CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761145Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Pharmaceutical Manufacturing Assessment
Division of Biotechnology Manufacturing

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Date: March 17, 2020
STN: 761145
Reviewer: Candace Gomez-Broughton, Ph.D. Microbiologist CDER/OPQ/OPMA/DBMB1
Secondary: Patricia Hughes, Ph.D., Secondary Reviewer CDER/OPQ/OPMA/DBMB2
Endorsed: Peter Qiu, Ph.D., Acting Division Director CDER/OPQ/OPMA/DBM
Subject: Original BLA
Applicant: Janssen Biotech, Inc.
License #: 1864
Facilities: Daratumumab: (b) (4)
rHuPH20: (b) (4)
Product: HuMax®-CD38 (daratumumab, JNJ-54767414 Recombinant Human Hyaluronidase (rHuPH20)
Dosage: Solution for subcutaneous injection (1800 mg daratumumab, 30000U rHuPH20 per 15 mL vial)
Indication: Multiple Myeloma
Action Date: May 12, 2020

Recommendation: This BLA is recommended for approval from a microbiology product quality perspective.

Introduction

Janssen has submitted a Biologic License Application (BLA) for the approval of daratumumab for subcutaneous (SC) administration co-formulated with recombinant human hyaluronidase (rHuPH20). The proposed proprietary name for this product is DARZALEX® and it is indicated for the treatment of adult patients with multiple myeloma.

Drug Substance Quality Microbiology Information Reviewed

Sequence number	Date	Description
001	07/12/2019	Original Submission
0023	04/09/2020	Response to Information Request

Assessment

S Drug Substance – daratumumab - all

S.1 General Information

Daratumumab is an anti-CD38 human immunoglobulin monoclonal cytolytic antibody. Daratumumab has been shown to inhibit CD38 expressing tumor cells.

S.2 Manufacture

S.2.1 Manufacturer (s)

Facilities involved in daratumumab manufacturing and testing are listed in the following table.

Site	Responsibilities
Janssen Biotech, Inc Malvern, PA	• Cell bank storage • Cell bank manufacturing • Analytical testing
(b) (4)	• Cell bank storage • Cell culture and Purification • Analytical testing

Janssen Biologics B.V. The Netherlands	• Analytical testing
Janssen Sciences Ireland UC Cork, Ireland	• Analytical testing
(b) (4)	• Analytical testing
	• Analytical testing

Reviewer comment: All proposed manufacturing and testing facilities are found to be acceptable. Pre-license inspections of DS manufacturing facilities were waived based on previous history. Full assessment of the facilities for this BLA are covered in a separate document prepared by Zhong Li, Ph.D.

S.2.2 Description of Manufacturing Process and Process Controls

(b) (4)

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Candace Gomez-Broughton

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Zhihao Peter Qiu

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Date: 4/20/2020 12:00:07PM
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Recommendation: Approval

BLA Number: 761145
Review Number: First round
Review Date: March 23, 2020

Drug Name/Dosage Form	DARZALEX Faspro, daratumumab and hyaluronidase, injection, solution
Strength/Potency	1800 mg daratumumab/30,000 U hyaluronidase/15 mL
Route of Administration	Subcutaneous administration
Rx/OTC dispensed	Rx
Indication	Treatment of patients with multiple myeloma • in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant • in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy • in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy • in combination with pomalidomide and dexamethasone (b) (4) • as monotherapy, 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.
Applicant/Sponsor	Janssen Biotech, Inc.
US agent, if applicable	Janssen Research & Development, LLC

