

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125388Orig1s000**

**MICROBIOLOGY REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Drug Evaluation and Research  
WO Bldg 51  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** 7/28/2011  
**To:** Administrative File, STN 125388/0, STN 125399/0  
**From:** Bo Chi, Ph.D., CDER/OC/OMPQ/DGMP/BMAB  
**Endorsement:** Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OC/OMPQ/DGMP/BMAB  
**Subject:** New Biologic License Applications (BLA)  
**Applicant:** Seattle Genetics, Inc.  
**US License:** 1853  
**Facility:** Manufacturing site for monoclonal antibody cAC10  
[REDACTED] (b) (4)  
Drug substance manufacturing site  
[REDACTED] (b) (4)  
**Product:** ADCETRIS™ (brentuximab vedotin)  
**Dosage:** 50 mg/vial, intravenous infusion  
**Indication:** Relapsed or refractory Hodgkin lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma  
**PDUFA date:** August 30<sup>st</sup>, 2011

**Recommendation:** The drug substance part of this application is recommended for approval from product quality microbiology perspective with the following post-market commitments:

1. 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.
2. Perform the bacteriostasis/fungistasis testing for the bioburden test of the bulk drug substance 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.

### Review Summary

Seattle Genetics has submitted this Biologics License Application (BLA) for brentuximab vedotin, a CD30-directed antibody drug conjugate (ADC) consisting of three components; a) the monoclonal antibody cAC10, specific for human CD30, b) anti-microtubule agent MMAE, and c) a protease-cleavable linker that covalently attaches MMAE to cAC10, for the treatment of relapsed or refractory Hodgkin lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma. The monoclonal antibody cAC10 is manufactured at [REDACTED] (b) (4)

- . The SGD-1006 intermediate is manufactured at (b) (4)
  - . The bulk drug substance (DS) is manufactured at (b) (4)
  - . The drug product (DP) is manufactured at (b) (4)
- . The application contains CMC information in an eCTD format.

This review contains the assessments of the manufacturing process of cAC10 and brentuximab vedotin bulk drug substance from microbiology perspective. For review of drug product aspects of the application, please see the review by Dr. Colleen Thomas.

(b) (4)

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**Conclusion**

- I. The drug substance section of the BLA is recommended for approval from a product quality microbiology perspective with the following post-market commitments:
- 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.
  - Perform the bacteriostasis/fungistasis testing for the bioburden test of the bulk drug substance 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.
- II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by an OBP reviewer.
- III. A pre-license inspection (6/6-10/2011) was conducted at (b) (4), the manufacturing site for cAC10 intermediate. Five 483 observations were issued. The compliance status of the facility is currently pending.  
A pre-license inspection (6/2-9/2011) was conducted at (b) (4), the drug substance manufacturing site. Four 483 observations were issued. The compliance status of the facility is currently pending.

Cc: WO51: Chi  
WO51: Hughes  
WO22: Akinsanya  
HFD-328, eCTD Blue Files (STN 125388, STN125399)

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BLA STN125388/0, STN125399/0, Seattle Genetics, brentuximab vedotin

SIGNATURES/DISTRIBUTION LIST

Primary BMAB Reviewer: Bo Chi, Ph.D.,



Date: 8/4/11

Concurring BMAB Acting Branch Chief: Patricia Hughes, Ph.D.,



Date: 8/5/11



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Drug Evaluation and Research  
WO Bldg 51, 10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Date:** 3 August 2011  
**To:** Administrative File, STN 125388  
**From:** Colleen Thomas, Ph.D., Reviewer, CDER/OC/OMPQ/DGMPA/BMAB  
Reyes Candau-Chacón, Ph.D., Reviewer, CDER/OC/OMPQ/DGMPA/BMAB  
Bo Chi, Ph.D., Reviewer, CDER/OC/OMPQ/DGMPA/BMAB  
**Endorsed:** Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/OC/OMPQ/DGMPA/BMAB  
**Subject:** Original BLA for brentuximab vedotin  
**US License:** 1853  
**Applicant:** Seattle Genetics, Inc.  
**Facility:** (b) (4)  
**Product:** Adcetris® (brentuximab vedotin)  
**Indication:** Relapsed or refractory Hodgkin's lymphoma  
**Dosage:** Sterile, preservative-free, white to off-white lyophilized cake supplied in single-use 30 ml vials (50 mg/vial). Reconstituted with 10.5 ml of sterile WFI. The required amount of reconstituted drug product is added to an infusion bag containing 0.9% sodium chloride for injection, 5% dextrose for injection, or lactated Ringer's for injection for a final concentration of 0.4-1.8 mg/ml. For intravenous infusion, 1.8 mg/kg over 30 minutes every 3 weeks. For patients over 100 kg, dose is calculated for 100 kg.  
**Due date:** 30 August 2011

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**Recommendation for approvability:** The BLA was reviewed from a product quality microbiology perspective and is recommended for approval. Two PMCs are listed at the end of this review memo.

