CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125388Orig1s000

<u>CHEMISTRY REVIEW(S)</u>

ONDQA Division Director's Memo
BLA 125-388 / 125-399 ADCETRIS (brentuximab vedotin) for Injection 50 mg/vial
Date: 16-AUG-2011

16-Aug-2011

Introduction

ADCETRIS (brentuximab vedotin) for Injection (lyophilized cake) is an antibody drug conjugate. After dilution, it is administered intravenously for the treatment of relapsed or refractory Hodgkin lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma

Administrative

The original submission of this BLA was received 25-FEB-2011 from Seattle Genetics, Inc. of Bothell, WA and was granted priority review status. ONDQA reviewed portions of the original submission and three amendments which were received between 28-JUN-2011 and 08-JUL-2011. This BLA is also supported by Seattle Genetics IND 71,634.

DMF (b) (4) for brentuximab drug substance was also reviewed. NOTE: This DMF is adequate ONLY for this BLA because the information in the BLA adequately addresses the deficiencies in this DMF

There are two post marketing commitments with Seattle Genetics. These are:

1. Reassess the acceptance limits for the bulk drug substance and drug product specifications for average drug load MR_D and % unconjugated cAC10 and further tighten the currently proposed limits. (Note: The target completion date for the fulfillment of the PMC may be coordinated with the related PMCs recommended by the Office of Biotechnology Products, as necessary).
2. Harmonize the CMC information contained in DMF (b) (4) and this BLA within three months post approval. (the Applicant committed to this timing in a 7/26/2011 teleconference).

There are **no outstanding CMC deficiencies from ONDQA that impact approvability**.

Chemical name Chimeric IgG1 cAC10 covalently linked to vcMMAE

Molecular formula (b) (4) MW = 153,352 Da

Brentuximab vedotin consists of cAC10 conjugated to SGD-1006 via thioether bonds. Each antibody molecule may have 0, 2, 4, 6, or 8 conjugated SGD-1006 (drug molecule + spacer arm) moieties. On average, the drug (SGD-1006 intermediate-1006) and antibody (cAC10) molar ratio is four. Brentuximab vedotin is a heterogeneous mixture, with respect to drug conjugation ratio and also with respect to the variety of post-translational modifications of the antibody. Hence, the calculated molecular formula and predicted average molar mass of brentuximab vedotin are

based on the average molar mass of cAC10 and assume an average of four drug-linkers conjugated per antibody.

Prior to conjugation to form antibody drug conjugate, two intermediates, cAC10 (reviewed by OBP) and SGD-1006 (reviewed by ONDQA), are manufactured by different contract manufacturers.

The cAC10 antibody is manufactured by [redacted] (b) (4) [redacted]. Evaluation of the CMC information for cAC10 antibody was conducted by the Office of Biotechnology Products, which is the lead office for CMC review of this BLA.

SGD-1006 intermediate is manufactured by the [redacted] (b) (4). The ONDQA review evaluates the CMC information for SGD-1006 intermediate, relevant drug related information for SGN-35 bulk drug substance. There are no outstanding deficiencies from ONDQA. Approval is recommended.

Drug Product (ASCETRIS)

ADCETRIS (brentuximab vedotin) for Injection single-use vial containing 50 mg of brentuximab vedotin as a white to off-white lyophilized cake or powder. Prior to administration, SGN-35 drug product is reconstituted with 10.5 mL of sterile Water for Injection, USP resulting in a clear to slightly opalescent, colorless solution containing 5 mg/mL SGN-35, [redacted] (b) (4) sodium citrate, [redacted] (b) (4) trehalose, 0.2 mg/mL polysorbate 80, pH 6.6. For administration, the reconstituted solution is added to an intravenous infusion bag containing sterile 0.9% Sodium Chloride Injection, USP.

The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. The vial containing 50 mg of brentuximab vedotin is reconstituted with Sterile Water for Injection, USP, to yield a 5 mg/mL brentuximab vedotin solution. Based on the dose the required amount of this reconstituted solution, is further diluted in 0.9% saline to achieve an infusion solution of 0.4 – 1.8 mg/mL brentuximab vedotin, which is to be used within 4 hours of vial reconstitution.

There are no outstanding deficiencies from ONDQA. Approval is recommended.

Rik Lostritto, Ph.D., Director, ONDQA Division III

18-AUG-2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies (DMA)

The Quality Team Leader's Executive Summary

From: Kathleen A. Clouse, Ph.D., Director
Division of Monoclonal Antibodies
DMA/OBP/OPS/CDER

Through: Patrick Swann, Ph.D., Deputy Director
DMA/OBP/OPS/CDER

BLA Number: STN 125388 & 125399
Product: Brentuximab vedotin (Adcetris™)
Sponsor: Seattle Genetics

Date of Review: August 5, 2011
Due Date of CDTL Memo: August 9, 2011

INDEX

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, has completed review of BLA 125388/0 and 125399/0 for Adcetris™ (brentuximab vedotin) manufactured by Seattle Genetics. The data submitted in this application are adequate to support the conclusion that the manufacture of Adcetris™ (brentuximab vedotin) is well-controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated and a consistent product was produced from the multiple production runs presented. From a Product Quality perspective, it is recommended that this product be approved for human use (under conditions specified in the package insert).

II. APPROVAL LETTER INFORMATION

The following information should be communicated to the sponsor in the approval letter:

Under this license, you are approved to manufacture the monoclonal antibody (cAC10) Intermediate for brentuximab vedotin at [redacted] (b) (4), and the SGD-1006 drug-linker intermediate at [redacted] (b) (4). The brentuximab vedotin (Adcetris™) formulated bulk drug substance, SGN-35, will be manufactured at [redacted] (b) (4), and the SGN-35 final drug product will be manufactured at [redacted] (b) (4) [redacted].

The expiration date for brentuximab vedotin (Adcetris™) drug product shall be 30 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of [redacted] (b) (4) of the formulated drug product. The expiration date for the drug substance shall be [redacted] (b) (4) when stored at [redacted] (b) (4). The expiration date for the brentuximab vedotin cA10 Intermediate will be [redacted] (b) (4) when stored at [redacted] (b) (4). We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of the brentuximab vedotin drug substance and drug product and the cA10 Intermediate under 21 CFR 601.12. Data supporting extension of the expiration dating period should be submitted to the BLA Annual Report.

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

1. 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 includes ≥25 lots cAC10 and ≥10 lots of SGD-1006 as input intermediates and, as part of your annual Product Quality Review for brentuximab vedotin.

2. Commit to harmonize all CMC information contained in the BLA application with that contained in DMI (b) (4).

3. Commit to perform additional experimental work to understand the impact of soluble CD30 in serum samples on the determination of anti-drug antibodies.

IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

None identified from a DMA product quality perspective.

V. EXECUTIVE SUMMARY

A. Description of Brentuximab vedotin (Adcetris™) Drug Product and Drug Substance

Brentuximab vedotin (SGN-35) is a first-in-class chimeric IgG1□ monoclonal antibody (cA10) specific for CD30 that is conjugated to monomethyl auristatin E (MMAE) for the treatment of Hodgkin's Lymphoma (HL) and Anaplastic Large Cell Lymphoma (ALCL). CD30 is a type 1 transmembrane glycoprotein of ~120 kDa which is a member of the TNF/NGF receptor super family and is expressed mainly on activated T and B lymphocytes. CD30 was first identified as an antigen expressed on Reed-Sternberg cells of HL and in some forms of NHL. MMAE is an anti-mitotic small molecule covalently linked to the monoclonal antibody via an enzyme-cleavable linker.

Brentuximab vedotin binds to CD30 on the surface of tumor cells and is subsequently internalized and trafficked to the lysosomal compartment. Within the lysosome, the MMAE is freed upon cleavage of the linker by proteases. Upon release, the free MMAE binds to tubulin thereby disrupting the microtubule network, inducing cell cycle arrest and apoptosis of the CD30+ tumor cells.

Adcetris™ (brentuximab vedotin; SGN-35) drug product is supplied as a sterile, preservative free, white to off-white lyophilized cake or powder in a single-use vial. One vial contains 50 mg of drug product. Adcetris™ drug product has a (b) (4) overfill ((b) (4) mg/vial) to ensure that the labeled quantity (50 mg/vial) can be withdrawn from the vial, but this does not constitute an excess or overage of available drug product per vial. Adcetris™ drug product is stored at 2-8°C.

The container closure system for Adcetris™ DP is a 30 mL clear Type I glass vial having a 20 mm opening with a blowback feature, a gray (b) (4) rubber lyophilization stopper with (b) (4) coating, and a 20 mm aluminum/plastic dark green push-off seal.

The final formulation for SGN-35 bulk drug substance was determined to be (b) (4) This was selected prior to the initiation of the IND-enabling toxicology studies (b) (4) The same formulation has been used in all of the non-clinical and clinical studies. There are no novel excipients used in the Adcetris™ (brentuximab vedotin; SGN-35) drug product formulation

Prior to administration, Adcetris™ (brentuximab vedotin) is reconstituted with 10.5 mL of sterile Water for Injection, USP (WFI) that is not supplied or packaged with the brentuximab vedotin drug product. This results in a clear to slightly opalescent, colorless solution with a final Adcetris™ formulation of 5 mg/mL SGN-35, (b)(4) sodium citrate, (b)(4) trehalose, and 0.2 mg/mL polysorbate 80, at pH 6.6. For administration, the reconstituted solution is diluted in an intravenous infusion bag generally containing sterile 0.9% Sodium Chloride Injection, USP. Adcetris™ can also be diluted into 5% Dextrose Injection or Lactated Ringer's Injection.

A claim for categorical exclusion has been submitted under 21 CFR § 25.31(b). As stated in 21 CFR Part 25.31(c), action on an application for marketing approval of a biologic product is categorically excluded from environmental assessment requirements if the action is for a substance which occurs naturally in the environment, when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. The applicant states that to the applicant's knowledge, no extraordinary circumstances exist. The drug substance and intermediates are not derived from plants or animals taken from the wild. There is no information indicating that additional environmental information is warranted. The claim of categorical exclusion is accepted.

B. Clinical Trial Information

Adcetris™ (brentuximab vedotin) is proposed for the treatment of patients with Hodgkin's Lymphoma (HL) who relapse after autologous stem cell transplantation (STN 125388) and for patients with relapsed or refractory systemic Anaplastic Large Cell Lymphoma (ALCL).

Route of Administration: Intravenous injection.

The recommended dose of Adcetris™ (brentuximab vedotin) is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Treatment is continued until a maximum of 16 cycles, disease progression or unacceptable toxicity is reached. Infusion-related reactions, including anaphylaxis, have occurred with Adcetris™.

The vial containing 50 mg of brentuximab vedotin is reconstituted with Sterile Water for Injection, USP, to yield a 5 mg/mL brentuximab vedotin solution. Based on the dose, the required amount of the reconstituted solution is further diluted in 0.9% saline to achieve an infusion solution of 0.4 – 1.8 mg/mL brentuximab vedotin, which should be used within 4 hours of vial reconstitution.

Adcetris™ (brentuximab vedotin) was studied in 102 patients with HL in a Phase 2, single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg administered every 3 weeks. Median duration of treatment was 27 weeks. This trial was supported by several other Phase 1 and 2 trials. Adcetris™ was also studied in 58 patients with systemic ALCL in a single arm clinical trial in which the recommended starting dose and schedule was the same as that noted previously. The median duration of treatment was 21 weeks.

Seattle Genetics was granted Orphan drug designation for HL in January 2007. The sponsor was informed in November 2010 that their proposed application for HL would be

considered under Accelerated Approval Regulations due to the need for adequate and well-controlled clinical trials establishing that this NME provides clinical benefit and has an acceptable benefit to risk ratio. A confirmatory trial will be required to convert from an accelerated approval to a regular approval.

C. Stability

(b) (4)

[redacted]

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VI. SIGNATURE BLOCK (BLA ONLY)

Name and Title	Signature and Date
Kathleen A. Clouse, Ph.D., Director Division of Monoclonal Antibodies (Author of Team Leader Review) (Secondary Reviewer of Primary Review) Patrick Swann, Ph.D., Deputy Director Division of Monoclonal Antibodies (Secondary Reviewer of Primary Review) (Secondary Reviewer of Team Leader Review)	Kathleen A. Clouse 08/05/2011 Patrick Swann 8-5-11
Marjorie Shapiro, Ph.D. Laboratory Chief, Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies (Author of Primary Review)	Marjorie A. Shapiro 8/5/11
Francisco Borrego, M.D., Ph.D. Primary Reviewer, Senior Staff Fellow, Division of Monoclonal Antibodies (Author of review of section 3.2.S.4.2 and 4.3)	8/5/11

CHEMISTRY REVIEW

8/1/2011

Concur -
Sarah Pope Mikinski
8/1/2011

BLA 125-388/125-399

ADCETRIS™ (brentuximab vedotin) for Injection

Seattle Genetics, Inc.

Xiao-Hong Chen, Ph.D.