Product Overview

DARZALEX Faspro is a fixed-dose combination of Darzalex and hyaluronidase (recombinant human) for subcutaneous administration of daratumumab for the treatment of multiple myeloma. Daratumumab is a human monoclonal IgG1κ antibody that binds to CD38 antigen on target cells to induce immune-mediated cell death. It has multiple potential mechanisms of action, including CDC, ADCC, ADCP, and induction of target cell apoptosis. CD38 antigen is expressed to varying degrees on a number of hematopoietic cells as a transmembrane glycoprotein; it is overexpressed on myeloma cells. The purpose of adding hyaluronidase, an endoglycosidase, to daratumumab DP is to increase the dispersion and absorption of daratumumab when administered subcutaneously, resulting in a significantly shorter infusion time for the patient as well as a reduced rate of infusion-related reactions.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance/Drug Product	Deborah Schmiel	OPQ/OBP/DBRR 1
Hyaluronidase	Shen Luo	OPQ/OBP/DBRR 4
Drug Substance Microbiology Drug Product Microbiology	Candace Gomez-Broughton Aimee Cunningham	OPQ/OPMA OPQ/OPMA
Facilities	Li Zhong	OPQ/OPMA/DBM/Branch 1

Labeling	Vicky Borders Hemphill	OPQ/OBP
Team Lead, Hyaluronidase	Serge Beaucage	OPQ/OBP/DBRR 4
Product Quality Team Lead Microbiology QAL Facility Branch Chief OBP Review Chief	Jennifer Swisher Patricia Hughes/Peter Qiu Thuy Thanh Nguyen Rachel Novak	OPQ/OBP/DBRR 1 OPQ/OPMA OPQ/OPMA/DBM/Branch 1 OPQ/OBP/DBRR 1
Business Regulatory Process Manager	Andrew Shiber	OPQ/OPRO
Application Team Lead	Jennifer Swisher	OPQ/OBP/DBRR 1

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Kimberly Scott, Natasha Kormanik	OND/OOD/DHMI
Cross-disciplinary Team Lead	Bindu Kanapuru	OND/OOD/DHMII
Medical Officer	Andrea Baines	OND/OOD/DHMII
Pharm/Tox	Emily Place/Christopher Sheth (TL)	OND/OOD/DHOT
Clinical Pharmacology	Yibo Wang/Hong Zhao (TL)	OTS/OCP/DCPI
Clinical Statistics	Haiyan Chen/Yute Wu (TL)	OTS/OB/DBV

Names:

- Proprietary Name: DARZALEX Faspro
- Trade Name: DARZALEX Faspro
- Non-Proprietary/USAN/INN: daratumumab and hyaluronidase
- CAS Registry number: 945721-28-8
- Company/Laboratory code: JNJ-54767414
- OBP systematic name: COMBINATION: MAB HUMAN (IGG1) ANTI P28907 (CD38_HUMAN) [HuMaxCD38] AND RPROTFRAG P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20]

Submissions Reviewed:

Submission(s) Reviewed /sequence number	**Document Date**
STN 761145/1	7/12/2019
STN 761145/5 (response to IR #1)	9/27/2019
STN 761145 /8 (response to IR #2)	1/6/2020
STN 761145 /10 (response to IR#3)	2/4/2020
STN 761145 /11 (response to IR#4)	2/14/2020
STN 761145/13 (response to IR #5)	3/2/2020
STN 761145 /17 (response to IR #6)	3/16/2020
STN 761145/22 (response to IR #7)	4/2/2020
STN 761145/23 (response to IR #8)	4/9/2020

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]
(b) (4)	II		(b) (4)	3	N/A
	II			3	N/A
	II			3	N/A
	II			3	N/A
	II			3	N/A
	III			3	N/A
	III			3	N/A
	V			3	N/A
	III			3	N/A
	III			3	N/A

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

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

B. Other documents: BLA 761036 (daratumumab), NDA 21859 (hyaluronidase)

3. Consults: None

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Biotechnology Products, OPQ, CDER, recommends approval of STN 761145 for DARZALEX Faspro (daratumumab and hyaluronidase) manufactured by Janssen, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of DARZALEX Faspro is well controlled and leads to a product that is pure and potent. We recommend that DARZALEX Faspro be approved for human use under the conditions specified in the package insert.

