CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761061Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: **4/20/2017**
To: Administrative File, **STN 761061/0**
From: Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
Endorsement: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead, CDER/OPQ/OPF/DMA/Branch IV
Subject: New Biologic License Application (BLA)
Applicant: Janssen Biotech, Inc.
US License: **1864**
Facility: Cilag AG, Schaffhausen, Switzerland
FEI: 3002806695
Product: guselkumab
Dosage: 100 mg/1 mL, Subcutaneous, solution for injection
Indication: Treatment of Adults with Moderate-to-Severe Plaque Psoriasis
PDUFA date: July 16, 2017

Recommendation: The drug product part of this BLA, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective with the following post-marketing commitment:

Provide additional data comparing the (b) (4) Include the (b) (4) in the (b) (4) revalidation program if the new information indicates that the (b) (4) .

Review Summary

Janssen has submitted this new Biologics License Application (BLA) for guselkumab, a recombinant human monoclonal antibody for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. (b) (4) of the drug substance (DS) process are manufactured at Biogen Inc., Research Triangle Park, NC. (b) (4) of the DS process are manufactured at Janssen Biologics, Cork, Ireland. The drug product (DP) is manufactured at Cilag AG, Schaffhausen, Switzerland. This application contains CMC information in an eCTD format.

This review contains an assessment of the guselkumab drug product section of the BLA from a sterility assurance and product quality microbiology perspective. The sponsor initially submitted manufacturing information pertaining to both (b) (4) and 100 mg/syringes presentations in the BLA. However, the proposed labeling specifies only the 100 mg/syringe dosage and includes no information on the (b) (4) presentation. The sponsor removed manufacturing

information related to the [redacted] DP presentation from Sections 3.2.P.1 (Description and Composition of the Drug Product), 3.2.P.3.2 (Batch Formula), 3.2.P.3.3 (pfs – Description of Manufacturing Process and Process Controls), 3.2.P.3.4 (pfs – In-process Control), 3.2.P.5.1 (pfs – Specifications), and 3.2.P.8.2 (Stability) of the BLA on 3/31/2017 per FDA's request. Information and data on the [redacted] presentation are still present in the rest of the sections of the BLA.

Assessment

Drug Product

Description of the Composition of the Drug Product (3.2.P.1):

Guselkumab drug product is supplied as a sterile solution in a single-use, prefilled syringe (PFS) assembled into [redacted] passive needle guard. The PFS is filled with [redacted] mL to deliver a nominal 100 mg in 1.0 mL per syringe. The DP contains no preservative. [redacted] DP contains 100 mg/mL guselkumab in a target final formulation composed of [redacted] mM histidine, [redacted] % (w/v) sucrose, and 0.05% (w/v) PS 80, pH 5.8.

Reviewer comment: The information on DP composition is adequately described.

Satisfactory

Pharmaceutical Development (3.2.P.2):

Guselkumab is a recombinant fully humanized monoclonal antibody that binds to the p19 subunit of IL-23 and neutralizes the biological activities of IL-23. Guselkumab is manufactured in [redacted] and consists of two identical light chains and two identical heavy chains. The 4 chains are linked together by covalent disulfide bonds and non-covalent protein-protein interactions.

Microbiological Attributes (3.2.P.2.5)

The guselkumab container closure DP is [redacted] 1 mL long prefilled syringe comprises a Type 1 glass syringe barrel with fixed stainless steel needle stoppered with a plunger stopper. The needle is covered with a rigid needle shield. The PFS is then assembled [redacted]

Container closure integrity (CCI) of the PFS is achieved by [redacted]

Assembly of the PFS [redacted] device and shipment of the [redacted] after assembly may impact CCI of the PFS. Therefore, additional studies were performed to demonstrate CCI post-assembly and post-shipment. The results are presented in Section 3.2.P.3.5.

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[redacted] *In addition, CCI test was conducted on PFS [redacted] post-assembly and post-shipping (simulation). See Section 3.2.P.3.5 below. All the units passed the CCI test. Therefore, the CCI of the guselkumab PFS has been validated. In addition, the PFS [redacted] assembly process does not negatively impact the CCI of the PFS.*

Satisfactory

Manufacture (3.2.P.3):

Manufacturers (3.2.P.3.1):

Cilag AG
Hochstrasse 201
8200 Schaffhausen
Switzerland
FEI: 3002806695
DP manufacturing, assembly with device, labeling and secondary packaging, and analytical testing [redacted] release, and stability testing of DS and DP)

AndersonBrecon, Inc.
4545 Assembly Drive
Rockford, Illinois 61109
FEI: 1421377
DP labeling and secondary packaging

Janssen Biologics B.V.
Einsteinweg 101
2333 CB, Leiden
The Netherlands
FEI: 3002806632
[redacted] release, and stability testing of DS and DP

Janssen Biologics (Ireland)
Barnahely,
Ringaskiddy, Co. Cork
Ireland
FEI: 3007029028
Drug substance manufacturing [redacted] release, and stability testing of DS and DP

Batch Formula (3.2.P.3.2)

[redacted]

(b) (4)

Description of the Manufacturing Process and Process Controls (3.2.P.3.3) and Controls of Critical Steps and Intermediates (3.2.P.3.4)

(b) (4)

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(b) (4)

Satisfactory

Stability (3.2.P.8)

The proposed shelf life for guselkumab drug product is 24 months when stored at 2-8°C and protected from light. One batch of the100 mg/syringe guselkumab DP batch will be added to the stability program annually if DP is manufactured. Container closure integrity and sterility tests are conducted initially, at 12, 24, 30, and 36 months on the stability program using guselkumab PFS.

The container closure integrity test by dye ingress is reviewed in Section 3.2.P.5.2 above.

> *Reviewer comment: The shelf life of the DP should be determined by the OBP reviewer. The CCI test is tested on guselkumab PFS on the stability program with adequate frequency. There is no microbiology test on PFS-U for the stability program, which is acceptable.*

Satisfactory

Conclusion

I. The drug product section of the BLA, as amended, is recommended for approval from a sterility assurance and product quality microbiology perspective with the following post-marketing commitment:

Provide additional data comparing (b) (4) . Include the (b) (4) in the (b) (4) revalidation program if the new information indicates that the (b) (4) .

II. Information and data in this submission not related to drug product sterility assurance and product quality microbiology perspective were not evaluated and should be reviewed by an OBP reviewer.

III. See Panorama for CGMP status of the relevant facilities.

Bo
Chi

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Reyes
Candau-Chacon

Digitally signed by Reyes Candau-Chacon
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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

Date: April 27, 2017
STN: BLA 761061/0
Reviewer: Candace Gomez-Broughton, Ph.D. Microbiologist, CDER/OPQ/OPF/DMA/Branch IV
Endorsed: Reyes Candau-Chacon, Ph.D. Quality Assessment Lead, CDER/OPQ/OPF/DMA/Branch IV
Subject: New Biologics License Application
Applicant: Janssen Biotech, Inc.
License #: 1864
Facilities: Biogen, Inc. Research Triangle, NC (FEI: 3000719749)
Janssen Biologics Cork, Ireland (FEI: 3007029028)
Product: TREMFYA® (guselkumab)
Dosage: solution for subcutaneous injection (100 mg/mL)
Indication: Treatment for adult moderate-to-severe plaque psoriasis
Action Date: July 16, 2017

Recommendation: The drug substance section of the BLA, as amended, is recommended for approval from a microbiology product quality perspective.

Introduction

Janssen Biologics, Inc. has submitted a Biologics License Application (BLA) for the approval of guselkumab for the treatment of adults with moderate to severe plaque psoriasis. Guselkumab is a human immunoglobulin G1 lambda (IgG1λ) mAb which binds to the p19 protein subunit of human interleukin 23 (IL-23). This binding disrupts the IL-23/IL-17 pathway which leads to inflammation.

This BLA was submitted in eCTD format. This assessment covers the drug substance sections of the application . Drug product sections were reviewed by Bo Chi, Ph.D.

Amendments Reviewed

- Sequence 0031 (07Apr2017)
- Sequence 0037 (20Apr2017)

Assessment

S Drug Substance

S.1 General Information

Guselkumab (CNTO 1959) has been shown to bind the p19 subunit of human IL-23 which ultimately inhibits IL-23-specific intracellular signaling.

S.2 Manufacture

S.2.1 Manufacturer(s)

The (b) (4) of drug substance (DS) manufacturing are completed at Biogen Inc. in Research Triangle, North Carolina. The remainder of the DS manufacturing process is completed at Janssen Biologics in Cork, Ireland. Analytical testing (bioburden and endotoxin) is done at both sites.

S.2.2 Description of Manufacturing Process and Process Controls

The guselkumab DS manufacturing process consists of (b) (4) which include (b) (4) . The manufacturing stages are outlined below:

(b) (4)

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CONCLUSIONS

I. The drug substance section of the BLA, as amended, is recommended for approval from a microbiology product quality perspective.

II. Information and data in this supplement not related to drug product sterility assurance should be reviewed by the OBP reviewer.

III. The drug substance facility in Research Triangle, NC was inspected on Dec. 19-23, 2016 and was classified as VAI. In addition, the drug substance facility in Cork, Ireland was inspected on Feb. 27 to Mar. 3, 2017 and was classified as VAI.

