> <tr><td>C10<sup>a</sup></td><td>N-demethylation, oxidation</td><td>ND</td></tr> <tr><td>C11</td><td>Oxidation</td><td>ND</td></tr> <tr><td>C12<sup>a</sup></td><td>Dehydrogenation, N-demethylation, oxidation (C8 + C10)</td><td>ND</td></tr> <tr><td>C13<sup>a</sup></td><td>O-demethylation, dehydrogenation (C4 + C8)</td><td>ND</td></tr> </tbody> </table> <p><sup>a</sup> Detected in human in vitro hepatocyte assays (KT-024007) or in vivo in excreta (SGN35-008). ND = not determined</p>		Metabolite Designation	Metabolic Pathway	IC <sub>50</sub> (nM)	C1	Oxidation	ND	C2	Oxidation	ND	C3 <sup>a</sup>	Oxidation	ND	C4 <sup>a</sup>	O-demethylation	0.09	C5 <sup>a</sup>	Amide hydrolysis	ND	C6 <sup>a</sup>	Oxidation	ND	C7 <sup>a</sup>	N-demethylation	31	C8 <sup>a</sup>	Dehydrogenation	0.01	C9 <sup>a</sup>	Oxidation	ND	C10 <sup>a</sup>	N-demethylation, oxidation	ND	C11	Oxidation	ND	C12 <sup>a</sup>	Dehydrogenation, N-demethylation, oxidation (C8 + C10)	ND	C13 <sup>a</sup>	O-demethylation, dehydrogenation (C4 + C8)	ND
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<b>Absorption</b>	<b>Absolute/Relative Bioavailability</b>	Not applicable IV route of administration																																										
	<b>T<sub>max</sub> Median (Range)</b>	<p style="text-align: center;">T<sub>max</sub> (days)</p> <table style="width: 100%; border-collapse: collapse;"> <tbody> <tr> <td style="width: 30%;">ADC</td> <td style="text-align: center;">0.089 (0.084, 0.254)</td> </tr> <tr> <td>MMAE</td> <td style="text-align: center;">2.093 (1.086, 3.934)</td> </tr> </tbody> </table> <p>1.8 mg/kg every 21 days (Study SG035-0001)</p>	ADC	0.089 (0.084, 0.254)	MMAE	2.093 (1.086, 3.934)																																						
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<b>Distribution</b>	<b>Vd/F or Vd</b>	<b>V<sub>m</sub> (L)</b> ADC 8.21 (24) 1.8 mg/kg every 21 days (Study SG035-0001)							
	<b>Geometric Mean (%CV)</b>								
	<b>% bound</b>	ADC: Not applicable MMAE: (Study <sup>(b) (4)</sup> 0025)							
	<b>Arithmetic Mean (%CV)</b>	<table border="1"> <thead> <tr> <th>MMAE Concentration (nM)</th> <th>Plasma Protein Binding (%)</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>67.9 (3)</td> </tr> <tr> <td>10</td> <td>77.5 (4)</td> </tr> <tr> <td>100</td> <td>82.2 (2)</td> </tr> </tbody> </table>	MMAE Concentration (nM)	Plasma Protein Binding (%)	1	67.9 (3)	10	77.5 (4)	100
MMAE Concentration (nM)	Plasma Protein Binding (%)								
1	67.9 (3)								
10	77.5 (4)								
100	82.2 (2)								
<b>Elimination</b>	<b>Route</b>	<ul style="list-style-type: none"> <li>Not applicable for ADC. Expected to be catabolized to amino acids</li> <li>Both hepatic (72%) and renal (28%) excretion of MMAE observed in a 7 day study. Approximately 23.5% of the equivalent MMAE received was recovered. (Study SGN35-008)</li> </ul>							
	<b>Terminal t<sub>1/2</sub></b>	<b>t<sub>1/2</sub> (days)</b>							
	<b>Geometric Mean (%CV)</b>	ADC 3.60 (25) MMAE 4.43 (38) 1.8 mg/kg every 21 days (Study SG035-0001)							
	<b>CL/F or CL</b>	<b>CL (L/day)</b>							
<b>Geometric Mean (%CV)</b>	ADC 1.76 (17) 1.8 mg/kg every 21 days (Study SG035-0001)								
<b>Intrinsic Factors</b>		Intrinsic factors were evaluated in a population PK model (RA2007002)							
	<b>Age</b>	Age was not a statistically significant covariate in the population PK model							
	<b>Sex</b>	The central compartment volume was approximately 14% lower for females patients compared to male patients for ADC. Sex was not a statistically significant covariate for other parameters in the population PK model.							
	<b>Race</b>	Race was not a statistically significant covariate in the population PK model							
	<b>Hepatic &amp; Renal Impairment</b>	ALT, AST, and bilirubin were not statistically significant covariates in the population PK model for ADC and MMAE. Albumin was a statistically significant covariate for MMAE clearance, volume of the peripheral compartment, and conversion from ADC. Albumin was not a statistically significant covariate for ADC.  Calculated creatinine clearance (CrCl) was not a							