B. Action letter language:

- Manufacturing location:
  - Drug substance
    - Daratumumab – (b) (4)
    - Hyaluronidase – (b) (4)
  - Drug product – (b) (4)
- Fill size and dosage form
  - 1800 mg daratumumab/30,000 Units hyaluronidase per vial
- Dating period:
  - Drug product – 12 months; 2-8°C
  - Drug substance (daratumumab) – (b) (4) months; (b) (4) °C
  - Drug substance (hyaluronidase) – (b) (4) months; (b) (4) °C
  - Stability option (select one below):
    - Not applicable – data for both drug substances and drug product support the requested expiration dating periods with no further extensions
- Exempt from lot release
    - Yes - specified product per 601.2a

C. Summary of Complete Response Issues: none

D. Benefit/Risk Considerations:

DARZALEX Faspro (daratumumab and hyaluronidase) is intended to deliver daratumumab subcutaneously. The benefit to patients is the reduced time at the infusion center as well as a reduction in infusion-related reactions. The manufacturing process is adequately controlled and the critical quality attributes of DARZALEX Faspro are comparable to DARZALEX. The higher concentration formulation does not result in higher levels of aggregates and the rates of immunogenicity to daratumumab between subcutaneous and intravenous delivery were comparable and low. Although the rate of immunogenicity against hyaluronidase was slightly higher, it did not affect daratumumab exposure and none of the responses were neutralizing.

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

1. Confirm the effectiveness of updates to the daratumumab SC drug substance manufacturing process to ensure the continued ability to meet expectations during drug product shelf life for levels of sub-visible particles. The effectiveness of the modifications should be supported by real-time and accelerated drug product stability data between material produced by the current manufacturing process and the improved process. Provide the statistical plans used to evaluate the data, as well as validation and supportive data for any process updates and manufacturing control strategy updates in the final report.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

DARZALEX Faspro for subcutaneous administration was developed to decrease the currently approved administration time of 6-20 hours for Darzalex IV. The control strategy for daratumumab for subcutaneous administration is based on the identification of critical quality attributes (CQAs), clinical and manufacturing experience, process and product characterization and understanding, stability data, and knowledge and experience from clinical and manufacturing experience with daratumumab for intravenous infusion.

Table 1, below, identifies critical quality attributes intrinsic to the API and risk management.

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

CQA	Risk	Origin	Control Strategy	Other notes
Daratumumab				
ADCC activity (potency)	Efficacy	Intrinsic to the molecule. Impacted by glycosylation, aggregation, glycation, and deamidation	(b) (4)	N/A
CDC activity (potency)	Efficacy	Intrinsic to the molecule. Impacted by glycosylation, aggregation, glycation, deamidation, and oxidation.		N/A
CD38 Binding (Potency)	Efficacy	Intrinsic to the molecule. Impacted by oxidation, glycation, and aggregation.		
Glycosylation (product-related species)	Efficacy (fucosylation and galactosylation impact ADCC and CDC; also some impact on FcRn binding)	Dependent on and affected by bioreactor conditions. Does not change during storage.		N/A
High Molecular Weight (HMW) /Aggregates (Product-related impurities)	Efficacy, PK, and safety/immunogenicity	Manufacturing process and exposure to heat, light, and pH extremes. Minimal increase expected on stability.		N/A

Fragments (LMW species)	Efficacy and PK	Manufacturing process and exposure to heat, light, and high pH stress. Minimal increase in fragments is expected during storage under recommended conditions.	(b) (4)	N/A
(b) (4) (product-related impurities)	(b) (4)	Manufacturing process and exposure to heat		N/A
(b) (4) (product-related impurities)		Manufacturing process and exposure to light		N/A
		Cell culture in the production bioreactor		N/A
Hyaluronidase (rHuPH20)				
Enzymatic activity (Potency)	MOA – Impact on daratumumab distribution, PK	Intrinsic to molecule	(b) (4)	
Aggregates (Purity)	Impact on MOA and immunogenicity	Formed in bioreactor		
Oxidized Species (Purity)	MOA – impact on enzymatic activity (b) (4)	Formed in bioreactor		(b) (4)

Hydrolyzed Species (Purity)	MOA- impact on enzymatic activity	Formed in bioreactor	(b) (4)	(b) (4)
Primary Sequence (Identity)	Impact on daratumumab distribution, PK, and immunogenicity	Expression construct and cell line		
N-linked Glycosylation (Identity)	MOA- impact on enzymatic activity	Formed in bioreactor		(b) (4)

B. Drug Substance Daratumumab Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance (Daratumumab) CQA Identification, Risk, and Lifecycle Knowledge Management.