Information Requested During Review

31 Mar 2017

1. Please express endotoxin limits in EU/mL.
2. Please provide the microbial quality (b) (4) validation study reports for all drug substance (b) (4). Please include microbial data (b) (4).
3. Please amend the BLA to include brief descriptions of the bacterial endotoxin and bioburden tests used for release and (b) (4)

17 Apr 2017

Endotoxin may be introduced during (b) (4)

Your proposed endotoxin limit of (b) (4) EU/mg (b) (4) is equivalent to an unacceptable endotoxin limit of approximately (b) (4) EU/mL. (b) (4)

Express the (b) (4) endotoxin limits in EU/mL and lower the endotoxin limits (b) (4)

APPEARS THIS WAY ON ORIGINAL

Candace Y. Gomez-broughton -A

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Date: 2017 05 01 14 03:17 04 00

Reyes
Candau-Chacon

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First Approval for Indication
Priority Review

Recommendation: Approval

BLA 761061
Review

Date: April 14, 2017
From: Qing Zhou, Ph.D.
Team Leader, DBRR I/OBP/OPQ

Through: Sarah Kennett, Ph.D.
Review Chief, DBRR I/OBP/OPQ

Kathleen Clouse, Ph.D.
Director, DBRR I/OBP/OPQ

Drug Name/Dosage Form	**guselkumab/injection (Trade name pending)**
Strength/Potency	**100 mg/1.0 mL prefilled syringe**
Route of Administration	**Subcutaneous injection**
Rx/OTC Dispensed	**Rx**
Indication	**Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.**
Applicant/Sponsor	**Janssen Biotech, Inc**
US agent, if applicable	**Janssen Research & Development, LLC**

Product Overview

Guselkumab is a human IgG1λ monoclonal antibody produced in (b) (4). Guselkumab targets the p19 protein subunit of extracellular human interleukin 23 (IL-23) and blocks the binding of IL-23 to the IL-23 receptor, leading to the reduction and/or inhibition of downstream production of IL-17A, a pro-inflammatory cytokine implicated in psoriasis pathogenesis. Guselkumab drug product is supplied at 100 mg/1.0 mL as a sterile, single-dose, preservative-free solution for subcutaneous (SC) injection in pre-filled syringes (PFS) assembled into (b) (4) passive needle guard. Guselkumab is proposed as a single agent for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Willie Wilson	DBRR I/OBP/OPQ
Drug Product	Willie Wilson	DBRR I/OBP/OPQ
Immunogenicity	Willie Wilson	DBRR I/OBP/OPQ
Labeling	Jibril Abdus-Samad	OBP/OPQ
Facility	Viviana Matta	DIA/OPF/OPQ
Microbiology	Bo Chi	DMA/OPF/OPQ
Microbiology	Candace Gomez-Broughton	DMA/OPF/OPQ
Business Process Manager	Kelly Ballard	RBPMBI/ OPRO/OPQ
Team Lead for OBP	Qing Zhou	DBRR I/OBP/OPQ
Tertiary Reviewer for OBP	Sarah Kennett	DBRR I/OBP/OPQ
Microbiology Team Lead	Maria Candau-Chacon	DMA/OPF/OPQ
Facilities Team Lead	Peter Qiu	DIA/OPF/OPQ

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Matthew White	CDER/OND/ODEIII/DDDP
Cross-disciplinary Team Lead	Gordana Diglisic	CDER/OND/ODEIII/DDDP
Medical Officer	Melinda McCord/Kevin Clark	CDER/OND/ODEIII/DDDP
Pharm/Tox	Renqin Duan	CDER/ODEIII/DDDP
Clinical Pharmacology	Anand Balakrishnan	CDER/OCP/DCPIII
Stats	Matthew Guerra	CDER/OM/DMS

a. Names
   i. Proprietary Name: Pending (“Tremfya” under review)
   ii. Trade Name: Pending (“Tremfya” under review)
   iii. Non-Proprietary/USAN: guselkumab
   iv. CAS name: 1350289-85-8
   v. INN Name: guselkumab
   vi. OBP systematic name: MAB HUMAN (IGG1) ANTI Q9NPF7 (IL23A_HUMAN) [CNTO1959]

b. Pharmacologic category: Therapeutic recombinant human monoclonal antibody

Quality Review Team – Signature Page

DISCIPLINE	REVIEWER	SIGNATURE
Microbiology Team Lead	Reyes Candau-Chacon	See electronic signature at the end of review
Facilities Team Lead	Peter Qiu	See electronic signature at the end of review
Application Technical Lead and DS and DP Team Lead	Qing Zhou	See electronic signature at the end of review
OBP Review Chief; DS, DP and Immunogenicity Tertiary Reviewer	Sarah Kennett	See electronic signature at the end of review
Director; Executive Summary Tertiary Reviewer	Kathleen Clouse	See electronic signature at the end of review

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. Submissions Reviewed

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
761061/0000	November 16, 2016	OBP, DMA, DIA
761061/0004	December 7, 2016	DMA, DIA
761061/0005	December 9, 2016	DMA, DIA
761061/0006	December 12, 2016	DMA
761061/0007	December 15, 2016	DMA
761061/0008	December 19, 2016	OBP, DMA, DIA
761061/0010	February 9, 2017	OBP
761061/0018	March 7, 2017	OBP
761061/0024	March 28, 2017	DMA
761061/0025	March 31, 2017	OBP
761061/0028	April 4, 2017	OBP
760161/0031	April 7, 2017	DMA
760161/0034	April 12, 2017	OBP
760161/0035	April 13, 2017	DMA

B. DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	Code[1]	STATUS[2]
(b) (4)	III		(b) (4)	3	N/A
	III			3	N/A
	III			3	N/A
	V			3	N/A

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

[2] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

C. Other Documents: None

3. CONSULTS: None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761061 for guselkumab manufactured by Janssen Biotech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of guselkumab 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 conditions specified in the package insert.

b. Approval action letter language

Under this license, you are approved to manufacture [redacted] (b) (4) [redacted] (b) (4) at Biogen Inc., Research Triangle Park, NC. You are approved to manufacture guselkumab drug substance at Janssen Sciences Ireland UC, Cork, Ireland. The 100 mg/1.0 mL drug product will be manufactured, assembled, labelled, and packaged at Cilag A.G., Schauffhausen, Switzerland. The 100 mg/1.0 mL drug product may also be labelled and packaged at AndersonBrecon, Inc., Rockford, IL.

The dating period for guselkumab drug product, 100 mg/1.0 mL, shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product.

The dating period for guselkumab drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

The dating period for the [redacted] (b) (4) shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

c. Benefit/Risk Considerations

Psoriasis is a chronic immune-mediated inflammatory skin disease associated with serious comorbidities and substantial impairment of physical and psychological quality of life. Approximately 90% of those affected with psoriasis have plaque psoriasis; 20% have moderate to severe plaque psoriasis with a body surface area (BSA) involvement of >5%. The current therapeutic options for moderate to severe plaque psoriasis include phototherapy, topical agents (e.g., corticosteroids), conventional systemic therapy (e.g., cyclosporine, methotrexate, and oral retinoids), and biologic therapy (e.g., adalimumab, etanercept, infliximab, ustekinumab, and secukinumab). However, these therapies have limitations due to due to tolerability, toxicity, safety risks, and/or issues with ease of use. Guselkumab targets the p19 protein subunit of extracellular interleukin 23 (IL-23) and blocks the interaction of IL-23 and IL-23 receptor, leading to an anti-inflammatory response in psoriasis patients.

The overall control strategy for guselkumab manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, process monitoring tests, release, and stability testing ensures process consistency, and drug substance (DS) and drug product (DP) that have appropriate quality and are free of adventitious agents.

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

PMC 1: To perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to both drug substance and drug product.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Drug Substance and Drug Product CQA Identification, Risk and Lifecycle Knowledge Management				
CQA	Risk	Origin	Control Strategy	Other notes
IL-23 binding (potency)	Efficacy	Intrinsic to the molecule Impacted by oxidation, glycation, deamidation, aggregation and fragmentation. Decrease (b) (4) is expected during DP storage through expiry.	(b) (4)	Guselkumab does not bind to IL-23 that is already bound to IL-23 receptor and no CDC activity was detected using an in vitro cell based assay
Identity	Safety and Efficacy	Intrinsic to the molecule		N/A
High Molecular Weight (HMW) species/Aggregates (product-related impurities)	Efficacy, Pharmacokinetics, and Safety/Immunogenicity Impacts IL-23 binding	Manufacturing process and exposure to heat, light and low and high pH stress. Minimal change is expected during (b) (4) DP storage through expiry.		N/A

Low Molecular Weight (LMW) Species (product-related impurities)	Efficacy and Pharmacokinetics	Manufacturing process and exposure to heat, light, and low and high pH stress. Minimal change is expected on stability.	(b) (4)	N/A
Heavy chain (b) (4)	Efficacy	(b) (4) Minimal change is expected on stability.		N/A
Heavy chain (b) (4)	Pharmacokinetics (FcRn binding)	Manufacturing process and exposure to acid treatment, light, heat, low and high pH stress. Minimal change is expected on stability.		N/A
Light chain (b) (4)	Efficacy	Manufacturing process and exposure to oxidative, light, heat, and high pH stress. Minimal change is expected on stability.		N/A
Light chain (b) (4)	Efficacy	Manufacturing process and		N/A

(b) (4)		exposure to light, heat, and high pH stress. Minimal change during storage is expected (b) (4) during DP storage through expiry.	(b) (4)	
Heavy chain (b) (4) (b) (4)	Efficacy	Manufacturing process and exposure to heat and high pH stress. Minimal change is expected on stability.		
Osmolality	Safety, Efficacy (control of degradation through formulation)	Formulation		N/A
pH	Safety and Efficacy	Formulation process		N/A
Protein Content	Efficacy	Manufacturing process		N/A
Polysorbate 80 (PS 80)	Safety	Formulation		N/A

B. Drug Substance [guselkumab] Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA	Risk	Origin	Control Strategy	Other notes
Appearance	Safety	Controlled by the manufacturing process	(b) (4)	N/A
Host Cell Proteins (Process-related impurity)	Safety and Immunogenicity	Production cell line		N/A
Host Cell DNA (Process-related impurity)	Safety	Production cell line		N/A
(b) (4) (Process-related impurity)	Safety and Immunogenicity	Process related impurity (b) (4)		N/A

Residual (b) (4) (Process-related impurity)	Safety	(b) (4)	N/A
Culture Medium additives (b) (4) (Process-related impurity)	Safety	(b) (4)	N/A
Viruses (Contaminant)	Safety	Contamination during manufacture, most likely during cell culture operations	N/A
Mycoplasma (Contaminant)	Safety	Mycoplasma would most likely be introduced during cell culture operations.	N/A
Leachables (Process-related impurity)	Safety	Process-related impurities potentially from manufacture and the DS container closure system (CCS)	N/A
Endotoxin	Safety and Purity	Raw materials or	N/A

		contamination during manufacturing	(b) (4)	
Bioburden	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials or contamination during manufacturing		N/A

a. Description

Guselkumab is a recombinant, human IgG1λ monoclonal antibody and consists of two heavy chains that are each composed of 447 amino acids and two light chains that are each composed of 217 amino acids. Each heavy chain contains an N-linked glycan site at asparagine 297 (Asn297). The molecular weight of deglycosylated guselkumab without C-terminal lysine is 144,258 Da.