		statistically significant covariate in the population PK model. Although not a statistically significant covariate, median CrCl appeared to correlate with MMAE clearance.			
Extrinsic Factors	Drug interactions	GMR (90% CI)			
		Perpetrator	Substrate	AUC <sub>0-∞</sub>	C <sub>max</sub>
		Brentuximab vedotin	Midazolam	0.94 (0.81, 1.10)	1.15 (0.76, 1.74)
		Rifampin	MMAE	0.54 (0.43, 0.68)	0.56 (0.42, 0.76)
		Ketoconazole	MMAE	1.34 (0.98, 1.84)	1.25 (0.90, 1.72)
		CYP3A4 based drug-drug interactions were evaluated in SGN35-008. Midazolam was dosed at the T <sub>max</sub> for MMAE following administration of brentuximab vedotin. No meaningful effect was observed for rifampin and ketoconazole on ADC exposures.			
	Food Effects	Not applicable			
Expected High Clinical Exposure Scenario	<p>Brentuximab vedotin ADC C<sub>max</sub> and AUC are not expected to be meaningfully increased due to any of the intrinsic or extrinsic factors evaluated.</p> <p>MMAE C<sub>max</sub> and AUC are expected to increase by 25% and 34%, respectively, following administration of a strong CYP3A4 inhibitor. These exposure levels are covered by those from the 2.7 mg/kg dose.</p>				

**Division of Hematology Products**

**REGULATORY PROJECT MANAGER LABELING REVIEW**

**Application:** STN 125388/0 and 125399/0

**Name of Drug:** ADCETRIS (brentuximab vedotin) injection

**Applicant:** Seattle Genetics. Inc.

**Labeling Reviewed**

**Submission Date:** February 25, 2011

**Receipt Date:** February 28, 2011

**Background and Summary Description:**

**Brentuximab vedotin is indicated for the treatment of patients with relapsed or refractory hodgkin lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma.**

Pre-BLA meeting: **August 12, 2010; November 18, 2010 and December 7, 2010**

Special Protocol Assessments (SPAs) meeting: **October 1, 2009**

**Review**

The PI for ADCETRIS submitted in the original submission dated February 25, 2011 follows the PLR format - no major issues with the labeling (PI, carton and container) was observed.

**Recommendations**

Minor editorial and format changes to the PI were communicated to the applicant on March 22, 2011. The sponsor provided a revised PI on March 25, 2011.

Lara Akinsanya

April 5, 2011

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Regulatory Project Manager

Date

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Chief, Project Management Staff

Date

**RPM FILING REVIEW**  
(Including Memo of Filing Meeting)

Application Information		
NDA # N/A BLA# 125388/0	NDA Supplement #:S- N/A BLA STN # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: N/A Established/Proper Name: <b>Brentuximab Vedotin</b> Dosage Form: <b>Injection</b> Strengths: <b>50 mg/vial</b>		
Applicant: <b>Seattle Genetics</b> Agent for Applicant (if applicable): N/A		
Date of Application: <b>February 25, 2011</b> Date of Receipt: <b>February 28, 2011</b> Date clock started after UN: N/A		
PDUFA Goal Date: <b>August 30, 2011</b>		Action Goal Date (if different):
Filing Date: <b>April 29, 2011</b>		Date of Filing Meeting: <b>March 30, 2011</b>
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): Relapsed or refractory Hodgkin's lymphoma		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>            and refer to Appendix A for further information.</i>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input checked="" type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): IND (b) (4) DMF # (b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		✓		
<i>If yes, explain in comment column.</i>			✓	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			✓	
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?			✓	

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input checked="" type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>✓</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>✓</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>✓</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  <b>Check the Electronic Orange Book at:</b>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="181 1446 1341 1587"> <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															<p>✓</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></p>			<p>✓</p>																	

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			✓	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes</b>, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>			✓	
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>			✓	
<p><b>If yes</b>, 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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			✓	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
<p><b>Overall Format/Content</b></p>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	✓			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	✓			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	✓			

1

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

<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)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?		✓		
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?		✓		Language included in AcKL Letter sent out 03/02/2011
<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>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	✓			

