CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761032Orig1s000

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date:	March 8, 2016
To:	Administrative File, STN 761032
From:	Donald C. Obenhuber, Ph.D., CDER/OPQ/OPF/DIA
Endorsement:	Zhihao Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject:	Original BLA
Applicant:	AstraZeneca
Mfg Facility:	Drug Substance: (b) (4)
	Drug Product: (b) (4)
Product:	brodalumab
Due Date:	November 16, 2016

Recommendation: This submission is recommended for approval based the facilities assessment.

SUMMARY

The drug substance is manufactured at (b) (4) The brodalumab drug substance manufacturing process consists of (b) (4) The drug product presentation is manufactured at (b) (4) manufacturing site, located in (b) (4) The brodalumab drug product manufacturing process consists of (b) (4) . Drug product assembly, packaging and labeling activities for the PFS occur at (b) (4)

Table 1 includes the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Table 1 Manufacturing facilities associated with BLA 761032

Site name and address	FEI and DUNS numbers	Onsite Contact Phone #, fax #, email	Manufacturing Step(s) or Type of Testing and DMF number (if applicable).
[redacted] (b) (4)			Drug substance: Drug substance manufacture, drug substance in-process, lot release and stability testing, working cell bank storage Drug product: Drug product lot release and stability testing
			Drug substance: Master cell bank and work cell bank storage, working cell bank production ,
			Drug product: Drug product lot release and stability testing, packaging and labeling, distribution
			Drug substance: [redacted] (b) (4) mycoplasma and adventitious viral testing Drug product: Container closure integrity for stability testing
		(b) (4)	testing
[redacted] (b) (4)			Drug product: Container closure integrity for stability testing
			Drug product: Drug product manufacture, drug product in-process and lot release testing, inspection

DRUG SUBSTANCE manufacturing

(b) (4)

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(b) (4)

[redacted]

Recommendation: Approve Facility
Reason: Based on Profile

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

The subject BLA is recommended for approval from a facilities assessment perspective.
Donald C. Obenhuber, Ph.D., CDER/OPQ/OPF/DIA.

Supervisor Comments and Concurrence:

I concur with the facility reviewer's assessment

Zhihao Peter Qiu, Ph.D.
Branch Chief, OPQ/OPF/DIA/Branch 1

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

/s/

JONATHAN T DOW
02/24/2017

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

DRUG SUBSTANCE AND DRUG PRODUCT MICROBIOLOGY QUALITY REVIEW
(Addendum to original BLA Review Memo)

Date:	11/14/2016
To:	Administrative File, STN 761032
From:	Maria Jose Lopez Barragan, PhD, Reviewer, CDER/OPQ/OPF/DMA/BIV
Through:	Reyes Candau-Chacon, PhD, Acting Quality Assessment Lead, CDER/OPQ/OPF/DMA/BIV
Subject:	Amendment to original BLA for Brodalumab (SILIQ™)
Applicant:	Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL): Acceptance of Ownership received by the Agency on 04/01/2016 (original applicant: Astra Zeneca UK Ltd.)
Facilities:	(b) (4)
Product:	Brodalumab (SILIQ™); AMG-827
Dosage:	Sterile, preservative free solution in 1.5 mL (140 mg/mL) pre-filled syringes for subcutaneous injection (dosing regimen is 210 mg subcutaneously at weeks 0, 1, and 2, followed by 210 mg every 2 weeks)
Indication:	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Goal date:	11/16/2016

Recommendation for approvability: The BLA, as amended, was reviewed from a product quality microbiology and sterility assurance perspective and it is recommended for approval.

Summary

Astra Zeneca UK Ltd submitted BLA 761032 to obtain approval of brodalumab (company internal product name: AMG-827). Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL) is the current owner of brodalumab (acceptance of ownership submitted to the Agency on 4/1/2016). Brodalumab is a monoclonal antibody antagonist to human IL-17 receptor A (IL-17RA) for the treatment of moderate to severe plaque psoriasis in adult patients that are candidates for systemic therapy or phototherapy.

BLA 761032 was submitted on 11/16/2015 in eCTD format. Additional information pertaining stability was submitted under section 3.2.P.8 on 12/15/2015 (eCTD 0001).

This addendum contains additional assessment of brodalumab drug product from a sterility assurance and microbiology product quality perspective. This addendum assesses microbiology responses submitted by the sponsor in amendments 0041 and 0048.

Drug Substance and Drug Product Quality Microbiology Information Reviewed

For amendments with multi-disciplinary information, only microbial quality information was reviewed.

IR Submission Date	Description	eCTD Sequence	Date
06/20/2016	Partial response to IR (Q#5)	0041	07/08/2016
08/08/2016	Response to IR (Microbiology Q#1-3)	0048	08/22/2016

3.2 DRUG PRODUCT

P.3 MANUFACTURE

P.3.4 Control of Critical Steps and Intermediates

Drug Product Process Controls

(b) (4)

[redacted]

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SIGNATURE PAGE

Maria Jose Lopez Barragan -S (Affiliate)

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DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=0012653737, cn=Maria Jose Lopez Barragan -S (Affiliate)
Date: 2016.11.14 11:56:50 -05'00'

Maria Jose Lopez Barragan
Primary Reviewer

Reyes Candau-Chacon
Quality Assessment Lead (Actg)

Reyes Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 11/14/2016 02:29:46PM
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Maria Jose Lopez-Barragan

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Date: 11/14/2016 02:33:31PM
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First Approval for Indication

Recommendation: Approval, provided residual issues are addressed prior to the action date. The review of these issues will be documented in an addendum to the BLA review.

BLA/NDA 761032
Review 1

Date: 7/1/2016
From: Qing Zhou, Ph.D.
Acting 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	**Siliq (brodalumab)/for injection**
Strength/Potency	**210 mg/1.5 mL**
Route of Administration	**Subcutaneous injection**
Rx/OTC Dispensed	**Rx**
Indication	**Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.**
Applicant/Sponsor	**Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)**
US agent, if applicable	**Valeant Pharmaceuticals North America LLC**

Product Overview

Siliq (brodalumab) is a human IgG2 monoclonal antibody produced in CHO cells. Brodalumab targets interleukin-17 receptor A (IL-17RA) and blocks the binding of IL-17A, IL-17F, and IL-17A/F, produced by T-helper cells and innate immune cells, to IL-17RA, leading to the reduction and/or inhibition of tissue inflammation and destruction observed in patients with psoriasis. Brodalumab drug product is supplied at 210 mg/1.5mL as a sterile, single-dose, preservative-free solution for injection in a pre-filled syringe (PFS) and is intended for subcutaneous dosing. Brodalumab 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	Donald Obenhuber	DIA/OPF/OPQ
Microbiology (DS and DP)	Maria Jose Lopez- Barragan	DMA/OPF/OPQ
Business Process Manager	Andrew Shiber	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	Reyes Candau-Chacon	DMA/OPF/OPQ
Facilities Team Lead	Peter Qiu	DIA/OPF/OPQ

