

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125496Orig1s000

CHEMISTRY REVIEW(S)



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

The Quality Team Leader's Executive Summary

From: Chana Fuchs, PhD, Team Leader
Division of Monoclonal Antibodies (DMA),

Through: Sarah Kennett, PhD
Review Chief, DMA

Kathleen Clouse, PhD
Director, DMA

BLA Number: 125496/0
Product: siltuximab (SYLVANT™)
Sponsor: Janssen Research and Development, LLC

Date of Review: April 10, 2014
Date of TL Memo: April 10, 2014

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, has completed review of BLA 125496 for siltuximab (SYLVANT™) manufactured by Janssen Research and Development, LLC. The data submitted in this application are adequate to support a conclusion that the manufacture of siltuximab is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert.

II. APPROVAL LETTER INFORMATION

Under this license, you are approved to manufacture the siltuximab (b) (4) intermediate at Janssen Biologics B.V. in Leiden, The Netherlands. You are approved to manufacture siltuximab Formulated Bulk Drug Substance at Janssen Biologics, Cork, Ireland. The final lyophilized drug product will be manufactured, (b) (4) at Cilag AG, Schaffhausen, Switzerland.

You may label your product with the proprietary name, SYLVANT, and will market it as an 8 mL single use vial containing 100 mg siltuximab lyophilized powder for injection and as a 30 mL single use vial containing 400 mg siltuximab lyophilized powder for injection.

The dating period for SYLVANT 100 mg vial shall be 24 months from the date of manufacture when stored at 2-8°C. The dating period for SYLVANT 400 mg vial shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as (b) (4) product.

The dating period for siltuximab (b) (4)

The dating period for siltuximab formulated bulk drug substance shall be (b) (4)

The dating period for siltuximab formulated bulk drug substance (b) (4)

III. POST MARKETING COMMITMENTS AND REQUIREMENTS
DMA CMC PMCs

1. To re-evaluate siltuximab 100 mg/vial final lyophilized product lot release and stability specifications using the commercial manufacturing process 5 years from the PDUFA date of April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 9 lots which were included in the analysis

SUMMARY BLA 125496 siltuximab (SYLVANT)

- of specifications submitted in the BLA and any subsequent FLP lots manufactured. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specification (b) (4)
- [REDACTED]
2. To re-evaluate siltuximab 400 mg/vial final lyophilized product lot release and stability specifications using the commercial manufacturing process 5 years from the PDUFA date of April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 7 lots which were included in the analysis of specifications submitted in the BLA and any subsequent FLP lots manufactured. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications (b) (4)

[REDACTED]

 3. To re-evaluate siltuximab formulated bulk lot release and stability specifications using the commercial manufacturing process 5 years from April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 13 lots which were included in the analysis of specifications submitted in the BLA and any subsequent FB lots manufactured. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications (b) (4)

[REDACTED]

 4. To re-evaluate siltuximab (b) (4) intermediate lot release and stability specifications using the commercial manufacturing process 2 years from April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 7 lots which were included in the analysis of cIEF specifications submitted in the BLA and any subsequent (b) (4) lots manufactured. The cIEF and SE-HPLC data from all lots manufactured using the commercial manufacturing process will be included in this evaluation. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications (b) (4)

[REDACTED]

 5. To confirm the anticipated amount of (b) (4) using a validated reduced scale model. Results of the study will be submitted by December 2014.
 6. To confirm the anticipated amount of (b) (4) using a validated reduced

SUMMARY BLA 125496 siltuximab (SYLVANT)

