

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125496Orig1s000

MICROBIOLOGY REVIEW(S)



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

REVIEW ADDENDUM

Date: April 7, 2014
To: Administrative File, STN 125496
From: Candace Gomez-Broughton, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsed: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Amended Biologic License Application
US License: 1864
Applicant: Janssen Biotech, Inc.
Facility: Cilag AG, Hochstrasse 201 Schaffhausen, Switzerland (FEI #3002806695)
Product: Sylvant (siltuximab)
Dosage: Lyophilized powder in single-use vial; reconstituted for intravenous injection (100 mg/vial and 400 mg/vial)
Indication: For the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus negative and human herpes virus-8 negative
Due date: April 30, 2014

Recommendation: The BLA was reviewed from a product quality microbiology perspective and is recommended for approval.

This is an addendum to the drug product quality microbiology review memo entered into DARRTS on 03-Feb-2014 for BLA 125496. Information requests were sent to the sponsor on 31-Jan-2014 and 19-Feb-2014. The responses were received on 7-Feb-2014 and 10-Mar-2014 and were included in Amendments 0026 and 0031 (sequences 0026 and 0031). The information requests and responses are discussed below. On 31-Mar-2014 the sponsor also submitted the endotoxin recovery study report 295.AB.ZV.432/A spiking study of drug product in the final container (vial) in Amendment 0041. In addition, the environmental assessment has been updated.

Amendment 0026

Reviewer Question 1: Regarding the hold time study endotoxin study data submitted in Amendment 0015, please submit the study report and protocol. Include descriptions of sample preparation, endotoxin concentration, type of endotoxin used, etc.

Sponsor Response: Study protocol 295.AA.ZV.238/A and report 295.AB.ZV.238/A were submitted in the amendment. IPC samples from two batches of (b) (4) bulk drug substance and one batch of placebo were used in the study. Samples were aliquoted in to Schott glass vials and spiked with 100 EU/mL endotoxin standard solution (E. coli 055:B5-CSE). The samples were analyzed at 0, 24, 48, 72 hours following storage at 2-8°C. Values detected at t=0 hours served at the 100% reference values. The results from the summary are shown in the table below.

Table 1: Validation Study Results

Batch ^a	Raw Endotoxin Content ^b (EU/mL)	Final Endotoxin Content of Sample (EU/mL) ^c	Endotoxin Recovery % Versus T=0 Value ^d	Spike Recovery of Positive Product Control (PPC) ^d	
				EU/mL	%
T = 0 hours					
9JS000	0.0242	1.21	100	0.119	119
9IS000	0.0214	1.07	100	0.118	118
9JS0L02	0.0216	1.08	100	0.118	118
T = 24 hours					
9JS000	0.0214	1.07	88	0.089	89
9IS000	0.0172	0.86	80	0.088	88
9JS0L02	0.0342	1.71	158	0.135	135
T = 48 hours					
9JS000	0.0207	1.03	85	0.099	99
9IS000	0.0178	0.89	83	0.104	104
9JS0L02	0.0287	1.44	133	0.130	130
T = 72 hours					
9JS000	0.0214	1.07	88	0.112	112
9IS000	0.0230	1.15	107	0.102	102
9JS0L02	0.0247	1.23	114	0.101	101

^a Siltuximab Batches - 9JS000 and 9IS000; Placebo Batch - 9JS0L02

^b Dilution of 1:50 is not included in the raw data value

^c Calculation = raw data result x used test dilution (1:50)

^d Acceptance Criterion: (b) (4) recovery

This study has demonstrated that endotoxin can be detected quantitatively in samples up to storage time of 72 at 2-8°C.

Reviewer Question 2: Submit the protocol for the endotoxin hold time study for formulated bulk planned for 2014. Ensure that the study is completed with undiluted samples. Also, clarify if the study will be conducted with formulated bulk drug substance.

Sponsor Response: The sponsor submitted the study protocol and has committed to completing the study with undiluted formulated bulk drug substance samples.

Reviewer Question 3: Provide re-validation/re-qualification schedules for major equipment to include (b) (4).