<p><b>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</b></p> <p><i>Note: Debarment Certification should use wording in FDCA 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>				
<p><b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b></p>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</b></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>			✓	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<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>			✓	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>			✓	
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>			✓	

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

<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>			✓	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>			✓	
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>			✓	
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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>	✓			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>			✓	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	✓			
Is the PI submitted in PLR format? <sup>4</sup>	✓			

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

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

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			✓	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)			✓	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
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)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>			✓	
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>			✓	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>			✓	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			✓	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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>	✓			IRT sent 03/30/11
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> N/A  <i>If yes, distribute minutes before filing meeting</i>				

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> August 12, 2010; November 18, 2010 and December 7, 2010;	✓			
<i>If yes, distribute minutes before filing meeting</i> Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> October 1, 2009	✓			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

**DATE:** March 30, 2011

**BLA/NDA/Supp #:** 125388/0

**PROPRIETARY NAME:** N/A

**ESTABLISHED/PROPER NAME:** Brentuximab vedotin

**DOSAGE FORM/STRENGTH:** Injection, 50 mg/vial

**APPLICANT:** Seattle Genetics

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):**

Indicated for the treatment of relapsed or refractory Hodgkin Lymphoma

**BACKGROUND:**

Brentuximab vedotin is a CD30-directed antibody drug conjugate (ADC) consisting of three components:

- the antibody cAC10, specific for human CD30,
- the highly potent antimicrotubule agent MMAE, and
- a protease-cleavable linker that covalently attaches MMAE to cAC10.

Brentuximab vedotin injection for intravenous infusion is supplied as a sterile, preservative free, white to off-white lyophilized cake, supplied in single-use 30mL vials (50 mg/vial).

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Lara Akinsanya	Y
	CPMS/TL:	Janet Jamison	Y
Cross-Discipline Team Leader (CDTL)	Virginia Kwitkowski		Y
Clinical	Reviewer:	Angelo de Claro	Y
	TL:	Virginia Kwitkowski	Y

Clinical Pharmacology	Reviewer:	Aakanksha Khandelwal and Bahru Habtemariam	Y
	TL:	Julie Bullock	Y
Biostatistics	Reviewer:	Kyung Yul Lee	Y
	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Yanli Ouyang	Y
	TL:	Haleh Saber	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (for BLAs/BLA efficacy supplements)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Xiao Hong Chen and Marjorie Shapiro	Y
	TL:	Janice Brown	Y
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	Bo Chi and Colleen Thomas	Y
	TL:	Patricia Hughes	Y
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Lauren Iacono-Connors	N
	TL:	Tejashri Purohit-Sheth	N
Other reviewers			
Other attendees	Ann Farrell, Edvardas Kaminskas, Anthony Murg, Kyung Lee, Francisco Borrego, Sarah Pope Miksinski, Kathleen Clouse, Ebla Ali Ibrahim, Mara Miller, and Karen Bengtson		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b> None</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b> Will provide information request to send to sponsor.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <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></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: July 13/14, 2011 <input type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<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
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<b><u>CMC Labeling Review</u></b>	
Comments: N/A	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Lara Akinsanya  <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):  <b>Comments:</b> None	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<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. List (optional):  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<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, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> </ul>

	<ul style="list-style-type: none"> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<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 checked="" type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

PMR/PMC Description: BL 125399, PMR under accelerated approval  
A randomized phase 3 trial of SGN-35 (brentuximab vedotin) in combination with CH-P versus CHOP as frontline therapy in patients with CD30-positive mature T- and NK-cell lymphomas and systemic ALCL (sALCL). Enrollment of approximately 300 patients is planned with a primary endpoint of progression free survival as determined by an independent review facility. Overall survival is a key secondary endpoint.

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/31/2012</u>
	Trial Completion:	<u>06/30/2018</u>
	Final Report Submission:	<u>06/30/2019</u>

---

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Brentuximab vedotin is a highly active agent in relapsed systemic anaplastic large cell lymphoma. This trial will prospectively test the efficacy and safety of the combination of Brentuximab with chemotherapy in an earlier stage of the disease.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

This Phase 3 trial is required per 21 CFR 601.40-46 subpart E, the accelerated approval regulations, to confirm and verify the clinical benefit of brentuximab vedotin, following the accelerated approval for the treatment of patients with relapsed systemic anaplastic large cell lymphoma.