The extinction coefficient was calculated and confirmed experimentally to be 1.70 mg^{-1} cm^{-1} mL at 280 nm. This value has been used during development and will continue to be used to determine the guselkumab protein concentration for commercial use.

b. Mechanism of action

Guselkumab binds to the p19 subunit of human IL-23 and blocks the binding of IL-23 to the IL-23 receptor. IL-23 is produced by activated antigen presenting cells and binds to IL-23 receptor complexes expressed on NK cells and T cells. IL-23, alone or in combination with other cytokines (e.g., IL-1β), has been shown to promote the production of IL-17A, IL-17F, IL-6, and tumor necrosis factor α (TNFα), which are proinflammatory cytokines shown to contribute to inflammatory response in autoimmune disease such as psoriasis. Therefore, blocking the interaction between IL-23 and IL-23 receptor could reduce tissue inflammation and destruction in psoriasis patients.

c. Potency Assay

A cell-based bioassay that measures inhibition of IL-23 dependent receptor dimerization in modified human osteosarcoma U2OS cells (U2OS:IL23R cells) is used to control DS and DP potency. The U2OS:IL23R cells stably express modified versions of the IL-23 receptor subunits IL-23R and IL-12Rβ1, each of which expresses a segment of the β-galactosidase enzyme. The β-galactosidase enzyme is activated upon the dimerization of the IL-23 receptor subunits following treatment with IL-23, leading to the cleavage of a chemical substrate, which yields a luminescence signal. The activity of β-galactosidase is reduced when IL-23 receptor dimerization is blocked by guselkumab, leading to a reduction of the luminescence signal. The luminescence signal obtained from samples is plotted against guselkumab concentration and analyzed by a 4-parameter logistic model. The potency of test articles is calculated as a percentage relative to the reference material (RM).

d. Reference material(s)

(b) (4)

e. Critical starting materials or intermediates

(b) (4)

(b) (4)

f. Manufacturing process summary

(b) (4)

g. Container closure

(b) (4) The container closure system is suitable for guselkumab, based on stability data and maintenance of closure integrity.

h. Dating period and storage conditions

The dating period for the (b) (4) and DS is (b) (4) and (b) (4) months, respectively, when stored at (b) (4) °C.

C. Drug Product [guselkumab] Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that are derived from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility	Safety and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination could be introduced throughout DP manufacturing or through a container closure integrity failure	(b) (4)	N/A
Endotoxin	Safety	Contamination could be introduced throughout DP manufacturing or through a container closure integrity failure		N/A
Container closure integrity	Safety	May be impacted by storage conditions		N/A
Color and turbidity of solution (general)	Safety and Efficacy	Formulation, contamination or degradation		N/A
Particulate Matter (translucent, visible and subvisible) (Product or Process Related Impurities)	Safety/ Immunogenicity	Manufacturing process and CCS		N/A
Polysorbate 80 concentration	Safety	Manufacturing process		N/A
Expelled Volume	Efficacy/Dosing	Manufacturing process		N/A

(general)			(b) (4)	
Glidability (piston release and travel force)	Efficacy/Dosing	Manufacturing process		N/A
Leachables (process-related impurities)	Safety	Manufacturing equipment and CCS		Submission of additional leachable study data and a risk assessment will be addressed as a PMC

a. Potency and Strength
Guselkumab is supplied at 100 mg/1.0 mL syringe. Potency is defined as the percent activity relative to the current guselkumab reference standard. The potency assay is the same as described in the DS section of this memo.

b. Summary of Product Design
Guselkumab is supplied as a sterile, single-dose, preservative-free solution for SC injection in a pre-filled syringe that is assembled into (b) (4) passive needle guard. The drug product formulation consists of (b) (4) mM histidine, 0.05% (w/v) polysorbate 80, and (b) (4) % (w/v) sucrose, pH 5.8. The extractable volume is 1.0 mL.

c. List of Excipients
Excipients include (b) (4) mM histidine, 0.05% (w/v) polysorbate 80, and (b) (4) % (w/v) sucrose.

d. Reference material(s)
(b) (4)

e. Manufacturing process summary
(b) (4)

f. Container closure
The primary container closure system for guselkumab DP consists of a 1-mL long syringe barrel (b) (4) with a 27-gauge x1/2" thin wall fixed stainless steel needle, (b) (4) rigid needle shield (RNS), and a plunger stopper composed of (b) (4)

(b) (4). Appropriate compatibility studies were performed for the container closure system.

The secondary container closure system consists of a tray insert, which is placed into a paperboard carton.

g. Dating period and storage conditions
The dating period for guselkumab DP is 24 months when stored at 2-8ºC, protected from light.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations

- Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF).
- Store in original carton until time of use.
- Protect from light until use.
- Do not freeze.
- Do not shake.

F. Establishment Information

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
Cell bank manufacture and storage; (b) (4)	Janssen Biotech, Inc.	3001610451	Based on File Review	VAI	Approve Facility
Drug substance manufacturing (b) (4)	Biogen, Inc.	3000719749	Pre-License Inspection (12/19-23/16)	4 item Form FDA 483	Approve Facility
Drug substance manufacturing (b) (4)	Janssen Sciences Ireland UC (Ireland)	3007029098 3007029098	Pre-License Inspection (12/27/17-03/02/17)	1 item Form FDA 483	Approve Facility
In vitro assay for adventitious agents and mycoplasma testing	(b) (4)		Based on File Review	NAI	Approve Facility
Release and stability testing of drug substance	Cilag A.G.	3002806695	Based on File Review	NAI	Approve Facility
In vitro assay for adventitious agents and mycoplasma testing	(b) (4)		Based on File Review	NAI	Approve Facility
Release and stability testing of drug substance	Janssen Biologics B.V.	3002806632	Based on File Review	NAI	Approve Facility
DRUG PRODUCT					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
Drug product manufacturing; assembly of device; packaging and labeling; (b) (4) ; release and stability testing (b) (4) (b) (4)	Cilag A.G.	3002806695	Based on File Review	NAI	Approve Facility

drug product.					
Release and stability testing of drug product.	Janssen Sciences Ireland UC (Ireland)	3007029028	Pre-License Inspection (12/27/17-03/02/17)	1 item Form FDA 483	Approve Facility
(b) (4) ; release and stability testing of (b) (4) and drug product.	Janssen Biologics B.V.	3002806632	Based on File Review	NAI	Approve Facility
Drug product release and stability testing (b) (4)	PPD Development Ireland Ltd.	3008676264	Based on File Review	NAI	Approve Facility
Drug product labeling and packaging (secondary)	AndersonBrecon, Inc.	1421377	Based on File Review	NAI	Approve Facility

G. Facilities

Guselkumab DS is manufactured at two facilities: [redacted] at Biogen Inc., Research Triangle Park, NC (FEI: 3000719749) and [redacted] at Janssen Sciences Ireland UC in Ringaskiddy, Cork County, Ireland (FEI: 3007029098). Cell banking operations occur at Janssen Biotech, Inc., Malvern PA (FEI: 3001610451).

A Pre-license Inspection was performed at Biogen Inc., 12/19/2016 – 12/23/2016. A three item Form FDA 483 was issued. The firm is acceptable. In addition, a Pre-license Inspection was performed at Janssen Sciences Ireland UC 2/27/2017 – 3/3/2017. A one item Form FDA 483 was issued. The firm is acceptable. The DS manufacturing and testing sites have been inspected multiple times within the recent past, demonstrating acceptable compliance.

The DP is manufactured and filled into the primary container closure at Cilag AG, Schaffhausen Switzerland (FEI: 3002806695). No inspections specific to guselkumab DP were conducted. The compliance status of the production and testing facilities associated with the manufacture of guselkumab DP is acceptable based on recent previous inspections and district recommendation. Secondary labeling and packaging is performed at Cilag AG, Schaffhausen Switzerland and AndersonBrecon, Inc., Rockford, IL, USA (FEI: 1421377). The compliance status of the secondary labelling and packaging facility and DP testing facilities are also acceptable.

H. Lifecycle Knowledge Management

a. Drug Substance

i. Protocols approved
   1. Annual stability protocols for [redacted] and DS
   2. Qualification of new reference material protocol

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: Adequacy of method verification for compendial methods used for [redacted] and DS lot release and stability testing at each testing site.

b. Drug Product

i. Protocols approved: Annual stability protocol

ii. Outstanding review issues/residual risk: The only residual risk noted is a low level risk related to potential leachables from the DP container closure, which will be mitigated through the implementation of a PMC (see above).

iii. Future inspection points to consider: Adequacy of method verification for compendial methods used for DP lot release and stability testing at each testing site.