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Strother Dixon	CDER/OND/ODEIII/DDDP
Cross-disciplinary Team Lead	David Kettl	CDER/OND/ODEIII/DDDP
Medical Officer	Gary Chiang	CDER/OND/ODEIII/DDDP
Pharm/Tox	Carmen Booker	CDER/ODEIII/DDDP
Clinical Pharmacology	Jie Wang	CDER/OCP/DCPIII
Biometrics	Carin Kim	CDER/OB/DBIII

a. Names
   i. Proprietary Name: Siliq
   ii. Trade Name: Siliq
   iii. Non-Proprietary/USAN: brodalumab
   iv. CAS name: 1174395-19-7
   v. INN Name: brodalumab
   vi. OBP systematic name: MAB HUMAN (IGG2) ANTI Q96F46 (I17RA_HUMAN) [AMG827]

b. Pharmacologic category: Therapeutic recombinant human monoclonal antibody

Quality Review Team – Signatures

DISCIPLINE	REVIEWER	SIGNATURE
Microbiology Team Lead	Reyes Candau-Chacon	Maria D. Candauchacon -S Digitally signed by Maria D Candauchacon S DN: c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 2000639745 cn Maria D Candauchacon S Date: 2016 07 01 16:59 19 04 00
Facilities Team Lead	Marion Michaelis for Peter Qiu	Marion Michaelis -S Digitally signed by Marion Michaelis S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=1300424646 cn=Marion Michaelis S Date: 2016 07 01 16:54:54 04 00'
Application Technical Lead and DS and DP Team Lead	Qing Zhou	Qing Zhou -S Digitally signed by Qing Zhou S DN: c US o U S Government ou HHS ou FDA ou People cn Qing Zhou S 0 9 2342 19200300 100 1 1 2000581275 Date: 2016 07 01 17:02:21 04'00'
Review Chief, OBP/DBRR I	Sarah Kennett	Sarah B. Kennett -S Digitally signed by Sarah B Kennett S DN: c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 2000597165 cn Sarah B Kennett S Date: 2016 07 01 17:04 17 04 00
Director, OBP/DBRR I	Wendy Weinberg for Kathleen Clouse	Wendy C. Weinberg -S Digitally s gned by Wendy C Weinberg S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=1300151936 cn=Wendy C Weinberg S Date: 2016 07 01 17 16:17 04 00

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
761032/0000	November 17, 2015	OBP, DMA, DIA
761032/0001	December 15, 2015	OBP
761032/0005	January 8, 2016	OBP, DMA, DIA
761032/0023	April 29, 2016	OBP, DMA
761032/0024	May 2, 2016	OBP, DMA, DIA
761032/0027	May 11, 2016	OBP
761032/0028	May 25, 2016	OBP
761032/0029	May 27, 2016	DMA
761032/0033	June 10, 2016	DMA
761032/0034	June 16, 2016	OBP
761032/39	June 27, 2016	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
	III			3	N/A
	III			3	N/A

[1] 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

1. Recommendation:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761032 for Siliq (brodalumab) manufactured by Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL), if the following issues are sufficiently addressed prior to the Action Date. With the exceptions noted below, the data submitted in this application are adequate to support the conclusion that the manufacture of Siliq 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. The review of the responses to these issues will be included in an addendum to the BLA review.

1. Inclusion of cIEF analysis as part of the lot release and post-approval stability specifications for drug substance (DS) and drug product (DP).

2. Inclusion of the bioassay as part of the lot release and post-approval stability specifications for DS and DP.

3. Updating of the [redacted] (b) (4) (in-process testing) to account for the differences observed between the [redacted] (b) (4) [redacted]

4. Inclusion of the reduced and non-reduced CE-SDS methods as part of the DS and DP lot release and stability specifications or providing appropriate justifications for their removal.

5. Providing acceptable process characterization and/or validation data to support the [redacted] (b) (4) ranges for each [redacted] (b) (4) step or tightening the ranges to those supported by process and [redacted] (b) (4) validation studies.

6. Providing acceptable data to support the [redacted] (b) (4) [redacted] with respect to brodalumab quality or revising the action limit to reflect historical experience.

7. Providing the specific strategies that will be used to monitor and control variation in brodalumab product quality due to changes in [redacted] (b) (4) [redacted]

8. Updating of the future WCB qualification protocol to include appropriate acceptance criteria or removal of the protocol from the BLA.

9. Tightening of or modification of the proposed potency criterion for qualification of future primary and working reference standards or removal of this protocol from the BLA.

10. Providing evidence of successful method validation or transfer of each test method at each facility identified as a testing facility or specifying the appropriate test(s) performed at each facility in Section 3.2.P.3.1 and Form 356h.

11. Providing information to justify the use of Ph.Eur./JP (b) (4), rather than USP/NF (b) (4), as a drug product excipient.

12. Updating of Sections 3.2.S.7 and 3.2.P.8 with appropriate drug substance and drug product expiry periods that are supported by stability data from fully representative lots.

13. Updating all applicable sections of the BLA to reflect that the bioburden test volume used for brodalumab (b) (4) and action limit have been updated appropriately to > (b) (4) mL.

14. Establishing a minimum volume required to (b) (4) and provide data to support that the minimum established (b) (4).

15. Providing the routine conditions used during the container closure integrity test performed for brodalumab stability samples.

16. Providing additional data to support the limits established for the plunger placement, including summary reports for the (b) (4) simulation studies.

2. Approval action letter language

Under this license, you are approved to manufacture brodalumab drug substance at (b) (4). The 210 mg/1.5 mL drug product will be manufactured at (b) (4) and packaged and labeled at (b) (4).

The dating period for brodalumab drug product, 210 mg/1.5 mL, shall be 12 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 brodalumab drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

We have approved the stability protocols in your license application for the purpose of extending the dating periods of the drug substance and drug product

under 21 CFR 601.12. Data supporting extension of the expiration dating period should be submitted to the BLA Annual Report.

3. Benefit/Risk Considerations

Psoriasis is a chronic and frequently life-altering immune-mediated inflammatory skin disease associated with serious comorbidities and substantial impairment of physical and psychological quality of life. The prevalence of psoriasis in the US is estimated at around 3.1% among adults, and approximately 18% of patients diagnosed with psoriasis are estimated to develop moderate to severe disease. 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 are associated with dose- and treatment-limiting options, minimal efficacy, and relapse. Brodalumab targets human IL-17 receptor and blocks the interaction of IL-17 cytokine family members (including IL-17A, IL-17F, IL-17A/F heterodimer, IL-17C, and IL-25) and IL-17 receptor A for rapid and sustained anti-inflammatory response in psoriasis patients.

The overall control strategy for brodalumab manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. With the changes expected in response to the final information requests, the manufacturing control strategy coupled with in-process, release, and stability testing will ensure process consistency and drug substance and drug product that have appropriate quality attributes and are free of adventitious agents.

