

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761036Orig1s000**

**CHEMISTRY REVIEW(S)**



## First Approval for Indication Expedited and Breakthrough Review

**Recommendation: Approval**

### BLA 761036 Review 1 October 22, 2015

<b>Drug Name/Dosage Form</b>	Darzalex (daratumumab)/Injection
<b>Strength/Potency</b>	100 mg/vial and 400 mg/vial (20 mg/ml concentration)
<b>Route of Administration</b>	Intravenous Infusion
<b>Rx/OTC Dispensed</b>	Rx
<b>Indication</b>	Treatment of patients with multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, or who are double-refractory to a PI and an immunomodulatory agent.
<b>Applicant/Sponsor</b>	Janssen Biotech, Inc.
<b>US agent, if applicable</b>	Janssen Research & Development, LLC

#### Product Overview

Darzalex (daratumumab) is a human monoclonal IgG1k antibody that binds to CD38 antigen on target cells to induce immune-mediated cell death. CD38 antigen is expressed to varying degrees on a number of hematopoietic cells as a transmembrane glycoprotein; it is overexpressed on myeloma cells. The indication for daratumumab is the treatment of multiple myeloma in patients who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, or who are double-refractory to a PI and an immunomodulatory agent.

### Quality Review Team

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
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Drug Product	Tura Camilli	Division of Biotechnology Review and Research I
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Microbiology Drug Substance	Maria Jose Lopez-Barragan	Division of Microbiology Assessment
Microbiology Drug Product	Natalia Pripuzova	Division of Microbiology Assessment
Business Regulatory Process Manager	Anita Brown	OPRO
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Microbiology Team Lead	Patricia Hughes	Division of Microbiology Assessment
Application Technical Lead and DS and DP Team Lead	Jee Chung	Division of Biotechnology Review and Research I

### Multidisciplinary Review Team

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Pharmacometrics	Lian Ma (Nitin Mehrotra, TL)	OCP/DPM
Statistics	Yaping Wang (Yuan-Li Shen, TL)	OB/DBV

a. Names

- i. Proprietary Name: Darzalex
- ii. Non-Proprietary/USAN: daratumumab
- iii. CAS name: 945721-28-8
- iv. INN Name: daratumumab
- v. OBP systematic name: MAB HUMAN (IGG1) ANTI P28907 (CD38\_HUMAN)[HuMaxCD38]

b. Pharmacologic category: Therapeutic recombinant human monoclonal antibody



**Submissions Reviewed:**

<b>SUBMISSION(S) REVIEWED</b>	<b>DOCUMENT DATE</b>
STN 761036/0 (1)	7/9/15
STN 761036/4 (5) (stability update)	8/7/15
STN 761036/8 (12) (IR1 response)	9/15/15
STN 761036/15 (20) (IR1 response)	9/30/15
STN 761036/18 (23) (IR2 response)	10/2/15
STN 761036/19 (24) (IR2-micro response)	10/5/15
STN 761036/20 (26) (SEC data correction)	10/5/15
STN 761036/25 (31) (IR3 response)	10/8/15
STN 761036/29 (36) (IR4 response)	10/15/15
STN 761036/31 (40) (IR6 response)	10/20/15
STN 761036/ (IR5 response)	10/16/15 via email

**Quality Review Team-Signature Page**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>	<b>e-Signature</b>
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Review Chief; DS, DP, and Immunogenicity Tertiary Reviewer	<b>Sarah Kennett</b>	<b>Division of Biotechnology Review and Research I</b>	<p><b>Sarah B. Kennett -S</b></p> <p>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: 2015.10.22 17:48:29 -04'00'</p>
Director; Executive Summary Tertiary Reviewer	<b>Kathleen Clouse</b>	<b>Division of Biotechnology Review and Research I</b>	<p><b>Kathleen A. Clouse Strebel -S</b></p> <p>Digitally signed by Kathleen A Clouse Strebel -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300054511, cn=Kathleen A Clouse Strebel -S            Date: 2015.10.22 19:07:00 -04'00'</p>

## Quality Review Data Sheet

**1. LEGAL BASIS FOR SUBMISSION: 351(a)**

**2. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>
(b) (4)	Type III	(b) (4)	(b) (4)	3	N/A
	Type III			3	N/A
	Type III			3	N/A
	Type III			3	N/A
	Type V			3	N/A

<sup>1</sup> 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")

<sup>2</sup> 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)

**B. Other Documents:** None

**3. CONSULTS:** None

## Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

##### a. Recommendation

The OPQ, CDER, recommends approval of STN 761036 for Darzalex (daratumumab) manufactured by Janssen Biotech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Darzalex (daratumumab) is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert.

##### b. Action letter language

Under this license, you are approved to manufacture daratumumab (b) (4)

You are approved to manufacture daratumumab drug substance at Janssen Biologics, Cork, Ireland. The 100 mg/vial drug product will be manufactured at Cilag A.G. Schaffhausen, Switzerland, and the 100 mg/vial and 400 mg/vial drug product will be manufactured at (b) (4)

The dating period for daratumumab drug product, 100 mg/vial and 400 mg/vial, shall be 18 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 daratumumab drug substance shall be 18 months from the date of manufacture when stored at (b) (4) °C.

The dating period for (b) (4) 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.

##### c. Benefit/Risk Considerations

Multiple myeloma is a cancer of the plasma cells that build up in the bone marrow. Although several treatment options are available for the disease, treatment options for patients who relapse or become refractory to therapeutic agents are limited. Darzalex (daratumumab) was granted fast track and breakthrough designations in April and May 2013, respectively, for

the treatment of multiple myeloma patients who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, or who are double-refractory to treatments of a PI and an immunomodulatory agent.

The overall control strategy for daratumumab manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process, release, and stability testing ensures 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 screening assay was not tolerant to the levels of daratumumab present in the clinical study serum samples. Because the development of anti-drug antibodies (ADA) to daratumumab can affect both safety and efficacy of the product, we will implement a post-marketing requirement to develop and validate screening and neutralizing activity assays that can accurately detect ADA in the presence of daratumumab levels that are expected in the serum or plasma at the time of patient sampling; a companion clinical PMR will be implemented for the testing of patient serum samples with these assays.

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

Below are draft PMRs and PMCs that are being negotiated with the applicant.

**PMR 1:** Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to daratumumab, including procedures for the accurate detection of binding antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

**PMR 2:** Conduct an assessment of the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 1 capable of sensitively detecting ADA responses in the presence of daratumumab levels that are expected to be present at the time of patient sampling.

**PMR 3:** Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to daratumumab, including procedures for the accurate detection of neutralizing antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

**PMC 1:** Perform a shipping study to confirm validation of the commercial daratumumab drug product shipping conditions. The study will include monitoring of

temperature during the shipment, testing of pre- and post-shipment samples for product quality (purity by SEC, cSDS reduced and non-reduced, cIEF, sub-visible particles, and potency of daratumumab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

**PMC 2:** Provide quantitative extractables study data and a toxicological risk assessment for all compounds extracted from the (b) (4) and drug substance long term storage containers.

**PMC 3:** Re-evaluate (b) (4) lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

**PMC 4:** Re-evaluate daratumumab drug substance lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

**PMC 5:** Re-evaluate daratumumab drug product lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

**PMC 6:** Provide data to demonstrate that the (b) (4) validation studies of (b) (4) has the same microbial growth promotion properties as daratumumab (b) (4) corresponding to (b) (4). These studies are needed to demonstrate that (b) (4) daratumumab product (b) (4) are adequate to support microbial quality.

## 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.



Executive Summary BLA 761036 Darzalex (daratumumab)



Table 1: Drug Substance API CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
CDC Activity (Potency)	Efficacy and safety	Intrinsic to the molecule Impacted by glycosylation, deamidation, oxidation, glycation, and aggregation	Potency is tested for (b) (4) DS and DP at release and during stability.	
ADCC Activity (Potency)	Efficacy and safety	Intrinsic to the molecule Impacted by glycosylation, deamidation, oxidation, glycation, and aggregation	Potency is tested for DS and DP at release and during stability.	
CD38 Binding (Potency)	Efficacy and safety	Intrinsic to the molecule Impacted by oxidation, glycation, and aggregation	CDC and ADCC, which require CD38 binding, are tested for (b) (4) DS and DP at release and during stability.	
Glycosylation (product-related species)	Efficacy (fucosylation and galactosylation impact ADCC and CDC; also some impact on FcRn binding)	Affected by (b) (4) conditions. Does not change during storage.	(b) (4) (b) (4) (b) (4) (b) (4) and DS.	
High Molecular Weight (HMW)/Aggregates (product-related)	Efficacy, PK and Safety/Immunogenicity (impact CD38 binding, FcγR binding, CDC, ADCC; also	Manufacturing process and exposure to heat, light, and high and low pH stress. Minimal increase is expected	Aggregate (b) (4) (b) (4) (b) (4)	



Executive Summary BLA 761036 Darzalex (daratumumab)



impurities)	some impact on FcRn binding)	on stability.	formulation. HMW is controlled during release and stability testing of (b) (4) DS and DP using SEC and cSDS methods. The impact on activity is also controlled through the potency tests.	
Fragmentation (product-related impurities)	Efficacy	Manufacturing process and exposure to heat, light, and high pH stress. Minimal change is expected on stability.	Fragmentation is monitored during release and stability testing of (b) (4), DS and DP using cSDS. The impact on activity is also controlled through the potency tests.	
(b) (4) (product-related impurities)	Efficacy (impacts CDC and ADCC activity, FcγR binding)	Manufacturing process and exposure to heat	Controlled by the manufacturing process and storage conditions. Controlled as charge variants during (b) (4) DS, and DP release and stability testing by cIEF. Also associated with fragmentation, therefore is partially controlled through the cSDS (b) (4) DS, and DP testing at release and stability.  Peptide mapping characterization and monitoring will be performed at DP release for re-evaluation of the control strategy after 30 lots.	
(b) (4) oxidation	Efficacy, PK and safety (impacts CD38 binding, CDC, ADCC, and FcRn	Manufacturing process and exposure to light	Controlled by the manufacturing process and storage conditions. Associated with specific charge	



Executive Summary BLA 761036 Darzalex (daratumumab)



(product-related impurities)	binding)		species, therefore partly controlled by the cIEF assay used for (b) (4) DS, and DP release and stability testing. Associated with aggregation, therefore partly controlled during (b) (4), DS, and DP release and stability testing by SEC at release and on stability.  Peptide mapping characterization and monitoring will be performed at DP release for re-evaluation of their control strategy after 30 lots.	
(b) (4) Glycation  (product-related impurities)	Efficacy (impacts CD38 binding)	Cell culture in the production  (b) (4)	Glycation is controlled by a consistent cell culture process and by release and stability testing by cIEF.	

## **B. Drug Substance [daratumumab] 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. For additional information see Appendix A and Appendix B.