Sponsor Response: Major equipment is re-validated/re-qualified on a (b) (4) month basis. In

the event of change control, nonconformance, critical maintenance or technical interventions, re-validation/re-qualification requirements are assessed.

Reviewer Question 4: Describe incubation conditions for biological indicators used in qualification/validation studies.

Sponsor Response: Biological indicators (BIs) used in [REDACTED] (b) (4) process qualification are incubated for [REDACTED] (b) (4). For [REDACTED] (b) (4) process qualification BIs are incubated for [REDACTED] (b) (4).

Reviewer Question 5: Do [REDACTED] (b) (4) stoppers have a bioburden limit?

Sponsor Response: Bioburden limits for [REDACTED] (b) (4) stoppers are listed below.

- total aerobic microbial count: [REDACTED] (b) (4) CFU/unit
- total combined yeasts and molds count: [REDACTED] (b) (4) CFU/unit

Reviewer comment: The sponsor has submitted adequate responses to the questions submitted.

SATISFACTORY

Amendment 0031

Reviewer Question: The information request submitted by the Agency on November 14, 2013, stated:

“The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and drug product and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug substance and drug product during hold.”

Your proposed study appears to be addressing the hold time of samples [REDACTED] (b) (4). Although the proposed study appears to be adequate for that purpose, it does not address our concern of low endotoxin recovery during maximum hold of formulated drug substance and drug product. Please conduct studies to demonstrate effects of hold on undiluted drug product or drug substance samples spiked with endotoxin; the study should cover the maximum hold times and should be conducted in containers of similar composition as those used for drug substance and drug product during hold. We recommend using standard endotoxin for the study to facilitate quantification (using standard curve with standard endotoxin) and for comparison with results from the previous study.

Sponsor Response: The sponsor gives three reasons why the spiking study is also valid for final drug product:

- The concentration of all ingredients in the formulated bulk (FB) is [REDACTED] (b) (4) than in the final lyophilized drug product after reconstitution, increasing the probability masking endotoxins.
- Containers used in the spiking study (100 mL glass flasks) are of similar composition [REDACTED] (b) (4) as the container used for both presentations of final drug product.
- The only difference the IPC sample and final drug product is that the final drug product is

lyophilized. The sponsor has considered that lyophilization has no negative impact on standard endotoxin because the standard endotoxin itself is often stored as a lyophilized powder.

Reviewer comment: The proposed endotoxin spiking studies appear to be adequate.

Amendment 0041

The sponsor has submitted the spiking study of siltuximab final drug product completed at the request of the Agency. The study was done to demonstrate that the (b) (4) holding time used in the previous study (with final bulk) can also be applied to reconstituted final lyophilized product (FLP) in its final container (400 mg vials).

Vials were reconstituted with 8 mL of LAL-H₂O which yielded a product (b) (4) than the reconstituted product used for injection which increased probability of endotoxin masking and thereby providing the worst case condition.

Three batches of FLP were used in the study. The vials were spiked with 120 µl 100 EU/mL control standard endotoxin solution then analyzed for endotoxin after 0, 24, 48, and 72 hours. Endotoxin values of spiked vials at 0 hours served as the 100% values. Acceptance criteria are listed below.

- Endotoxin concentration at 0 hours must be within (b) (4) % of the detected endotoxin concentration in the positive control
- Endotoxin levels at 24, 48, and 72 hours must be within (b) (4) % of the initial endotoxin level
- Recovery of the positive product control of the sample dilutions must be within (b) (4) % of the known added endotoxin concentration after subtraction of endotoxin detected in the unspiked sample
- The correlation coefficient of the standard curve must be (b) (4)

The study results are provided below:

Tab.2: Endotoxin content of the samples at time point t = 0h, 24h, 48h and 72h , Endotoxin recovery in % in reference to the 0h-value and recovery of the Positive Product control (PPC) in EU/ml and in % (Spike Recovery)