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
	Product Type			
1.	Recombinant Product	x		
2.	Naturally Derived Product		x	
3.	Botanical		x	
4.	Human Cell Substrate/Source Material		x	
5.	Non-Human Primate Cell Substrate/Source Material		x	
6.	Non- Primate Mammalian Cell Substrate/Source Material	x		
7.	Non-Mammalian Cell Substrate/Source Material		x	
8.	Transgenic Animal Sourced		x	
9.	Transgenic Plant Sourced		x	
10.	New Molecular Entity	x		
11.	PEPFAR Drug		x	
12.	PET Drug		x	
13.	Sterile Drug Product	x		
14.	Other_____		x	
	Regulatory Considerations			
15.	Citizen Petition and/or Controlled Correspondence		x	

	Linked to the Application (#_____)				
16.	Comparability Protocol(s)			x	
17.	End of Phase II/Pre-NDA Agreements tem)			x	
18.	SPOTS (Special Products On-line Tracking System			x	
19.	USAN Name Assigned			x	
20.	Other_____			x	
Quality Considerations					
21.	Drug Substance Overage			x	
22.	Design Space	Formulation		x	
23.		Process		x	
24.		Analytical Methods		x	
25.		Other		x	
26.	Other QbD Elements		x		
27.	Real Time Release Testing (RTRT)			x	
28.	Parametric Release in lieu of Sterility Testing			x	
29.	Alternative Microbiological Test Methods			x	
30.	Process Analytical Technology in Commercial Production			x	
31.	Non-compendial Analytical Procedures	Drug Product	x		
32.		Excipients		x	

33.		Drug Substance	x		
34.	Excipients	Human or Animal Origin		x	
35.		Novel		x	
36.	Nanomaterials			x	
37.	Genotoxic Impurities or Structural Alerts			x	
38.	Continuous Manufacturing			x	
39.	Use of Models for Release			x	
40.	Other _____			x	

Sarah Kennett

Digitally signed by Sarah Kennett
Date: 4/14/2017 05:14:16PM
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Reyes Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 4/14/2017 04:40:38PM
GUID: 508da7160002977f7ca389c8f849b707

Kathleen Clouse Strebel

Digitally signed by Kathleen Clouse Strebel
Date: 4/17/2017 09:58:02AM
GUID: 508da6d70002630c9a2555c796176955

Qing Zhou

Digitally signed by Qing Zhou
Date: 4/14/2017 04:41:07PM
GUID: 508da7430002bbad737ae8d4b9c59845

Zhihao Peter Qiu

Digitally signed by Zhihao Peter Qiu
Date: 4/15/2017 08:49:28AM
GUID: 508da7480002bfb5825e149b2b4eb91d

BLA STN 761061

guselkumab
(trade name is under review)

Janssen Biotech, Inc.

Willie Wilson, Ph.D., Chemist
Qing (Joanna) Zhou, Ph.D., Team Lead

Division of Biotechnology Review and Research I

OBP CMC Review Data Sheet

1. **BLA#:** STN 761061

2. **REVIEW DATE:** April 14, 2017

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Melinda McCord, Kevin Clark, Gordana Diglisic
Pharm/Tox: Renqin Duan and Barbara Hill
Product Quality Team: Willie Wilson and Joanna Zhou
BMT or Facilities: Candace Gomez-Broughton, Bo Chi, Maria Jose Lopez-Barragan and Viviana Matta
Clinical Pharmacology: Anand Balakrishnan and Yow-Ming Wang
Statistics: Matthew Guerra and Mohamed Alosh
OBP Labeling: Jibril Abdus-Samad
Labeling: Matthew White and Nancy Xu
CDRH: Onwuatuegwu Echezona
OBP RBPM: Kelly Ballard
RPM: Matthew White

4. **MAJOR GRMP DEADLINES**
Filing Meeting: December 15, 2017
Mid-Cycle Meeting: February 16, 2017
Wrap-Up Meeting: June 9, 2017
Primary Review Due: April 14, 2017
Secondary Review Due: April 14, 2017
CDTL Memo Due: June 23, 2017
PDUFA Action Date: July 16, 2017

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

Communication/Document	Date
Filing Review Memo	1-12-17
Information Request 1	2-21-17
Mid-Cycle Communication	3-2-17
Information Request 2	3-20-17
Information Request 3	3-28-17
Information Request 4	4-7-17
Teleconference with the sponsor	4-11-17
Late-Cycle Communication	5-16-17

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed
STN 761061/0 (BLA Original Submission)	11-16-16	Yes
STN 761061/9 (Introduction of new clinical	1-19-17	Yes

products at Biogen Inc.)		
STN 761061/11 ((b) (4) deviation in process validation batch 859498C)	2-9-17	Yes
STN 761061/19 (Sponsor's response to IR1)	3-7-17	Yes
STN 761061/26 (Sponsor's response to IR2)	3-31-17	Yes
STN 761061/29 (Sponsor's response to IR3)	4-4-17	Yes
STN 761061/35 (Sponsor's response to IR4)	4-12-17	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**

a. Proprietary Name: Under Review
b. Trade Name: Under Review
c. Non-Proprietary/USAN: Guselkumab
d. CAS name: 1350289-85-8
e. Common name: CNTO-1959
f. INN Name: Guselkumab
g. Compendial Name: N/A
h. OBP systematic name: MAB HUMAN (IGG1) ANTI Q9NPF7 (IL23A_HUMAN) [CNTO1959]
i. Other Names: JNJ-54160366

8. **PHARMACOLOGICAL CATEGORY:** human IgG1 monoclonal antibody against the p19 subunit of human interleukin-23 (IL23A)

9. **DOSAGE FORM:** Injection

10. **STRENGTH/POTENCY:**

- The guselkumab Drug Product is supplied as a 100 mg/1.0 mL (100 mg/mL) solution in a single-dose pre-filled syringe.
- Potency is defined as the percent activity relative to the reference standard, using a cell-based bioassay that measures the ability of guselkumab to inhibit IL-23-mediated receptor dimerization (IL-23R/IL-12β1) in modified human osteosarcoma cells (U2OS).
- The dating period for guselkumab drug product is 24 months when stored at 2°C – 8°C, protected from light.

11. **ROUTE OF ADMINISTRATION:** Subcutaneous injection

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Provided in the BLA	Type III, Sufficient information was provided in the BLA for its intended use.

(b) (4)		
	Provided in the BLA	Type III, Sufficient information was provided in the BLA for its intended use.
	Provided in the BLA	Type III, Sufficient information was provided in the BLA for its intended use.
	Provided in the BLA	Type III, Sufficient information was provided in the BLA for its intended use.
	Provided in the BLA	Type III, Sufficient information was provided in the BLA for its intended use.
	Provided in the BLA	Type V, Sufficient information was provided in the BLA for its intended use.

13. **INSPECTIONAL ACTIVITIES**

Two pre-license inspections (PLI) for guselkumab drug substance manufacturing were conducted. Inspection of the Biogen, Research Triangle Park, North Carolina facility (FEI: 3000719749) was conducted from December 18 to December 23, 2016 by DIA (Viviana Matta and Thuy Thanh Nguyen) and OBP (Joanna Zhou) reviewers. The site is responsible for manufacturing the (b) (4) . The PLI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. The recommendation by the inspection team is VAI.

Inspection of the Janssen Sciences Ireland UC, Cork, Ireland facility (FEI: 3007029098), formerly Janssen Biologics – Ireland, was conducted from February 27 – March 3, 2017 by DIA reviewer (Viviana Matta) and OBP reviewer (Willie Wilson). The site is responsible for the manufacturing of drug substance (b) (4) and release testing. The PLI inspection was combined with a routine surveillance GMP inspection by Surveillance Inspector (Carla Lundi). The PLI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. One 483 item was issued by the Surveillance Inspector. The issue was related to the reports of analysis from component suppliers being accepted in lieu of testing each component for conformity with all appropriate written specifications, without establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals. The recommendation for the classification of the inspection is VAI.

The requirement for conducting a PLI for the drug product manufacturing facility was waived based on a facility profile evaluation, which was found to be acceptable.

14. **CONSULTS REQUESTED BY OBP:** None. A CDRH consult was requested by OND.

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

Design of Experiments studies were performed as part of process development.

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The data submitted in this Biologics License Application support the conclusion that the manufacture of guselkumab 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 has been manufactured from the multiple production runs presented. It is recommended that guselkumab be approved for human use (under conditions specified in the package insert).

I recommend an expiry period of 24 months for guselkumab DP when stored at 2 – 8°C, protected from light.

I recommend an expiry period of (b) (4) months for guselkumab DS and (b) (4) months for (b) (4) when stored at (b) (4) °C.

II. List Of Deficiencies To Be Communicated

None

III. List Of Post-Marketing Commitments/Requirement

PMC 1: To perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

IV. Review Of Common Technical Document-Quality Module 1

Environmental Assessment or Claim of Categorical Exclusion:
A claim for categorical exclusion under 21 CFR 25.31 (c) was made. To the sponsor's knowledge, no extraordinary circumstances exist relative to this action.

V. Primary Container Labeling Review

The CMC labeling review was performed by Jibril Abdus-Samad, OBP.

VI. Review Of Common Technical Document-Quality Module 3.2

This document contains the review of the information provided for guselkumab DS (Section 3.2.S), DP (Section 3.2.P), the adventitious agents safety evaluation (3.2.A) and the method validation package and batch records (3.2.R).