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

CQA (Type)	Risk	Origin	Control Strategy	Other
Bioburden (contaminant)	Safety; product quality due to degradation or modification of product	Bioburden can be introduced during the manufacturing process	Multiple (b) (4) and release testing. DS specification acceptance criterion is $\leq$ (b) (4).	
Endotoxin (contaminant)	Safety	Endotoxin can be introduced during the manufacturing process	Controlled via the (b) (4). DS specification acceptance criterion is (b) (4).	
(b) (4) (Process-related impurity)	Safety and Immunogenicity	Process-related impurity from (b) (4)	Removal occurs at (b) (4)	
(b) (4) (Process-related)	Safety	Process-related impurity from (b) (4)	Removal occurs at (b) (4)	



Executive Summary BLA 761036 Darzalex (daratumumab)



impurity)			(b) (4)	
(b) (4) (Process-related impurity)	Safety and Immunogenicity	Process-related impurity from (b) (4)	Removal occurs (b) (4)	
(b) (4) (Process-related impurity)	Safety	Production (b) (4)	Predefined amounts are added on pre-specified days or as needed, but not to exceed (b) (4). Removal to below the assay LOQ of (b) (4)  Toxicological risk assessment confirmed LOQ level provides acceptable exposure limit.	
(b) (4) (Process-related impurity)	Safety	(b) (4)	Removal to below the assay LOQ of (b) (4)  . Toxicological risk assessment confirmed LOQ level provides acceptable exposure limit.	
(b) (4) (Process-related	Safety	Culture medium used prior (b) (4)	Removal to below the assay LOQ of (b) (4)	



Executive Summary BLA 761036 Darzalex (daratumumab)



impurity)			(b) (4) Toxicological risk assessment confirmed LOQ level provides acceptable exposure limit.	
Viruses (Contaminant)	Safety	Contamination during manufacture, most likely (b) (4)	Cell bank testing, unprocessed bulk in-process testing and validation of the manufacturing process to remove/inactivate viruses	
Mycoplasma (Contaminant)	Safety	Mycoplasma would most likely be introduced (b) (4)	Cell bank testing, unprocessed bulk in-process testing	
Leachables (Process-related impurity)	Safety	Process-related impurities due to single use plastics in manufacturing and leaching from the DS container closure system (CCS)	<p>The majority of the leachables from manufacturing components will be cleared by the process.</p> <p>Extractables studies were conducted on the (b) (4) and DS.</p> <p>Real time, accelerated, and stressed stability studies have the potential to detect leachables that impact product quality.</p> <p>Risk for leachables from the (b) (4) and DS is low because the DS and (b) (4)</p>	Submission of additional extraction study data and a toxicological risk assessment will be addressed as a PMC.

a. Description

Daratumumab is a full length recombinant, human IgG1k monoclonal antibody that binds to CD38 antigen expressed on multiple myeloma cells. Daratumumab consists of  (b) (4)



The extinction coefficient was calculated to be  (b) (4) and confirmed experimentally. This value has been used during development and will continue to be used to determine the daratumumab protein concentration.

For additional information see Appendix A.

b. Mechanism of action

The main mechanisms of action for daratumumab are the induction of complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and antibody-dependent cell-mediated cytotoxicity (ADCC) in multiple myeloma cells that overexpress CD38 antigen. CD38 antigen is expressed to varying degrees as a transmembrane glycoprotein on a number of hematopoietic cells and can act as a receptor or an ectoenzyme to induce cell signaling events leading to cell adhesion, proliferation, activation, and calcium influx. Published literature indicates that blood cancer cells, such as myeloma and leukemia cells, overexpress CD38 antigen, thus providing the rationale for daratumumab therapy in multiple myeloma patients. For additional information see Appendix A.

c. Potency Assay

Daratumumab utilizes two cell-based assays to measure potency, a CDC assay and an ADCC assay.

- CDC Bioactivity Assay:  (b) (4)



**C. Drug Product [Established Name] 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 C.

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

<b>CQA (Type)</b>	<b>Risk</b>	<b>Origin</b>	<b>Control Strategy</b>	<b>Other</b>
Sterility and Container Closure Integrity (contaminant)	Safety Efficacy (degradation or modification of the product by contaminating microorganisms)	Contaminants could be introduced during the manufacturing process or through a container closure integrity failure.	Control of (b) (4) of the (b) (4). Sterilization of equipment and components that contact the sterile product. (b) (4) validation and (b) (4) integrity testing. (b) (4) processing qualification. Control of the environment. Maintenance of container closure system integrity. Validation of assembly and shipping processes for maintenance of container closure integrity. Sterility testing of DP release and stability samples. Container closure integrity testing of DP stability samples.	
Endotoxin (contaminant)	Safety	Contamination could be introduced throughout DP manufacturing or through a container closure integrity failure.	The control strategies described for sterility also limit the introduction of endotoxin. The container closure system (b) (4). The DP is tested for endotoxin at release. The DP endotoxin specification provides a large safety margin.	



## Executive Summary BLA 761036 Darzalex (daratumumab)



Color of solution (general)	Safety and Efficacy	Formulation, contamination or degradation	Controlled through the manufacturing/formulation process and by release and stability testing	
Osmolality (general)	Safety	Formulation	Controlled through the formulation process and by release and stability testing. Osmolality is a surrogate test for excipients levels.	
Particulate Matter (product or process related impurities)	Safety/Immunogenicity	Manufacturing process and CCS	Controlled through the manufacturing process and preparation of the CCS. Controlled by release and stability testing	
Polysorbate 20 (general/critical excipient)	Safety and Efficacy (impacts aggregate)	Formulation	Controlled through the formulation process and by release and stability testing	
pH (general)	Safety and Efficacy	Formulation	Controlled through the formulation process and by release and stability testing	
Turbidity (general and process or product related impurities)	Safety	Manufacturing process and formulation	Controlled through the formulation process and by release and stability testing	
Extractable Volume (general)	Efficacy/Dosing	Manufacturing process	Controlled through the filling process and by release testing	
Protein Concentration (general)	Efficacy and Safety	Formulation	Controlled through the formulation process and by release and stability testing	
Identity (general)	Safety and Efficacy	Intrinsic to molecule	Controlled by release testing	
Leachables (process-related impurities)	Safety	Manufacturing equipment and CCS	Extractables study conducted on DP CCS. Leachables study on CCS is on-going and will continue to DP expiry.	

- a. Potency and Strength  
Daratumumab is supplied at two strengths, 100 mg/vial and 400 mg/vial. The drug product concentration is 20 mg/ml.
  
- b. Description/Commercial Image  
Daratumumab is supplied as a sterile, preservative-free solution containing daratumumab at either 100 mg per (b) (4) vial or 400 mg per (b) (4) vial. The drug product formulation consists of 25 mM acetic acid, 60 mM sodium chloride, 140 mM mannitol, and 0.04% (w/v) polysorbate 20, pH 5.5. The extractable volume of each 100 mg/vial is 5 mL and the extractable volume of each 400 mg/vial is 20 mL.
  
- c. Summary of Product Design  
Daratumumab is supplied in single-use (b) (4) vials.
  
- d. List of Excipients  
The excipients used in the formulation buffer are listed above in b.
  
- e. Reference material(s)  
The same reference material is used for drug substance and drug product.
  
- f. Manufacturing Process  
The drug product manufacturing process consists of (b) (4)  
  
  
  
Container Closure Integrity was assessed as part of validation and is included in the drug product stability program. For additional information see Appendix A and Appendix C.
  
- g. Container Closure

The primary container closure system for the drug product consists of (b) (4) glass vials for 100 mg and 400 mg strengths, respectively, (b) (4)

Appropriate compatibility studies were performed for the container closure system. For additional information see Appendix A.

h. Expiration Date & Storage Conditions

The dating period for the drug product is 18 months when stored at 2-8°C.

**D. Novel Approaches/Precedents**

None

**E. Any Special Product Quality Labeling Recommendations**

Store at 2-8°C. Protect from light. Do not freeze or shake. Once diluted with 0.9% sodium chloride solution, the infusion bag may be stored for up to 24 hours in a refrigerator at 2°C to 8°C (36°F to 46°F), protected from light, followed by additional time at room temperature for temperature equilibration prior to infusion.

**F. Establishment Information**

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Daratumumab (b) (4)	(b) (4)	(b) (4)	PLI Inspection Requested	4 Item 483	Pending Final Facility Recommendation
Process (b) (4) testing	(b) (4)	(b) (4)			
Daratumumab (b) (4) DS manufacture	Janssen Biologics (Ireland)	3007029098	PLI Inspection Requested	No 483	Pending Final Facility Recommendation
Process (b) (4) testing	Cork, Ireland				
Release testing of drug substance					
Manufacture of working cell bank	Janssen Biotech, Inc.	3001610451	Acceptable based on facility profile		
Biological and characterization assays	Malvern, PA			N/A	Approved based on facility profile
Release testing of bulk drug substance and drug product					
Bulk DS stability testing	Janssen Biologics B. V.	3002806632	Acceptable based on facility profile		
DP stability and release testing for all tests but CCIT Mycoplasma and In Vitro Assay for Adventitious Agents	Leiden, The Netherlands			N/A	Approved based on facility profile



**Executive Summary BLA 761036 Darzalex (daratumumab)**



Mycoplasma and In Vitro Assay for Adventitious Agents	(b) (4)		Acceptable based on facility profile	N/A	Approved based on facility profile
Mycoplasma and In Vitro Assay for Adventitious Agents	(b) (4)		Acceptable based on facility profile	N/A	Approved based on facility profile
DRUG PRODUCT					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
DP-100mg/ vial liquid DP release and stability testing for CCIT DP in process testing DP labelling and packaging	Cilag A G.  Schaffhausen, Switzerland	3002806695	Inspection waived- Acceptable based on facility profile	N/A	Approved based on facility profile
DP-100mg and 400mg/ vial liquid  Endotoxin and sterility	(b) (4)		Inspection waived- Acceptable based on facility profile	N/A	Approved based on facility profile
DP release testing	Janssen Biologics (Ireland)  Cork, Ireland	3007029098	PLI Inspection Requested	No 483	Pending Final Facility Recommendation
Biological and characterization assays	Janssen Biotech, Inc.  Malvern, PA	3001610451	Acceptable based on facility profile	N/A	Approved based on facility profile
DP release and stability testing for all test except CCIT	Janssen Biologics B. V.  Leiden, The Netherlands	3002806632	Acceptable based on facility profile	N/A	Approved based on facility profile
Polysorbate 20 only	(b) (4)		Acceptable based	N/A	Approved based on



Executive Summary BLA 761036 Darzalex (daratumumab)



	(b) (4)	on facility profile		facility profile
Endotoxin and sterility		Acceptable based on facility profile	N/A	Approved based on facility profile
Visual inspection only		Acceptable based on facility profile	N/A	Approved based on facility profile
Visual inspection only		Acceptable based on facility profile	N/A	Approved based on facility profile
Polysorbate 20 only		Acceptable based on facility profile	N/A	Approved based on facility profile
DP labelling and packaging		Acceptable based on facility profile	N/A	Approved based on facility profile

## G. Facilities

The subject BLA proposes manufacture of Daratumumab Drug Substance and Drug Product at the following facilities:

The drug substance is manufactured at two facilities: (b) (4)

(b) (4) Janssen Biologics 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 (b) (4). A four item Form FDA 483 was issued. The recommendation for the firm is VAI; however, the inspection is pending final classification. In addition, a Pre-license Inspection was performed at Janssen Biologics 10/5/2015 – 10/9/2015. No Form FDA 483 was issued. The recommendation for the firm is NAI; however, the inspection is pending final classification. The drug substance manufacturing and testing sites have been inspected multiple times within the recent past, demonstrating acceptable compliance.