- scale model [REDACTED] (b) (4) The results of this study will be submitted by December 2014.
7. To tighten the [REDACTED] (b) (4) reference material requalification acceptance criteria based on appropriate statistical evaluation and a sufficient amount of data points required for such an evaluation. The updated acceptance criterion and supporting data will be submitted as a CBE0 by November 2014.
 8. To implement specific siltuximab master cell bank (MCB) and working cell bank (WCB) stability programs. The protocols (SOP) for the MCB and WCB stability programs and supporting data for the protocols will be submitted as a CBE0 by August 2014.
 9. To establish a control strategy for the [REDACTED] (b) (4). The updated control strategy and supporting data will be submitted as a CBE0 in August 2014.
 10. To re-evaluate the [REDACTED] (b) (4) using data from drug substance batches manufactured up to October 2016. The analysis and supporting data will be submitted as a CBE30 by December 2016.
 11. To provide confirmatory data by executing manufacturing run of the 100 mg/vial FLP batch at [REDACTED] (b) (4). The drug product from this run will be placed on a stability protocol. The study report, release and stability data will be submitted in Annual Reports.
Study Completion Date: 09/2017
Final Report Submission Date: 12/2017
 12. To provide confirmatory data by executing manufacturing run of the 400 mg/vial FLP batch at [REDACTED] (b) (4). The drug product from this run will be placed on a stability protocol. The study report, release and stability data will be submitted in Annual Reports.
Study Completion Date: 09/2017
Final Report Submission Date: 12/2017
 13. To provide confirmatory data by executing a manufacturing run of the 100 mg/vial FLP batch at [REDACTED] (b) (4). The drug product from this run will be placed on a stability protocol. The study report, release and stability data will be submitted in Annual Reports.
Study Completion Date: 09/2017
Final Report Submission Date: 12/2017
 14. To provide confirmatory data by executing a manufacturing run of the 400 mg/vial FLP batch at [REDACTED] (b) (4). The drug product

from this run will be placed on a stability protocol. The study report, release and stability data will be submitted in Annual Reports.

Study Completion Date: 09/2017

Final Report Submission Date: 12/2017

IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

None

V. EXECUTIVE SUMMARY

A. Description of siltuximab (SYLVANT) Drug Product (DP) and Drug Substance (DS)

Siltuximab (CNTO 328) is a full length recombinant chimeric (human-mouse) IgG1 kappa monoclonal antibody that is directed to interleukin-6 (IL-6), a proinflammatory cytokine. Siltuximab is comprised of (b) (4)

Siltuximab drug product is supplied as a sterile, preservative free, lyophilized powder in two presentations:

100 mg of lyophilized powder in an 8 mL single-use vial.

400 mg of lyophilized powder in a 30 mL single-use vial.

Each carton of SYLVANT contains one single-use glass vial and one package insert.

Siltuximab is to be reconstituted with sterile Water for Injection (WFI), USP, to a concentration of 20 mg/mL. 5.2 mL of WFI are used to reconstitute the 100 mg/vial presentation, and 20 mL of WFI are used to reconstitute the 400 mg/vial presentation. The reconstituted, 20 mg/mL solution is to be further diluted into infusion bags containing 250 mL of Dextrose 5% in Water (D5W) by (b) (4)

The D5W bags must be made of PVC (polyvinyl chloride) with DEHP [Di(2-ethylhexyl) phthalate] or PO (polyolefin). These were the only materials for which compatibility of siltuximab was assessed. Final diluted siltuximab in D5W is to be administered by intravenous infusion over a period of 1 hour using an infusion set containing a 0.2 micron inline, polyethersulfone, (b) (4) filter.

Reconstituted SYLVANT solution in the vial should only be stored for up to 2 hours prior to addition into the infusion bag. Infusion should be completed within 4 hours of dilution of the reconstituted SYLVANT solution into the infusion bag.

SUMMARY BLA 125496 siltuximab (SYLVANT)

The amount of overfill in the siltuximab 100 mg/vial is (b) (4) to account for the volume remaining in the vial, syringe and needle when the contents of the reconstituted product are withdrawn and delivered.

The amount of overfill in the siltuximab 400 mg/vial) is (b) (4) to account for the volume remaining in the vial, syringe and needle when the contents of the reconstituted product are withdrawn and delivered.

SYLVANT drug product 100 mg vial contains 100 mg siltuximab, 3.7 mg L- histidine, 0.8 mg polysorbate 80, and 169 mg sucrose. These are the nominal amounts.

SYLVANT drug product 400 mg vial contains 400 mg siltuximab, 14.9 mg L-histidine, 3.2 mg polysorbate 80, and 677 mg sucrose. These are the nominal amounts.

The inclusion of histidine (b) (4)
Polysorbate 80 (b) (4)
Sucrose (b) (4)
(b) (4)
(b) (4)

Following reconstitution with Sterile Water for Injection, USP, the resulting solution contains 20 mg/mL siltuximab at a pH of 5.2.

SYLVANT should be refrigerated at 2°C to 8°C protected from light.

There is no preservative in the formulation, (b) (4)

The container closure system used for the 100 mg/vial DP is an (b) (4) clear glass vial closed with a (b) (4) aluminum seal with a (b) (4) Gray colored (b) (4) flip-off button.

The container closure system used for the 400 mg/vial DP is a (b) (4) clear glass (b) (4) tubing vial closed with a (b) (4) gray butyl (b) (4) stopper and a 20 mm aluminum seal with a Garnet colored (b) (4) flip-off button.