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I

CMC Review of NDA 125-388/125-399

For the Division of Hematology Products (HFD-160)

Table of Contents

Chemistry Review Data Sheet

1. BLA 125-388/125-399

2. REVIEW #1

3. REVIEW DATE: 20-July-2011

4. REVIEWERS: Xiao-Hong Chen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 71,634	27-JUN-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	25-FEB-2011
Amendment	28-JUN_2011
Amendment	30-JUN-2011
Amendment	08-JUL-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Seattle Genetics, Inc.
Address:	21823 30th Drive Southeast Bothell, Washington 98021
Representative:	Elaine Waller, PharmD, MBA Senior Vice President, Regulatory Affairs
Telephone:	425-527-4312

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Adcetris™
b) Non-Proprietary Name (USAN): brentuximab vedotin for injection
c) Chemical Name: Chimeric IgG1 cAC10 covalently linked to vcMMAE
Code Name/#: SGN-35
Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: BLA, 21 CFR Part 601

10. PHARMACOL. CATEGORY: Treatment of Relapsed or refractory Hodgkin lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma

11. DOSAGE FORM: For Injection, Lyophilized cake

12. STRENGTH/POTENCY: 50 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

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

___X___SPOTS product – Form Completed

_____Not a SPOTS product

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

Chimeric IgG_1 cAC10 covalently linked to vcMMAE

Molecular formula: (b) (4)

Molecular weight: 153,352 Da

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II	(b) (4)	brentuximab drug substance	1	Inadequate	7/20/2011	DMF is reviewed only in reference to this BLA. It is adequate only to support this BLA.

*There was a typographical error in the spelling of (b) (4) in the 3/23/07 review. It was incorrectly spelled as "(b) (4)."

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

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

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	71,634	Seattle Genetics	

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	N/A			

Chemistry Review Data Sheet

Pharm/Tox	Drug related impurities	April 8, 2011	July 19, 2011	Informal email consult regarding the qualification of drug related impurities in the SGD-1006 intermediate and SGN-35.
Biopharm	N/A			
ODS/DMEPA	N/A			
Methods Validation	N/A			
EA	N/A			
Microbiology	N/A			

The Chemistry Review for NDA 125-388/125-399

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The BLA is recommended for approval based on the adequate CMC information provided in the BLA and the post-marketing commitments Seattle Genetics has provided (Number 1 and 2 below).

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

1. Reassess the acceptance limits for the bulk drug substance and drug product specifications for average drug load MR_D and % unconjugated cAC10 and further tighten the currently proposed limits. (Note: The target completion date for the fulfillment of the PMC may be coordinated with the related PMCs recommended by the Office of Biotechnology Products, as necessary).
2. Harmonize the CMC information contained in DMF (b) (4) and this BLA within three months post approval. (the Applicant committed to this timing in the 7/26/2011 teleconference).

II. Summary of Chemistry Assessment

Regulatory Background

The initial IND for SGN-35 was submitted on June 28, 2011. Throughout the drug development program, several major industrial meetings were held to discuss the pertinent CMC issues, which include pre IND meeting dated Jun, 30, 2005, a Type B meeting on November 13, 2008, a CMC specific End-of-Phase-2 meeting on January 19, 2010, a CMC specific pre NDA meeting on December 7, 2010. The BLA for brentuximab vedotin for injection dated 25-FEB-2011 was submitted per 21 CFR Part 601, and the application was filled on April 29, 2011, with a priority review clock of six month.

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

Brentuximab vedotin (SGN-35) consists of cAC10 conjugated to SGD-1006 via thioether bonds. Each antibody molecule may have 0, 2, 4, 6, or 8 conjugated SGD-1006 molecules. On average, the drug (SGD-1006 intermediate-1006) and antibody (cAC10) molar ratio is four. Brentuximab vedotin is a heterogeneous mixture, with respect to drug conjugation ratio and also with respect to the variety of post-translational modifications of the antibody. Hence, the calculated molecular formula and predicted average molar mass of brentuximab vedotin are based on the average molar mass of cAC10 and assume an average of four drug-linkers conjugated per antibody.

Executive Summary Section

Prior to conjugation to form antibody drug conjugate, two intermediates, cAC10 and SGD-1006, are manufactured by two different contract manufacturers. cAC10 antibody is manufactured by [redacted] (b) (4). Evaluation of the CMC information for cAC10 antibody is conducted by Dr. Marjorie Shapiro in the Office of Biotechnology Products, which is the lead office for CMC review of this BLA. SGD-1006 intermediate is manufactured by the [redacted] (b) (4). This review evaluates the CMC information for SGD-1006 intermediate, relevant drug related information for SGN-35 bulk drug substance.

SGD-1006 intermediate

CMC information for SGD-1006 intermediate is submitted both in the BLAs and the referenced DMF [redacted] (b) (4). Most of the SGD-1006 intermediate CMC information provided in the BLA and the DMF are the same. Review of SGD-1006 intermediate is conducted in the BLA review when the same information is submitted in both BLA and DMF. DMF [redacted] (b) (4) is reviewed for the CMC information that is only submitted in the DMF but not BLA. DMF review concludes that it is only adequate to support this BLA. Refer to the review for the DMF dated July 21, 2011.

SGD-1006 is manufactured at a commercial scale of [redacted] (b) (4). The process consists of [redacted] (b) (4). During drug development three manufacturing processes were used to produce SGD-1006 intermediate, Process A, B and C. [redacted] (b) (4) Process C is the proposed commercial process. Comparability between Process A, B and C was assessed based on the results of in-process control tests, the test results from the stage intermediates, and the final intermediate SGD-1006, and the results demonstrated the lots produced by the three processes are comparable.

Specifications for SGD-1006 intermediate are proposed based on historical batch data, analytical method capability, and results of process characterization studies. Although the acceptance limits for the specified impurities levels are higher than the ICH Q3A recommended qualification thresholds, their levels at bulk drug substance are well below the ICH limit after the conjugation and purification process. Pharm/tox input for the qualification of impurities was sought, and is found to be acceptable. Method validation studies and the results are provided in the DMF.

SGD-1006 intermediate is packaged in [redacted] (b) (4). The proposed [redacted] (b) (4) retest date for SGD-1006 intermediate stored at [redacted] (b) (4) is acceptable.

SGN-35 Drug Substance

SGN-35 bulk drug substance is manufactured at [redacted] (b) (4) scale by a contract manufacturer, [redacted] (b) (4). SGN-35 manufacturing starts with [redacted] (b) (4)

(b) (4)

Structural characterization of SGN-35 has been conducted using a comprehensive set of methods. The data confirm that SGN-35 conjugation site is at the cysteine residues (b) (4) resulting in many active forms with up to eight possible conjugation sites per antibody. Drug load distribution studies were conducted using HIC and RP-HPLC methods, The amount of various isoforms of drug antibody conjugates have been measured. And the relative abundance of the conjugation isoforms with respect to the average drug average drug load MR_D have been determined. Historical data for drug loading distribution and average drug load MR_D showed certain correlation.