The review of the assays used to evaluate the immunogenicity rates in the clinical trials indicated that the neutralization assay was not tolerant to the levels of brodalumab present in the clinical study serum samples. Because the impact of brodalumab anti-drug antibodies (ADA) on safety and efficacy of the product is not clear, implementation of a post-marketing requirement (PMR) (b) (5) (b) (5) (b) (5) s under consideration. The final decision for such a PMR is pending on an overall risk assessment of brodalumab immunogenicity from the clinical and clinical pharmacology review team.

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

Note: The PMCs are dependent on the final information request responses.

(b) (5)


(b) (5)

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. For additional information see Appendix A.

Note: The tables (1-3) include the requests communicated to the sponsor for which a response has not been received.

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

CQA (type)	Risk	Origin	Control Strategy	Other notes
Identity	Safety and Efficacy	Intrinsic to the molecule	Identity is tested for at DS and DP lot release.	N/A
IL-17 receptor binding (potency)	Efficacy	Intrinsic to the molecule. Can be impacted by the manufacturing process and storage.	Potency is included on the DS and DP release and stability specifications.	Brodalumab shows no ADCC activity using an in vitro cell based assay.
High Molecular Weight (HMW) species/Aggregates (product related impurities)	Efficacy, Pharmacokinetics, and Safety/Immunogenicity Impact IL-17R binding	Manufacturing process and exposure to heat, light, and high pH stress. Minimal increase is expected on stability	(b) (4)	N/A
Low Molecular Weight (LMW) Species (product related impurities)	Efficacy and Pharmacokinetics	Manufacturing process. Minimal change is expected on stability. Minimal changes were observed in forced degradation studies.		N/A

			(b) (4)	
Charge Variant Profile (deamidation, C-terminal and N-terminal variants and oxidation; product related impurities)	Efficacy, Pharmacokinetics, and Potency	Cell culture and degradation during manufacturing and storage. Exposure to light.		N/A
Osmolality	Safety, Efficacy (control of degradation through formulation)	Formulation		N/A
Endotoxin	Safety and Purity	Raw materials or contamination during manufacturing process		N/A
Bioburden	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials or contamination during manufacturing process		N/A
Protein Content	Efficacy	Manufacturing process		N/A

B. Drug Substance [brodalumab] Quality Summary

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. For additional information see Appendix A and Appendix B.

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

CQA (type)	Risk	Origin	Control Strategy	Other notes
(b) (4)	Pharmacokinetics and Efficacy	(b) (4)	(b) (4)	N/A
	Safety and Immunogenicity			N/A
	Safety			N/A
	Safety and Efficacy			N/A
	Safety and Immunogenicity			N/A
	Safety			(b) (4)

(b) (4)

	Safety		
	Safety		
	Safety		
	Safety		

(b) (4)

		(b) (4)	(b) (4)	
(b) (4)	Safety			
	Safety			
	Safety			N/A
	Safety			
Appearance	Safety	Controlled by the manufacturing process		N/A
(b) (4)	Safety and Efficacy (b) (4) (b) (4)	Formulation		N/A
Leachables (b) (4)	Safety	Manufacturing components and the DS container closure system (CCS) during storage		N/A

			(b) (4)	
Endotoxin	Safety and Purity	Raw materials or contamination during manufacturing process	Controlled via the bioburden control strategy (b) (4) (b) (4). Tested (b) (4) (b) (4) (b) (4) for DS release. DS release specification is ≤ (b) (4) EU/mg.	N/A
Bioburden	Safety, Purity and Efficacy (b) (4)	Raw materials and contamination during manufacturing	(b) (4) (b) (4) ested (b) (4) (b) (4) for DS release. DS release specification is ≤ (b) (4)	N/A

a. Description

Brodalumab is a full length recombinant, human IgG2 monoclonal antibody and consists of two heavy chains that are each composed of 442 amino acids and two light chains that are each composed of 214 amino acids. Each heavy chain contains an N-linked glycan at asparagine 292 (Asn^{292}). (b) (4)

The extinction coefficient was calculated and confirmed experimentally to be 1.5 mg^{-1} cm^{-1} mL at 280 nm. This value has been used during development and will continue to be used to determine the brodalumab protein concentration for commercial use.

For additional information see Appendix A.

b. Mechanism of action

Brodalumab binds to the human interleukin-17 receptor A (IL-17RA) and blocks the biological activities of IL-17A, IL-17F, IL-17A/F heterodimer, and IL-25. IL-17RA is a type I transmembrane receptor expressed on various cell types including, but not limited to, fibroblasts, epithelial cells, and monocytes. Interleukin-17A, IL-17F, and IL-17A/F are proinflammatory cytokines shown to contribute to the inflammatory response in autoimmune diseases such as psoriasis. Therefore, blocking the interaction between IL-17RA and IL-17 cytokine family members could reduce tissue inflammation and destruction in psoriasis patients. For additional information see Appendix A.

c. Potency Assay

A cell-based bioassay that measures the brodalumab dose-dependent inhibition of IL-8 secretion from IL-17A stimulated human foreskin fibroblast (HFF) cells is used to control brodalumab DS and DP potency. IL-17 receptor expressing HFF cells are incubated with IL-17A and various concentration of brodalumab, and the cell supernatant is tested for the level of IL-8 using either a traditional ELISA method or a bead-based luminescence assay (AlfaLISA; primary method) that utilizes the same principle. The IL-8 in the cell supernatant is captured using anti-IL-8 antibody coated plates (for ELISA) or using a layer of hydrogel containing a thioxene derivative (acceptor beads, AlfaLISA) and is detected using a biotinylated anti-IL-8 antibody (ELISA) or a biotinylated anti-IL8 antibody linked to beads coated with a hydrogel that contains phthalocyanine, a photosensitizer (donor beads, AlfaLISA). Luminescence signals resulting from the oxygen initiated energy transfer when the acceptor and donor beads are in proximity are measured for the AlfaLISA method. Optical density is measured for the ELISA method. Sample potency is determined relative to the reference standard. For additional information see Appendix A.

d. Reference material(s)

(b) (4)

(b) (4). The RMs are suitable for their intended uses in brodalumab testing. The procedures and criteria used to establish and qualify future WRMs were provided. For additional information see Appendix A.

e. Critical starting materials or intermediates

(b) (4)

f. Manufacturing process summary

(b) (4)

g. Container closure

The drug substance is stored in (b) (4) The container closure system is suitable for brodalumab

manufacturing based on stability data and maintenance of closure integrity. For additional information see Appendix A and Appendix B.

h. Dating period and storage conditions

The dating period for the drug substance is (b) (4) months when stored a (b) (4) °C, (b) (4) .

C. Drug Product [brodalumab] 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. For additional information see Appendix A and Appendix B.