The Formulated Bulk Drug Substance (FB) contains (b) (4) siltuximab in a (b) (4) histidine, (b) (4) polysorbate 80 (PS 80), pH 5.2. (b) (4) FB is stored at (b) (4) containers with (b) (4) closures containing a (b) (4) liner.

The calculated extinction coefficient for siltuximab is (b) (4). This was used throughout development and in the validation studies to calculate (b) (4).

A claim for a categorical exclusion from the Environmental Assessment (EA) requirement has been submitted under 21CFR section 25.31(c), which states that any application for marketing approval of a biologic product for substances that occur naturally in the environment, or supplement to such an application, is categorically excluded and ordinarily does not require an EA or an Environmental Impact Statement when there is not a significant alteration of the concentration or distribution of the substance, its metabolites or degradation product in the environment. The sponsor states that no extraordinary circumstances exist with respect to this product. There is no indication that additional environmental information is warranted. The claim of categorical exclusion is deemed acceptable.

B. Clinical Trial Information

SYLVANT™ (siltuximab) is indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are HIV-negative and HHV-negative.

The route of administration of siltuximab is intravenous infusion.

The recommended dosing is 11 mg/kg by intravenous infusion every 3 weeks. Infusions are carried out over 60 minutes.

Clinical efficacy data are mainly from protocol CNTO0328MCD2001, a randomized, double blind placebo controlled phase 2 study comparing every 3 week infusions of SYLVANT and best supportive care to placebo and best supportive care in patients with MCD who are HIV and HHSV-8 negative. Additional supporting efficacy data were from MCD patients in clinical trial C0328T03, a phase 1 dose finding study in patients with hematologic malignancies. According to Dr. Dinndorf, results identified that siltuximab treated patients showed durable tumor and symptomatic responses as compared to patients receiving placebo.

This BLA was granted priority review status.

C. Stability

The BLA submission contained adequate stability data to support establishment of (b) (4) FB and DP shelf-life. Stability studies have been conducted in accordance with ICH Q1A(R2) and Q5C. (b) (4), FB and DP stability protocols, including specifications, conditions and testing intervals, were provided and the final versions submitted were determined to be acceptable.

Expiration dating for both the 100 mg/vial and 400 mg/vial presentations of siltuximab lyophilized drug product (FLP) is 24 months from the date of manufacture when stored at 2-8 °C and protected from light. The date of manufacture is defined as the (b) (4)

VI. SIGNATURE BLOCK

Name and Title	Signature and Date
Kathleen Clouse, Ph.D., Director, Division of Monoclonal Antibodies	Signature executed electronically through DARRTS
Sarah Kennett, Ph.D., Review Chief Division of Monoclonal Antibodies	Signature executed electronically through DARRTS
Chana Fuchs, PhD Product Quality Team Leader Division of Monoclonal Antibodies	Signature executed electronically through DARRTS

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/s/

CHANA FUCHS
04/11/2014

SARAH B KENNETT
04/11/2014

KATHLEEN A CLOUSE STREBEL
04/11/2014

BLA STN 125496

SYLVANT™ (Siltuximab)

Janssen Research and Development, LLC

**Audrey Yunhua Jia, M.D, Ph.D.
Bazarragchaa Damdinsuren, M.D., Ph.D.**

Division of Monoclonal Antibodies; HFD-123

OBP CMC Review Data Sheet

1. **BLA#:** STN 125496
2. **REVIEW DATE:** April 10, 2014
3. **PRIMARY REVIEW TEAM:**
 - Medical Officer:** Pat Dinndorf
 - Pharm/Tox:** Pedro DelValle
 - Product Quality Team:** Audrey Y. Jia, M.D., Ph.D. (DS)
 Bazarragchaа Damdinsuren, M.D., Ph.D. (DP)
 Chana Fuchs, Ph.D., Product Quality Team Leader
 - BMT or Facilities:** Maria Candauchaon (DS), and Candace Gomez-Broughton (DP)
 - Clinical Pharmacology:** Jeanne Fourie Zirkelbach
 - Statistics:** Kiki Ko
 - CMC Labeling:** Bazarragchaа Damdinsuren, M.D., Ph.D.
 - RPM:** Patricia Garvey, OMPT/CDER/OND/OHOP/DHP
 - OBP RPM:** Lyndsay Hennessey