(b) (4)

Guselkumab DP is manufactured, assembled with needle safety device and packaged/labeled at Cilag AG, Schaffhausen, Switzerland. Secondary packaging/labeling can also be performed at AndersonBrecon, Inc., Rockford, Illinois. The manufacturing process for guselkumab DP is comprised of (b) (4) The container closure system is a single-use, 1 mL Type 1 glass syringe (b) (4) with a stainless steel needle, (b) (4) needle shield (b) (4) and (b) (4) plunger-stopper. Syringes are filled to 1.0 mL guselkumab DP (100 mg/mL). The pre-filled syringes are packaged in cardboard secondary containers and stored at 2 – 8°C, protected from light.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

A review of the immunogenicity assays is provided at the end of the primary review document. The immunogenicity evaluation is composed of four assays: anti-drug antibody (ADA) screening, ADA specificity, ADA titration and neutralizing ADA confirmation. The ADA screening/titration/specificity/neutralization assays are electrochemiluminescence (ECL)-based immunoassays (ECLIA). The drug-tolerant (0.95 – 1.23 µg/mL guselkumab) sensitivity of the screening and neutralization assays is acceptable. Overall, the ADA rate for guselkumab is low and the presence of ADA does not appear to be correlated with a loss in efficacy or an alteration in PK. The immunogenicity assays are suitable for their intended use.

TABLE OF CONTENTS

DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

S. DRUG SUBSTANCE

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

Descriptive Name(s):	MAB HUMAN (IGG1) ANTI Q9NPF7 (IL23A_HUMAN) [CNTO1959]
International Non-proprietary Name (INN):	guselkumab
United States Adopted Name (USAN):	guselkumab
Chemical Name:	Immunoglobulin G1-lambda 2, anti-human interleukin 23, IL-23
Company Code:	CNTO 1959; JNJ-54160366
Chemical Abstracts Service (CAS) Registry Number:	1350289-85-8

3.2.S.1.2 Structure

Guselkumab is a human monoclonal immunoglobulin G1 (IgG1, λ) consisting of two identical heavy chains (HC) and two identical light chains (LC). Each HC and LC is composed of 447 and 217 amino acids, respectively. Bi-antennary N-linked glycan structures (b) (4) were detected on asparagine residue 297 in each HC. Guselkumab contains a total of 32 cysteine residues that make up both intrachain and interchain disulfide bonds. (b) (4)

A majority of guselkumab species (>90%) contain variants without the HC C-terminal lysine. The guselkumab HC and LC amino acid sequences are shown in the figure below. The complementary determining regions (CDR) are underlined and the disulfide bonds are shown in red font.

Heavy Chain

```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFS NYWIGWVRQM PGKGLEWMGI IDPSNSYTRY      60
                          HC 22-96
SPSFQGQVTI SADKSISTAY LQWSSLKASD TAMYYCARWY YKPFDVWGQG TLVTVSSAST      120

KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY      180
                          HC 144-200
SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV      240
                                    LC216-HC220 HC2-HC226  HC229-HC2
FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY      300
                          HC 261-321                              N-Glycan
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSRDELTK      360

NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG      420
      HC 367-425
NVFSCSVMHE ALHNHYTQKS LSLSPGK                                          447
```

Light Chain

```
QSVLTQPPSV SGAPGQRVTI SCTGSSSNIG SGYDVHWYQQ LPGTAPKLLI YGNSKRPSGV      60
                          LC 22-90
PDRFSGSKSG TSASLAITGL QSEDEADYYC ASWTDGLSLV VFGGGTKLTV LGQPKAAPSV      120

TLFPPSSEEL QANKATLVCL ISDFYPGAVT VAWKADSSPV KAGVETTTPS KQSNNKYAAS      180
                          LC 139-198
SYLSLTPEQW KSHRSYSCQV THEGSTVEKT VAPTECS                               217
                                    LC 216-HC 220
```

3.2.S.1.3 General Properties

Detailed information on the mechanism of action and the physicochemical, biochemical and biophysical characteristics of guselkumab are provided in Section 3.2.S.3.1.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The manufacturing and testing facilities and their responsibilities are shown in the tables below.

Table 1: Drug Substance Manufacturing and Test Sites

Company	Address	Cell Bank Manufacturing	Cell Bank Storage	Cell Culture and Purification	Analytical Testing
Janssen Biotech, Inc.	200 Great Valley Parkway Malvern, PA 19355-1307 USA	X	X		X
(b) (4)					
Biogen Inc. (b) (4) Note: Biogen Idec Inc. has changed its name to Biogen Inc.	5000 Davis Drive Research Triangle Park, NC 27709 USA			X	X
(b) (4)					
Janssen Sciences Ireland UC Note: Janssen Biologics (Ireland) has changed its name to Janssen Sciences Ireland UC	Barnahely, Ringaskiddy, Co. Cork Ireland			X	X
(b) (4)					X
Cilag AG	Hochstrasse 201 8200 Schaffhausen Switzerland				X
(b) (4)					X
Janssen Biologics B.V.	Einsteinweg 101 2333 CB Leiden The Netherlands				X

Table 2: Detailed List of Analytical Procedures and Test Sites

(b) (4)

3.2.S.2.2 Description of Manufacturing Process and Process Controls

Overview of Drug Substance Manufacturing Process

(b) (4)

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

Reviewer Comment: *Data from Phase 3 process and process validation lots support stability of commercial [(b) (4)] stored at [(b) (4)]°C for [(b) (4)] months.*

3.2.P DRUG PRODUCT

Reviewer comment: *The sponsor included manufacturing and testing information for commercial guselkumab DP in 100 mg/1.0 mL and [(b) (4)] PFS presentations. However, the proposed labeling states that the dosage form and strength is 100 mg/1.0 mL, that is "supplied as a 100 mg prefilled syringe," and that the patients should "inject the full amount (1 mL), which provides 100 mg." The labeling includes no information regarding [(b) (4)] presentation. In response to IR1, IR2 and IR4, the sponsor removed all information related to [(b) (4)] presentation from Module 3, with exception of development data that are used to support the 100 mg/1.0mL presentation, to reflect the intended commercial DP specified in the label.*

3.2.P.1 Description and Composition of the Drug Product

Commercial DP is supplied as a sterile, single-use, 1 mL pre-filled syringe (PFS) containing 100 mg/mL guselkumab in [(b) (4)] mM histidine, [(b) (4)]% (w/v) sucrose and [(b) (4)]% (w/v) PS80, pH 5.8. The PFS is filled with [(b) (4)] mL DP to deliver a nominal 100 mg p ringe. A description of the PFS container closure system is provided in Section 3.2.P.7. The grade and function of DP components are presented in the table below.

Table 1: Composition of the Drug Product[a]

Component	Grade	Function	Amount per Dose 100 mg/syringe	Amount per 100 mg/syringe[b]
Guselkumab	Company Standard	Active	100 mg	[(b) (4)]
Sucrose	NF/Ph. Eur./JP	[(b) (4)]	79 mg	
L-Histidine	USP/Ph. Eur./JP		0.6 mg	
L-Histidine monohydrochloride monohydrate	Ph. Eur./JP		1.5 mg	
Polysorbate 80[c]	NF/Ph. Eur./JP		0.5 mg	
Water for injection	USP/Ph. Eur./JP		q.s. to 1.0 mL	

[a] Amounts calculated based on measurements of process validation drug substance batches, as described in 3.2.S.2.5, Process Validation and Evaluation, [(b) (4)] for all the excipients. Target values used for active.
[b] Amount [(b) (4)] allow an expelled volume of 1.0 mL.
[c] [(b) (4)]

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance and 3.2.P.2.1.2 Excipients

The composition of the DS includes [(b) (4)]

(b) (4)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

(b) (4)

(b) (4)

Reviewer Comment: *The information provided is sufficient from a product quality perspective. The information on the design control and management system to ensure the quality of the primary container closure system is reviewed by CDRH.*

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

The recommended storage condition for commercial guselkumab DP is 2 – 8ºC, protected from light (b) (4). The stability program to support DP expiry consists of eight Phase 3 clinical batches and three process validation batches stored at the 2 – 8ºC (0, 3, 6, 9, 12, 18, 24, 30 and 36 months), 25ºC/60% RH (0, 3, 6, 9 and 12 months) and 40ºC/75% RH (0, 1, 2 and 3 months). A total of four Phase 3 process and three process validation batches (b) (4) were included as supporting batches. Additional testing was included in the stability program to assess photostability, temperature cycling and the stability of the assembled PFS (b) (4) batches stored at 2 – 8ºC through 36 months. All DP batches in the stability program were manufactured at full scale at the commercial manufacturing facility by the commercial process. Stability studies are performed with DP stored in the commercial container closure system described in Section 3.2.P.7.

Stability Test Methods

DP stability evaluation included testing for primary container appearance, color, pH, osmolality, turbidity, visible/sub-visible particulate matter, polysorbate 80, expelled volume, glidability, identity, charge heterogeneity (cIEF), purity (reduced/non-reduced cSDS and SE-HPLC), protein concentration, potency (U2OS bioassay), endotoxin, sterility and container closure integrity (CCI). Testing was performed at each time under the respective storage condition with the exception of sterility and CCI testing, which were performed annually for batches stored at 2 – 8ºC. The stability acceptance criteria and justification for specifications are described in Section 3.2.P.5.1 and 3.2.P.5.6, respectively. The U2OS bioassay replaced the NKL bioassay after the Phase 3 and process validation batches were introduced into the stability program. Stability data prior to the U2OS bioassay introduction were obtained from retain samples stored at (b) (4) ºC.