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Color and clarity of solution (general)	Safety and Efficacy	Formulation, contamination or degradation	(b) (4)	
Particulate Matter (Product or Process Related Impurities)	Safety/Immunogenicity	Manufacturing process and container closure system (CCS)		N/A
pH (general)	Safety and efficacy	Formulation		N/A
Deliverable Volume (general)	Efficacy/Dosing	Manufacturing process		N/A
Leachables (process related impurities)	Safety	Manufacturing equipment and CCS		Submission of additional leachable study data and a toxicological risk assessment will be addressed as a PMC
Sterility	Safety (infection) Purity and Efficacy (degradation or	Contamination could be introduced throughout DP manufacturing or through a container closure integrity		(b) (4) will

	modification of the product by contaminating microorganisms)	failure	(b) (4)	be required as a PMC
Endotoxin	Safety and Purity	Contamination could be introduced throughout DP manufacturing or through a container closure integrity failure		N/A

a. Potency and Strength

Brodalumab is supplied at 210 mg/1.5 mL. The DP concentration is 140 mg/mL. Potency is defined as the percent activity relative to the current brodalumab reference standard. The potency assay is the same as described in the DS section and in Appendix A.

b. Summary of Product Design

Brodalumab is supplied as a sterile, single-dose, preservative-free solution for SC injection in a pre-filled syringe. The drug product formulation consists of 30 mM glutamate, 2.4% (w/v) proline, and 0.01% (w/v) polysorbate 20, pH 4.8. The extractable volume is 1.5 mL.

c. List of Excipients

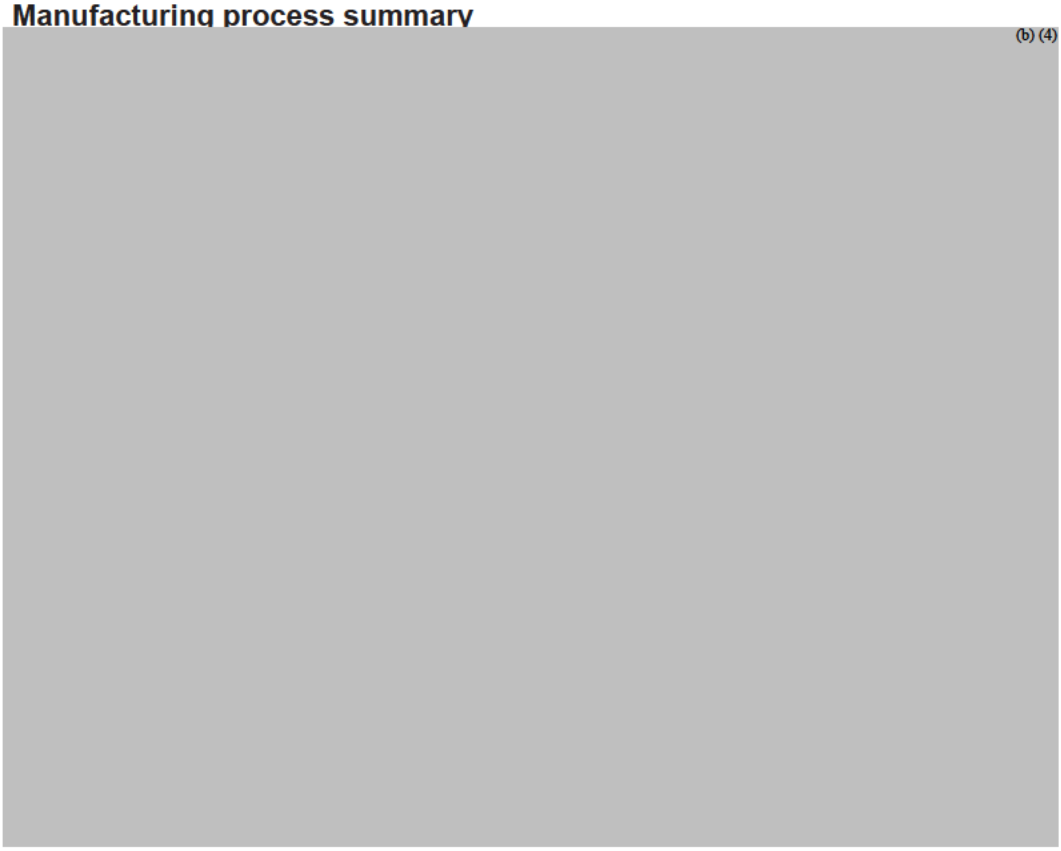
Excipients include glutamate, polysorbate 20, and proline.

d. Reference material(s)

The same reference material is used for drug substance and drug product.

e. Manufacturing process summary

(b) (4)



f. Container closure

The primary container closure system for brodalumab DP consists of a 2.25 mL Long glass (Type 1) syringe with a staked-in-place stainless steel needle covered with (b) (4) needle shield and a (b) (4) plunger-stopper (b) (4) .

The secondary container closure system consists of a plastic tray, which is placed into a paperboard carton with the corresponding leaflets.

For additional information see Appendix A.

g. Dating period and storage conditions
The dating period for brodalumab drug product is 12 months when stored at 2-8ºC, protected from light.

D. Novel Approaches/Precedents:
None

E. Any Special Product Quality Labeling Recommendations:
There are no special product quality labeling recommendations as compared to those used for similar marketed protein products.

F. Establishment Information

Note: Testing sites will be finalized following receipt of the final information request responses.

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
Drug substance manufacture Drug substance and drug product (b) (4), lot release and stability testing except breakloose/extrusion force and container closure integrity testing. Working cell bank storage	(b) (4)		Pre-Approval Inspection (b) (4)	3 item 483	Pending final facility recommendation
Master cell bank and working cell bank storage; Working cell bank production			District Recommendation	VAI	Approve Facility
(b) (4) mycoplasma and adventitious viral testing			District Recommendation	VAI	Approve Facility
DRUG PRODUCT					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
Drug product manufacture Drug product (b) (4) and lot release testing including endotoxin and bioburden	(b) (4)		Based on Profile	VAI	Approve Facility
Secondary Packaging, labeling and Distribution; Drug product lot release and stability testing including break loose and extrusion force			Based on Profile	VAI	Approve Facility

Container closure integrity for drug product stability testing	(b) (4)	District Recommendation	VAI	Approve Facility
Container closure integrity for drug product stability testing		Based on Profile	VAI	Approve Facility

G. Facilities

Brodalumab drug substance is manufactured at (b) (4) A Pre-license Inspection was performed at (b) (4). A three item Form FDA 483 was issued. The recommendation for the firm is VAI; however, the inspection is pending final recommendation. The drug substance manufacturing and testing sites have been inspected multiple times within the recent past, demonstrating acceptable compliance.

The drug product is manufactured and filled into the primary container closure at (b) (4) No inspections specific to brodalumab drug product were conducted. The compliance status of the production facility associated with the manufacture of brodalumab DP is acceptable based on recent previous inspections and district recommendation. Secondary labelling and packaging is performed at (b) (4) The compliance status of the secondary labelling and packaging facility and drug product testing facilities were also acceptable.