4. **MAJOR 21st Century Review DEADLINES**

- Filing Meeting:** October 22, 2013
- Mid-Cycle Meeting:** December 9, 2013
- Wrap-Up Meeting:** March 18, 2014
- Primary Review Due:** January 30, 2014
- Secondary Review Due:** February 6, 2014
- CDTL Memo Due:** March 30, 2014
- PDUFA Action Date:** April 30, 2014

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
CMC pre-BLA teleconference meeting	July 16, 2013
Information request letter 1	October 21, 2013
Filing review memo	October 22, 2013
Information request letter 2	January 17, 2014
Information request letter 3	January 27, 2014
Information request letter 4	February 14, 2014
Teleconference	March 20, 2014
Information request letter 5	March 21, 2014
PMC Discussion Comments	April 1, 2014
Teleconference	April 8, 2014

6. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
125496/0	August 29, 2013	Yes
125496/4 (Stability update)	September 26, 2013	Yes
125496/9 (Response to IR #1)	October 29, 2013	Yes
125496/23 (Response to IR #2)	January 28, 2014	Yes
125496/24 (Response to IR #2)	February 5, 2014	Yes
125496/27 (Response to IR #3)	February 21, 2014	Yes
125496/30 (Response to IR #4)	March 7, 2014	Yes
125496/32 (PMC update from the sponsor)	March 14, 2014	Yes
125496/40 (Response to IR #5)	March 28, 2014	Yes
125496/41 (Response to IR#4)	March 31, 2014	Yes
125496/42 (Response to PMC Discussion)	April 3, 2014	Yes
125496/43 (Response to PMC Discussion)	April 10, 2014	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: SYLVANT
- b. Trade Name: SYLVANT
- c. Non-Proprietary/USAN: Siltuximab
- d. CAS name: Immunoglobulin G1, anti-(human interleukin 6 (BSF-2, interferon beta-2)); human mouse chimeric monoclonal CNTO 328 γ 1 heavy chain (222-213')-disulfide with human mouse chimeric monoclonal CNTO 328 κ light chain, dimer (228-228":231-231")-bisdisulfide
- e. Common name: CNTO 328
- f. INN Name: Siltuximab
- g. Chemical Name:  (b) (4)
- i. Other Names: CNTO 328

8. PHARMACOLOGICAL CATEGORY: Chimeric IgG1 kappa immunoglobulin molecule

9. DOSAGE FORM: Injection, Powder, Lyophilized, For Solution

10. STRENGTH/POTENCY:

- a) The concentration of siltuximab drug product is 20 mg/mL after reconstitution
- b) Potency is defined as percent activity relative to reference standard, using a cell based assay which measures the inhibition of IL-6 mediated proliferation of 7TD1 cells (a murine hybridoma cell line that depends on IL-6 for its growth and responds to human IL-6).
- c) Sylvant 100 mg is filled into 8 mL glass vials containing 100 mg siltuximab
Sylvant 400 mg is filled into 30 mL glass vials containing 400 mg siltuximab

11. ROUTE OF ADMINISTRATION: intravenous infusion

12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)	(b) (4)	(b) (4)	Provided	Adequate. No review required as all the relevant information related to compatibility with the product was in the BLA.
(b) (4)	(b) (4)	(b) (4)	Provided	Adequate. No review was required as relevant information is provided in the BLA.
(b) (4)	(b) (4)	(b) (4)	Provided	(b) (4) Review in DARRTS 12/23/2002 found this acceptable for use for (b) (4). No further review required as all the relevant information related to compatibility with the product was in the BLA.
(b) (4)	(b) (4)	(b) (4)	Provided	(b) (4) No review required as all the relevant information related to compatibility with the product was in the BLA.
(b) (4)	(b) (4)	(b) (4)	Provided	Adequate. No review was required as relevant information is provided in the BLA.

13. INSPECTIONAL ACTIVITIES

There were two pre-license inspections (PLI) at siltuximab drug substance manufacturing facilities. Inspection of Janssen Biologics (Cork, Ireland), at which siltuximab (b) (4) are performed, was conducted on November 18 -22, 2013 by BMAB reviewer Maria Candauchacon and DMA reviewers Gerald Feldman and Yunhua Jia. This site is responsible for manufacturing the formulated drug substance and release testing of formulated drug substance (FB). No 483 observation was issued at the end of this inspection.