Batch	Raw endotoxin content in EU/ml*	Endotoxin content in EU/ml	Endotoxin recovery in reference to the 0h-value in %	Spike Recovery of the PPC	
				EU/ml	%
Time point t= 0 h (LAL run 14032405D)					
CES2E02	0.0273	1.37	100	0.112	112
CID66015	0.0247	1.24	100	0.104	104
CID66016	0.0244	1.22	100	0.106	106
Time point t=24 h (LAL run 14032507D)					
CES2E02	0.0252	1.26	92	0.109	109
CID66015	0.0252	1.26	102	0.101	101
CID66016	0.0244	1.22	100	0.0986	99
Time point t= 48 h (LAL run 14032608D)					
CES2E02	0.0270	1.35	99	0.105	105
CID66015	0.0270	1.35	109	0.109	109
CID66016	0.0247	1.24	102	0.101	101
Time point t=72 h (LAL run 14032709D)					
CES2E02	0.0260	1.30	95	0.110	110
CID66015	0.0267	1.34	108	0.105	105
CID66016	0.0238	1.19	98	0.103	103

* Dilution of 1:50 is not included in the raw value

The results show that any potential endotoxin present in the FLP can be detected quantitatively in its final container after 72 hours at 2-8°C.

SATISFACTORY

ENVIRONMENTAL ASSESSMENT

Siltuximab meets the criteria of a categorical exclusion as defined in the regulations (21 CFR 25.31 [c]). No extraordinary circumstances exist therefore; no environment assessment will be completed.

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/s/

CANDACE GOMEZ-BROUGHTON
04/07/2014

PATRICIA F HUGHES TROOST
04/07/2014



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

Date: 17 March, 2014
To: Administrative File, STN 125496/0
From: Reyes Candau-Chacon, PhD. Reviewer, OC/OMPQ/DGMPA/BMAB
Through: Patricia Hughes, Ph.D., Team Leader, OC/ OMPQ/DGMPA/BMAB
Subject: Addendum New Biologic License Application (BLA) to address potential Low Endotoxin Recovery in the formulated drug substance
US License: 1864
Applicant: Janssen Biotech, Inc.
Facilities: Janssen Biologics B.V., Einsteinweg 101, 2333 CB Leiden, The Netherlands (FEI 3002806632)
Janssen Biologics (Ireland), Barnahely, Ringaskiddy, Co. Cork, Ireland (FEI 3007029098)
Product: Sylvant (siltuximab)
Dosage: Sterile lyophilized powder for reconstitution with WFI to be delivered as injectable intravenous infusion in 8 mL glass vials containing 100 mg of siltuximab and in 30 mL glass vials containing 400 mg of siltuximab
Indication: For the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus negative and human herpesvirus-8 negative
Due date: 29 April 2014

Recommendation for Approvability: The drug substance part of BLA 125496, as amended, is recommended for approval from a microbial control and microbiology product quality perspective with the following post-marketing commitment:

“To conduct study for endotoxin recovery from formulated drug substance held in [REDACTED] ^{(b) (4)} at process conditions and submit summary report to the Agency per 21CFR601.12 by July 30, 2014”

Summary

This addendum addresses potential Low Endotoxin Recovery in the formulated drug substance. FDA submitted an information request on November 14, 2013 to address the effect of hold times on endotoxin recovery from undiluted drug substance and drug product. Janssen Biotech submitted a response in amendment 0015 indicating that it would conduct a hold time study to be completed in March 2014. This review only covers the effects of hold times on endotoxin recovery from undiluted

drug substance; for the effects on endotoxin recovery on undiluted drug product refer to review by Dr. Candace Gomez-Broughton.

Amendments Reviewed for this addendum

Information Request date	Question numbers	Amendment sequence	Amendment date
14-Nov-2013	9-d	0015	05-Dec-2013
31-Jan-2014	9-d	0026	07-Feb-2014
18-Feb-2014	9-d	0031	10-Mar-2014
27-Feb-2014	9-d	0032	14-Mar-2014

FDA Information Request 9-b sent on November 14, 2013

Recent studies suggest that the LAL endotoxin assay may underestimate the amount of endotoxin in formulations containing polysorbate (J. Chen, "Low Endotoxin Recovery in Common Biologics Products." 2013 PDA Annual Meeting, Orlando, FL, April 2013; K. Williams, "Endotoxin test concerns of Biologics." American Pharmaceutical Review (2013)). The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and drug product and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug substance and drug product during hold.