The drug product is filled into vials at 100 mg/vial and 400 mg/vial strengths. Both strengths are filled at (b) (4)

(b) (4) Additionally the 100 mg/vial strength is filled at Cilag A. G., Schaffhausen, Switzerland (FEI: 3002806695). No inspections specific to daratumumab drug product were conducted. The compliance status of the production and testing facilities associated with the manufacture of daratumumab DP is acceptable based on recent previous inspections and district recommendation. Recent inspections of both Cilag A. G. (FEI: 3002806695) and (b) (4) (b) (4) found the establishments compliant for related product types (b) (4).

Secondary labelling and packaging is performed at Cilag A. G. (FEI: 3002806695) and (b) (4). The compliance status of the secondary labelling and packaging facilities and drug product the testing facilities were also acceptable.

For a complete summary see Appendix D.

## H. Lifecycle Knowledge Management

### a. Drug Substance

- i. Protocols approved
  1. Annual stability protocol
  2. Stability protocol for the extension of shelf-life
  3. New working cell bank qualification protocol
  4. New primary and working reference material protocol

5. Lifetime [REDACTED] <sup>(b) (4)</sup> verification protocols
  6. [REDACTED] <sup>(b) (4)</sup> verification protocols
- ii. Outstanding review issues/residual risk: All identified residual risk is mitigated through the PMCs listed above.
  - iii. Future inspection points to consider: None identified

**b. Drug Product**

- i. Protocols approved
  1. Annual stability protocol
  2. Stability protocol for the extension of shelf-life
- ii. Outstanding review issues/residual risk: All identified residual risk is mitigated through the PMCs listed above.
- iii. Future inspection points to consider: Review of raw data for the method transfers to Leiden

Janssen commits to re-evaluate specifications after data from [REDACTED] <sup>(b) (4)</sup> [REDACTED] drug substance, and drug product lots have been manufactured. These commitments are listed a post-marketing commitments.

## Quality Assessment Summary Tables

**Table 1: Noteworthy Elements of the Application**

#	Checklist	Yes	No	N/A
<b>Product Type</b>				
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 _____			
<b>Regulatory Considerations</b>				
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	x		
18.	SPOTS		x	

	(Special Products On-line Tracking System)				
19.	USAN Name Assigned		x		
20.	Other _____				
<b>Quality Considerations</b>					
21.	Drug Substance Overage			x	
22.	Design Space	Formulation		x	
23.		Process		x	
24.		Analytical Methods		x	
25.		Other			
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 _____				



## Appendices

**BLA STN 761036**

**DARZALEX<sup>TM</sup> (daratumumab)**

**Janssen Biotech, Inc.**

**Tura C. Camilli, Ph.D., Product Quality Reviewer  
Jee Chung, Ph.D., Acting Team Leader, ATL  
Division of Biotechnology Research and Review I**

# Product Quality Review Data Sheet

1. **BLA# 761036**

2. **REVIEW DATE:** October 22, 2015

3. **PRIMARY REVIEW TEAM:**

Medical Officer: Barry Miller and Albert Deisseroth [Team Leader (TL) and CDTL]  
 Pharm/Tox: Emily Place and Chris Sheth (TL)  
 Product Quality Team: Tura C. Camilli and Jee Chung (TL)  
 BMT or Facilities: Maria Jose Lopez-Barragan, Natalia Pripuzova and Patricia Hughes (TL)  
 Wayne Seifert, Laura Fontan and Steve Fong (TL)  
 Clinical Pharmacology: Jeanne Fourie Zirkelbach and Bahru Habtemariam (TL)  
 Statistics: Yaping Wang and Yuan-Li Shen (TL)  
 Pharmacometrics: Lian Ma and Nitin Mehrotra (TL)  
 OBP Labeling: Jibril Abdus-Samad  
 OBP RBPM: Anita Brown  
 RPM: Jessica Boehmer

4. **MAJOR GRMP DEADLINES:**

**Filing Meeting: September 7, 2015**  
**Mid-Cycle Meeting: September 24, 2015**  
**Wrap-Up Meeting: November 4, 2015**  
**Primary Review Due: October 18, 2015**  
**Secondary Review Due: October 22, 2015**  
**CDTL Memo Due: October 25, 2015**  
**PDUFA Action Date: November 17, 2015**

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

Communication/Document	Date
CMC Pre-BLA Meeting	December 12, 2015
IR in filing letter	September 4, 2015
Information Request #1	September 28, 2015
Information Request #2 (DMA)	September 29, 2015
Information Request #3	October 2, 2015
Information Request #4	October 10, 2015
Information Request #5	October 14, 2015
Teleconference	October 15, 2015
Information Request# 6	October 16, 2015

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

Submission	Date Received	Review Completed (Yes/No)
STN 761036/0	July 9, 2015	yes
STN 0004 /5 (stability update)	August 7, 2015	yes
STN 0008 /12 (response to IR in filing letter)	September 15, 2015	yes
STN 0015/20 (response to IR#1)	September 30, 2015	yes
STN 0018/23 (response to IR#1)	October 2, 2015	
STN 0019 /24 (response to IR#2)	October 5, 2015	yes
STN 0020 /26 (data correction)	October 5, 2015	yes
STN 0025 /31 (response to IR#3)	October 8, 2015	yes
STN 0029 /36 (response to IR#4)	October 15, 2015	yes
Teleconference	October 15, 2015	
Received via email (response to IR#5)	October 19, 2015	yes

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

- a. Proprietary Name: Darzalex
- b. Trade Name: Darzalex
- c. Non-Proprietary/USAN: daratumumab
- d. CAS name: Immunoglobulin G1, anti-(human CD38 (antigen)) (human monoclonal (b) (4))  
[REDACTED]
- e. Common name: HuMax-CD38
- f. INN Name: daratumumab
- g. Compendial Name: N/A
- h. OBP systematic name: MAB HUMAN (IGG1) ANTI P28907 (CD38\_HUMAN) [HuMaxCD38]
- i. Other Names: JNJ-54767414
- j. CAS Registry number: 945721-28-8

**8. PHARMACOLOGIC CATEGORY:** CD38 directed monoclonal antibody

**9. DOSAGE FORM:** injection, 100 mg/5 mL in a single use vial  
injection, 400 mg/20 mL in a single use vial

**10. STRENGTH/POTENCY:**

- a) The concentration of (daratumumab) Drug Product is 20 mg/ml for both the 100 mg/vial and the 400 mg/vial presentations
- b) Potency is defined as percent activity relative to the reference material, using a CDC cell based assay that measures the concentration [REDACTED] (b) (4)
- c) Potency acceptance criteria are [REDACTED] (b) (4) % of the reference material for the ADCC and CDC potency assays, respectively.
- d) Dating period for vial drug product is 18 months when stored at 2-8°C.

**11. ROUTE OF ADMINISTRATION:** Intravenous infusion

**12. RELATED/SUPPORTING DOCUMENTS:**

**REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCE D	Letter of Cross-Reference	COMMENTS (STATUS)
<div style="background-color: #cccccc; width: 100%; height: 100%; display: flex; align-items: center; justify-content: center;"> <span>(b) (4)</span> </div>			provided	No review required. Information was in the BLA or previous DMF reviews.
			provided	No review required. Information was in the BLA or previous DMF reviews.
			provided	No review required. Information was in the BLA or previous DMF reviews.
			provided	No review required. Information was in the BLA or previous DMF reviews.
			provided	No review required. Information was in the BLA or previous DMF reviews.
			provided	No review required. Information was in the BLA or previous DMF reviews.
			provided	No review required. Information was in the BLA or previous DMF reviews.

**13. INSPECTIONAL ACTIVITIES**

Two pre-approval inspections (PAI) for daratumumab drug substance manufacturing were conducted. Inspection of the (b) (4) was conducted from (b) (4) by OPF/DIA reviewers Wayne Seifert and Peter Qiu and OBP reviewer Tura Camilli. The site is responsible for (b) (4). The inspection was conducted in conjunction with the PAI inspection for BLA 761029 for daclizumab. An observation was issued regarding the (b) (4) for the daratumumab process, which was inadequately cleaned to mitigate microbial contamination. Another observation regarding both products was issued for inadequate deviation investigations and ineffective initial corrective actions with respect to several equipment leaks. The recommendation by

the inspection team is VAI. Inspection of the Cork facility (Cork, Ireland) was conducted from October 1 to October 5, 2015 by OPF/DIA reviewer Laura Fontan and OBP reviewers Milos Dokmanovic and Sarah Kennett. The site is responsible for manufacturing of drug substance (b)(4) and release testing. No 483 observation was issued at the end of the inspection. The recommendation by the inspection team is NAI. The PAI inspection for daratumumab drug product manufacturing at the Cilag and (b)(4) manufacturing facilities were waived.

**14. CONSULTS REQUESTED BY OBP**

None

**15. QUALITY BY DESIGN ELEMENTS**

Risk assessments and design of experiments based studies were used as part of process development.

**16. PRECEDENTS**

None

**17. ADMINISTRATIVE**

<b>Discipline</b>	<b>Reviewer</b>	<b>Branch/Division</b>	<b>e-Signature</b>
OBP- DS, DP, Immunogenicity	Tura C. Camilli	Division of Biotechnology Review and Research I	
Review Chief	Sarah B. Kennett	Division of Biotechnology Review and Research I	
Application Technical Lead	Jee Chung	Division of Biotechnology Review and Research I	

## SUMMARY OF QUALITY ASSESSMENTS

### I. Primary Reviewer Summary Recommendation

We recommend approval of this BLA. The data submitted in this Biologics License Application support the conclusion that the manufacture of Darzalex (daratumumab) is well controlled and leads to a product that is pure and potent. The product is free of 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 multiple production runs. It is recommended that Darzalex (daratumumab) be approved for human use (under conditions specified in the package insert).

We recommend an expiration dating period of (b) (4) months for daratumumab (b) (4) when stored at (b) (4) °C.

We recommend an expiration dating period of 18 months for daratumumab drug substance when stored at (b) (4) °C.

We recommend an expiration dating period of 18 months for daratumumab drug product when stored at 2-8°C protected from light.

### II. List Of Deficiencies To Be Communicated

None

### III. List Of Post-Marketing Commitments/Requirement

PMR 1: Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to daratumumab, including procedures for the accurate detection of binding antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMR 2: Conduct an assessment of the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 4 capable of sensitively detecting ADA responses in the presence of daratumumab levels that are expected to be present at the time of patient sampling.

PMR 3: Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to daratumumab, including procedures for the accurate detection of neutralizing antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMC1: Perform a shipping study to confirm validation of the commercial daratumumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipment samples for product quality (purity by SEC, cSDS reduced and non-reduced, cIEF, sub-visible particles, and potency of daratumumab), and

confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

PMC 2: Provide quantitative extractables study data and a toxicological risk assessment for all compounds extracted from the (b)(4) and drug substance long term storage containers.

PMC 3: Re-evaluate (b)(4) lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC 4: Re-evaluate daratumumab drug substance lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC 5: Re-evaluate daratumumab drug product lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

#### IV. Review Of Common Technical Document-Quality Module 1

##### A. Environmental Assessment or Claim of Categorical Exclusion

As specified in 21 CFR 25.15(d), Janssen states that this Biologic License Application qualifies for a categorical exclusion to the environmental assessment requirement under 21CFR 25.31(c), based on consideration of its effects when exposed to the environment. Daratumumab is considered to be a nonhazardous, biodegradable product. The environmental impact in terms of use and disposal is considered to be negligible and, therefore, does not require the preparation of an environmental assessment.