Reviewer Comment: *Based on DS data, minimal stability change is expected for DP samples stored at* (b) (4) *ºC.*

Statistical Evaluation of Shelf-life

A statistical analysis was performed on the real-time stability data set to propose a DP shelf-life of 24 months at 2 – 8ºC. Pooled data sets from the 100 mg/syringe (b) (4) DP batches were included in the statistical analysis of DP shelf life if a significant p-value ($p \leq 0.05$) was observed for the likelihood ratio significance test. The statistical approach used for trending and outlier analysis is the same as described in Section 3.2.S.7.1.

Reviewer Comment: *Data from the (b) (4) DP batches are used as supportive information; therefore, stability data for (b) (4) and 100 mg/syringe in Section 3.2.P.8.3 were reviewed separately for the purpose of an evaluation of commercial DP expiry.*

3.2.P.8.2 Post-Approval Stability Commitment

The sponsor commits to continue ongoing stability studies for the Phase 3, process validation and assembled PFS (b) (4) batches. The sponsor also commits to place one 100 mg/syringe DP batch into the post-approval stability program each year that the DP is manufactured. The post-approval stability program includes testing under real-time (2 – 8°C), accelerated (25°C/60% RH) and stressed (40°C/75% RH) storage conditions. The current stability protocols are described below. The acceptance criteria for each test method are described in Section 3.2.P.5.1.

Table 1: Stability-monitoring Program for the DP (Recommended Condition: 2-8 °C)

Test Method	Months of Storage						
	0[a]	3	6	12	24	30	36
Color of solution	√	√	√	√	√	√	√
pH	√	√	√	√	√	√	√
Protein concentration by A_{280}	√	√	√	√	√	√	√
cIEF	√	√	√	√	√	√	√
cSDS (Reduced)	√	√	√	√	√	√	√
cSDS (Non-reduced)	√	√	√	√	√	√	√
DW-SE-HPLC	√	√	√	√	√	√	√
(b) (4)	√	√	√	√	√	√	√
U2OS bioassay	√	√	√	√	√	√	√
Turbidity	√	√	√	√	√	√	√
Particulate matter (Visible translucent MDI)	√	√	√	√	√	√	√
Particulate matter (Sub-visible)	√	√	√	√	√	√	√
Expelled volume	√	√	√	√	√	√	√
Glidability	√	√	√	√	√	√	√
Sterility	√	NR	NR	√	√	√	√
Container closure integrity	√	NR	NR	√	√	√	√

[a] Test results at time zero will be derived from release testing.

√ = Required test
NR = Not required
cIEF = Capillary isoelectric focusing
cSDS = Capillary sodium dodecyl sulfate electrophoresis
DW-SE-HPLC = Dual wavelength size exclusion high performance liquid chromatography
(b) (4)

Reviewer Comment: *In response to IR2, the DP annual stability program was updated with a statement that the annual stability data will be filed to the BLA in the Annual Report (b) (4) The stability protocol includes testing time points beyond the DP expiry (30 and 36 months).* (b) (4) .

3.2.P.8.3 Stability Data

Reviewer Comment: *Graphical representations of stability trends were provided in Section 3.2.P.8.1. Stability results were provided for* [redacted] *and 100 mg/syringe DP (primary) batches. The review of the container closure integrity and glidability results is deferred to the DMA and CDRH reviewers, respectively.*

Recommended Storage Condition (2 – 8°C)

Stability data were provided for the following DP lots stored under the recommended storage condition:

Primary lots (100 mg/syringe):

- Phase 3 DP batches stored up to 6 months (1 batch), 12 months (1 batch), 18 months (1 batch), 24 months (1 batch), 30 months (1 batch) and 36 months (2 batches)
- Process validation batches stored up to 6 months (3 batches)

Supporting lots [redacted]

- Phase 3 batches stored up to 12 months (1 batch), 18 months (1 batch), 30 months (1 batch) and 36 months (1 batch)
- Process validation batches stored up to 6 months (3 batches)

Stability specifications were met for the primary and supporting lots stored for up to 36 months. No adverse trends in stability were observed with the exception of acidic variants and aggregates measured by cIEF and SE-HPLC, respectively. Increasing acidic variants (~4%) and aggregate species (approx. 0.6%), associated with decreasing main charge isoform, monomer and potency, were observed for the primary and supporting lots stored up to 36 months at 2 – 8°C. Data for the initial U2OS bioassay time point were available for one out of four Phase 3 batches [redacted] and three out of eight Phase 3 batches (100 mg/syringe). The available data set for the 100 mg/syringe batches (including T=0) shows a decreasing trend in potency ([redacted]) upon real-time storage up to 24 months. [redacted]

Accelerated Storage Condition (25°C)

Stability data were provided for the primary and supporting stability lots stored at the 25°C for 12 months. The primary and supporting stability lots had OOS results for potency, monomer by SE-HPLC and purity by reduced cSDS at the 9 and 12 month time points. OOS results were also observed for purity by non-reduced cSDS and acidic peaks at the 6, 9 and 12 month time points. All other test results were within the specification limits. Significant increasing trends in aggregate by SE-HPLC, acidic and basic peaks, turbidity, and sub-visible particles, associated with decreasing trends in potency, purity and main charge isoform were observed. The overall stability profiles were similar between the primary and supporting stability lots.

Stressed Storage Conditions (40°C)

Stability data were provided for the primary and supporting stability lots stored at 40°C for up to 3 months. The primary and supporting stability lots showed OOS results for potency, monomer and aggregate by SE-HPLC, basic peaks, turbidity, polysorbate 80 and sub-visible particles at the 3 month time point. New peaks were detected by cIEF at the 3 month time point. OOS results

were also observed for the purity by reduced/non-reduced cSDS and acidic peaks at the 1 and 3 month time points. All other test results were within the specification limits and no other adverse stability trends were observed. The overall stability profiles were similar between the primary and supporting stability lots.

Reviewer Comment: *The overall stability data provided for the primary stability batches support the storage of commercial DP at 2 – 8°C for 24 months.* [redacted] *The stability profiles between the supporting* [redacted] *and primary (100 mg/syringe) DP batches appear similar. Data from both supporting and primary batches demonstrate a guselkumab degradation consisting of changes in charge heterogeneity, potency and the formation of aggregates.*

Additional Stability Studies

Photostability

Photostability studies were performed in one primary and supporting DP lot in the following configurations: PFS alone, PFS [redacted] alone, PFS [redacted] in surrogate package and PFS- [redacted] in surrogate package with light-proof foil. The DP configurations were exposed to no less than 1.2 million lux hours of cool white fluorescent and 200 watt hour/m^2 of near UV light at 25°C/60% RH. Samples were evaluated for potency (NKL bioassay), protein concentration, purity (SE-HPLC, cSDS), charge heterogeneity (cIEF), color, pH, visible/sub-visible particles, turbidity, glidability, expelled volume and polysorbate 80. Results were evaluated against the stability acceptance criteria described in Section 3.2.P.5.1. The NKL bioassay was evaluated against the 50 – 150% relative potency acceptance criterion. For the PFS alone configuration, OOS results were observed for aggregate/monomer (SE-HPLC), purity (reduced/non-reduced cSDS) and acidic peaks. SE-HPLC OOS results were also observed for the PFS- [redacted] alone configuration. All other specifications were met for the other DP configurations. Results were also evaluated against the batch analysis for the respective PFS lots not exposed to the test light condition. The batch analysis was consistent with data generated for the PF [redacted] in the surrogate packaging (with and without foil). Compared to lot release data, the unpackaged PFS and PFS [redacted] showed an increase in aggregate ([redacted] and acidic peaks ([redacted] and a corresponding decrease in main peak following light exposure.

Reviewer Comment: *The data provided demonstrate that the packaging for commercial DP is sufficient to protect against light induced stress during storage.*

Temperature Cycling

Temperature cycling studies were performed on 100 mg [redacted] DP batches early (3 month old) and late (10 and 16 month old) in their shelf life. DP batches were exposed to five temperature cycles consisting of -20°C for at least 2 days and 25°C for at least 2 days followed by storage at the recommended 2 – 8°C. The early phase DP batches were placed on long-term stability after temperature cycling and data are currently available through 12 months. The late phase DP batches were tested directly after temperature cycling. Samples were evaluated with the same specifications described in the photostability study with the exception of the exclusion of PS 80 testing. All stability specifications were met for the early and late phase DP batches. A similar trend of increasing aggregates [redacted] and acidic peaks [redacted]) were observed for the

early and late phase DP batches. [redacted]

Reviewer Comments: *The data support sufficient product stability under extreme temperature excursions that may occur during shipping, handling and storage.*

Long-term Stability of Assembled PFS [redacted]
One batch each of the 100 mg [redacted] PFS [redacted] were placed on a long-term stability protocol consisting storage at 2 – 8°C for 36 months (0, 3, 6, 9, 12, 18, 24, 30 and 36 months). Samples were evaluated for potency (U2OS bioassay), protein concentration, purity (SE-HPLC, cSDS), charge heterogeneity (cIEF), color, pH, visible/sub-visible particles, turbidity, glidability, expelled volume and polysorbate 80. Results were evaluated against the stability acceptance criteria described in Section 3.2.P.5.1. Data were provided for up to 6 months for both PFS [redacted] batches. All stability specifications were met and no adverse stability trends were observed. Overall stability profiles between the 100 mg and [redacted] PF [redacted] were similar.

Reviewer Comment: *These data and the photostability data for PFS and PFS [redacted] support that the needle guard device assembly process does not have a significant impact on the product quality of guselkumab. See Section 3.2.P.5.1 for additional comments.*

3.2.A Appendices Table of Contents
3.2.A.1 Facilities and Equipment

Reviewer Comment: *Review of information provided on the facilities and equipment is deferred to the OPF review team.*

3.2.A.2 Adventitious Agents Safety Evaluation
The potential sources of endogenous and adventitious agent contamination and the corresponding control strategies were summarized in Table 1. No animal-derived raw materials were used during the guselkumab production process and cell bank preparation; [redacted] discussed in Section 3.2.S.2.3, above.