Janssen response submitted in amendment 0015

Janssen plans to conduct an endotoxin hold time study to be completed March 2014; the report will be submitted to the FDA prior to the end of the review cycle.

FDA Information Request sent on January 31, 2014

Submit the protocol for the endotoxin hold time study for formulated bulk planned for 2014. Ensure that study is completed with undiluted samples. Also, clarify if the study will be conducted with formulated bulk drug substance.

Janssen response submitted in amendment 0026

Janssen acknowledges the requirement for the study to be completed with undiluted drug substance samples and agree to conduct that study. In addition, study protocol DS-TEC-44347 "Endotoxin hold time verification study for CNTO328 samples" is included in the amendment. The study is intended to demonstrate that (b) (4) hour hold time has no impact on endotoxin recovery for CNTO328 in-process and formulated bulk. The study will be conducted by adding from *R. pickettii* (in-house isolate), *P. aeruginosa*, or equivalent to the samples and incubating the samples at 30 to 35°C for 24 to 48 hours. After incubation, the samples will be tested for the presence of endotoxin (T = 0) and will be stored at 2 to 8°C for (b) (4) hours and tested for endotoxin (T = (b) (4)). The acceptance criteria is be endotoxin recovery at T = (b) (4) between (b) (4) and (b) (4) % of endotoxin recovery at T = 0.

FDA Information Request sent on January 31, 2014

The information request submitted by the Agency on November 14, 2013, stated:

“The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and drug product and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug substance and drug product during hold.”

Your proposed study appears to be addressing the hold time of samples (b) (4). Although the proposed study appears to be adequate for that purpose, it does not address our concern of low endotoxin recovery during maximum hold of formulated drug substance and drug product. Please conduct studies to demonstrate effects of hold on undiluted drug product or drug substance samples spiked with endotoxin; the study should cover the maximum hold times and should be conducted in containers of similar composition as those used for drug substance and drug product during hold. We recommend using standard endotoxin for the study to facilitate quantification (using standard curve with standard endotoxin) and for comparison with results from the previous study.

Janssen response submitted in amendment 0031

The formulated drug substance can be held in (b) (4) at (b) (4); samples are testing within 24 hours. Ongoing studies will address the hold time of endotoxin samples (b) (4) (DS-TEC-44347). In addition, Janssen proposes to conduct a study spiking formulated drug substance held in (b) (4) at process conditions followed by a recovery study for a minimum of 48 hours using standard endotoxin; the study will be conducted in parallel with the production of the next three available batches of Siltuximab formulated drug substance.

FDA Information Request sent on February 27, 2014

a. Indicate when the study will be completed and when the report will be submitted to the Agency. b. Indicate which actions will be taken if the proposed study determines low endotoxin recovery in the formulated drug substance after hold.

Janssen response submitted in amendment 0032

a. Indicate when the study will be completed and when the report will be submitted to the Agency.

Janssen Biologics (Cork) expects to submit the summary report for endotoxin recovery from formulated bulk held in (b) (4) at process conditions by (b) (4). In addition, due to changes in the manufacturing

schedule, sample hold time studies for endotoxin in formulated bulk drug substance and in-process intermediates previously committed to be available prior to the end of the review cycle (refer to response to question 9-d in amendment 0015) will be delayed; Janssen Biologics (Cork) expects to submit the summary report for endotoxin recovery from samples held under test conditions by (b) (4).

Satisfactory

Post-marketing Commitment 1

To conduct study for endotoxin recovery from formulated drug substance held in (b) (4) at process conditions and submit summary report to the Agency per 21CFR601.12 by July 30, 2014

b. Indicate which actions will be taken if the proposed study determines low endotoxin recovery in the formulated drug substance after hold.