For a complete summary see Appendix C.

H. Lifecycle Knowledge Management

a. Drug Substance

i. Protocols approved (pending final IR response)
   1. Annual stability protocol
   2. Stability protocol for the extension of shelf-life
   3. Qualification of new working reference material protocol

ii. Outstanding review issues/residual risk: All identified residual risk is mitigated through the PMCs listed above. Outstanding review issues are listed at the beginning of this document.

iii. Future inspection points to consider: None identified.

b. Drug Product

iv. Protocols approved (pending final IR response)
   1. Annual stability protocol
   2. Stability protocol for the extension of shelf-life

v. Outstanding review issues/residual risk: All identified residual risk is mitigated through the PMCs listed above. Outstanding review issues are listed at the beginning of this document.

vi. Future inspection points to consider: None identified.

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 Linked to the Application (#_____)			x	
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			x	

	Production				
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	

BLA STN 761032

Siliq
(brodalumab)

Valeant Pharmaceuticals
Luxembourg S.a.r.l.

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 761032

2. **REVIEW DATE:** July 1, 2016

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Gary Chiang and David Kettl
Pharm/Tox: Carmen Booker and Barbara Hill
Product Quality Team: Willie Wilson and Joanna Zhou
BMT or Facilities: Maria Jose Lopez-Barragan, Maria Candauchacon
Clinical Pharmacology: Jie Wang and Yow-Ming Wang
Statistics: Carin Kim and Mohamed Alosh
OBP Labeling: Jibril Abdus-Samad
Labeling: Nancy Xu, Carlos Mena-Grillasca, Rowell Medina, Tara Turner
OBP RBPM: Andrew Shiber
RPM: Strother Dixon

4. **MAJOR GRMP DEADLINES**
Filing Meeting: January 5, 2016
Mid-Cycle Meeting: April 20, 2016
Advisory Committee Meeting: July 19, 2016
Wrap-Up Meeting: August 26, 2016
Primary Review Due: July 1, 2016
Secondary Review Due: July 1, 2016
CDTL Memo Due: September 7, 2016
PDUFA Action Date: November 16, 2016

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

Communication/Document	Date
Filing Review Memo	1-11-16
Information Request 1	4-15-16
Information Request Regarding Future DS Manufacturing Plans	4-14-16
Mid-Cycle Communication	4-26-16
Information Request 2	5-16-16
Information Request 3	6-9-16
Late-Cycle Communication	6-28-16

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

Submission	Date Received	Review Completed (Yes/No)
STN 761032/0 (BLA Original Submission)	11-16-15	Yes
STN 761032/24 (Sponsor's response to IR1)	4-29-16	Yes

STN 761032/25 (Sponsor's response to IR regarding manufacturing plans)	5-2-16	Yes
STN 761032/27 (Sponsor's response to IR1)	5-3-16	Yes
STN 761032/28 (Sponsor's response to IR1)	5-11-16	Yes
STN 761032/29 (Sponsor's response to IR2)	5-25-16	Yes
STN 761032/35 (Sponsor's response to IR3, part 1)	6-16-16	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Siliq
   b. Trade Name: Siliq
   c. Non-Proprietary/USAN: Brodalumab
   d. CAS name: 1174395-19-7
   e. Common name: AMG-827
   f. INN Name: Brodalumab
   g. Compendial Name: N/A
   h. OBP systematic name: MAB HUMAN (IGG2) ANTI Q96F46 (I17RA_HUMAN) [AMG827]
   i. Other Names: AMG-827

8. **PHARMACOLOGICAL CATEGORY:** human IgG2 monoclonal antibody against human interleukin-17 Receptor A (IL-17RA)
9. **DOSAGE FORM:** For Injection
10. **STRENGTH/POTENCY:**
    - The Siliq (brodalumab) Drug Product is supplied as a 210 mg/1.5 mL (140 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 binding assay that measures the ability of brodalumab to inhibit IL-17RA signaling (i.e., IL-8 secretion) in IL-17-treated human foreskin fibroblast cells.
    - The dating period for Siliq drug product is 12 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.
			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.

13. **INSPECTIONAL ACTIVITIES**

A pre-licensure inspection (PLI) of the biologics drug substance manufacturing facility was conducted at (b) (4) by DMA reviewers (Maria Candauchacon and Maria Jose Lopez-Barragan), DIA reviewer (Donald Obenhuber) and OBP product quality reviewers (Willie Wilson and Joanna Zhou). The PLI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls.

A three-item 483 was issued; the 483 issues were related to the standard operating procedures (b) (4) (b) (4) (b) (4). The initial 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.

16. PRECEDENTS: None

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Sarah Kennett, Ph.D. Review Chief Office of Biotechnology Products Division of Biotechnology Review and Research 1	
Qing (Joanna) Zhou, Ph.D. Acting Team Leader Office of Biotechnology Products Division of Biotechnology Review and Research 1	
Willie Wilson, Ph.D. Primary Reviewer Office of Biotechnology Products Division of Biotechnology Review and Research 1	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

With the exceptions noted below, the data submitted in this Biologics License Application support the conclusion that the manufacture of Siliq (brodalumab) 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 Siliq (brodalumab) be approved for human use (under conditions specified in the package insert), provided that the following issues are sufficiently addressed prior to the Action Date. The review of these issues will be included in an Addendum to the BLA review.

1. Inclusion of cIEF analysis as part of the lot release and post-approval stability specifications for drug substance (DS) and drug product (DP).

2. Inclusion of the bioassay as part of the lot release and post-approval stability specifications for DS and DP.

3. Updating of the [redacted] (b) (4) (in-process testing) to account for the differences observed between the [redacted] (b) (4).

4. Inclusion of the reduced and non-reduced CE-SDS methods as part of the DS and DP lot release and stability specifications or providing appropriate justifications for their removal.

5. Providing acceptable process characterization and/or validation data to support the [redacted] (b) (4) ranges for each [redacted] (b) (4) step or tightening the ranges to those supported by process and [redacted] (b) (4) validation studies.

6. Providing acceptable data to support the [redacted] (b) (4) with respect to brodalumab quality or revising the action limit to reflect historical experience.

7. Providing the specific strategies that will be used to monitor and control variation in brodalumab product quality due to changes in [redacted] (b) (4).

8. Updating of the future WCB qualification protocol to include appropriate acceptance criteria or removal of the protocol from the BLA.

9. Tightening of or modification of the proposed potency criterion for qualification of future primary and working reference standards or removal of these protocols from the BLA.

10. Providing evidence of successful method validation or transfer of each test method at each facility identified as a testing facility or specifying the appropriate test(s) performed at each facility in Section 3.2.P.3.1 and Form 356h.

11. Providing information to justify the use of Ph.Eur./JP [redacted] (b) (4), rather than USP/NF [redacted] (b) (4), as a drug product excipient.