Through process characterization studies, Seattle Genetics identified the critical step (cAC10 (b) (4)) and CPP ((b) (4)) that affect the CQAs. Studies have demonstrated that variation on (b) (4) results in the change of average drug load MR_D, % unconjugated cAC10, and drug loading distribution. The AOR and NOR for (b) (4) have been identified. By controlling (b) (4) within the NOR, the SGN-35 bulk drug substance produced should have average drug load MR_D and % unconjugated cAC10 well within the proposed specification limits. Whether testing for drug load distribution should be included as part of the release testing has been evaluated. Considering the observed correlation between average drug load MR_D and drug loading distribution as well as the process understanding and process controls, testing for average drug load MR_D without drug load distribution appears to be adequate. A post-marketing commitment to reassess the acceptance limits for the bulk drug substance and drug product specifications for average drug load MR_D and % unconjugated cAC10 and further tighten the currently proposed limits is recommended, and was agreed to (7/26/2011) by Seattle Genetics. The target completion date for the fulfillment of the PMC may be coordinated with the related PMCs recommended by the Office of Biotechnology Products as needed.

<u>SGN-35 Drug Product</u>

ADCETRIS (brentuximab vedotin) for Injection single-use vial containing 50 mg of brentuximab vedotin as a white to off-white lyophilized cake or powder. Prior to administration, SGN-35 drug product is reconstituted with 10.5 mL of sterile Water for Injection, USP resulting in a clear to slightly opalescent, colorless solution containing 5 mg/mL SGN-35, (b) (4) sodium citrate, (b) (4) trehalose, 0.2 mg/mL polysorbate 80, pH 6.6. For administration, the reconstituted solution is added to an intravenous infusion bag containing sterile 0.9% Sodium Chloride Injection, USP.

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

ADCETRIS (brentuximab vedotin) for Injection is a CD30-directed antibody-drug conjugate indicated for treatment of patients with Hodgkin lymphoma (HL) who relapse after autologous stem cell transplant (STN 125388) and Relapsed or refractory systemic anaplastic large cell lymphoma (STN 125399)

The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. The vial containing 50 mg of brentuximab vedotin is reconstituted with Sterile Water for Injection, USP, to yield a 5 mg/mL brentuximab vedotin solution. Based on the dose the required amount of the reconstituted solution, is further diluted in 0.9% saline to achieve an infusion solution of 0.4 – 1.8 mg/mL brentuximab vedotin, which should be used within 4 hours of vial reconstitution.

C. Basis for Approvability or Not-Approval Recommendation

Based on the CMC information submitted, this BLA is recommended for approval. There are no outstanding CMC deficiencies from the small molecule (CMC) perspective.

III. Administrative

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

Reviewer Name/Date: Xiao-Hong Chen, Ph.D.
Branch Chief Name/Date: Sarah Pope Miksinski, Ph.D.

C. CC Block

Lara Akinsanya/OODP/DHP/Regulatory PM
Janice Brown/ONDQA/CMC Lead
Tu-Van Lambert/ONDQA/PM
Sarah Pope Miksinski/ONDQA/Branch Chief
Richard Lostritto/ONDQA/DNQA I Director

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Review Cover Sheet

BLA STN 125388/125399

Brentuximab Vedotin

Seattle Genetics

Marjorie A. Shapiro, Ph.D.
Francisco Borrego, M.D., Ph.D.
Division of Monoclonal Antibodies

OBP CMC Review Data Sheet

1. **BLA#:** STN 125388 and **125399**

2. **REVIEW DATE:** June 27, 2011

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Angelo de Claro (NHL 125388); Karen McGinn (ALCL 125399)
Pharm/Tox: Yanli Ouyang
Product Quality Team: DMA: Marjorie Shapiro, Francisco Borrego:
ONDQA Xiao-Hong Chen
BMAB/Facilities: Bo Chi and Colleen Thomas
Clinical Pharmacology: Aakanksha Khandelwal and Bahru Habtemariam
Statistics: Kyung Lee (NHL 125388); Kallappa Koti (ALCL 125399)
OBP Labeling: Kim Raines
RPM: Lara Akinsanya

4. **MAJOR GRMP DEADLINES**
Mid-Cycle Meeting: May 26, 2011
Primary Review: August 2, 2011
CDTL Memo Due: August 9, 2011
PDUFA Action Date: August 30, 2011

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS:**

Communication/Document	Date
CMC Pre-BLA Meeting	January 19, 2010, December 17, 2010
Filing Review Memo.	March 30, 2011
Teleconference 1	July 26, 2011
Teleconference 2	
Information Request Email #1	June 20, 2011
Information Request Email #2	June 27, 2011
Information Request Email #3	June 29, 2011
Information Request Email #4	July 18, 2011
Information Request Email #5	July 18, 2011
EIR 483 Seattle Genetics	May 19, 2011
EIR (b) (4)	June 9, 2011
EIR	June 10, 2011

6. **SUBMISSION(S) REVIEWED: (Note: where two amendment numbers are provided, the first indicates 125388 and the second indicates the same submission to 125399)**

Submission(s) Reviewed	Document Submission Date
STN 125388.**125399/0**	February 28, 2011
STN 125388/18 (Errata Summary of Changes)	June 13, 2011

(b) (4)	
	Type III. Review in DARRTS 9/7/10 found this acceptable for use for NDA 19-155. No further review required as all the relevant information related to compatibility with the product was in the BLA.
	Type III. No review required as all the relevant information related to compatibility with the product was in the BLA
	Type III. No review required as all the relevant information related to compatibility with the product was in the BLA.
	Type III. No review required as all the relevant information related to compatibility with the product was in the BLA.
	No review required as all the relevant information related to compatibility with the product was in the BLA.
	Type II. No review required as all the relevant information related to compatibility with the product was in the BLA.