Janssen has submitted summary report for protocol DS-TEC-45632 “Endotoxin hold time verification study for CNTO328 (siltuximab) formulated bulk in (b) (4) at room temperature”. Certified endotoxin standard was added to one batch of formulated bulk at a final concentration of (b) (4) EU/mL, mixed and held in (b) (4). The samples were held at room temperature for (b) (4) hours and assayed for endotoxin immediately (T0), after (b) (4) hours, and after 48 hours of spike. The results were compared with the theoretical spike; acceptance criterion was endotoxin result at T48 between (b) (4) % of the theoretical spike and corresponding T0 addition. The results were:

- Endotoxin recovery after (b) (4) hours:
 - (b) (4) % of theoretical spike
 - (b) (4) % of recovery at T0
- Endotoxin recovery after (b) (4) hours:
 - (b) (4) % of theoretical spike
 - (b) (4) % of recovery at T0

The results suggest no impact of formulated drug substance held in production conditions on endotoxin recovery. Once additional batches of siltuximab formulated drug substances become available, Janssen Biologics (Cork) will conduct a comprehensive study and will submit it to the Agency (refer to previous response). The applicant will notify the Agency immediately in the event of any change in the current data profile during the planned study.

Reviewer comment

Janssen Biologics (Cork) has already submitted endotoxin recovery results of formulated drug substance held in production conditions using one batch of formulated DS and will repeat the study with three additional batches. The provisional results show no impact of formulated DS in endotoxin recovery.

Satisfactory

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/s/

REYES CANDAU-CHACON
03/17/2014

PATRICIA F HUGHES TROOST
03/18/2014



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

Date: 7 February, 2014
To: Administrative File, STN 125496/0
From: Reyes Candau-Chacon, PhD. Reviewer, OC/OMPQ/DGMPA/BMAB
Through: Patricia Hughes, Ph.D., Team Leader, OC/ OMPQ/DGMPA/BMAB
Subject: New Biologic License Application (BLA)
US License: 1864
Applicant: Janssen Biotech, Inc.
Facilities: Janssen Biologics B.V., Einsteinweg 101, 2333 CB Leiden, The Netherlands (FEI 3002806632)
Janssen Biologics (Ireland), Barnahely, Ringaskiddy, Co. Cork, Ireland (FEI 3007029098)
Product: Sylvant (siltuximab)
Dosage: Sterile lyophilized powder for reconstitution with WFI to be delivered as injectable intravenous infusion in 8 mL glass vials containing 100 mg of siltuximab and in 30 mL glass vials containing 400 mg of siltuximab
Indication: For the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus negative and human herpesvirus-8 negative
Due date: 29 April 2014

Recommendation for Approvability: The drug substance part of this application is recommended for approval from a microbial control and microbiology product quality perspective.

Review Summary

Janssen Biotech Inc. has submitted BLA 125496 to license siltuximab drug substance and drug product. Siltuximab is a chimeric (human-murine) immunoglobulin G1 κ (IgG1 κ) that binds and neutralizes the biological activity of human Interleukin-6 (IL-6) for the treatment of multicentric Castleman's disease.

BLA 125496 was submitted in eCTD on August 29, 2013. This review contains the assessment of the manufacturing process of siltuximab bulk drug substance from microbiological perspective. For review of drug product aspects of the application, please see review by Dr. Candace Gomez-Broughton.

Amendments Reviewed for Drug Substance Quality

Information Request date	Question numbers	Amendment sequence	Amendment date
14-Nov-2013	1 to 9	0015	05-Dec-2013
17-Jan-2014	3g, 3j, 8b	0023	28-Jan-2014
24-Jan-2014	3g, 8b	0025	5 Feb-2014

Review Narrative

S DRUG SUBSTANCE

S.1 General Information

Siltuximab is a chimeric human-murine monoclonal immunoglobulin G1 containing (b) (4)

[Redacted]

The drug product is a lyophilized powder for reconstitution and intravenous infusion.

Satisfactory

S.2 Manufacture

S.2.1 Manufacturer(s)

The following facilities are involved in the manufacture, release testing, and stability testing of siltuximab drug substance:

- Janssen Biologics B.V., Einsteinweg 101, 2333 CB Leiden, The Netherlands Drug Substance Manufacturing (Stages 1-3); analytical testing of process intermediates and bulk drug substance; testing of final lyophilized product FEI 3002806632
- Janssen Biologics (Ireland), Barnahely, Ringaskiddy, Co. Cork, Ireland Drug Substance Manufacturing (Stage 4-9), analytical testing of process intermediates and bulk drug substance; testing of final lyophilized product FEI 3007029098

- [Redacted] (b) (4)
FEI [Redacted] (b) (4)

Reviewer comments:

Refer to the cGMP status section of this review for the compliance status of the manufacturing facilities.