12. Updating of Sections 3.2.S.7 and 3.2.P.8 with appropriate drug substance and drug product expiry periods that are supported by stability data from fully representative lots.

I recommend an expiry period of 12 months for brodalumab DP when stored at 2 – 8°C, protected from light. Note: Additional data to extend this recommendation may be provided.

I recommend an expiry period of [redacted] (b) (4) months for brodalumab DS when stored at [redacted] (b) (4).

The post-approval stability protocols are acceptable with the exception of the testing noted above. Updated stability data will be reported to the BLA in the Annual Report.

With exceptions noted above, I recommend approval of the proposed release specifications for brodalumab DS and DP.

II. List Of Deficiencies To Be Communicated

None (remaining issues were communicated)

III. List Of Post-Marketing Commitments/Requirement

There is the potential for the following PMR/PMCs. The PMR is dependent on the final determination made by the clinical review team. The PMCs are dependent of the final responses provided by Valeant.

[redacted] (b) (5)

(b) (4)

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion
A claim for categorical exclusion under 21 CFR 25.31 (c) and 21 CFR 25.34 (b) 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 brodalumab 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).

Brodalumab DS is manufactured at (b) (4)
(b) (4)

Brodalumab DP is manufactured at (b) (4) and is packaged and labeled at (b) (4). The manufacturing process for brodalumab DP is comprised of (b) (4)
(b) (4)

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 confirmation, neutralizing ADA screening and neutralizing ADA confirmation.

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

S. DRUG SUBSTANCE

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

Recommended International Non-proprietary Name (INN):	brodalumab
Chemical name(s):	anti IL-17RA monoclonal antibody
Chemical abstracts service (CAS) registry number:	1174395-19-7
Amgen laboratory code name:	AMG 827
United States Adopted Name (USAN):	brodalumab

3.2.S.1.2 Structure

Brodalumab is a human monoclonal IgG2 antibody consisting of 2 heavy chains (HC) and 2 kappa light chains (LC). (b) (4) (b) (4) (b) (4) The theoretical amino acid sequences of the HC and LCs of brodalumab were provided in the submission and were verified by LC MS/MS analysis of peptide fragments. (b) (4) (b) (4) The structure of brodalumab, including the disulfide bonding pattern, is presented in Figure 1 below.

Figure 1. Schematic of Brodalumab Structure

(b) (4)

3.2.S.1.3 General Properties

Physical and Chemical Properties

Table 1. Physical and Chemical Properties of Brodalumab

Immunoglobulin subclass	IgG2
Sequence	Human
Biological Target	Specific binding to human IL-17RA
Molecular Mass[a]	(b) (4)
Cysteines	36
Number of disulfide bonds	18
Glycosylation	N-linked site: Asn^{292} on each heavy chain
Extinction coefficient	Theoretical: 1.5 mg^{-1} cm^{-1} mL at 280 nm Determined: 1.5 mg^{-1} cm^{-1} mL at 280 nm
Isoelectric point (pI)	Theoretical: 8.7[b] Determined: 8.6
T_m (melting temperatures)[c]	67°C for C_H2 77°C for Fab

[a] Experimentally determined molecular mass
[b] Theoretical isoelectric point with heavy chain C-terminal glycine
[c] Experimentally determined melting temperatures

Biological Properties

The biological characterization of brodalumab is discussed in Section 3.2.S.3.1.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The manufacturer, testing facilities, and their responsibilities are shown in tables below.

Table -1 Drug Substance Facility Responsibilities

Facility	Address	Responsibility	US FDA Registration Number
(b) (4)	(b) (4)	Drug substance manufacture Drug substance in-process, lot release and stability testing Working cell bank storage	FEI: (b) (4) DUNS
		Master cell bank and working cell bank storage Working cell bank production	FEI: (b) (4) DUNS:

FEI = Facility Establishment Identifier,
DUNS = Data Universal Numbering System Number

Table -2 Contract Testing Laboratories

Facility	Address	Type of Testing	US FDA Registration Number
(b) (4)	(b) (4)	(b) (4) mycoplasma and adventitious viral testing	FEI: (b) (4) DUNS:

FEI = Facility Establishment Identifier
DUNS = Data Universal Numbering System Number

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

Reviewer Comment: *This section incorporates the review of the description of the manufacturing process, process parameters (PPs) and their acceptable ranges (ARs), in-process controls (IPCs) and their limits (Sections 3.2.S.2.2 and 3.2.S.2.4), and the relevant information and data from process characterization (Section 3.2.S.2.6) used to support the ARs and action/rejection limits established for each step in the brodalumab DS manufacturing process. Information and data provided in Section 3.2.S.2.6 are identified by their location in the BLA. Review of information provided on the control of bioburden and endotoxin is deferred to the DMA review team.*

Overview of Drug Substance Manufacturing Process

(b) (4)

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

DRUG SUBSTANCE AND DRUG PRODUCT MICROBIOLOGY QUALITY REVIEW

Date: 07/01/2016

To: Administrative File, STN 761032/0

From: Maria Jose Lopez Barragan, PhD, Reviewer, CDER/OPQ/OPF/DMA/BIV

Through: Reyes Candau-Chacon, PhD, Acting Quality Assessment Lead, CDER/OPQ/OPF/DMA/BIV

Subject: New Biologic License Application (BLA)

Applicant: Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL): Acceptance of Ownership received by the Agency on 04/01/2016 (original applicant: Astra Zeneca UK Ltd.)

Facilities: (b) (4) (Drug Substance Manufacturer)
(b) (4) (Drug Product Manufacturer)

Product: Brodalumab (SILIQ™); AMG-827

Dosage: Sterile, preservative free solution in 1.5 mL (140 mg/mL) pre-filled syringes for subcutaneous injection (dosing regimen is 210 mg subcutaneously at weeks 0, 1, and 2, followed by 210 mg every 2 weeks)

Indication: Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy

PDUFA date: 11/16/2016

Recommendation for approvability: The drug substance and drug product parts of BLA 761032 were reviewed from a microbial control, sterility assurance and microbiology product quality perspective. No approvability issues have been identified at this point and the review of a pending information request will be included as an addendum to this review.

Summary

Astra Zeneca UK Ltd submitted BLA 761032 to obtain approval of brodalumab (company internal product name: AMG-827). Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL) is the current owner of brodalumab (acceptance of ownership submitted to the Agency on 4/1/2016). Brodalumab is a

monoclonal antibody antagonist to human IL-17 receptor A (IL-17RA) for the treatment of moderate to severe plaque psoriasis in adult patients that are candidates for systemic therapy or phototherapy.

BLA 761032 was submitted on 11/16/2015 in eCTD format. Additional information pertaining stability was submitted under section 3.2.P.8 on 12/15/2015 (eCTD 0001). This review contains the assessment of brodalumab drug substance and drug product from a sterility assurance and microbiology product quality perspective.