Inspection of Janssen Biologics B.V. (Leiden, The Netherlands) was conducted on December 16-20. This manufacturing facility is responsible for the manufacturing steps (b) (4)

(b) (4) as well as QC testing of the stability of siltuximab formulated drug substance and lyophilized final drug product (FLP). A 483 with 3 observations was issued at the end of inspection. These observations are:

1. Microbial quality of (b) (4) is not adequately controlled. Specifically,
 - A) maximum hold time validation of (b) (4)
 - B) (b) (4)
2. Bioburden test procedures are not adequately conducted. Specifically, (b) (4)
3. Warehouse is not adequately maintained. Specifically, during the tour to the warehouse a minivan was parked inside the warehouse.

The sponsor provided responses on January 10, 2014 to FDA/CDER/IOC/OMPQ/DIDQ. Communication with the BMAB reviewer Dr. Maria Candauchaon indicated that the final compliance status for both Leiden and Cork facilities is acceptable.

Inspection of the drug product manufacturing site at Cilag, AG facility is waived, based on recent compliance history [last inspection under the (b) (4) profile was on February 17-18, 2014), the current GMP status, and the fact that Cilag AG has been approved to manufacture multi-licensed products including (b) (4) (b) (4) (b) (4). BMAB reviewer Dr. Maria Candauchaon stated that the ORA inspection in Cilag on February 18, 2014 has an initial classification of "Acceptable."

14. CONSULTS REQUESTED BY OBP: None

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS: None**17. ADMINISTRATIVE****A. Signature Block**

Name and Title	Signature and Date
Chana Fuchs, Ph.D. Team Leader, Division of Monoclonal Antibodies	
Primary Reviewers: Audrey Yunhua Jia, M.D, Ph.D. Product quality reviewer Division of Monoclonal Antibodies Bazarragchaa Damdinsuren, M.D., Ph.D. Senior Staff Fellow Division of Monoclonal Antibodies	

B. CC Block

Recipient	Date
Clinical Division BLA RPM Patricia Garvey, R.Ph.CAPT OMPT/CDER/OND/OHOP/DHP	
Division of Monoclonal Antibodies, File/BLA STN 125496	

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/s/

BAZARRAGCHAA DAMDINSUREN
04/11/2014

YUNHUA JIA
04/11/2014

CHANA FUCHS
04/11/2014

**Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum**

Date: March 26, 2014

From: Candace Gomez-Broughton, Ph.D., OC/OMPQ/DGMP/BMAB
Bazarragchaa Damdinsuren, Ph.D., OPS/OBP/DMA

To: BLA File, STN 125496/0

Through: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMP/BMAB

Subject: Biological License Application (BLA)

Applicant: Janssen Biotech, Inc.

Facility: Cilag AG, Hochstrasse 201, CH-8200 Schaffhausen, Switzerland (FEI# 3002806695)

Product: Sylvant™ (siltuximab)

Dosage: Single-use, powder for injection, for Intravenous administration. 100 mg vial and 400 mg vial

Indication: For the treatment of Multicentric Castleman's Disease (MCD) in patients who are immunodeficiency virus negative (HIV-1) and human herpes virus-8 negative (HHV-8).

Waiver Recommendation

Based on the compliance history of the firm, the current GMP status, and the fact that Cilag AG, Schaffhausen, Switzerland has been approved to manufacture (b) (4) we recommend that the pre-approval inspection of the Cilag AG drug product manufacturing facility in Schaffhausen, Switzerland (FEI: 3002806695) be waived for STN 125496/0.

Summary

Janssen has submitted BLA 125496/0 for approval of siltuximab (proposed name: Sylvant™) which provides for the treatment of MCD in HIV-1 and HHV-8 negative patients. Siltuximab drug product is supplied as a sterile powder for injection, for intravenous administration in USP Type 1 glass vials. Each vial contains either 100 mg or 400 mg of siltuximab, for injection after reconstitution with sterile water for injection (WFI).

The drug substance is manufactured (b) (4)



Facility Information

Siltuximab

(b) (4)

(b) (4)

Supporting Information

The following information is provided in support of waiving the pre-approval inspection:

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

(b) (4)

2. *FDA has not inspected the establishment in the last 2 years.*

The establishment was inspected by IOG from 2/17/14-2/18/14. The site is acceptable from a cGMP perspective.

3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

The inspection was classified VAI with acceptable GMP status. The inspection covered biotech (b) (4) profiles) as well as (b) (4) manufacturing operations.