*The claim of categorical exclusion is acceptable.*

#### V. Primary Container Labeling Review

The CMC review of DP labeling was generated by Jibril Abdus-Samad, OBP.

#### VI. Review of Common Technical Document-Quality Module 3.2

The review of module 3.2 is provided below.

#### VII. Review of Immunogenicity Assays – Module 5.3.1.4

A review of the product immunogenicity assays is included at the end of the primary review document.

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### 3. QUALITY

#### 3.2.S Drug Substance

##### 3.2.S.1 General Information

###### 3.2.S.1.1 Nomenclature

- INN: daratumumab
- Chemical name: [REDACTED] (b) (4)
- USAN name: daratumumab
- Chemical Abstract Service (CAS) registry number: 945721-28-8
- CAS Index Name: Immunoglobulin G1, anti-(human CD38 (antigen)) (human monoclonal [REDACTED]) (b) (4)
- Other names: HuMax-CD38, JNJ-54767414, anti-CD38 monoclonal antibody, Human IgG1  $\kappa$  monoclonal antibody against CD38

###### 3.2.S.1.2 Structure

Daratumumab is a human recombinant IgG1 $\kappa$  monoclonal antibody that targets human CD38.

Relative molecular mass: 148,000Da

Structural formula: The amino acid sequences for the [REDACTED] (b) (4) deduced from the DNA sequence and confirmed by peptide mapping are shown below.



### 3.2.S.1.3 General Properties

Physical state: clear to pale yellow solution

pH: 5.3-5.8

Molar extinction coefficient: (b) (4) determined theoretically and verified experimentally. This extinction coefficient was used throughout product development.

### 3.2.S.2 Manufacture

#### 3.2.S.2.1 Manufacturer(s)

- Cell bank manufacture and storage:  
Janssen Biotech, Inc. I  
200 Great Valley Parkway  
Malvern, PA 19355-1307
- Cell culture, recovery, purification, and testing (b) (4) :  
(b) (4)  
(b) (4)  
Janssen Biologics (Ireland) Barnahely  
Ringaskiddy, Co. Cork, Ireland
- Testing of the bulk drug substance (formulated bulk)
  - Janssen Biologics B.V. (Stability testing)  
Einsteinweg 101  
2333 CB Leiden, The Netherlands
  - Janssen Biologics (Ireland) (Release testing)  
Barnahely  
Ringaskiddy, Co. Cork, Ireland
  - Janssen Biotech, Inc. (Biological assays and characterization assays)  
200 Great Valley Parkway  
Malvern, PA 19355-1307
- Mycoplasma and In Vitro Assay for Adventitious Agents:
  - (b) (4)
  - Janssen Biologics B.V.  
Einsteinweg 101  
2333 CB Leiden, The Netherlands

○ [Redacted] (b) (4)

The specific functions and tests performed at each site were clarified in response to the information request (IR) sent on September 4, 2015. All tests are performed at Leiden and Cork, with the exception of Polysorbate 20 testing that is performed [Redacted] (b) (4) mapping that is only performed at Cork.

### 3.2.S.2.2 Description of Manufacturing Process

#### 3.2.S.2.2. Description of manufacturing process and process controls

##### **Batch numbering system:**

An individual batch record and unique batch number is assigned for each production batch using a computerized inventory management system.

[Redacted] (b) (4)

##### **Definitions:**

In-process controls (IPCs) and process monitoring tests (PMTs) are defined by the sponsor as follows:

**In-process controls (IPCs)** are tests, checks, and measurements performed during the course of manufacturing to monitor, and if necessary, adjust the process to ensure that the resulting drug substance (DS) will meet the defined specifications. IPCs have acceptance criteria that will lead to rejection when not met; a subset of IPCs have action limits, in addition to acceptance criteria; when action limits are not met, an immediate investigation and correction is required. A number of IPCs have predefined instructions for process adjustment.

**Process Monitoring Tests (PMTs)** are tests, checks, and measurements performed during the course of manufacturing to monitor, and if necessary, adjust the process to ensure consistent process stage performance. The PMTs are subject to action limits or pre-defined instructions. When are not met, an investigation is performed before lot release.

**Reviewer comment:** Refer to section 3.2.S.2.6 for discussion of the control strategy.

**Description of the process:**

The daratumumab DS manufacturing process occurs

(b) (4)

[Redacted]

[Redacted]

(b) (4)

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

### 3.2.P.1 Description and Composition of the Drug Product - 100 mg and 400 mg

Each vial contains 100 mg or 400 mg of daratumumab in a 5 ml nominal fill volume with an excess of at least (b) (4) or in a 20 ml nominal fill volume with an excess of at least (b) (4). The container closure consists of a (b) (4) Type 1 glass vial with an (b) (4) closure and an aluminum seal with a flip-off cap. The nominal composition of daratumumab DP 100 mg is included in the table below. Both DP strengths are preservative-free and are for single-use. In both cases, the DP is administered by the intravenous route after dilution in commercially available 0.9% sodium chloride.

Table 1: Composition of 100 mg Daratumumab DP

Component <sup>a</sup>	Grade	Function	Nominal Amount per Vial (5 mL)	Concentration
daratumumab	Company Standard	Active	100 mg	20 mg/mL
Glacial acetic acid	Ph. Eur./USP/JP	(b) (4)	0.9 mg	25 mM <sup>b</sup>
Sodium acetate trihydrate	Ph. Eur./USP/JP	(b) (4)	14.8 mg	
Sodium chloride	Ph. Eur./USP/JP	(b) (4)	17.5 mg	60 mM
Mannitol	Ph. Eur./USP/JP	(b) (4)	127.5 mg	140 mM <sup>c</sup>
Polysorbate 20	Ph. Eur./NF/JPE	(b) (4)	2.0 mg	0.4 mg/mL <sup>d</sup>
Water for injection	Ph. Eur./USP/JP	(b) (4)	q.s.	q.s.

(b) (4)

q.s. = sufficient quantity

### 3.2.P.2 Pharmaceutical Development

#### 3.2.P.2.1 Components of the Drug Product

##### 3.2.P.2.1.1 Drug Substance

Table 1: Composition of Daratumumab Drug Substance

Component	Concentration <sup>a</sup>
Daratumumab	20 (b)(4) mg/mL
Sodium Acetate (b)(4)	25 mM
Sodium chloride	(b)(4)
Mannitol	(b)(4)
Polysorbate 20	0.04% w/v
Water for injection	q.s.

<sup>a</sup> Target concentrations for the active and excipients were used to produce Phase 3 clinical and process validation batches of drug substance; average measured concentrations are reported.

<sup>b</sup> (b)(4) (b)(4)

### 3.2.P.2.1.2 Excipients

The excipient in the DS and DP are the same. The selection of the excipients was based on formulation development studies (section 3.2.P.2.2.1).

### 3.2.P.2.2 Drug Product

#### 3.2.P.2.2.1 Formulation Development

During Phase 1 and 2 clinical studies, the DP (100mg/vial) was manufactured by Genmab at Vetter Langenargen, Germany. The formulation for daratumumab in these early phase clinical studies was selected based on development/screening studies performed at Genmab and consisted of 20 mg/ml daratumumab in 25mM acetate, 60 mM sodium chloride, 140 mM mannitol, (b)(4)% w/v Polysorbate 20 (PS20), pH 5.5. The DP presentation was a 100 mg vial, and it was stored at 2-8°C. The formulation for the phase 3 DP and commercial DP manufactured at Cilag AG, Switzerland and (b)(4), includes a (b)(4) concentration of PS20 (0.04% w/v).

**Early formulation screening studies:** The early formulation studies were designed to evaluate the impact of pH, ionic strength, (b)(4) type, (b)(4) on the stability of daratumumab solution. The studies were focused on ranges of pH (4-7) and osmolality (270-330 mOsm/kg). (b)(4)

(b)(4) The studies evaluated thermal stability, robustness against agitation and freeze/thaw cycles and the formulation listed above was selected. The early phase formulation resulted in a stable DP (see section 3.2.P.7).

**Studies to support development of the phase 3/commercial formulation:** The formulation changes implemented at the beginning of phase 3 and commercial development included the (b)(4) PS20 concentration from (b)(4) 0.04% (w/v); this change, which is based on a change in the DS formulation, accompanied a change in storage (b)(4). The impact of these changes on DP quality was evaluated.

**Effect of PS20 concentration on robustness of the formulation:** Studies were performed to evaluate the effect of PS20 (b)(4) on the stability of daratumumab under stress conditions (agitation and temperature).

*Reviewer comment: The results for other attributes were not included in the submission; however aggregates are the most likely to be impacted.*

### 3.2.P.8 Stability

#### 3.2.P.8.1 Stability Summary and Conclusion

The proposed shelf life for both the 100 mg/vial and the 400 mg/vial DP presentations is 18 months at 2-8°C protected from light.

**Reviewer comment:** *The proposed shelf life for the 100 mg/vial and 400 mg/vial presentations manufactured at (b) (4) are supported by the 100 mg/vial presentation manufactured at Cilag.*

**Batches manufactured at Cilag:** Available data for phase 3 clinical 100 mg/vial DP batches stored under recommended long term conditions (2-8°C) include up to 18 months for three 100 mg/vial batches, 12 months for two batches and 9 months for one batch. In addition, up to 6 months of data are available for three 100 mg/vial process validation batches. Up to 12 months of data are available for five of the phase 3 clinical 100 mg/vial DP batches and up to 6 months for one batch stored under accelerated conditions (25°C). Up to 6 months of data are also available for all three validation batches stored under accelerated conditions. Data for up to 6 months under stress conditions (40°C) are available for all phase 3 batches.

**Batches manufactured at (b) (4):** Available data for phase 3 clinical DP batches stored under recommended long term conditions include up to 9 months for one 100 mg/vial phase 3 clinical batch and one 400 mg/vial phase 3 clinical batch. In addition, up to 12 months of data are available for one phase 3 engineering batch of the 100mg/vial DP and one 400mg/vial DP, and up to 6 months of data are available for three 100 mg/vial and three 400 mg/vial validation

batches. Up to 6 months of data are available for all clinical and engineering batches (100 mg/vial and 400 mg/via) stored under accelerated and stressed conditions. Up to 6 months of data are also available for one of the 100mg/vial validation batches and for two of the 400mg/vial validation batches. For all other validation batches, up to 3 months data are available. Supportive stability data are also included for phase1/2 clinical batches through 36 months at 2-8°C.

**Reviewer comment:** *A simple stability update was provided within 30 days of the original submission of the BLA.*

The following studies were also performed:

**Photostability studies:** Samples were exposed to not less than 1.2 million lux hrs of cool white fluorescent and 200 watt hrs/m<sup>2</sup> of near UV light for a total of 140 hours at 25°C in a surrogate market package or without packaging.

**Temperature cycling study:** The study was conducted by subjecting DP batch EIS2U/EIS02 stored for <6 months at 2-8°C to 3 temperature cycles followed by storage under recommended conditions. One temperature cycle consisted of storage at -20°C for no less than 3 days followed by storage at 2-8°C for one day.