Non-viral Adventitious Agents
Microbial and mycoplasma contamination during the guselkumab manufacturing process is controlled through routine in-process testing as described in Sections 3.2.S.2.2 and 3.2.S.2.4.

Reviewer Comment: *Review of the microbial control strategy is deferred to the DMA review team.*

Viral Adventitious Agents
The control strategy for adventitious viral agents during the guselkumab manufacturing process is composed of [redacted]

Cell Bank Characterization

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Willie Wilson

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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: 03/14/17
To: Administrative File, STN 761061/0
From: Viviana Matta, Consumer Safety Officer, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: New Biologic License Application (BLA)
US License: 1864
Applicant: **Janssen Biotech, Inc.**
Mfg Facility: Drug Substance: Biogen, Inc., Research Triangle Park, NC (FEI 3000719749) & Janssen Biologics, Ringaskiddy, Cork (Ireland) (FEI 3007029098)
Drug Product: Cilag A.G., Schauffhausen, Switzerland (FEI 3002806695)
Product: Guselkumab
Dosage: Single-dose pre-filled syringe with sterile solution, 100 mg/ 1.0 mL
Indication: For the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
Due Date: 05/16/2017

Recommendation: Compliance decisions are pending for the 12/19/16 to 12/23/16 inspection of the Biogen site (FEI 3000719749) proposed for [redacted] (b) (4) DS manufacture, and the 02/27/17 to 03/03/17 inspection of the Janssen Biologics site (FEI 3007029098) proposed for [redacted] (b) (4) DS manufacture. Both of these sites are currently in acceptable compliance standing. The compliance status of the drug product site, Cilag A. G., Schaffhausen, Switzerland (FEI: 3002806695) also has an acceptable compliance standing. Final recommendation for the proposed manufacturing and testing sites is pending final compliance decisions for the DS manufacturing facilities.

SUMMARY

The subject BLA proposes manufacture of guselkumab Drug Substance and Drug Product at the following facilities.

Biogen, Inc. in Research Triangle Park, NC (FEI #3000719749) is responsible for DS manufacturing [redacted] (b) (4) and release testing of the DS. A PLI was conducted from 12/19/16 to 12/23/16. This inspection was a system-based covered Quality, Laboratory, Raw Materials, Facilities and Equipment, and Production Systems. A 4-item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection for the following: Inadequate event/deviation investigations, inadequate [redacted] (b) (4) operation to minimize the risk for product contamination, [redacted] (b) (4)

(b) (4)

(b) (4) The initial recommendation is VAI. *The EIR is pending compliance review.*

Janssen Biologics (Ireland) in Ringaskiddy, Cork Ireland (FEI #3007029098) is responsible for DS manufacturing (b) (4). In addition, release and stability testing of (b) (4) drug substance and drug product. A PLI was conducted on 02/27/17 to 03/03/17. An FDA 483 observation was issued related to the lack of qualification of materials for acceptance on Certificate of Analysis without full testing. No observations were noted with respect to the application under review. The initial recommendation is VAI. *The EIR is pending compliance review.*

The manufacturing of (b) (4) pre-filled syringe, analytical testing (b) (4) (b) (4) for guselkumab DP is performed at Cilag A.G., Schauffhausen, Switzerland (FEI #3002806695). The last inspection was a PLI completed 04/08/16 (b) (4)
No FDA-483 Inspectional Observations form was issued and the inspection was classified as NAI. Approval was recommended for the BLA product per Inspection Waiver Memorandum dated 02/13/17.

All other facilities preforming secondary packaging, and/or testing on DS and DP are currently in acceptable compliance status. The facility descriptions submitted in this BLA have been reviewed and found to be adequate to support the manufacture of guselkumab Drug Substance and Drug Product.

ASSESSMENT

DRUG SUBSTANCE
3.2.S.2.1 Manufacturers

The proposed guselkumab DS manufacturing, storage, release testing, and stability testing sites are listed below in Table 1.

Table 1. (b) (4) Drug Substance Facilities.

Site Name	Address	FEI	Responsibilities
Janssen Biotech, Inc.	200 Great Valley Parkway, Malvern, PA 19355	3001610451	Cell bank manufacture and storage; (b) (4) (b) (4)
Biogen, Inc.	5000 Davis Dr., Research Triangle Park, NC 27709	3000719749	Drug substance manufacturing (b) (4) (b) (4)
Janssen Biologics (Ireland)	Barnahely, Ringaskiddy, Cork, Ireland	3007029098	Drug substance manufacturing (b) (4) (b) (4) Release and stability testing of (b) (4) drug substance and drug product.
Janssen Biologics B.V.	Einsteinweg 101, 2333 CB, Leiden, The Netherlands	3002806632	(b) (4) release and stability testing of (b) (4) drug substance and drug product.

		(b) (4)	In vitro assay for adventitious agents and mycoplasma testing
			In vitro assay for adventitious agents and mycoplasma testing
Cilag A.G.	Hochstrasse 201, Schauffhausen, Switzerland	3002806695	Drug product manufacturing; assembly of device; packaging and labeling; (b) (4) release and stability testing of (b) (4) drug substance and drug product.
PPD Development Ireland Ltd.	Building C, IDA Business and Technology Park, Garrycastle, Althone, Co, Westmeath, Ireland	3008676264	Drug product release and stability testing for (b) (4)
AndersonBrecon, Inc.	4545 Assembly Drive, Rockford, IL	1421377	Drug product labeling and packaging (secondary)

Review comment: The facilities for the manufacturing, storage, release testing, and stability testing for the guselkumab drug substance are adequately described.

—Satisfactory—

Facility Inspection:

Prior Inspection History

The last three inspections of Janssen Biotech, Inc. manufacturing, testing and storage site (FEI #3001610451) occurred on 09/24/2014 (VAI), 09/25/2012 (NAI) and 06/15/2012 (VAI). The 09/24/2014 inspection covered CBI. The facility is currently in compliance.

The last three inspections of Biogen, Inc. manufacturing and testing site (FEI #3000719749) occurred on 12/23/16 (VAI), 01/15/2016 (NAI), and 09/25/2015 (VAI). The 01/15/2016 inspection was a surveillance inspection covering CBI operations and the 09/25/2015 inspection was a PLI covering BLAs 761029 and 761036. The aforementioned applications covered during the PLI were recommended for approval. Corrections to issued observations have been deemed adequate. A PLI was conducted on 12/19/16 to 12/23/16. This inspection was a system-based covered Quality, Laboratory, Raw Materials, Facilities and Equipment, and Production Systems. A 4-item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection for the following: Inadequate event/deviation investigations, (b) (4) (b) (4) The initial recommendation is VAI. *The EIR is pending compliance review.*

The last three inspections of Janssen Biologics (Ireland) manufacturing and testing site (FEI #3007029098) occurred on 03/03/17 (VAI), 10/09/2015 (NAI) and 03/07/2014 (VAI). The 10/09/2015 inspection was a PLI covering BLA 761036. The aforementioned application covered during the PLI was recommended for approval. The 03/07/2014 inspection was a surveillance inspection covering CBI processing. Corrections to issued observations have been deemed adequate. A PLI was conducted on 02/27/17 to 03/03/17. An FDA 483 observation was issued related to the lack of qualification of materials for acceptance on Certificate of Analysis

without full testing. No observations were noted with respect to the application under review. The initial recommendation is VAI. *The EIR is pending compliance review.*

The last three inspections of Janssen Biologics B.V. testing site (FEI #3002806632) occurred on 05/27/2016 (NAI), 07/11/2014 (VAI) and 12/20/2013 (VAI). The 05/27/2016 inspection covered the laboratory system. The facility is currently in compliance.

The last three inspections of (b) (4). testing site (FEI # (b) (4)) occurred on (b) (4) (NAI) and (b) (4) (NAI). The (b) (4) inspection covered CTL. The facility is currently in compliance.

The last three inspections (b) (4) testing site (FEI # (b) (4)) occurred on (b) (4)(NAI), (b) (4) (NAI) and (b) (4) (NAI). The (b) (4) inspection covered CTL. The facility is currently in compliance.

The last three inspections of Cilag A.G. manufacturing and testing site (FEI #3002806695) occurred on 04/08/2016 (NAI), 09/08/2015 (NAI) and 02/18/2014 (NAI). The last inspection was a PLI for Simponi (Golimumab) pre-filled syringe (PFS) BLA-125289/131 and covered syringe filling operations and the same line utilized for the subject product. Approval was recommended for the aforementioned application covered during the PLI. The facility is currently in compliance.

The last three inspections of PPD Development Ireland Ltd. testing site (FEI #3008676264) occurred on 06/22/2016 (NAI) and 11/09/2011 (VAI). The 06/22/2016 inspection covered CTL. The facility is currently in compliance.

The last three inspections of AndersonBrecon, Inc secondary packaging and labeling site (FEI #1421377) occurred on 05/16/2016 (NAI), 08/30/2013 (NAI) and 04/19/2012 (VAI). The 05/16/2016 inspection covered the SVS profile and packaging/labeling operations. The facility is currently in compliance and no further evaluation is required.

Current PAI Outcome

Biogen, Inc. (FEI #3000719749) was inspected from 12/19/16 to 12/23/16 under FACTS assignment #11710768 with an initial recommendation of VAI. *The EIR is pending compliance review.*

Janssen Biologics (Ireland) (FEI #3007029098) was inspected on 02/27/17 to 03/03/17 under eNSpect Operation ID 48231 with an initial recommendation of VAI. *The EIR is pending compliance review.*

Review comment: The compliance status of the facilities associated with the manufacture of guselkumab drug substance is pending PAI compliance review for PLI.