STN 125388.**125399** /22 or **20** (Updated DP stability)	June 24, 2011
STN 125388.**125399** /28 or **25** (Response to 6/20/11 IR)	July 1, 2011
STN 125388.**125399** /30 or **27** (Response to 6/27/11 IR)	July 8, 2011
STN 125388.**125399** /31 or **28** (Response to 6/30/11 IR)	July 13, 2011
STN 125388.**125399** /33 or **30** (Response to 7/18/11 IR)	July 20, 2011
STN 125388.**125399** /35 or **32** (Response to 7/18/11 IR)	July 22, 2011
STN 125388.**125399** /36 or **33** (Response to 7/18/11 IR)	July 25, 2011
STN 125388.**125399** /37 or **34** (b) (4) updates)	July 28, 2011

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: ADCETRIS
   b. Trade Name: ADCETRIS
   c. Non-Proprietary/USAN: brentuximab vedotin
   d. CAS name: 914088-09-8
   e. Common name: SGN-35
   f. Chemical Type: antibody drug conjugate
   g. WHO Number:
   h. INN Name: brentuximab vedotin
   i. Compendial Name:
   j. OBP systematic name:
   k. Other Names:

8. **PHARMACOLOGICAL CATEGORY:** Chimeric monoclonal antibody against CD30 conjugated to the tubulin inhibitor, MMAE, with a cleavable linker

9. **DOSAGE FORM:** Lyophilized cake or powder in single use vials

10. **STRENGTH/POTENCY:**
   (i) 50 mg/vial
   (ii) Cytotoxicity assay, Binding ELISA and Average Drug-to-Antibody Molar Ratio

11. **ROUTE OF ADMINISTRATION:** intravenous infusion

12. **Referenced Master Files:**

DMF #	HOLDER	ITEM REFERENCED	COMMENTS (STATUS)
		(b) (4)	Type V. No review required as all relevant information is in BLA and the facility was inspected
			No review required. Validation reports for tests performed on SGN-35, including the SOP for the methods, are included in the BLA.

(b) (4)	
	Type V. No review required as all relevant information is in BLA and the facility was inspected
	Type II. Reviewed by Dr. Xiao-Hong Chen, ONDQA
	Type III. No review required as all the relevant information related to compatibility with the product was in the BLA.

13. **Inspectional Activities**

There are five facilities involved in the manufacture of brentuximab vedotin and its intermediates; the cAC10 mAb and the SGD-1006 vc-MMAE drug-linker.

The cAC10 mAb intermediate is manufactured by (b) (4). This facility was inspected from June 6-10, 2011 by Patricia Hughes and Maria Candauchacon (BMAB); Francisco Borrego and Laurie Graham (DMA); and Mark McClain and Susanne Richardson (ORA, Northeast Region).

The SGD-1006 drug-linker intermediate is manufactured by (b) (4). This inspection was waived.

SGN-35 BDS is manufactured at (b) (4). This facility was inspected by Bo Chi (BMAB) and Marjorie Shapiro (DMA) from June 2 – June 10, 2011.

SGN-35 DP is manufactured at (b) (4). This inspection was conducted by the field as part of a follow-up inspection to a Warning Letter issued in (b) (4) and unrelated to SGN-35.

SGN-35 BDS and DP release and stability testing is performed at Seattle Genetics, Bothell, WA. This facility was inspected by Mary Farbman (BMAB), Marjorie Shapiro (DMA) and Heika Tait (ORA, Pacific Region) from May 17-19, 2011.

17. **Consults Requested by OBP**

None

18. **Quality by Design Elements.**

This BLA is not claiming a design space; however elements of Quality by Design were incorporated into the cAC10, SGN-35 BDS and SGN-35 DP manufacturing processes. Normal Operating Ranges (NOR) and Acceptable Operating Ranges (AOR) were determined for most

steps in the manufacturing process. Multivariate and univariate DoE studies were used to define the NORs and AORs where applicable. There were fewer such studies for the SGN-35 DP process. However, the overall control strategy started with an analysis of critical quality attributes of DP. These attributes were then linked back to SGN-35, cAC10 and/or SGD-1006 where appropriate. The criticality of the quality attributes was determined and coupled with process characterization and capability, an integrated strategy for control of product quality was implemented.

For cAC10, SGN-35 BDS and SGN-35 DP, each process is controlled within the NORs or at setpoints which fall at or within the established AORs. These NORs or setpoints are defined in the batch records and are established based on manufacturing experience, an understanding of process capability, and extensive process characterization studies. Operating outside of an established NOR or setpoint results in an investigation.

The AORs established for the cAC10 process are similar to the AORs established for other recent mAbs.

NORs or setpoints may be revised within an AOR. Such changes will be managed though the contract manufacturing organization (CMO) and Seattle Genetics. The Quality agreements with each CMO provide that proposed changes to NORs or setpoints are justified in written change requests that will be reviewed by a multidisciplinary team at Seattle Genetics and requires a written authorization from Seattle Genetics. This review will include an assessment of the potential impact of the change on product quality and whether additional characterization, validation and/or regulatory submissions will be required to implement the change. Seattle Genetics Regulatory Affairs will determine the appropriate strategy for notifying the FDA of such changes per 21 CFR 601.12 and 21 314.70 based on the type of change implemented.

19. Administrative

A. Signature Block

Name and Title	Signature and Date
Patrick Swann, Ph.D., Deputy Director Division of Monoclonal Antibodies Kathleen Clouse, Ph.D.DirectorDivision of Monoclonal Antibodies	Patrick Swann 8-2-2011 Kathleen Clouse 08/02/2011
Marjorie A. Shapiro, Ph.D. Chief, Laboratory of Molecular and Developmental Immunology Division of Monoclonal Antibodies	Marjorie A. Shapiro 8/2/2011
Francisco Borrego, M.D., Ph.D. Senior Staff Fellow	8/2/2011

Laboratory of Molecular and Developmental Immunology Division of Monoclonal Antibodies	

B. CC Block

Recipient	Date
Lara Akinsanya, RPM Division of Hematology Products Office of Oncology Drug Products	August 2, 2011
Division of Monoclonal Antibodies/Therapeutic Proteins File/BLA STN 125388 & 125399	August 2, 2011

(b) (4)

430 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number:	Applicant:	Stamp Date:
125388/125389	Seattle Genetics	

Established/Proper Name:	BLA/NDA Type: Original
Adcetris	Submission/Priority Review

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	(Y) N	
Form 356h completed	Y N	
❑ including list of all establishment sites and their registration numbers	(Y) N	
Comprehensive Table of Contents	(Y) N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	(Y) N	
Labeling:	Y N	
❑ PI –non-annotated	Y N	
❑ PI –annotated	Y N	
❑ PI (electronic)	Y N	
❑ Medication Guide	Y N	
❑ Patient Insert	Y N	
❑ package and container	Y N	
❑ diluent	Y N	
❑ other components	Y N	
❑ established name (e.g. USAN)	Y N	
❑ proprietary name (for review)	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?:	(Y) N	
Examples include:		
❑ legible	Y N	
❑ English (or translated into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	
❑ interpretable data tabulations (line listings) & graphical displays	Y N	
❑ summary reports reference the location of individual data and records	Y N	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y N	
Companion application received if a shared or divided manufacturing	Y N	Not applicable