#### Summary of results:

**Recommended storage conditions:** The data show that the three phase 3 clinical 100 mg/vial batches manufactured at Cilag remain within the acceptance criteria through 18 months under the recommended storage condition. The data through 9 months and 12 months for the other clinical 100 mg/vial DP are also within the acceptance criteria through these time points. Very little change in quality attributes was observed under these storage conditions. Levels of aggregates increased from (b)(4)%, with corresponding decreases in % monomer, and % monomer by cSDS (reduced and non-reduced) decreased from (b)(4)%. The 100 mg/vial and the 400 mg/vial batches manufactured at (b)(4) also remained within the acceptance criteria after 9 months under the recommended storage conditions. Levels of aggregates were also increased (b)(4)% with corresponding decreases in % monomer. No other notable changes were observed.

**Accelerated conditions:** The data included show that for phase 3 clinical 100 mg/vial batches manufactured at Cilag, there was a (b)(4)% increase in acidic variants, a (b)(4)% decrease in main charge variants, and a (b)(4)% increase in basic variants after 12 months of storage. Decreases in purity by cSDS reduced ((b)(4)%) and non-reduced ((b)(4)%) were measured after 12 months, as well as decrease in monomer ((b)(4)%), (b)(4)%) and increases in fragments ((b)(4)%) after 12 months storage. ADCC activity was decreased by (b)(4)% and CDC activity by (b)(4)% after 12 months. The same changes, within similar ranges, were observed for the batches manufactured at (b)(4).

**Stressed temperature conditions:** (b)(4)  
(b)(4)% decrease in main charge variants and a (b)(4)% increase in acidic variants after 6 months of storage. Decreases in purity by cSDS reduced ((b)(4)%) and non-reduced ((b)(4)%) were measured after 6 months, as well as increases in aggregates ((b)(4)%) and fragments ((b)(4)%) after 6 months storage. CDC activity was decreased by (b)(4)% and

ADCC activity by (b) (4) % after 6 months storage. The same changes and similar ranges were observed for the batches manufactured at (b) (4).

**Photostability studies:** The data showed that while all attributes remained unchanged when the samples were shielded from exposure to light, changes in color of the solution and in the results from SE-HPLC, cSDS reduced and non-reduced, potency, cIEF and peptide mapping were observed in the samples exposed to light. As is described in section 3.2.P.5.5, levels of translucent particles were also increased following exposure to light.

**Reviewer comment:** *Data were not included for these studies; however, data for photostability studies were provided as part of the development studies. As described in section 3.2.P.3.3, a number of steps were implemented to reduce exposure to light during the manufacturing process at both Cilag and (b) (4).*

**Temperature cycling study:** The data showed that temperature cycling had no effect on product quality [CD 38 binding, CDC and ADCC activities, protein concentration, purity (SE-HPLC and cSDS reduced and non-reduced), charge variants (cIEF), color of the solution, pH, subvisible and visible particles, turbidity and peptide mapping].

### 3.2.P.8.2 Post-Approval Stability Commitment

The sponsor commits to continuing the stability studies for the 100 mg/vial phase 3 clinical DP batches and 400 mg/vial DP batches through 36 months at 2-8°C and through 12 months at 25°C. The sponsor also commits to continuing the stability studies through 36 months at 2-8°C and through 12 months at 25°C for all validation batches and through 6 months at 40°C for specific validation batches. The sponsor commits to placing one DP batch on the stability monitoring program under long term storage conditions (2-8°C) every year that a DP batch is manufactured.

**Reviewer comment:** *In response to the IR sent on 10/02/15, the sponsor confirmed that the stability protocol is intended to support a shelf life (b) (4) months. The sponsor also confirmed that the commitment to placing one batch of 100 mg DP on stability annually includes one batch manufactured at each site ((b) (4) and Cilag). Section 3.2.P.8 was updated with this information.*

The specifications are the same as for release with the exception that appearance, osmolality, visible particles, extractable volume and identity are only tested at release. Refer to section 3.2.P.5.1 for release and stability specifications. Confirmed out of specification (OOS) results obtained for stability samples under recommended storage conditions will be reported to the Agency.

### 3.2.P.8.3 Stability Data

Refer to section 3.2.P.8.1 above.

### 3.2.A Appendices

### 3.2.A.2 Adventitious Agents Safety Evaluation

The virus inactivation/clearance studies were performed using four model viruses. The viruses used, their properties and the steps at which their inactivation/clearance were studied are listed in the table below.

Table 2: Viruses Studied

Virus	Genome	Envelope	Family	Size (nm)	Chemical Resistance	Step used
(b) (4)						

**Reviewer comment:** *The selection of the model viruses represents an appropriate variety of virus types.*

The viral clearance studies were performed at (b) (4). Studies to determine indicator cell cytotoxicity and potential viral interference and viral genome recovery for PCR detection were performed. The abilities of the (b) (4) inactivate /clear viruses was evaluated using scale down models. The parameters were adjusted to provide worst case conditions in terms of clearance for each of the steps. (b) (4)

The raw materials used for the small scale models were equivalent to those used during commercial manufacturing, (b) (4) with the model viruses were representative of the manufacturing process.



***SUMMARY OF POST-MARKETING COMMITMENTS:***

See summary at the beginning of the review document.



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

**Date:** 10/19/15  
**To:** Administrative File, STN 761036/0  
**From:** Maria Jose Lopez Barragan, PhD., Reviewer, CDER/OPQ/OPF/DMA/BIV  
**Through:** Patricia F. Hughes, PhD., Acting Branch Chief, CDER/OPQ/OPF/DMA/BIV  
**Subject:** New Biologic License Application (BLA)  
**US License:** 2018  
**Applicant:** Janssen Research & Development, LLC  
**Facilities:** Biogen Inc., Research Triangle Park, NC; FEI: 3000719749  
Janssen Biologics (Ireland), Ringaskiddy, Cork, Ireland; FEI: 3007029028  
**Product:** Daratumumab (DARZALEX<sup>®</sup>)  
**Dosage:** 100 mg/vial and 400 mg/vial in sterile liquid solution for intravenous injection  
**Indication:** Treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or are double refractory to a PI and an IMiD  
**Due date:** 11/17/2016

**Recommendation for approvability:** The drug substance part of BLA 761036 is recommended for approval from a microbial control and microbiology product quality perspective.

There is one post-marketing commitment:

1. Provide data demonstrating that the (b) (4) validation studies of (b) (4) has the same microbial growth promotion properties than the daratumumab (b) (4). Sponsor has agreed to complete these studies by 06/30/2016.

### Summary

Janssen Research & Development, LLC has submitted BLA 761036 to obtain approval of daratumumab. Daratumumab is a fully human immunoglobulin G1k monoclonal antibody (HuMax-CD38) that binds an extracellular domain on the transmembrane glycoprotein CD-38, which is overexpressed in plasma cells of patients with multiple myeloma.

BLA 761036 was submitted in eCTD format as a rolling BLA. The original application was submitted on 06/05/2015 and contained a partial module 5. Module 4 was submitted on 06/15/2015 under supplement sequence 0001 and modules 1, 2, 3 and remaining module 5 were submitted on 07/09/2015 under supplement sequence 0002.

This review contains the assessment of daratumumab bulk drug substance from a microbiological quality perspective.

### Drug Substance Quality Microbiology Information Reviewed

Information Request Date	Document Type	eCTD Sequence	Date
Not applicable	Original BLA	0002	07/09/2015
09/04/2015	Amendment	0008	09/15/2015
09/29/2015	Amendment	0019	10/05/2015
10/02/2015	Amendment (question 5c)	0025	10/08/2015
10/14/2015	Amendment	N/A	10/18/2015*

N/A: Not applicable (eCTD sequence not available at the time of completion of this review). \*: date in which responses were received by the Agency.

## 3.2.S DRUG SUBSTANCE

### S.1 General Information

Daratumumab is a human monoclonal immunoglobulin G1 (IgG1) targeted against CD-38 a transmembrane glycoprotein that functions as a receptor and as ectoenzyme and which is overexpressed in plasma cells of multiple myeloma patients. Daratumumab contains (b) (4).

*The description is satisfactory*

### S.2 Manufacture

#### S.2.1 Manufactures

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

Site	Responsibilities
(b) (4)	<ul style="list-style-type: none"> <li>Drug substance manufacturing (b) (4)</li> <li>DS in-process testing</li> </ul>
Janssen Biologics (Ireland), Barnahely, Ringaskiddy (Cork), Ireland FEI: 3007029028	<ul style="list-style-type: none"> <li>Drug substance manufacturing (b) (4)</li> <li>DS in-process testing</li> <li>Testing of formulated DS bulk</li> </ul>
Janssen Biotech, Inc., 200 Great Valley Parkway, Malvern, PA FEI: 3001610451	<ul style="list-style-type: none"> <li>Testing of formulated DS bulk</li> </ul>

Janssen Biologics B.V., Einsteinweg 101, 2333 CB, Leiden, The Netherlands FEI: 3002806632	<ul style="list-style-type: none"><li>• Testing of formulated DS bulk</li></ul>
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**S.2.2 Description of Manufacturing Process and Process Controls**

Daratumumab DS is manufactured in (b) (4)

[Redacted]

[Redacted] (b) (4)

*The description is satisfactory*

[Redacted] (b) (4)

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Maria Jose Lopez Barragan, Primary Reviewer

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Patricia Hughes, Acting Branch Chief



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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

## PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

**REVIEWER:** Natalia Pripuzova, Ph.D.

**ACTING BRANCH CHIEF:** Patricia Hughes, Ph.D.

Date: 08 October, 2015

BLA: 761036

Applicant: Janssen Biotech, Inc.

US License Number: 1864

Submission Reviewed: Original BLA (Breakthrough Therapy Designation)

Product: Daratumumab (HuMax®-CD38, human IgG1κ monoclonal antibody)

Indication: Treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or are double refractory to a PI and an IMiD

Dosage Form: 100 mg/vial and 400 mg/vial, sterile liquid solution for infusion supplied in vials, intravenous

Manufacturing Sites: Cilag A.G., Hochstrasse 201, 8200 Schaffhausen, Switzerland (FEI: 3002806695); (b) (4)

FDA Receipt Date: 09 July 2015

Action Date: 17 November 2015

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**Approvability Recommendation:** The BLA was reviewed from drug product quality microbiology prospective and recommended for approval.

**Summary:** BLA761036, Module 3, “Quality”, was submitted in electronic format on 09-July-2015 as a part of the rolling submission to license daratumumab for treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or are double refractory to a PI and an IMiD. Daratumumab (HuMax-CD38) is a monoclonal antibody which specifically binds an epitope of the CD38 molecule present on the extracellular surface. Given the multiple effects of CD38, daratumumab functions as a targeted immunotherapy. The concentrated (b) (4) is manufactured by (b) (4). The drug substance (DS) is manufactured in Cork, Ireland. The Drug product (DP) is manufactured by Cilag A.G. in Schaffhausen, Switzerland (100mg/vial) and (b) (4) (100 and 400 mg/vial). The daratumumab DP is supplied as a sterile, 20 mg/mL liquid concentrate for infusion in two presentations: 100 mg/vial and 400 mg/vial. It is intended for administration by the intravenous (IV) route after dilution in commercially available 0.9% sodium chloride.