(b) (4)

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/s/

CANDACE GOMEZ-BROUGHTON
03/26/2014

PATRICIA F HUGHES TROOST
03/26/2014

BAZARRAGCHAA DAMDINSUREN
03/27/2014

KATHLEEN A CLOUSE STREBEL
03/30/2014

JOSEPH D DOLESKI
03/31/2014

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

BLA/NDA Number: 125496 **Applicant:** Janssen Research & Development, LLC **Stamp Date:** 8/30/2013

Established/Proper Name: **BLA/NDA Type:** Priority review
 Siltuximab/SYLVANT
 (proposed)

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	Y	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y	
<input type="checkbox"/> PI –non-annotated	Y	
<input type="checkbox"/> PI –annotated	Y	
<input type="checkbox"/> PI (electronic)	Y	
<input type="checkbox"/> Medication Guide	Y	
<input type="checkbox"/> Patient Insert	Y	
<input type="checkbox"/> package and container	Y	
<input type="checkbox"/> diluent	N	Not applicable
<input type="checkbox"/> other components	N	Not applicable
<input type="checkbox"/> established name (e.g. USAN)	Y	
<input type="checkbox"/> proprietary name (for review)	Y	Submitted as an amendment on 9/6/2013.

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	
<input type="checkbox"/> legible	Y	
<input type="checkbox"/> English (or translated into English)	Y	
<input type="checkbox"/> compatible file formats	Y	
<input type="checkbox"/> navigable hyper-links	Y	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a	N	Not applicable

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

Examples of Filing Issues	Yes?	If not, justification, action & status
shared or divided manufacturing arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	No novel excipients are used in the formulations of siltuximab final lyophilized product (100 mg/vial and 400 mg/vial). As a result 3.2.A.3 Novel Excipients is not provided in Module 3.
<input type="checkbox"/> Drug Substance	Y	
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y	
<input type="checkbox"/> Novel Excipients	Y	
<input type="checkbox"/> Executed Batch Records	Y	
<input type="checkbox"/> Method Validation Package	Y	
<input type="checkbox"/> Comparability Protocols	Y	

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

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

CTD Module 3 Contents	Present?	If not, justification, action & status
<p>including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)</p> <ul style="list-style-type: none"> <input type="checkbox"/> controls of critical steps and intermediates <input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> <input type="checkbox"/> Filter validation <input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation <input type="checkbox"/> Validation of aseptic processing (media simulations) <input type="checkbox"/> Environmental Monitoring Program <input type="checkbox"/> Lyophilizer sterilization validation <input type="checkbox"/> Other needed validation data (hold times) <input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) <input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF & LOAs <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results 		
<p>Other components to be marketed (full description and supporting data, as listed above):</p> <ul style="list-style-type: none"> <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part 	N	Not Applicable: No components to be marketed with siltuximab.

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

CTD Module 3 Contents	Present?	If not, justification, action & status
of kit)		
Appendices for Biotech Products [3.2.A]		
<input type="checkbox"/> facilities and equipment	Y	
<input type="checkbox"/> manufacturing flow; adjacent areas	Y	
<input type="checkbox"/> other products in facility	Y	
<input type="checkbox"/> equipment dedication, preparation, sterilization and storage	Y	
<input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination	Y	
<input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.:	Y	
<input type="checkbox"/> avoidance and control procedures	Y	
<input type="checkbox"/> cell line qualification	Y	
<input type="checkbox"/> other materials of biological origin	Y	
<input type="checkbox"/> viral testing of unprocessed bulk	Y	
<input type="checkbox"/> viral clearance studies	Y	
<input type="checkbox"/> testing at appropriate stages of production	Y	
<input type="checkbox"/> novel excipients	Y	No novel excipients were used.
USA Regional Information [3.2.R]		
<input type="checkbox"/> executed batch records	Y	
<input type="checkbox"/> method validation package	Y	
<input type="checkbox"/> comparability protocols	N	No new comparability study was proposed.
Literature references and copies [3.3]	Y	

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	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y	
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities	Y	

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

Examples of Filing Issues	Yes?	If not, justification, action & status
have occurred)		
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	
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: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility		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	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

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

Audrey Y. Jia (signature through DARRTS)

Product Quality Reviewer(s)

Date

Bazarragchaа Damdinsuren (signature through DARRTS)

Product Quality Reviewer(s)

Date

Chana Fuchs (signature through DARRTS)

Branch Chief/Team Leader/Supervisor

Date

Kathleen A. Clouse (signature through DARRTS)

Division Director

Date

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

/s/

YUNHUA JIA
10/22/2013

BAZARRAGCHAA DAMDINSUREN
10/22/2013

CHANA FUCHS
10/22/2013

KATHLEEN A CLOUSE STREBEL
10/22/2013