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/s/

REYES CANDAU-CHACON
02/07/2014

PATRICIA F HUGHES TROOST
02/10/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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

Date: January 30, 2013
To: Administrative File, STN 125496/0
From: Candace Gomez-Broughton, Ph.D. Reviewer CDER/OC/OMPQ/DGMPA/BMAB
Endorsed: Patricia Hughes, Ph.D. Team Leader CDER/OC/OMPQ/DGMPA/BMAB
Subject: New Biologic License Application
US License: 1864
Applicant: Janssen Biotech, Inc.
Facility: Cilag AG, Hochstrasse 201 Schaffhausen, Switzerland (FEI #1018495)
Product: Sylvant (siltuximab)
Dosage: Lyophilized powder in single-use vial; reconstituted for intravenous injection (100 mg/vial and 400 mg/vial)
Indication: For the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus negative and human herpes virus-8 negative.
Due date: April 30, 2014

Recommendation: BLA 125496, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitment:

To determine the volume of the (b)(4) necessary to achieve consistent (b)(4) test conditions, provide the supportive data, and use the determined volume in the (b)(4) test of the drug product (b)(4) by May 2014.

REVIEW SUMMARY

Janssen Biotech Inc. has submitted BLA 125496 in eCTD format on 30-Aug-2013 to license siltuximab for treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) and human herpes virus-8 (HHV-8) negative. Siltuximab is a chimeric (human-murine) immunoglobulin G1κ (IgG1κ) monoclonal antibody that binds to human Interleulin-6 (IL-6), neutralizing its biological activity. The drug substance (DS) is manufactured at Janssen Biologics B.V. in Leiden, The Netherlands, and Janssen Biologics (Ireland) in Cork, Ireland and is designated formulated bulk (FB) in the application.

This review covers the product quality microbiology of the drug product final lyophilized product (FLP) as presented in BLA section 3.2.P. The product quality microbiology review for the DS was completed by Reyes Candau-Chacon, Ph.D. in a separate memo.

DRUG PRODUCT QUALITY MICROBIOLOGY ASSESSMENT

Amendments Reviewed For Drug Product Quality Microbiology

- Amendment 0015 – response to information request sent 14-Nov-2013
- Amendment 0019 – response to information request sent 6-Dec-2013

Reviewer Question: Information and validation of (b) (4) processes of product contact parts and equipment is included in the appendix section. Amend the BLA to include that information in Section 3.2.P.3.5.

Sponsor Response in Amendment 0019: The sponsor agreed to amend BLA 125496 to include in Module 3 the validation (performance qualification) of (b) (4) processes, originally submitted in the Appendix section. The following dossier sections are relocated to Module 3.2.P.3.5:

- (b) (4)

The following dossier section is revised to align with this dossier re-location:

- 3.2.A.1 Facilities and Equipment - Equipment (b) (4)

P DRUG PRODUCT

P.1 Description and Composition of the Drug Product

Siltuximab is supplied as a sterile, single-use lyophilized dosage for intravenous infusion. The DP is provided in two presentations; 100mg/vial (8 mL vial) and 400 mg/vial (30 mL vial). Both presentations are supplied in Type 1 glass vials with elastomeric closure and aluminum seal with flip-button. The 100- and 400-mg/vial presentations are reconstituted with 5.2 and 20.0 mL of sterile water-for-injection (WFI) respectively. The quantitative composition of the final lyophilized product (FLP) for both presentations is provided in the table below.