## **Product Quality Microbiology Assessment: Drug Product**

### **Drug Product Quality Microbiology Information Reviewed**

<b>Sequence number</b>	<b>Date</b>	<b>Description</b>
0002	09 July 2015	Original BLA, Module 3
0004	07 August 2015	3.2.P.8 Stability data
0008	15 September 2015	Response to IR

## **Drug Product Review**

### **Module 3.2**

#### **P.1 Description and Composition of the Drug Product**

The daratumumab DP is supplied as a sterile, 20 mg/mL liquid concentrate for infusion in two dosage forms 100 mg/vial and 400 mg/vial. Each vial contains 100 mg of daratumumab in a 5 mL nominal fill volume and an excess volume of at least (b) (4) or 400 mg of daratumumab in a 20 mL nominal fill volume and an excess volume of at least (b) (4). The primary packaging consists of a (b) (4) Type 1 or (b) (4) Type 1 glass vial with an (b) (4) closure and an aluminum seal with a flip-off cap. The DP contains no preservative and is for single use only. The DP is intended for administration by the intravenous (IV) route after dilution in commercially available 0.9% sodium chloride. The nominal composition of the DP along with the function and grade of the excipients used in preparation of the DP are shown in two tables copied below from the submission.

Table 1: Composition of 100 mg Daratumumab DP

Component <sup>a</sup>	Grade	Function	Nominal Amount per Vial (5 mL)	Concentration
daratumumab	Company Standard	Active	100 mg	20 mg/mL
Glacial acetic acid	Ph. Eur./USP/JP	(b)(4)	0.9 mg	25 mM <sup>b</sup>
Sodium acetate trihydrate	Ph. Eur./USP/JP	(b)(4)	14.8 mg	
Sodium chloride	Ph. Eur./USP/JP	(b)(4)	17.5 mg	60 mM
Mannitol	Ph. Eur./USP/JP	(b)(4)	127.5 mg	140 mM <sup>c</sup>
Polysorbate 20	Ph. Eur./NF/JPE	(b)(4)	2.0 mg	0.4 mg/mL <sup>d</sup>
Water for injection	Ph. Eur./USP/JP	(b)(4)	q.s.	q.s.

(b) (4)

(b) (4)

q.s. = sufficient quantity

Table 1: Composition of 400 mg Daratumumab DP

Component <sup>a</sup>	Grade	Function	Nominal Amount per Vial <sup>c</sup> (20 mL)	Concentration
daratumumab	Company Standard	Active	400 mg	20 mg/mL
Glacial acetic acid	Ph. Eur./USP/JP	(b)(4)	3.7 mg	25 mM <sup>b</sup>
Sodium acetate trihydrate	Ph. Eur./USP/JP	(b)(4)	59.3 mg	
Sodium chloride	Ph. Eur./USP/JP	(b)(4)	70.1 mg	60 mM
Mannitol	Ph. Eur./USP/JP	(b)(4)	510.0 mg	140 mM <sup>d</sup>
Polysorbate 20	Ph. Eur./NF/JPE	(b)(4)	8.0 mg	0.4 mg/mL <sup>e</sup>
Water for injection	Ph. Eur./USP/JP	(b)(4)	q.s.	q.s.

(b) (4)

q.s. = sufficient quantity

*Reviewer's comment: This information is provided in this review memo for reference.*

## P.2 Pharmaceutical Development

### P.2.5 Microbiological Attributes

#### Container Closure Integrity

Using the blue dye immersion test, samples from 3 Clinical batches of 100 mg/vial DP and 3 Process Validation batches of 400 mg/vial DP were evaluated for container closure integrity (CCI). The results for 100 mg/vial (Table 1, batches DHS4G, etc.) and 400 mg/vial DP at Cilag (Table 1, batches CDNJ02, etc.) and for 100 mg/vial at (b)(4) (Table 2) are copied below from the submission. No blue dye was observed in any samples tested. All positive controls exhibited blue dye ingress and the negative controls had no blue dye present.

Table 1: Blue Dye Immersion CCIT Results

Batch	Number of Vials Tested	Number of Failures <sup>a</sup>	Result
DHS4G	315	0	Pass
DJS5G	315	0	Pass
DLS0H	315	0	Pass

<sup>a</sup> Vials must not show any blue dye ingress

Table 1: Blue Dye Immersion CCIT Results

Batch	Number of Vials Tested	Number of Failures <sup>a</sup>	Result
CDNJ02	108	0	Pass
CDNJ032	50	0	Pass
CDNL051	50	0	Pass

<sup>a</sup> Any visual incursion of blue dye into the test unit constitutes a failure

Table 2: Blue Dye Immersion CCIT Results

Batch	Number of Vials Tested	Number of Failures <sup>a</sup>	Result
CDNJ031	52	0	Pass
CDNK04	78	0	Pass
CDNL052	78	0	Pass

<sup>a</sup> Any visual incursion of blue dye into the test unit constitutes a failure

### Container Closure Integrity after Shipment

Samples from a Process Validation batch of 100 mg DP and 400 mg DP were evaluated by CCI test (CCIT) following a simulated transport study, which included distribution hazards representative of the anticipated commercial shipping lanes (air and ground). DP vials were packed into qualified 2–8°C shippers and subjected to a simulated transportation sequence. The results are presented in Tables 3 (100 mg DP) and 2 (400 mg DP) copied below from the submission and confirm the integrity of the DP.

Table 3: CCIT by Blue Dye Immersion Results After Simulated Transportation Sequence<sup>a</sup>

Batch	Number Tested	Number of Failures	Container Integrity
<sup>(b) (4)</sup> Batch CDNL052	20	0	Passed

<sup>a</sup> Samples were tested according to the validated procedure described in 3.2.P.5.2, Analytical Procedures, Container Closure Integrity, which is also used for stability monitoring.

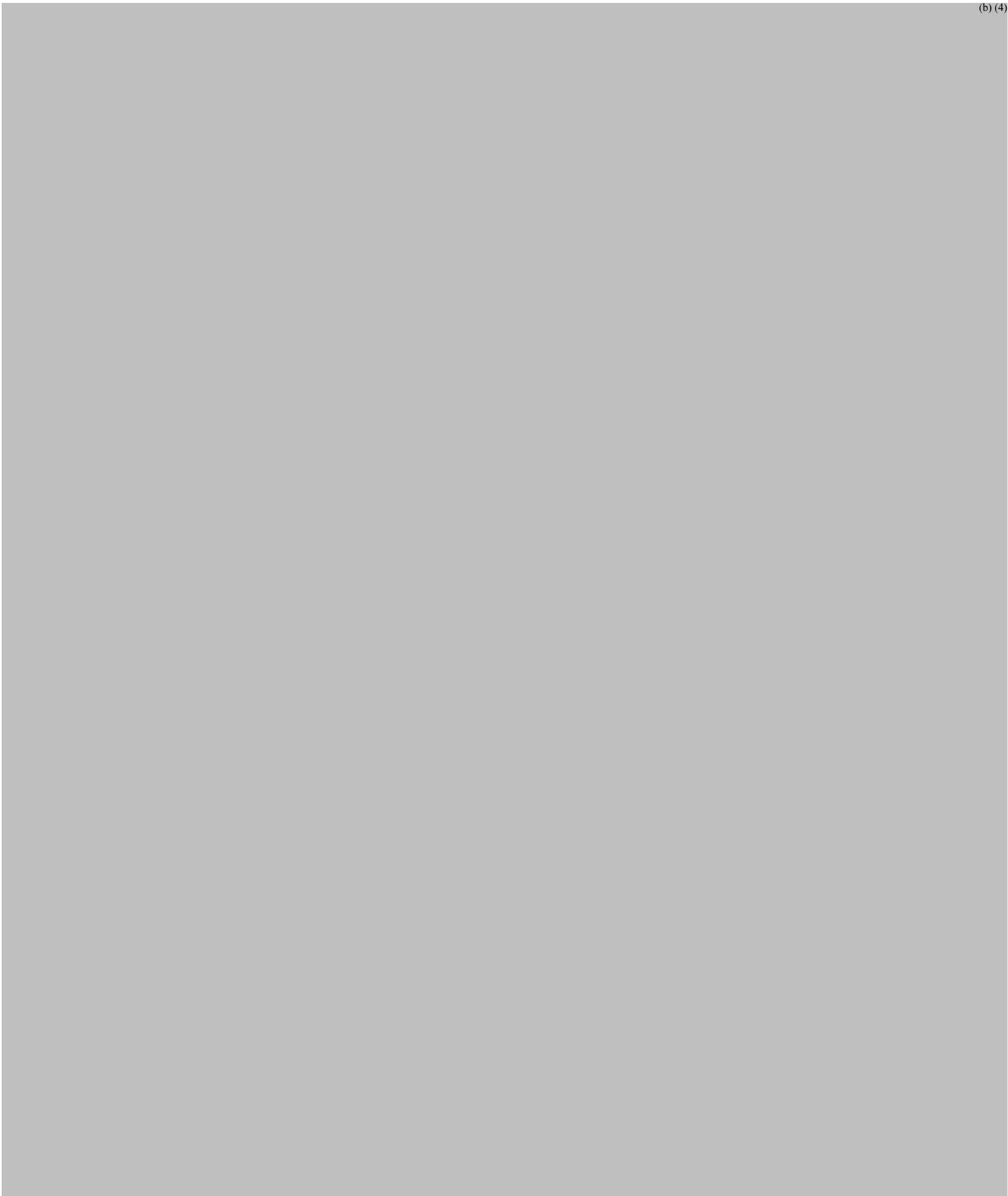
Table 2: CCIT by Blue Dye Immersion Results After Simulated Transport Sequence<sup>a</sup>

Batch	Number of Vials Tested	Number of Failures	Result
<sup>(b) (4)</sup> Batch CDNL051	20	0	Pass

<sup>a</sup> Samples were tested according to the validated procedure described in 3.2.P.5.2, Analytical Procedures, Container Closure Integrity, which is also used for stability monitoring.

### Blue Dye Immersion Test—Cilag

<sup>(b) (4)</sup>



***Reviewer's comment:** The results of the study confirmed that the container closure system used for the packaging of DP passed the CCIT. Additional information on CCIT method and the method validation are reviewed under P.5.3, Validation of Analytical Procedures.*

#### SATISFACTORY

### **Microbiology Data in Support of the Proposed Label Storage Statement**

The microbial growth challenge study was performed to evaluate microbial growth in the dilute DP over the specified hold time. The studies were performed using 100 mg/vial DP as a representation for both vial strengths (both containing 20 mg/ml of DP). The study was conducted using a final compounded solution based on average patient dose (~2.4 mg/mL protein concentration after dilution in saline) and a representative infusion container type (b) (4) bag). The challenge was performed using (b) (4) cfu/mL of five USP <51> microorganisms plus a typical skin contaminant isolated from the environment. These preparations held at refrigerated conditions (2-8°C) for 48 hours immediately followed by room temperature (RT) (20-25°C) for 48 hours. Additionally, microbial growth was studied for 48 hours at RT only. Testing was performed at several time points covering at least twice the required in-use hold time. The final compounded solutions for administration were evaluated for their bacteriostatic/fungistatic properties and relative resistance to microbial proliferation. The results of the microbial challenge study are presented in Tables 9 and 10 copied below from the submission.