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y N	
Quality overall summary [2.3]	Y N	
❑ Drug Substance	Y N	
❑ Drug Product	Y N	
❑ Facilities and Equipment	Y N	
❑ Adventitious Agents Safety Evaluation	Y N	
❑ Novel Excipients	Y N	
❑ Executed Batch Records	Y N	
❑ Method Validation Package	Y N	
❑ Comparability Protocols	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y N	
Drug Substance [3.2.S]		Module 3 Drug Substance 3.2.S is applicable to brentuximab vedotin DS and the cAC10 mAb intermediate. See Initial Quality Assessment memo by Janice Brown regarding the fileability of the SGD-1006 intermediate.
❑ general info ○ nomenclature ○ structure (e.g. sequence, glycosylation sites) ○ properties	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ description of manufacturing process and process control ○ batch numbering and pooling scheme ○ cell culture and harvest ○ purification ○ filling, storage and shipping	Y N	
❑ control of materials ○ raw materials and reagents ○ biological source and starting materials ○ cell substrate: source, history, and generation ○ cell banking system, characterization, and testing	Y N	
❑ control of critical steps and intermediates	Y N	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
○ justification of specifications ○ stability		
❑ process validation (prospective plan, results, analysis, and conclusions)	Y N	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	
❑ characterization of drug substance		
❑ control of drug substance		
○ specifications		
○ justification of specs.	Y N	
○ analytical procedures	Y N	
○ analytical method validation		
○ batch analyses		
❑ reference standards	Y N	
❑ container closure system	Y N	
❑ stability		
❑ summary	Y N	
❑ post-approval protocol and commitment	Y N	
❑ pre-approval	Y N	
○ protocol		
○ results		
○ method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y N	
❑ pharmaceutical development	Y N	
○ preservative effectiveness	Y N	
○ container-closure integrity	Y N Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance:	Y N	
○ Filter validation		

CTD Module 3 Contents	Present?	If not, justification, action & status
○ Component, container, closure depyrogenation and sterilization validation ○ Validation of aseptic processing (media simulations) ○ Environmental Monitoring Program ○ Lyophilizer validation ○ Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y N	
❑ reference standards or materials	Y N	
❑ container closure system [3.2.P.7] ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ○ administration device(s)	Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	Y N	
Diluent (vials or filled syringes) [3.2P′]		Not applicable
❑ description and composition of diluent	Y N	
❑ pharmaceutical development	Y N	
○ preservative effectiveness	Y N	
○ container-closure integrity	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N Y N Y N	
❑ controls of critical steps and intermediates		
❑ process validation including aseptic processing & sterility assurance:	Y N	
o Filter validation		
o Component, container, closure depyrogenation and sterilization validation	Y N	
o Validation of aseptic processing (media simulations)	Y N	
o Environmental Monitoring Program	Y N	
o Lyophilizer sterilization validation		
o Other needed validation data (hold times)	Y N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system		
o specifications (vial, elastomer, drawings)		
o availability of DMF & LOAs	Y N	
❑ stability		
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
Other components to be marketed (full description and supporting data, as listed above):		

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ other devices ❑ other marketed chemicals (e.g. part of kit)	Y N Y N	
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	 Y N Y N Y N	Facilities will be covered by DMPQ
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y N Y N Y N	
Literature references and copies [3.3]	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y N	
Includes data demonstrating consistency of manufacture	Y N	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	(Y) N	
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	(Y) N	
Certification that all facilities are ready for inspection	(Y) N	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	(Y) N	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	Y N	Not applicable
❑ LAL instead of rabbit pyrogen	Y N	
❑ mycoplasma	Y N	
❑ sterility	Y N	
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	(Y) N	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	See DMPQ
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	See DMPQ

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? **Yes** **No**

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Maryone Shapiro 3/30/11

Product Quality Reviewer(s) Date

Branch Chief/Team Leader/Supervisor Date

Division Director Date

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number:	Applicant:	Stamp Date:
125388/125389	Seattle Genetics	

Established/Proper Name:	BLA/NDA Type: Original
Adcetris	Submission/Priority Review

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	(Y) N	
Form 356h completed	Y N	
❑ including list of all establishment sites and their registration numbers	(Y) N	
Comprehensive Table of Contents	(Y) N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	(Y) N	
Labeling:	Y N	not reviewed for details
❑ PI –non-annotated	Y N	
❑ PI –annotated	Y N	
❑ PI (electronic)	Y N	
❑ Medication Guide	Y N	
❑ Patient Insert	Y N	
❑ package and container	Y N	
❑ diluent	Y N	
❑ other components	Y N	
❑ established name (e.g. USAN)	Y N	
❑ proprietary name (for review)	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	(Y) N	
❑ legible	Y N	
❑ English (or translated into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	
❑ interpretable data tabulations (line listings) & graphical displays	Y N	
❑ summary reports reference the location of individual data and records	Y N	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y N	
Companion application received if a shared or divided manufacturing	Y N	Not applicable

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y N	
Quality overall summary [2.3]	Y N	
❑ Drug Substance	Y N	
❑ Drug Product	Y N	
❑ Facilities and Equipment	Y N	
❑ Adventitious Agents Safety Evaluation	Y N	
❑ Novel Excipients	Y N	
❑ Executed Batch Records	Y N	
❑ Method Validation Package	Y N	
❑ Comparability Protocols	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y N	
Drug Substance [3.2.S]		Module 3 Drug Substance 3.2.S is applicable to brentuximab vedotin DS and the cAC10 mAb intermediate. See Initial Quality Assessment memo by Janice Brown regarding the fileability of the SGD-1006 intermediate.
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ description of manufacturing process and process control o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	Y N	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	Y N	
❑ control of critical steps and intermediates	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
○ justification of specifications ○ stability ❑ process validation (prospective plan, results, analysis, and conclusions) ❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) ❑ characterization of drug substance ❑ control of drug substance ○ specifications ○ justification of specs. ○ analytical procedures ○ analytical method validation ○ batch analyses ❑ reference standards ❑ container closure system ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	
Drug Product [3.2.P] [Dosage Form] ❑ description and composition ❑ pharmaceutical development ○ preservative effectiveness ○ container-closure integrity ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ batch formula ❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) ❑ controls of critical steps and intermediates ❑ process validation including aseptic processing & sterility assurance: ○ Filter validation	Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
○ Component, container, closure depyrogenation and sterilization validation ○ Validation of aseptic processing (media simulations) ○ Environmental Monitoring Program ○ Lyophilizer validation ○ Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y N	
❑ reference standards or materials	Y N	
❑ container closure system [3.2.P.7] ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ○ administration device(s)	Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	Y N	
Diluent (vials or filled syringes) [3.2P′]		Not applicable
❑ description and composition of diluent	Y N	
❑ pharmaceutical development	Y N	
○ preservative effectiveness	Y N	
○ container-closure integrity	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N Y N Y N	
❑ controls of critical steps and intermediates		
❑ process validation including aseptic processing & sterility assurance:	Y N	
o Filter validation		
o Component, container, closure depyrogenation and sterilization validation	Y N	
o Validation of aseptic processing (media simulations)	Y N	
o Environmental Monitoring Program	Y N	
o Lyophilizer sterilization validation		
o Other needed validation data (hold times)	Y N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system		
o specifications (vial, elastomer, drawings)		
o availability of DMF & LOAs	Y N	
❑ stability		
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
Other components to be marketed (full description and supporting data, as listed above):		