—Satisfactory—

3.2.A.1 Facilities and Equipment

Facility Overview and Guselkumab Manufacturing Areas

(b) (4)

[redacted]

—Satisfactory—

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(b) (4)

[redacted]

—Satisfactory—

DRUG PRODUCT

3.2.P.2.1 Manufacturers

The manufacturing, storage, release testing, and stability testing for the guselkumab drug product is shown in Table 2.

Table 2. Guselkumab Drug Product Facilities.

Site Name	Address	FEI	Responsibilities

Cilag A.G.	Hochstrasse 201 Schauffhausen Switzerland	3002806695	Drug product manufacturing; assembly of device; packaging and labeling; (b) (4); release and stability testing of (b) (4) drug substance and drug product.
PPD Development Ireland Ltd.	Building C IDA Business and Technology Park Garrycastle, Althone, Co, Westmeath Ireland	3008676264	Drug product release and stability testing (b) (4)
Janssen Biologics (Ireland)	Barnahely, Ringaskiddy, Cork, Ireland	3007029098	Release and stability testing of (b) (4), drug substance and drug product.
Janssen Biologics B.V.	Einsteinweg 101, 2333 CB, Leiden, The Netherlands	3002806632	In-process control testing; release and stability testing of (b) (4) drug substance and drug product.
AndersonBrecon, Inc.	4545 Assembly Drive Rockford, IL	1421377	Drug product labeling and packaging (secondary)

Review comment: *The provided information regarding the identity of the facilities for manufacturing, storage, release testing, and stability testing for guselkumab drug product is adequate.*

—Satisfactory—

Prior Inspection History

The last three inspection of Cilag A.G. (FEI #3002806695) resulted in NAI outcomes, and were conducted 04/08/2016, 09/08/2015 and 02/18/2014. The 04/08/2016 inspection was a PAI and covered (b) (4) pre-filled syringe (PFS) processing. The most recent inspection also included a review of the quality, material, facilities and equipment, production, packaging, and laboratory control operation systems. The facility is currently in compliance. Approval was recommended for the BLA product per Inspection Waiver Memorandum dated 02/13/17.

The last three inspections of PPD Development Ireland Ltd. testing site (FEI #3008676264) occurred on 06/22/2016 (NAI) and 11/09/2011 (VAI). The 06/22/2016 inspection covered CTL. The facility is currently in compliance.

The last three inspections of Janssen Biologics (Ireland) manufacturing and testing site (FEI #3007029098) occurred on 03/03/17 (VAI), 10/09/2015 (NAI) and 03/07/2014 (VAI). The 10/09/2015 inspection was a PLI covering BLA 761036. The aforementioned application covered during the PLI was recommended for approval. The 03/07/2014 inspection was a surveillance inspection covering the laboratory system. Corrections to issued observations have been deemed adequate. A PLI was conducted on 02/27/17 to 03/03/17. An FDA 483 observation

was issued related to the lack of qualification of materials for acceptance on Certificate of Analysis without full testing. No observations were noted with respect to the application under review. The initial recommendation is VAI. *The EIR is pending compliance review.*

The last three inspections of Janssen Biologics B.V. testing site (FEI #3002806632) occurred on 05/27/2016 (NAI), 07/11/2014 (VAI) and 12/20/2013 (VAI). The 05/27/2016 inspection covered the laboratory system. The facility is currently in compliance.

The last three inspections of AndersonBrecon, Inc secondary packaging and labeling site (FEI #1421377) occurred on 05/16/2016 (NAI), 08/30/2013 (NAI) and 04/19/2012 (VAI). The 05/16/2016 inspection covered the SVS profile and packaging/labeling operations. The facility is currently in compliance and no further evaluation is required.

Review comment: The compliance status of the facilities associated with the manufacture of guselkumab drug product is adequate.

—Satisfactory—

3.2.A.1 Facilities and Equipment

Facility Overview

(b) (4)

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(b) (4)

[redacted]

—*Satisfactory*—

Conclusion:

Adequate descriptions were provided for the following sites proposed for guselkumab DS and DP manufacture:

- Biogen, Inc in Research Triangle Park, NC (FEI: 3000719749)
- Janssen Biologics in Ringaskiddy, Cork County, Ireland (FEI: 3007029098).
- Cilag A. G. in Schaffhausen, Switzerland (FEI: 3002806695).

In addition, the proposed manufacturing and testing sites are recommended for approval from a facilities assessment standpoint pending final compliance decisions for the 12/19/16 to 12/23/16 inspection of the Biogen site (FEI 3000719749) and the 02/27/17 to 03/03/17 inspection of the Janssen Biologics site (FEI 3007029098).

Viviana Matta -A

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Viviana Matta
Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1

Zhihao Qiu -S

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Date: 2017.03.14 14:07:01 -04'00'

Zhihao (Peter) Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

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

Date: 02/13/2017
From: Viviana Matta, Facility Reviewer, OPQ/OPF/DIA/IAB1
Bo Chi, Ph.D., DP Microbiology Reviewer, OPQ/OPF/DMA
Candace Gomez-Broughton, Ph.D., DS Microbiology Reviewer, OPQ/OPF/DMA
Willie Wilson, Ph.D., Product Quality Reviewer, OPQ/OBP/DBRRI
To: BLA File, STN 761061/0
Through: Zhihao (Peter) Qiu, Ph.D., Branch Chief, OPQ/OPF/DIA/IAB1
Subject: Inspection Waiver Memo for Manufacture of Guselkumab Drug Product at Cilag A.G. Facility in Schauffhausen, Switzerland
Applicant: Janssen Biotech, Inc.
Facility: Cilag A.G.
Hochstrasse 201, Schauffhausen, Switzerland
FEI #3002806695
Product: Guselkumab
Dosage: Single-dose pre-filled syringe with sterile solution, 100 mg/ 1.0 mL
Indication: For the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Waiver Recommendation

Guselkumab 100 mg/ 1.0 mL single-dose pre-filled syringe (PFS) with sterile solution (BLA STN 761061/0) drug product (DP) will be manufactured at the Cilag A.G. facility in Schauffhausen, Switzerland.

(b) (4) (b) (4) The facility was last inspected by the FDA on 04/08/2016 and the inspection was classified as NAI. The inspection covered the quality system, material, facilities and equipment, production, packaging, and laboratory control operation related to (b) (4) and Simponi (Golimumab) PFS, and the facility was found to be in compliance.

Based on the firm's compliance history, current acceptable cGMP status, and the (b) (4) manufacture of other licensed and approved (b) (4) products (b) (4) (b) (4) we recommend that a pre-license inspection of the Cilag A.G. facility (b) (4) be waived for STN 761061/0.

Summary

BLA STN 761061/0, submitted by Janssen Biotech, Inc., provided information and data to support the manufacture of single-dose PFS with sterile solution. The manufacture of guselkumab drug substance is performed at Biogen, Inc. (FEI# 3000719749) and Janssen Biologics (Ireland) (FEI# 3007029098). The manufacture of guselkumab DP is carried out at

Cilag A.G. (FEI# 3002806695). This waiver recommendation is in regards to guselkumab DP [redacted] (b) (4)

Facility Information

[redacted] (b) (4)

Evaluation of criteria that may warrant 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.

Cilag A.G. is a multi-product facility manufacturer that has been licensed to manufacture another licensed product, Simponi (Golimumab) PFS under BLA-125289/131, [redacted] (b) (4)

2. The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission [redacted] (b) (4)) or systematic problems, such as QC/QA oversight.

The facility was most recently inspected by FDA on 04/08/2016. This was a Pre-Approval Inspection that covered the quality system, material, facilities and equipment, production, packaging, and laboratory control operation related to [redacted] (b) (4) and Simponi (Golimumab) pre-filled syringe (PFS). The following objectives were covered during this inspection: readiness for commercial manufacturing, data integrity and conformance to application. Records reviewed during the current inspection included but were not limited to SOPs, complaints,

change controls, laboratory and manufacturing investigations, equipment and room logbooks, exhibit batch records, packaging records, finished and in-process testing results, analytical method validation, equipment qualification, and process validation reports. No FDA 483, Inspectional Observations was issued. The inspection was classified as NAI and approval was recommended for the pending applications.

3. The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.

(b) (4)

4. The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.

(b) (4)

Signed:

Viviana Matta -A

Digitally signed by Viviana Matta -A
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Date: 2017.02.14 08:59:26 -05'00'

Viviana Matta, OPF/DIA Reviewer

Bo Chi -S

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Date: 2017.02.14 09:04:37 -05'00'

Bo Chi, Ph.D., OPF/DMA Reviewer

Candace Gomez-Broughton, Ph.D., OPF/DMA Reviewer

Candace Y. Gomez-broughton -A

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Willie Wilson, Ph.D., OBP/ DBRRI Reviewer

Willie Wilson III -S (Affiliate)

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Zhihao Qiu, Ph.D., OPF/DIA Branch Chief

Zhihao Qiu -S

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Patricia Hughes, Ph.D., OPF/DMA Branch Chief

Patricia F. Hughestroost -S

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Sarah Kennett, Ph.D., OBP/DBRRI Review Chief

Sarah B. Kennett -S

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Marjorie A. Shapiro -S

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Date: 2017.02.14 18:27:50 -05'00'

CONCUR ~~DO NOT CONCUR~~ DATE

Marjorie Shapiro, Ph.D., Acting Director, Division of Biotechnology Review and Research III
Office of Biotechnology Products, Office of Pharmaceutical Quality, CDER