Drug Substance and Drug Product Quality Microbiology Information Reviewed

For amendments with multi-disciplinary information, only microbial quality information was reviewed.

IR Submission Date	Description	eCTD Sequence	Date
Not applicable	Original BLA	0000	11/16/2015
Not applicable	Amendment (Section 3.2.P.8)	0001	12/15/2015
04/15/2016	Response to IR (Q 12-18)	0023	04/29/2016
05/20/2016	Partial response to IR (Q 1-9, 10 (a, b), 11 (b, c, d), 12 (a, d, e), 13, 14 and 18)	0029	05/27/2016
05/20/2016	Partial response to IR (Q 11a, 12 (b, c), 15-17)	0033	06/10/2016
06/09/2016	Response to IR (Q7)	0034	06/16/2016
06/20/2016	Partial response to IR (Q1- 4 and 6-9)	0039	06/27/2016
06/20/2016	Partial response to IR (Q5)	*Pending*	*Pending*

3.2.S DRUG SUBSTANCE

S.1 GENERAL INFORMATION

Brodalumab is an anti-IL-17RA (interleukin-17 receptor A) human monoclonal antibody of the immunoglobulin G2 (IgG2) subclass. Brodalumab consists of two heavy chains and two light chains that are covalently linked by a total of 18 disulfide bonds with a theoretical molecular weight of (b) (4) Brodalumab is expressed in recombinant Chinese Hamster Ovary (CHO) cells.

The description is satisfactory

S.2 MANUFACTURE

S.2.1 Manufacture(s)

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

Site	Responsibilities
(b) (4)	• Drug substance manufacture • DS in-process, release and stability testing • Working cell bank storage
	• Master cell bank and working cell bank storage • Working cell bank production
	• (b) (4) mycoplasma and adventitious viral testing

Reviewer comments: Refer to Panorama for the cGMP compliance status of these facilities.

S.2.2 Description of Manufacturing Process and Process Controls

(b) (4)

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S.7 STABILITY

S.7.1 Stability Summary and Conclusions

The proposed shelf-life for brodalumab drug substance is (b) (4) months at the recommended storage condition of (b) (4) in (b) (4) containers.

The current stability programs include:

- Primary stability program: 3 lots manufactured at clinical scale (b) (4) using the commercial process at the development manufacturing site (b) (4) There are stability data for up to 48 month time point.
- Production stability program: 3 lots manufactured at commercial scale (b) (4) using the commercial process at the commercial scale manufacturing facility (b) (4) There are data available for up to 18 month for one lot and up to 12 month for the two remaining lots.
- Supporting stability program: 1 additional lot manufactured at (b) (4) using the commercial process at clinical scale (b) (4) was used to assess comparability between processes 1 and 2. There are data available for up to the 48 month time point.

The storage conditions (recommended, experimental, accelerated and stressed, respectively) and time points proposed for the stability programs are summarized in Table 3 below submitted by sponsor:

Table 3 Time Points for Drug Substance Stability

(b) (4)

The container closure system used for the shelf-life stability studies is a (b) (4) . The stability closure container has been described as representative of the commercial container and is qualified to avoid any influence over stability results.

S.7.2 Post-Approval Stability Protocol and Stability Commitment

(b) (4) commits to complete the ongoing stability studies and to add a minimum of one lot of brodalumab DS annually to the ongoing post-approval stability program.

S.7.3 Stability Data

The stability programs for experimental ((b) (4)), accelerated ((b) (4)) and stressed ((b) (4)) conditions are completed with the latest times points available for 1, 6 and 3 months, respectively. The studies at the recommended storage conditions are still ongoing with the last time points available for 48, 18 and 54 months, respectively.

> *Reviewer's comment: no microbial attributes (bioburden or endotoxin) data was monitored during the stability studies. Microbial quality data is not required during stability studies for drug substance recommended for frozen storage.*

Satisfactory

3.2.P DRUG PRODUCT

P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Brodalumab drug product (DP) is a sterile, preservative-free, (b) (4) solution for subcutaneous injection in single-use prefilled syringes (PFS). Each PFS contains 140 mg/mL brodalumab in 30 mM glutamate, 2.4% (w/v) proline, and 0.01% (w/v) polysorbate 20 with a pH of 4.8. The PFS are filled to deliver a volume of 1.5 mL to provide 210 mg of brodalumab. The table below, which was provided by sponsor in section P.1, lists the DP unit formula.

Table 1. Composition of Brodalumab Drug Product

				1.5 mL fill in 2.25 mL syringe
Component	Grade	Function	Concentration	Quantity
Brodalumab	In house [a]	Active ingredient	140 mg/mL	210 mg
Proline	USP, PhEur, JP	(b) (4)	2.4% w/v	36 mg
Polysorbate 20	NF, PhEur, JPE		0.01% w/v	0.15 mg
(b) (4)	PhEur, JP		30 mM	6.5 mg
Water for injection	USP, PhEur, JP		qs to target volume	qs to target volume

qs = quantum sufficit
[a] Tested to internal specifications as described in 3.2.S.4.1 (Specification).
[b] The drug product is formulated with (b) (4) glutamate (b) (4) in final drug product as described in 3.2.P.2.1 (Components of the Drug Product [140 mg/mL PFS]).

The description is satisfactory

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.4 Container Closure System

Two container closure systems have been developed to accommodate three volume presentations: 1 mL Long syringe (for 0.75 mL and 1.0 mL fill volumes) and 2.25 mL syringe (for 1.5 mL fill volume). Both PFS closure systems are provided by (b) (4) and both are designed by a type I glass syringe barrel and 27G x ½" stacked-in needles. Both syringe systems have (b) (4) rigid needle shield (RNS), and a (b) (4) plunger-stopper. (b) (4)

Certificates of conformance (b) (4) have been submitted by the sponsor for the (b) (4) syringe barrels and plunger stoppers for the 1 mL Long and 2.25 mL syringes.