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	
Certification that all facilities are ready for inspection	Y N	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	Y N Y N Y N Y N	Not applicable
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	See DMPQ
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	See DMPQ

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ other devices ❑ other marketed chemicals (e.g. part of kit)	Y N Y N	
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	 Y N Y N Y N	Facilities will be covered by DMPQ
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y N Y N Y N	
Literature references and copies [3.3]	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y N	
Includes data demonstrating consistency of manufacture	Y N	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? **Yes** **No**

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Maryrose Shepherd 3/30/11
Product Quality Reviewer(s) Date

Kathleen A. Clouse 03/30/2011
Branch Chief/Team Leader/Supervisor Date

Kathleen A. Clouse 03/30/2011
Division Director Date

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number: STN125388/125399	**Applicant:** Seattle Genetics, Inc.	**Stamp Date:**
Established/Proper Name: Brentuximab vedotin	**BLA/NDA Type:** Priority review	

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed ❑ including list of all establishment sites and their registration numbers	Y Y	
Comprehensive Table of Contents	Y N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	OBP lead.

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
❑ legible	Y	
❑ English (or translated into English)	Y	
❑ compatible file formats	Y	
❑ navigable hyper-links	Y	
❑ interpretable data tabulations (line listings) & graphical displays	Y	
❑ summary reports reference the location of individual data and records	Y	
❑ all electronic submission components usable (e.g. conforms to published	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
guidance)		
Companion application received if a shared or divided manufacturing arrangement	Y N	Not applicable.

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y N	OBP lead.
❑ Novel Excipients	Y N	OBP review.
❑ Executed Batch Records	Y N	OBP review.
❑ Method Validation Package	Y	Microbiological tests and container-closure integrity. Provided in Module 3.
❑ Comparability Protocols	Y N	Not applicable.

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y N	
Drug Substance [3.2.S]		
❑ general info	Y	
○ nomenclature		
○ structure (e.g. sequence, glycosylation sites)		
○ properties		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control	Y	
○ batch numbering and pooling scheme		
○ cell culture and harvest		
○ purification		
○ filling, storage and shipping		
❑ control of materials	Y	
○ raw materials and reagents		
○ biological source and starting materials		

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
○ cell substrate: source, history, and generation ○ cell banking system, characterization, and testing		
❑ control of critical steps and intermediates	Y	
○ justification of specifications ○ stability		
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	OBP review.
❑ characterization of drug substance	Y	
❑ control of drug substance	Y	
○ specifications ○ justification of specs.		
○ analytical procedures	Y	
○ analytical method validation	Y	
○ batch analyses	Y	
❑ reference standards	Y	
❑ container closure system	Y	
❑ stability	Y	
❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
○ preservative effectiveness	Y N	Not applicable.
○ container-closure integrity	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y N	OBP review.
❑ description of manufacturing process for production through	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)		
❑ controls of critical steps and intermediates	Y	Microbial controls.
❑ process validation including aseptic processing & sterility assurance: ○ Filter validation ○ Component, container, closure depyrogenation and sterilization validation ○ Validation of aseptic processing (media simulations) ○ Environmental Monitoring Program ○ Lyophilizer validation ○ Other needed validation data (hold times)	Y	Microbial control and sterility assurance.
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	OBP review.
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	Sterility and endotoxin.
❑ reference standards or materials	Y N	OBP review.
❑ container closure system [3.2.P.7] ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ○ administration device(s)	Y	OBP lead.
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	Y	Container closure integrity test.
Diluent (vials or filled syringes) [3.2P′] ❑ description and composition of	Y N	Not applicable. Diluent is not supplied with the drug product.

CTD Module 3 Contents	Present?	If not, justification, action & status
diluent		
❑ pharmaceutical development	Y N	
○ preservative effectiveness	Y N	
○ container-closure integrity	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging	Y N	
(including all steps performed at outside [e.g., contract] facilities)	Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance:	Y N	
○ Filter validation		
○ Component, container, closure depyrogenation and sterilization validation	Y N	
○ Validation of aseptic processing (media simulations)		
○ Environmental	Y N	
Monitoring Program	Y N	
○ Lyophilizer sterilization validation		
○ Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system	Y N	
○ specifications (vial, elastomer,		

CTD Module 3 Contents	Present?	If not, justification, action & status
drawings) ○ availability of DMF & LOAs ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results	Y N	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	 Y N Y N	Not applicable.
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients	Y Y N Y N	 OBP lead. OBP review.
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y Y Y N	 OBP lead. Microbiological tests and container-closure integrity. Not applicable

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
Literature references and copies [3.3]	Y N	OBP review.

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	OBP review.
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	OBP review.
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	OBP review.
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	Container closure integrity.
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	N	See comment below.
❑ LAL instead of rabbit pyrogen	N	Rabbit pyrogen data will be requested.
❑ mycoplasma	Y N	OBP review.
❑ sterility	Y	
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to	Y	

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment		

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

3/30/11

Product Quality Reviewer(s) for DMPQ/BMT: Bo Chi (DS), Colleen Thomas (DP) Date

3/30/11

Branch Chief/Team Leader/Supervisor: Patricia Hughes Date

for RF 3/30/11

Division Director Date

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number:
STN125388/125399

Applicant:
Seattle Genetics, Inc.

Stamp Date:

Established/Proper Name:
Brentuximab vedotin

BLA/NDA Type:
Priority review

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed ❑ including list of all establishment sites and their registration numbers	Y Y	
Comprehensive Table of Contents	Y N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	OBP lead.

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
❑ legible	Y	
❑ English (or translated into English)	Y	
❑ compatible file formats	Y	
❑ navigable hyper-links	Y	
❑ interpretable data tabulations (line listings) & graphical displays	Y	
❑ summary reports reference the location of individual data and records	Y	
❑ all electronic submission components usable (e.g. conforms to published	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
guidance)		
Companion application received if a shared or divided manufacturing arrangement	Y N	Not applicable.

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y N	OBP lead.
❑ Novel Excipients	Y N	OBP review.
❑ Executed Batch Records	Y N	OBP review.
❑ Method Validation Package	Y	Microbiological tests and container-closure integrity. Provided in Module 3.
❑ Comparability Protocols	Y N	Not applicable.