3. If the study/clinical trial is a PMR, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See above.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other  
Prospective comparative clinical trial for efficacy and safety
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

PMR/PMC Description: BL 125388 - PMR

A randomized phase 3 trial of SGN-35 (brentuximab vedotin) in combination with AVD versus ABVD as frontline therapy in patients with advanced Hodgkin Lymphoma. Enrollment of approximately 880 patients is planned with a primary endpoint of progression free survival determined by an independent review facility. Overall survival is a key secondary endpoint.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/30/2012</u>
	Study/Trial Completion:	<u>06/30/2018</u>
	Final Report Submission:	<u>06/30/2019</u>

---

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Brentuximab vedotin is a highly active agent in Hodgkin Lymphoma that has relapsed after autologous stem cell transplantation. There are no approved treatments for use in this setting.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This Phase 3 trial is required per 21 CFR 601.40-46 subpart E, the accelerated approval regulations, to confirm and verify the clinical benefit of brentuximab vedotin, following accelerated approval for the treatment of patients with Hodgkin Lymphoma that has relapsed after autologous stem cell transplantation.

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See above.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Prospective comparative clinical trial for efficacy and safety
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: BLA-STN 125388: PMR  
Adcetris (brentuximab vedotin) Injection

Reversibility/Resolution of drug-induced peripheral neuropathy

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

We anticipate an accelerated approval for the reasons above. A cumulative peripheral neuropathy is a common adverse drug reaction. Information on the duration and reversibility of neuropathy is lacking.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Sponsor to characterize the duration and reversibility of treatment emergent neuropathy in a prospective trial.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Prospective open label trial to assess reversibility of treatment-emergent neuropathy

Required

- Observational pharmacoepidemiologic study  
 Registry studies  
 Primary safety study or clinical trial  
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
 Thorough Q-T clinical trial  
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: Perform additional experimental work to understand the impact of soluble CD30 in serum samples on the determination of anti-drug antibodies.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Some patients in the clinical studies secrete soluble CD30, the antigen recognized by the cAC10 monoclonal antibody component of brentuximab vedotin. Soluble CD30 could interfere with the detection of anti-drug antibodies in the immunogenicity assay. The rates of immunogenicity in the clinical studies to date were low and do not appear to impact efficacy, therefore this information will not provide information needed to support approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

If soluble CD30 interferes with the detection of anti-drug antibodies in the immunogenicity assay, the true rate of immunogenicity cannot be known and will not be properly reported on the package insert. The goal of this additional study is to attain a more complete understanding of the immunogenicity profile of brentuximab vedotin.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Perform additional studies as part of the validation of the immunogenicity assay to understand what, if any, levels of soluble CD30 samples interfere in the detection of anti-drug antibodies, and what additional steps may be taken in the preparation of patient samples to mitigate this interference.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Additional validation study for the immunogenicity assay.
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: SGN-35 PMC  
Provide summary data for validating all in-process product intermediate maximum hold times for the cAC10 manufacturing process at scale in a CBE0 by 12/31/2012.

---

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>12/31/2012</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The validation studies of in-process product intermediate hold times need to be conducted at the next product campaign. This is appropriate for a PMC because this PMC does not affect the safety of the product. The risk of microbial contamination is also mitigated by other microbial controls in place during manufacturing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The product intermediate hold times need to be validated at scale for microbial control. The hold times have been validated for chemical stability only.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Provide summary data for validating all in-process product intermediate maximum hold times for the cAC10 manufacturing process at scale in a CBE0 by 12/31/2012.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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PMR/PMC Description: SGN-35 PMC:  
Perform bacteriostasis/fungistasis testing for the bioburden test of the bulk drug substance (BDS) using three batches of BDS samples stored under routine sample storage conditions at 2-8°C. The summary data will be provided in an Annual Report by 12/31/2012.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>12/31/2012</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Bulk drug substance (BDS) samples need to be obtained during the next campaign for the bioburden test qualification studies. This is appropriate for a PMC because this PMC does not affect the safety of the product. The risk of frozen samples losing bacteriostasis/fungistasis effect is not very high. In addition, the BDS is manufactured under adequate microbial control, (b) (4) under controlled environment. However, the bioburden test should be qualified adequately as it is one of the specifications of the BDS.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The bulk drug substance (BDS) samples used for the bioburden test qualification studies were stored at (b) (4) prior to testing. It is not clear if the bacteriostasis/fungistasis effect of the samples was impacted by the storage condition or the freeze/thaw process. The bioburden test needs to be qualified using BDS samples stored under routine sample storage conditions.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Perform the bacteriostasis/fungistasis testing for the bioburden test of the bulk drug substance (BDS) using three batches of BDS samples stored under routine sample storage conditions at 2-8oC. The summary data will be provided in an Annual Report by 12/31/2012.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: Commit to reassess brentuximab vedotin drug substance and drug product specifications based on the combination of Intermediate lots used to manufacture SGN-35 BDS and DP when the total number of BDS and DP lots include  $\geq 25$  lots cAC10 and  $\geq 10$  lots of SGD-1006 as input intermediates and, as part of your annual Product Quality Review for brentuximab vedotin.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: _____	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Brentuximab vedotin is an antibody-drug conjugate manufactured from two pivotal intermediates, the cAC10 monoclonal antibody and the SGD-1006 drug-linker. Each lot of intermediate can be used to manufacture multiple lots of drug substance. Even though the BLA provides information on ~25-30 lots each of drug substance and drug product, the number of combinations of intermediates used to manufacture these lots is limited, therefore lot-to-lot variability has yet to be fully established. Additional post-approval manufacturing will be necessary to manufacture a sufficient number of DS and DP lots that will be representative of the range of quality attributes