Table 9: In-use Microbial Challenge Data at Refrigerated Condition and Followed by 48 Hours at Room Temperature Storage

Organism	Initial Count (cfu/mL)	Log of Initial Count (Positive Control)	48 hours at Refrigerated Condition (2-8 °C)													
			Followed by 48 hours at Room Temperature (20-25 °C)													
			0 (Refrigerated)		8 (Refrigerated)		24 (Refrigerated)		48 (Refrigerated)		60 (48 h Refrigerated + 12 h RT)		72 (48 h Refrigerated + 24 h RT)		96 (48 h Refrigerated + 48 h RT)	
log	logΔ	log	logΔ	log	logΔ	log	logΔ	log	logΔ	Log	logΔ	log	logΔ			
<i>S. aureus</i>																
<i>S. warneri</i>																
<i>P. aeruginosa</i>																
<i>E. coli</i>																
<i>C. albicans</i>																
<i>A. brasiliensis</i>																

<sup>a</sup> Failing result, i.e., log increase >0.5 log<sub>10</sub> unit higher compared to positive control occurred after 48 hours refrigerated + 48 hours room temperature storage, which is greater than 2x intended hold times of 24 hours refrigerated + 12 hours room temperature.

logΔ = log increase calculated from non-rounded values; negative results correspond to decrease compared to initial count  
RT = Room temperature

Table 10: In-use Microbial Challenge Data at Room Temperature

Organism	Initial Count (cfu/mL)	Log of Initial Count (Positive Control)	48 hours at Room Temperature (20-25 °C)													
			0		4		8		12		24		30		48	
			log	logΔ	log	logΔ	log	logΔ	log	logΔ	log	logΔ	Log	logΔ	log	logΔ
<i>S. aureus</i>																
<i>S. warneri</i>																
<i>P. aeruginosa</i>																
<i>E. coli</i>																
<i>C. albicans</i>																
<i>A. brasiliensis</i>																

<sup>a</sup> Failing result, i.e., log increase >0.5 log<sub>10</sub> unit higher compared to positive control occurred after 48 hours room temperature storage, which is greater than 2x intended hold times of 12 hours room temperature storage.

logΔ = log increase calculated from non-rounded values; negative results correspond to decrease compared to initial count

No increase in number (not more than 0.5 log<sub>10</sub>) was shown for all microorganisms when stored at RT for 24 hours or when stored refrigerated for 48 hours followed by 24 hours at RT. *E. coli* exceeded 0.5 log<sub>10</sub> increase, but only after storage times (48 hours refrigerated followed by 48 hours at RT, or 48 hours RT alone), which is twice greater than the intended allowable hold times. The results support the total in-use time of 24 hours refrigerated and 12 hours at room temperature for DP in 0.9% saline infusion bags.

The impact of bag size, which may result in variation of oxygen level in the head space, and IV bag (b)(4) type on microbial growth, was also studied and the results are presented in Tables 11 and 12 copied below from the submission. Daratumumab formulation buffer (placebo) was used instead of DP solution and only the room temperature condition was evaluated, as a worst case. The results demonstrated that, for all bag sizes and (b)(4) types, microbial growth over 48 hours at RT is less than 0.5 log<sub>10</sub> relative to the initial count for all microorganisms.

Table 11: Microbial Challenge Data for Placebo Diluted in 0.9% Saline IV Bags (of PVC) at Room Temperature

Organism	Bag Size (mL)	48 hours at Room Temperature (20-25 °C)	
		Log Differential Relative to T = 0 At 24 h	Log Differential Relative to T = 0 At 48 h
<i>S. aureus</i>			(b) (4)
<i>S. warneri</i>			
<i>P. aeruginosa</i>			
<i>E. coli</i>			
<i>C. albicans</i>			
<i>A. brasiliensis</i>			

Table 12: Microbial Challenge Data for Placebo Diluted in 500 mL 0.9% Saline IV Bags at Room Temperature

Organism	(b) (4) Type (mL)	48 hours at Room Temperature (20-25 °C)	
		Log Differential relative to T = 0 At 24 h	Log Differential relative to T = 0 At 48 h
<i>S. aureus</i>			(b) (4)
<i>S. warneri</i>			
<i>P. aeruginosa</i>			
<i>E. coli</i>			
<i>C. albicans</i>			
<i>A. brasiliensis</i>			

**Reviewer's comments:** Sponsor simulated potential contamination during dilution/preparation, hold, and infusion. The results support the total in-use time of DP at concentration of 2.4 mg/mL of 12 hours at room temperature with or without 24 hours prior refrigeration for daratumumab DP in 0.9% saline infusion bag. Sponsor has provided sufficient information on the growth promotion of the diluted DP to support labeling (additionally discussed in Module 1, Labeling Review).

SATISFACTORY

### P.3 Manufacture

#### P.3.1 Manufacturers

Manufacture of the drug product is performed at the following facilities:

100 mg

Cilag A.G.  
Hochstrasse 201  
8200 Schaffhausen  
Switzerland  
FEI: 3002806695

100 and 400 mg

(b) (4)

Testing may be performed at the following facilities:

Cilag A.G.  
Hochstrasse 201  
8200 Schaffhausen  
Switzerland  
FEI: 3002806695

(b) (4)

Janssen Biologics B.V.  
Einsteinweg 101  
2333 CB Leiden  
The Netherlands  
FEI: 3002806632

Janssen Biotech, Inc.  
200 Great Valley Parkway  
Malvern, PA 19355-1307  
USA  
FEI: 3001610451

(b) (4)

(b) (4)

Janssen Biologics (Ireland)  
Bamahely  
Ringaskiddy Co. Cork  
Ireland  
FEI: 3001610451

Secondary packaging of the drug product is performed at the following facilities:

Cilag A.G.  
 Hochstrasse 201  
 8200 Schaffhausen  
 Switzerland  
 FEI: 3002806695

(b) (4)

### P.3.2 Batch Formula

The target composition and theoretical vial output for the minimum and maximum DP batch sizes at 20 mg/mL daratumumab are provided in tables copied below from the submission.

#### Cilag:

Table 1: Target Quantitative Ingredient Statement for the Drug Product (100 mg/vial) for Minimum (b) (4) and Maximum (b) (4) Batch Sizes

Ingredient <sup>a</sup>	Reference	Minimum Batch Size, (b) (4) (g)	Maximum Batch Size, (b) (4) (g)
Daratumumab			(b) (4)
Glacial acetic acid	USP/Ph. Eur./JP		
Sodium acetate trihydrate	USP/Ph. Eur./JP		
Sodium chloride	USP/Ph. Eur./JP		
Mannitol	USP/Ph. Eur./JP		
Polysorbate 20	NF/Ph. Eur./JPE		
Water for injection, q.s. to	USP/Ph. Eur./JP		
Theoretical number of vials (100 mg/vial) <sup>b</sup>			

<sup>a</sup> (b) (4)

<sup>b</sup> Batch sizes are approximations

(b) (4) :

Table 1: Target Quantitative Ingredient Statement for the Drug Product (100 and 400 mg/vial) for Minimum (b) (4) and Maximum (b) (4) Batch Sizes

Ingredient <sup>a</sup>	Reference	Minimum Batch Size, (b) (4) (g)	Maximum Batch Size, (b) (4) (g)
Daratumumab			(b) (4)
Glacial acetic acid	USP/Ph. Eur./JP		
Sodium acetate trihydrate	USP/Ph. Eur./JP		
Sodium chloride	USP/Ph. Eur./JP		
Mannitol	USP/Ph. Eur./JP		
Polysorbate 20	NF/Ph. Eur./JPE		
Water for injection, q.s. to	USP/Ph. Eur./JP		
Theoretical number of vials (100 mg/vial) <sup>b</sup> :			
Theoretical number of vials (400 mg/vial) <sup>b</sup> :			

<sup>a</sup> (b) (4)

<sup>b</sup> Batch sizes are approximations

### P.3.3 Description of the Manufacturing Process and Process Controls

The 100 and 400 mg/vial DP for intravenous infusion (IV) is manufactured from 20 mg/mL DS at Cilag AG, Schaffhausen, Switzerland or (b) (4). The DS is stored (b) (4) bottles. The manufacturing process consists of (b) (4)

### **P.8.3 Stability Data**

Stability data for the 100 mg DP Phase 3 clinical Batches DHS55/DHS4G, DKS2Q/DJS5G, DLS0X/DLS0H, EDS1B/EDS0P, EDS5J/EDS4B, EIS3U/EJS00, VVNF68, and CDNI012 stored at the recommended (5°C) temperature condition, accelerated temperature (25°C/60% RH), and stressed temperature conditions (40°C/75% RH) are presented.

Stability data for the 400 mg drug product (DP) Phase 3 clinical Batches VVNF79 and CDNI011 stored at the recommended (5°C) temperature condition, accelerated temperature (25°C/60% RH), and stressed temperature conditions (40°C/75% RH) are presented.

Stability data for the 100 mg drug product (DP) process validation Batches CDNJ02, CDNJ032, and CDNL051 stored at the recommended (5 °C) temperature condition, accelerated temperature (25 °C/60% RH), and stressed temperature conditions (40 °C/75% RH) are presented. Stability samples were stored in inverted positions.

***Reviewer's comments:** CCIT, Sterility and Endotoxin tests results are available for initial time point and 12 months point of the long-term storage at 2-8°C, and for initial time point only for accelerated temperature (25°C/60% RH), and stressed temperature conditions (40°C/75% RH) for the 100 mg DP Phase 3 clinical batches. There have been no out of specification results. The remainder of the stability data should be reviewed by OBP.*

## **Module 1**

### **Labeling Review: Prescribing Information**

The daratumumab DP is supplied as a sterile, 20 mg/mL liquid concentrate for infusion in two dosage forms 100 mg/vial and 400 mg/vial: 100 mg/5 mL in a single use vial for intravenous infusion and 400 mg/20 mL in a single use vial for intravenous infusion. The vials should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F).

The prescribing information indicates that, using aseptic technique, a volume equal to the required volume of DARZALEX (daratumumab) solution of 0.9% Sodium Chloride have to be removed from the infusion bag/container. The necessary amount of DARZALEX solution has to be withdrawn and diluted to the appropriate volume by adding to the infusion bag/container containing 0.9% Sodium Chloride. Any unused portion left in the vial should be discarded. Following dilution the infusion bag/container may be stored for up to 24 hours at refrigerated conditions, protected from light. After allowing the bag/container to come to room temperature, DARZALEX solution has to be used immediately. Infusion should be completed within <sup>(b)</sup><sub>(4)</sub> hours. Any unused portion of the infusion solution should not be used.

***Reviewer's comment:** Data on the potential contamination during infusion preparation of daratumumab infusions in 0.9% sodium chloride injection (NS) in infusion bags were described and reviewed under **Section P.2.5.2, Microbiology Data in Support of the Proposed Label Storage Statement**. The results support the total in-use time of DP at concentration of 2.4 mg/mL of <sup>(b)</sup><sub>(4)</sub> hours at room temperature with or without 24 hours prior refrigeration for daratumumab DP in 0.9% saline infusion bag. Enough information is provided on the growth promotion of the reconstituted and diluted DP to support labeling.*

SATISFACTORY

## Conclusion

- I. The BLA was reviewed from a product quality microbiology perspective and is recommended for approval.
- II. Product quality aspects other than microbiology should be reviewed by OBP.
- III. No inspection follow-up items were identified.