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y N	
Drug Substance [3.2.S]		
❑ general info	Y	
o nomenclature		
o structure (e.g. sequence, glycosylation sites)		
o properties		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control	Y	
o batch numbering and pooling scheme		
o cell culture and harvest		
o purification		
o filling, storage and shipping		
❑ control of materials	Y	
o raw materials and reagents		
o biological source and starting materials		

CTD Module 3 Contents	Present?	If not, justification, action & status
○ cell substrate: source, history, and generation ○ cell banking system, characterization, and testing		
❑ control of critical steps and intermediates	Y	
○ justification of specifications ○ stability		
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	OBP review.
❑ characterization of drug substance	Y	
❑ control of drug substance	Y	
○ specifications ○ justification of specs.		
○ analytical procedures	Y	
○ analytical method validation	Y	
○ batch analyses	Y	
❑ reference standards	Y	
❑ container closure system	Y	
❑ stability	Y	
❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
○ preservative effectiveness	Y N	Not applicable.
○ container-closure integrity	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y N	OBP review.
❑ description of manufacturing process for production through	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)		
❑ controls of critical steps and intermediates	Y	Microbial controls.
❑ process validation including aseptic processing & sterility assurance: o Filter validation o Component, container, closure depyrogenation and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer validation o Other needed validation data (hold times)	Y	Microbial control and sterility assurance.
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	OBP review.
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	Sterility and endotoxin.
❑ reference standards or materials	Y N	OBP review.
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF & LOAs o administration device(s)	Y	OBP lead.
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y	Container closure integrity test.
Diluent (vials or filled syringes) [3.2P'] ❑ description and composition of	Y N	Not applicable. Diluent is not supplied with the drug product.

CTD Module 3 Contents	Present?	If not, justification, action & status
diluent		
❑ pharmaceutical development	Y N	
o preservative effectiveness	Y N	
o container-closure integrity	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging	Y N	
(including all steps performed at outside [e.g., contract] facilities)	Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance:	Y N	
o Filter validation		
o Component, container, closure depyrogenation and sterilization validation	Y N	
o Validation of aseptic processing (media simulations)		
o Environmental Monitoring Program	Y N Y N	
o Lyophilizer sterilization validation		
o Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system	Y N	
o specifications (vial, elastomer,		

CTD Module 3 Contents	Present?	If not, justification, action & status
drawings) ○ availability of DMF & LOAs ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results	Y N	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	 Y N Y N	Not applicable.
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination	Y	
❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production	Y N	OBP lead.
❑ novel excipients	Y N	OBP review.
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y Y Y N	 OBP lead. Microbiological tests and container-closure integrity. Not applicable

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
Literature references and copies [3.3]	Y N	OBP review.

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	OBP review.
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	OBP review.
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	OBP review.
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	Container closure integrity.
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	N	See comment below.
❑ LAL instead of rabbit pyrogen	N	Rabbit pyrogen data will be requested.
❑ mycoplasma	Y N	OBP review.
❑ sterility	Y	
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to	Y	

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment		

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Product Quality Reviewer(s) for DMPQ/BMT: Bo Chi (DS), Colleen Thomas (DP) — Date 3/28/11

Branch Chief/Team Leader/Supervisor: Patricia Hughes — Date 3/29/11

Division Director — Date 3/28/11

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

OND Division:	Division of Hematology Products
BLA:	STN 125388 & 125399
Applicant:	Seattle Genetics, Inc.
Stamp Date:	25-Feb-2011
PDUFA Date:	30-Aug-2011
Proprietary (Brand) Name of Drug Product:	Adcetris™
Established Name:	brentuximab vedotin
Dosage Form(s):	Lyophilized single use vial
Strength(s):	50 mg
Route of Administration:	Intravenous infusion
Proposed Indication(s):	Hodgkin Lymphoma: Treatment of patients with relapsed or refractory Hodgkin lymphoma (HL) Systemic Anaplastic Large Cell Lymphoma: Treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL).
CMC Lead:	Janice Brown, Branch II/DPA1/ONDQA
Chief, Branch II:	Sarah Pope, Ph.D., DPA1/ONDQA
Review team recommendation:	Team review

	Yes	No
ONDQA Fileability:	X	☐
Comments for 74-Day Letter	☐	X

CONSULTS/ CMC RELATED REVIEWS

Consult	Comment
Biopharm/ClinPharm	Not Applicable
CDRH	Not Applicable
EA	To be assessed by Primary Reviewer in Office of Compliance
EES	NA OBP/OC responsibility (See attachment 1 for manufacturing sites)
DMETS	Labeling consult request will be sent as part of DHP request.
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.
Microbiology	Office of Compliance will review the sterile processing
Pharm/Tox	To be determined by Primary Reviewer.

Initial Quality Assessment

Summary

Brentuximab vedotin is an antibody-drug conjugate (ADC) consisting of a chimeric IgG1 monoclonal antibody (cAC10) covalently linked to a linker-drug. The drug + peptide linker moiety is referred to as SGD-1006. The drug is monomethyl auristatin E (MMAE), a antimicrotubule agent and a protease-cleavable peptide linker consisting of a thiol-reactive maleimide, a caproyl spacer, a dipeptide valine-citulline, and p-aminobenzyloxycarbonyl. Each antibody has (b) (4) an average of four SGD-1006 molecules per antibody, with a distribution of 0-8 MMAE molecules per antibody. Upon exposure to proteases, the linker undergoes proteolytic degradation at the citrulline residue. The resulting aniline is spontaneously fragmented releasing the free drug MMAE.

The applicant hypothesize that the biological activity of brentuximab vedotin results from binding of the ADC to CD30 on the tumor cell surface that initiates internalization of the ADC-CD30 complex. Following internalization, lysosomal degradation and release of the MMAE-containing cytotoxic components occur which then bind to tubulin to disrupt the microtubule network resulting in inhibition of cell division and cell growth and eventually apoptotic death of the CD30-expressing tumor cell. This approach takes advantage of the targeting capability of the antibody and the potent cytotoxicity of MMAE.

This NDA provides for 50 mg of brentuximab vedotin supplied in a single use vial as a preservative-free sterile lyophilized powder. Each vial is reconstituted with 10.5 mL of Sterile Water for Injection (SWFI), USP to yield a 5 mg/mL solution of brentuximab vedotin. The reconstituted product contains 70 mg/mL trehalose dihydrate, 5.6 mg/mL sodium citrate dihydrate, 0.21 mg/mL citric acid monohydrate, and (b) (4) polysorbate 80 and Water for Injection. The pH is approximately 6.6.

The reconstituted solution is diluted in an infusion bag containing 0.9% Sodium Chloride Injection, USP in order to achieve a final concentration of 0.4-1.8 mg/mL brentuximab vedotin. Reconstituted solution can also be diluted into 5% Dextrose Injection or Lactated Ringer's Injection.

(b) (4)

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