Component	Concentration Post-Reconstitution (mg/mL)	100 mg/vial		400 mg/vial	
		Amount per vial (mg)	Nominal Amount per vial (mg)	Amount per vial (mg)	Nominal Amount per vial (mg)
Siluximab	20 (b) (4)	(b) (4)	100	(b) (4)	400
Sucrose	(b) (4)	(b) (4)	169	(b) (4)	677
L-histidine	(b) (4)	(b) (4)	3.7	(b) (4)	14.9
Polysorbate 80	(b) (4)	(b) (4)	0.8	(b) (4)	3.2

SATISFACTORY

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This BLA meets the criteria of a categorical exclusion as defined in the regulations (21 CFR 25.31 [c]), and that to the sponsor's knowledge, no extraordinary circumstances exist. Thus, no environmental assessment needs to be completed.

cGMP STATUS

Please see TB-EER in DARRTS.

CONCLUSION

- I. The BLA, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitments;

To determine the volume of the (b) (4) necessary to achieve consistent (b) (4) test conditions, provide the supportive data, and use the determined volume in the (b) (4) test of the drug product (b) (4) by May 2014.

- II. The supplement was reviewed from microbial control, CMC sterility assurance, and microbiology product quality perspective.
- III. No additional inspectional follow-up items were identified.

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/s/

CANDACE GOMEZ-BROUGHTON
01/31/2014

PATRICIA F HUGHES TROOST
02/03/2014

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

BLA Number:

Applicant:

Stamp Date:

STN 125496

Janssen Biotech, Inc.

October 17, 2013

Established/Proper Name: BLA Type:

Siltuximab

Priority

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 N	Not required
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y	Defer to OBP
<input type="checkbox"/> PI –non-annotated	Y N	
<input type="checkbox"/> PI –annotated	Y N	
<input type="checkbox"/> PI (electronic)	Y N	
<input type="checkbox"/> Medication Guide	Y N	
<input type="checkbox"/> Patient Insert	Y N	
<input type="checkbox"/> package and container	Y N	
<input type="checkbox"/> diluent	Y N	
<input type="checkbox"/> other components	Y N	
<input type="checkbox"/> established name (e.g. USAN)	Y N	
<input type="checkbox"/> 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	
<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	Y N	Not Applicable

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

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]	N	Not necessary
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	Defer to OBP Defer to OBP Defer to OBP; referred to section 3.2.R Included in Section 3.2.R Not Applicable
<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 N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		Defer to OBP OBP has the lead; BMAB reviews bioburden and endotoxin. Defer to OBP. OBP has the lead; BMAB reviews
<input type="checkbox"/> general info	Y	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> 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="checkbox"/> batch numbering and pooling scheme	Y	
<input type="checkbox"/> cell culture and harvest	Y	
<input type="checkbox"/> purification	Y	
<input type="checkbox"/> filling, storage and shipping	Y	
<input type="checkbox"/> control of materials	Y	
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input type="checkbox"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and	Y	

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CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> <input type="checkbox"/> batch formula <input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) <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 		
Other components to be marketed (full description and supporting data, as listed		NA

**PRODUCT QUALITY (Biotechnology)
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CTD Module 3 Contents	Present?	If not, justification, action & status
above): <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part of kit)		
Appendices for Biotech Products [3.2.A] <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> ○ 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 <input type="checkbox"/> novel excipients	Y	Defer to OBP
USA Regional Information [3.2.R] <input type="checkbox"/> executed batch records <input type="checkbox"/> method validation package <input type="checkbox"/> comparability protocols	Y	BMAB reviews microbial control
Literature references and copies [3.3]		

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)		
Includes data demonstrating consistency of manufacture		
Includes complete description of product lots and manufacturing process utilized for clinical studies		
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots		
Data demonstrating comparability of		

**PRODUCT QUALITY (Biotechnology)
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Examples of Filing Issues	Yes?	If not, justification, action & status
product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)		
Certification that all facilities are ready for inspection		
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.		
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		
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		
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product		
Description of precautions taken to 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 (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

Reyes Candau-Chacon	October 17, 2013
Product Quality Microbiology Reviewer (Drug Substance)	Date
Candace Gomez-Broughton	October 17, 2013
Product Quality Microbiology Reviewer (Drug product)	Date
Patricia Hughes, PhD	October 17, 2013
Team Leader	Date

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

/s/

CANDACE GOMEZ-BROUGHTON
10/28/2013

REYES CANDAU-CHACON
10/28/2013

PATRICIA F HUGHES TROOST
10/28/2013