Reviewer's comments: the only presentation proposed for commercial use is the 1.5 mL fill volume in 2.25 mL syringe. The 0.75 mL and 1.0 mL presentations (1 mL Long syringe) were used during brodalumab development program and they are included in this memo exclusively as supporting data. (b) (4)

Satisfactory

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(b) (4)

Satisfactory

P.3 MANUFACTURE

P.3.1 Manufacturers

Brodalumab DP is manufactured at (b) (4) The sponsor updated section 3.2.P.3.1 upon Agency's request dated 06/20/2016 to provide further clarification on the sites intended to perform DP release testing (see amendment 0039 dated 06/27/2016). The table below (submitted under section 3.2.P.3.1) provides an update on the facilities involved in manufacturing, in-process and release testing, packaging and labeling of brodalumab DP:

Table 1. Drug Product Facility Responsibilities

Facility	Address	Responsibility	US FDA Registration Numbers
(b) (4)		Drug product manufacture (b) (4) Drug product lot release testing (Gravimetric) Inspection	FEI: (b) (4) DUNS: (b) (4)
		Drug product lot release testing (Breakloose and Extrusion force) Packaging and labeling	FEI: (b) (4) DUNS: (b) (4)
		Drug product lot release testing (Appearance, Color, Clarity, Subvisible particulates, ID ELISA, SE-HPLC, Bacterial endotoxins, Bioburden, and Sterility) Drug product stability testing (Subvisible particulates, SE-HPLC, and Sterility)	FEI: (b) (4) DUNS: (b) (4)
		Drug product lot release testing and stability testing	FEI: (b) (4) DUNS: (b) (4)
		Container closure integrity for stability testing	FEI: (b) (4) DUNS: (b) (4)

FEI = Facility Establishment Identifier
DUNS = Data Universal Numbering System Number

Reviewer's comment: the sponsor clarified in amendment 0029 (and further in amendment 0039) that sterility and endotoxin testing for brodalumab DP lot release is performed only at (b) (4). Upon further request, the sponsor amended the BLA (section 3.2.P.3.1 Manufacturers) to clarify the responsibility of each brodalumab DP testing facility (see amendment 0039 dated 06/27/2016).

Satisfactory

P.3.2 Batch Formula [PFS]

(b) (4)

(b) (4)

The description is satisfactory

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

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(b) (4)

Satisfactory

Secondary packaging

Labeled PFS are placed into plastic trays and each tray is placed into a paperboard carton.

P.8 STABILITY

P.8.1 Stability Summary

An expiry period of (b) (4) months is proposed for brodalumab DP when stored at the recommended storage temperature of (b) (4) °C. This proposed shelf life is based on data accrued from 9 commercial scale lots including the 0.5 mL, 0.75 mL and 1.0 mL PFS (3 lots for each presentation) extrapolated to the 1.5 mL commercial presentation due to analytical comparability and same product strength (140 mg/mL). Additionally, three 1.5 mL clinical-scale lots and two supporting lots (0.5 mL and 1.0 mL manufactured at (b) (4)) were placed on stability.

Currently, three lots of the 1.5 mL presentation manufactured at commercial scale during process validation at (b) (4) were placed on stability with up to 9 months of data available at the time of the BLA submission.

An optional storage of up to 2 weeks at 20-25°C after removal from storage has been proposed for consumer convenience. In order to support this additional storage time, DP was stored at 25°C or 30°C for 2 months (or 40°C for 3 days) after storage at the recommended temperature for 46 months. These studies included sterility testing at 2-week and 2-month time points (or 3-day time point at 40°C) and the results met in all cases the acceptance criterion.

> *Reviewer's comment: brodalumab is provided in a single-use prefilled syringe for subcutaneous injection. Neither dilutions nor manipulations of the product are recommended by the manufacturer prior to administration therefore, additional storage at room temperature is not expected to impact product quality from a microbial quality perspective.*

Satisfactory

During brodalumab DP shelf life stability studies, the sterility test is scheduled to be performed at release and CCI test is scheduled to be performed at annual time points and at expiry ((b) (4) months). During stability studies under accelerated conditions (25°C, 30°C and 40°C), only sterility testing will be performed at release.

> *Reviewer's comment: sterility testing is required only at release. The current FDA guidelines recommend performing CCI testing in lieu of sterility every 12 months and at expiry during shelf life stability studies.*

Satisfactory

P.8.2 Post-Approval Stability Commitment

(b) (4) commits to complete the currently ongoing stability studies. Additionally, a minimum of 1 lot of brodalumab DP for each primary container (1 mL Long or 2.25 mL PFS) presentation will be added to the ongoing post-approval stability program annually.

P.8.3 Stability Data

All lots placed on stability met the acceptance criteria for sterility and CCI.

Satisfactory

cGMP Status

Refer to Panorama for cGMP status of the relevant facilities.

Conclusion

I. The drug substance and drug product parts of BLA 761032 were reviewed from a microbial control, sterility assurance and microbiology product quality perspective. No approvability issues have been identified at this point and the review of a pending information request will be included as an addendum to this review.

II. Non-microbial information and data from the Drug Substance and Drug Product sections of this BLA should be also reviewed by OBP.

III. A pre-license inspection was conducted at (b) (4) (b) (4) by OPF/DMA (Reyes Candau-Chacon and Maria Jose Lopez-Barragan), OBP (Qing Zhou and Willie Wilson) and DIA (Donald Obenhuber).

FDA Information Request for STN 761032/0 submitted on 04/15/2016. Sponsor responses in amendment 0023 (04/29/2016)

Description of the Manufacturing Process and Process Controls (Section 3.2.S.2)

(b) (4)

[redacted]

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SIGNATURE PAGE

Maria Jose Lopez Barragan
Primary Reviewer

Reyes Candau-Chacon
Acting Quality Assessment Lead

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: March 8, 2016
To: Administrative File, STN 761032
From: Donald C. Obenhuber, Ph.D., CDER/OPQ/OPF/DIA
Endorsement: Zhihao Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
Applicant: Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
Mfg Facility: Drug Substance: (b) (4)
Drug Product: (b) (4)
Product: brodalumab
Due Date: November 16, 2016

Recommendation: This submission is pending a final recommended for approval based the facilities assessment.

SUMMARY

The drug substance is manufactured at (b) (4) . The brodalumab drug substance manufacturing process consists of (b) (4) . The drug product presentation is manufactured at (b) (4) manufacturing site, located in (b) (4) The brodalumab drug product manufacturing process consists of (b) (4) . Drug product assembly, packaging and labeling activities for the PFS occur at (b) (4) .

Table 1 includes the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Table 1 Manufacturing facilities associated with BLA 761032

Site name and address	FEI and DUNS numbers	Onsite Contact Phone #, fax #, email	Manufacturing Step(s) or Type of Testing and DMF number (if applicable).
(b) (4)			Drug substance: Drug substance manufacture, drug substance in-process, lot release and stability testing, working cell bank storage Drug product: Drug product lot release and stability testing
			Drug substance: Master cell bank and work cell bank storage, working cell bank production. ,
			Drug product: Drug product lot release and stability testing, packaging and labeling, distribution
			Drug substance: (b) (4) mycoplasma and adventitious viral testing Drug product: Container closure integrity for stability
(b) (4)			testing
			Drug product: Container closure integrity for stability testing
			Drug product: Drug product manufacture (b) (4) (b) (4) and lot release testing, inspection

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(b) (4)

Recommendation: Approve Facility
Reason: Based on Profile

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Final approval is pending the outcome of the last inspections.

Donald C. Obenhuber, Ph.D., CDER/OPQ/OPF/DIA.

Supervisor Comments and Concurrence:

I concur with the facility reviewer's assessment

STN 761032 (brodalumab) Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)

Zhihao Peter Qiu, Ph.D.
Branch Chief, OPQ/OPF/DIA/Branch 1