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The proposed commercial release specifications for DS and DP are supported by the data provided and many have been tightened since the pivotal studies. However, the actual results suggest that some release specifications could be narrowed further. However, due to the limited number of intermediate lot combinations used to manufacture DS and DP to date, it will take post-marketing manufacturing experience to collect sufficient data to support a re-assessment and possible change in DS and DP release specifications.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

No clinical studies or additional studies required. This is a collection of DS and DP release data with a full statistical analysis of the data in order to determine if any specifications should be changed.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)  
Analysis of DS and DP release data.

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  - Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- X Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)

---

  - Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: Harmonize all CMC information contained in your application with that contained in DMF (b)(4)

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- X Other

Seattle Genetics proposed harmonizing the BLA and DMF within 3 month after approval, once the release specifications for the SGD-drug linker, described in DMF (b)(4), were clear. In addition, Seattle Genetics was requested to perform additional characterization to submit to the DMF and the study will not be completed prior to the PDUFA deadline.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The DMF describing the manufacture of the SGD-1006 drug-linker and the BLA should be harmonized to contain identical information regarding release specifications and other attributes. The purpose of this PMC is to ensure that the BLA and DMF will be harmonized in a timely fashion. Also, an additional study that is not required for approval was requested to further characterize SGD-1006. This study will not be complete until after the BLA PDUFA deadline.

3. If the study/clinical trial is a PMR, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

One additional study to further characterize the SDG-1006 intermediate was requested to be submitted to the DMF. No additional studies are required to harmonize release specifications between the BLA and DMF.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 

X Other

Complete additional characterization study and harmonize BLA and DMF within 3 months of BLA approval.

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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description:   Reevaluate the Limit of Detection (LOD) of methylene blue using standard curve with different concentrations of dye that include concentrations below the LOD. Results of the LOD determination will be appended to the method validation report and communicated to the FDA before the end of December 2011.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>12/31/2011</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This study will improve an assay that is used to test container closure integrity of stability samples. This study is appropriate for a PMC because suitability of the container closure system has been demonstrated by other tests, and release testing has confirmed drug product sterility. The study cannot be completed prior to BLA approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the study is to more accurately define the limit of detection for the dye used in the container closure integrity test for stability samples.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Reevaluate the Limit of Detection (LOD) of methylene blue using standard curve with different concentrations of dye that include concentrations below the LOD. Results of the LOD determination will be appended to the method validation report and communicated to the FDA before the end of December 2011.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

**Attachment B: Sample PMR/PMC Development Template**

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: The CDRH guidance referenced for biological indicator (BI) incubation time has been superseded by the CDRH Guidance on BI Premarket Notification 510(k) Submissions. The guidance refers to BIs used to monitor sterilization processes in health care facilities. BIs intended for use in a manufacturing setting are excluded. The <sup>(b) (4)</sup>Test BIs used for <sup>(b) (4)</sup> validation studies should be <sup>(b) (4)</sup> to confirm that all BIs are negative. This change should be made to the <sup>(b) (4)</sup> validation protocols at <sup>(b) (4)</sup> and reported in the next annual report.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>MM/DD/YYYY</u>
	Other: Report change to the FDA in the next annual report.	<u>12/31/2012</u>

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1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This is appropriate as a PMC because other data indicated that <sup>(b) (4)</sup> validation was adequate.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the PMC is to improve one of the methods used to evaluate validation studies. (b) (4)

3. If the study/clinical trial is a PMR, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The (b) (4) Test BIs used for (b) (4) validation studies should be (b) (4) to confirm that all BIs are negative. This change should be made to the (b) (4) validation protocols at (b) (4) and reported in the next annual report.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Quality study without a safety endpoint.

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)