## DP Quality Microbiology Information Requests Sent

### 04 September 2015 – response in amendment 0008

- 1) Provide the worst-case (b)(4) process parameters validated with CCIT in comparison to the parameters used for routine production (Section 3.2.P.2.5). Indicate which CCIT method was used to qualify (b)(4) process parameters.
- 2) Provide the sample volume for the bioburden test performed for DS (b)(4)  
(b)(4)
- 3) Submit the (b)(4) validation data and information for Cilag and (b)(4) Drug Product processes (in section 3.2.P.3.5).
- 4) Shipping validation studies should be provided in section 3.2.P.3.5.
- 5) The current acceptance criterion for endotoxin is set at (b)(4) (3.2.P.5.6). This is based on the (b)(4) endotoxin limit of (b)(4) and the (b)(4) dose of Drug Product (DP) of 24 mg/kg. However, the daratumumab DP is intended for administration by the intravenous (IV) route after dilution in commercially available 0.9% sodium chloride. No sodium chloride solution contribution was considered during the endotoxin specification limit calculation (Section 3.2.P.5.6). A (b)(4) safety factor is recommended for the commercial endotoxin release specification. Taking into account that the endotoxin levels at release and during stability of DP at 2-8°C ranged from (b)(4) (Section 3.2.P.5.6) the adjustment of the limit appears to be possible. Please readjust the endotoxin limits (b)(4) (Section P.3.4, Control of Critical Steps (b)(4)) and release specification (Section 3.2.P.5.6) for DP. Alternatively, provide justification for the proposed specification.

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PRIPUZOVA NATALIA  
(REVIEWER)  
10/08/2015

PATRICIA HUGHES  
10/08/2015



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

**Date:** 10/19/2015  
**To:** Administrative File, STN 761036/0  
**From:** Laura Fontan, Consumer Safety Officer, CDER/OPQ/OPF/DIA  
**Endorsement:** Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA  
**Subject:** Original BLA  
**US License:** 1864  
**Applicant:** Janssen Biotech, Inc.  
**Mfg Facility:** Drug Substance [redacted] (b) (4)  
[redacted]  
Drug Substance (b) (4): Janssen Biologics, Barnahely, Ringaskiddy, Co.  
Cork, Ireland (FEI: 30007029098)  
Drug Product: [redacted] (b) (4)  
[redacted]  
Drug Product: Cilag A.G., Hochstrasse 201, 8200 Schaffhausen, Switzerland  
(FEI: 3002806695)  
**Product:** daratumumab (human IgG1k monoclonal antibody) Injection  
**Dosage:** 100 mg/mL and 400 mg/mL sterile liquid concentrate intended for intravenous  
infusion after dilution in commercially available 0.9% sodium chloride  
**Indication:** Treatment of patients with multiple myeloma who have received at least three  
prior lines of therapy including a proteasome inhibitor and an immunomodulatory  
agent  
**Due Date:** 03/09/2016

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**RECOMMENDATION:** Compliance decisions are pending for the [redacted] (b) (4) inspection  
of the [redacted] (b) (4) DS manufacture, and the 10/5-  
9/2015 inspection of the Janssen Biologics site (FEI 3007029098) [redacted] (b) (4) DS  
manufacture. Both of these sites are currently in acceptable compliance standing. The  
compliance status of drug product sites, [redacted] (b) (4)  
[redacted] and Cilag A. G., Schaffhausen, Switzerland (FEI:  
3002806695) are also acceptable compliance standing. Final recommendation for the proposed  
manufacturing and testing sites is pending final compliance decisions for the DS manufacturing  
facilities.

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**SUMMARY**

The subject BLA proposes manufacture of Daratumumab (HuMax®-CD38) DS and DP at the following facilities. The drug substance is manufactured at two facilities; [REDACTED] (b) (4) at Janssen Biologics in Ringaskiddy, Cork County, Ireland (FEI: 3007029098). The drug product is filled into vials at 100mg/ml and 400 mg/ml strengths. Both strengths are filled at [REDACTED] (b) (4). Additionally the 100 mg/vial strength is filled at Cilag A. G., Schaffhausen, Switzerland (FEI: 3002806695). Cell banking operations will occur at Janssen Biotech, Inc., Malvern PA (FEI: 3001610451). A complete list of facilities associated with Daratumumab manufacturing is provided in Tables 1 and 7.

Daratumumab is a fully human immunoglobulin G1k monoclonal antibody that binds with high affinity and specificity to the extracellular domain of human CD38 and is a transmembrane glycoprotein. The DP is provided in two strengths, 400 mg/mL and 100 mg/mL.

**ASSESSMENT**

**DRUG SUBSTANCE FACILITIES**

**3.2.S.2.1 DS Manufacturers.**

The sites proposed for daratumumab DS manufacture, cell banking operations, and testing are presented below in Table 1.

**TABLE 1. Proposed Sites for Daratumumab DS Manufacture, Cell Banking and Testing Operations**

Site Name	Address	FEI Number	Responsibilities
[REDACTED]	[REDACTED]	[REDACTED] (b) (4)	-Daratumumab [REDACTED] (b) (4) DS manufacture -Process intermediate testing
Janssen Biologics (Ireland)	Barnahely Ringaskiddy, Cork, Ireland	3007029098	-Daratumumab [REDACTED] (b) (4) DS manufacture -Process intermediate testing -Release testing of drug substance
Janssen Biotech, Inc	200 Great Valley Parkway Malvern, PA	3001610451	-Manufacture of working cell bank -Biological and characterization assays -Release testing of bulk drug substance and drug product
Janssen Biologics B. V.	Einsteinweg 101 23333 CB Leiden Netherlands	3002806632	- Bulk DS stability testing - DP stability and release testing for all tests but CCIT -Mycoplasma and In Vitro Assay for Adventitious Agents
[REDACTED]	[REDACTED]	[REDACTED] (b) (4)	-Mycoplasma and In Vitro Assay for Adventitious Agents
[REDACTED]	[REDACTED]	[REDACTED] (b) (4)	-Mycoplasma and In Vitro Assay for Adventitious Agents

**Reviewer Comment:** *The facilities for manufacture of Daratumumab DS are adequately described.*

—Satisfactory—

- **Prior Inspection History for DS Manufacturing and Testing Sites:**

(b) (4)

**Daratumumab DS Manufacturing and IPC Testing.**



(b) (4)

Inspection performed (b) (4). The inspection was conducted in accordance with Compliance Programs 7556.002 and 7356.002M . Quality, Facilities and

BLA 761036 Daratumumab DS and DP Manufacture

Equipment, Materials, Production, and Laboratory Control systems were covered. A ten item FDA 483 was issued. The inspection was classified VAI.

**Janssen Biologics (FEI 3007029098) Daratumumab DS Manufacturing and IPC Testing.**

Pre-license Inspection performed 10/5/2015 – 10/9/2015 by CDER-DIA and CDER-OBP.

This inspection was in support of STN 761036/0, daratumumab drug substance manufacturing. It was an ICH Q7A based inspection and covered PAC code (b) (4). The Quality, Production, Laboratory, Raw Materials, Facilities and Equipment Systems were covered for (b) (4) areas for this product only. No Form FDA 483 was issued. The recommendation for the firm is NAI, however, the inspection is pending final classification.

Inspection performed 03/03/2-14-03/07/2014 by the Division of Foreign Field Investigations, DFFI (HFC-130). The inspection was conducted according to CP 7356.002M and CP 7356.002F to evaluate the firm's overall compliance with cGMPs and to evaluate corrective actions implemented. The inspection covered Quality, Facilities and Equipment, Production, and Materials Systems. A two item Form FDA 483 was issued. The inspection was classified VAI.

(b) (4)

(b) (4)

**DS Testing sites:**

**Table 2: Testing site Compliance summary**

Site Name	FEI Number	Inspection dates/ Compliance outcome	Status
Janssen Biotech, Inc Malvern, PA	3001610451	Sep 2014-VAI	Acceptable
		Sep 2012-NAI	
		(b) (4)	
[REDACTED]	[REDACTED]	May 2011-VAI	Acceptable
		(b) (4)	
Janssen Biologics B. V. Leiden, Netherlands	3002806632	July 2014-VAI	Acceptable
		(b) (4)	
		Sep 2012-VAI	
[REDACTED]	[REDACTED]	Jul 2010-NAI	Acceptable
		(b) (4)	

**Reviewer Comment:** Compliance decisions are pending for the (b) (4) inspection of the (b) (4) and the 10/5-9/2015 inspection of the Janssen Biologics site (FEI 3007029098). The drug substance manufacturing and testing sites have been inspected multiple times within the recent past demonstrating acceptable compliance.

—Pending—

**3.2.S.2.2. Overview of Daratumumab DS Manufacturing Operations at (b) (4).**  
The Daratumumab DS is manufactured in (b) (4)

[REDACTED]

[REDACTED]

## CONCLUSION

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

- [REDACTED] (b) (4)
- Janssen Biologics in Ringaskiddy, Cork County, Ireland (FEI: 3007029098).
- [REDACTED] (b) (4)
- Cilag A. G., Schaffhausen, Switzerland (FEI: 3002806695).

In addition, proposed manufacturing and testing sites are recommended for approval from a facilities assessment standpoint pending final compliance decisions for the [REDACTED] (b) (4) and the 10/5-9/2015 inspection of the Janssen Biologics site (FEI 3007029098).

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Laura Fontan  
Consumer Safety Officer  
OPF Division of Inspectional Assessment  
Branch 1

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

**BLA STN 761036**

**DARZALEX<sup>TM</sup> (daratumumab)**

**Janssen Biotech, Inc.**

**Tura C. Camilli, Ph.D., Product Quality Reviewer  
Jee Chung, Ph.D., Acting Team Leader, ATL  
Division of Biotechnology Research and Review I**

# Product Quality Review Data Sheet

1. **BLA# 761036**

2. **REVIEW DATE:** October 22, 2015

3. **PRIMARY REVIEW TEAM:**

Medical Officer: Barry Miller and Albert Deisseroth [Team Leader (TL) and CDTL]  
 Pharm/Tox: Emily Place and Chris Sheth (TL)  
 Product Quality Team: Tura C. Camilli and Jee Chung (TL)  
 BMT or Facilities: Maria Jose Lopez-Barragan, Natalia Pripuzova and Patricia Hughes (TL)  
 Wayne Seifert, Laura Fontan and Steve Fong (TL)  
 Clinical Pharmacology: Jeanne Fourie Zirkelbach and Bahru Habtemariam (TL)  
 Statistics: Yaping Wang and Yuan-Li Shen (TL)  
 Pharmacometrics: Lian Ma and Nitin Mehrotra (TL)  
 OBP Labeling: Jibril Abdus-Samad  
 OBP RBPM: Anita Brown  
 RPM: Jessica Boehmer

4. **MAJOR GRMP DEADLINES:**

**Filing Meeting: September 7, 2015**  
**Mid-Cycle Meeting: September 24, 2015**  
**Wrap-Up Meeting: November 4, 2015**  
**Primary Review Due: October 18, 2015**  
**Secondary Review Due: October 22, 2015**  
**CDTL Memo Due: October 25, 2015**  
**PDUFA Action Date: November 17, 2015**

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

Communication/Document	Date
CMC Pre-BLA Meeting	December 12, 2015
IR in filing letter	September 4, 2015
Information Request #1	September 28, 2015
Information Request #2 (DMA)	September 29, 2015
Information Request #3	October 2, 2015
Information Request #4	October 10, 2015
Information Request #5	October 14, 2015
Teleconference	October 15, 2015
Information Request# 6	October 16, 2015

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 See Attached 10/22/15 Review on epage 30 above for this review.