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Seattle Genetics, Inc. submitted BLAs 125388 and 125399 to license brentuximab vedotin and the associated drug substance and drug product manufacturing processes. Brentuximab vedotin is a CD30-directed antibody drug conjugate consisting of three components: cAC10 antibody specific for human CD30, the highly potent anti-microtubule agent MMAE, and a protease-cleavable linker that attaches cAC10 to MMAE. The drug product is supplied as a sterile, preservative-free, lyophilized powder for intravenous infusion. Brentuximab vedotin is indicated for treatment of relapsed or refractory Hodgkin's lymphoma (BLA 125388) and for treatment of

relapsed or refractory systemic anaplastic large cell lymphoma (BLA 125399). Because the manufacturing information is the same for both indications, the product quality microbiology information submitted under BLA 125388 was reviewed for both. The amendment numbers listed in the review memo refer to amendments to BLA 125388. The table below indicates BLA 125388 amendments that were reviewed. The corresponding BLA 125399 amendment numbers are provided for reference.

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125388	125399	Date	Content
0015	0016	26-May-2011	BMAB request: DP quality microbiology
0018	0017	10-Jun-2011	corrections to data tables
0022	0020	24-Jun-2011	stability update
0029	0026	7-Jul-2011	BMAB request: DP container closure integrity
0031	0028	13-Jul-2011	OBP request (responses related to DP quality microbiology)
0032	0029	15-Jul-2011	BMAB request: DP quality microbiology
0034	0031	20-Jul-2011	BMAB request: DP [REDACTED] (b) (4)
0035	0032	22-Jul-2011	OBP/BMAB request: DP shipping
0038	0035	29-Jul-2011	BMAB request: storage time for reconstituted DP

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Amendment 0037 (BLA 125399 amendment 0034) was submitted on 28-Jul-2011 to update section 3.2.P.3.5 with a list of validation reports provided in response to information requests. This information was reviewed in previous amendments.

The following CDER/OC/OMPQ/DGMPA/BMAB reviewers covered section 3.2.P as follows:

- Reyes Candau-Chacon, Ph.D.
  - container closure integrity (section 2.5)
- Bo Chi, Ph.D.
  - [REDACTED] (b) (4) (in section 3.5)
  - rabbit pyrogen test (in section 5.2)
- Colleen Thomas, Ph.D.
  - all other sections

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(b) (4)

## Conclusion

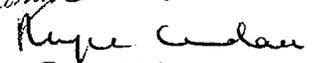
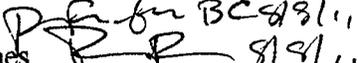
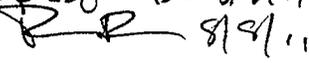
- I. The BLA was reviewed from a product quality microbiology perspective and is recommended for approval.
- II. Product quality aspects other than microbiology should be reviewed by OBP.
- III. A pre-approval inspection of (b) (4) was conducted in May 2011. The compliance status of the facility is acceptable.

## **Microbiology Product Quality PMCs**

1. 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.
2. 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)</sup><sub>(4)</sub> Test BIs used for <sup>(b)</sup><sub>(4)</sub> <sup>(b)</sup><sub>(4)</sub> validation studies should be <sup>(b)</sup><sub>(4)</sub> to confirm that all BIs are negative. This change should be made to the <sup>(b)</sup><sub>(4)</sub> validation protocols at <sup>(b)</sup><sub>(4)</sub> and reported in the next annual report.

**Signatures and Distribution List**

BMAB Reviewer: Colleen Thomas, Ph.D. Date: 8 Aug 2011  
BMAB Reviewer: Reyes Candau-Chacon, Ph.D. Date: 4 Aug 2011  
BMAB Reviewer: Bo Chi, Ph.D. Date: 8 Aug 2011  
Concurring BMAB Acting Branch Chief: Patricia Hughes, Ph.D. Date: 8 Aug 2011

CC: OC/OMPQ/DGMPA/BMAB/Building 51, Thomas  8 Aug 2011  
OC/OMPQ/DGMPA/BMAB /Building 51, Candau-Chacon  8/4/2011  
OC/OMPQ/DGMPA/BMAB /Building 51, Chi  BC 8/3/11  
OC/OMPQ/DGMPA/BMAB /Building 51, Hughes  8/4/11  
OND/OODP/DHP, Building 22, Akinsanya  
OND/OODP/DHP, Building 22, Kwitkowski  
OC/OMPQ/DGMPA/BMAB /Building 51, eCTD Files (STN:125388)

Archived File: S:\archive\BLA\125388\STN125388.rev.mem.BLA.DP.8-3-2011.doc