CQA	Risk	Origin	Control Strategy	Other notes
Appearance	Safety	Controlled by the manufacturing process	(b) (4)	N/A
Bioburden (Contaminant)	Safety, Purity and Efficacy due to degradation or modification of product by microbial contamination	Raw materials and the manufacturing process		N/A
Endotoxin (contaminant)	Safety, Purity	Raw materials and the manufacturing process		N/A

Host Cell Protein (Process-related impurity)	Safety and Immunogenicity	Production cell line	(b) (4)	N/A
Host Cell DNA (Process-related impurity)	Safety	Production cell line		N/A
(b) (4) impurity)	Safety and Immunogenicity	Process related impurity (b) (4)		N/A
(b) (4) (Process-related impurity)	Safety, immunogenicity	Production bioreactor		Evaluated by pharm/tox review team also.
(b) (4) (Process-related	Safety, immunogenicity	Cell bank cryopreservation medium, or culture medium		N/A

impurity)				
Viruses (Contaminant)	Safety	Contamination during manufacture, most likely during cell culture operations	(b) (4)	N/A
Mycoplasma (Contaminant)	Safety	Mycoplasma would most likely be introduced during cell culture operations		N/A
Leachables (Process-related impurity)	Safety	Manufacturing components and the DS container closure system		N/A

a. **Description:**
Daratumumab is a recombinant, human IgG1κ monoclonal antibody that binds to CD38 antigen expressed on multiple myeloma cells. Daratumumab consists of two heavy chains that are each 452 amino acids long, including the C-terminal lysine residue, which is typically not present, and two light chains that are each 214 amino acids long. The Fc region of daratumumab contains an N-linked glycosylation site on residue Asn302. The molecular weight of glycosylated daratumumab is 148,025 Da (the predominant glycoform) and the molecular weight of deglycosylated daratumumab is 145,833 Da. The extinction coefficient was calculated to be 1.524 $(mg/mL)^{-1}$ cm^{-1} and confirmed experimentally. This value has been used during development and will continue to be used to determine the daratumumab protein concentration.

b. **Mechanisms of Action (MoA):**
The main mechanisms of action for daratumumab are the induction of complement-dependent CDC, ADCP, and 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.

c. **Potency Assays:**
Daratumumab utilizes two cell-based assays to measure potency, a CDC assay and an ADCC assay.

- CDC Bioactivity Assay: Daudi cells that express CD38 antigen are exposed to varying concentrations of daratumumab; daratumumab binds to CD38 on the Daudi cells. Normal human serum is added, and the Fc portion of daratumumab binds the C1q complement protein present in the serum, leading to C1q activation through the classical complement pathway and the formation of the membrane attack complex (MAC) on the surface of the Daudi cells. The MAC forms a transmembrane pore, resulting in cell lysis. Viable cells are measured using a metabolic substrate that produces levels of luminescence proportional to the amount of ATP present after lysis of the cells. The luminescence measured as a function of the antibody concentration is used as a measure of CDC activity. Potency is determined as percent of the reference material activity.
- ADCC Bioactivity Assay: Two cell lines, Daudi and Jurkat, are used to measure ADCC activity and serve as the target and effector cells, respectively. Daudi cells are exposed to varying concentrations of daratumumab, which binds to CD38 on the surface of Daudi cells. The Jurkat cells are then introduced to the culture containing the daratumumab bound Daudi cells, and the FcγRIIIa receptors expressed on the Jurkat cells bind to the Fc portion of daratumumab. However, rather than measuring cell death, the activation of FcγRIIIa elicits downstream signaling events that lead to NFAT-regulated luciferase reporter gene expression. The luciferase activity is a measure of FcγRIIIa activation and serves as a surrogate for ADCC. Potency is determined as percent of the reference material activity.

d. **Reference Standards (RS):**

(b) (4)

e. **Critical starting materials or intermediates:**

(b) (4)

f. **Manufacturing process summary:**

(b) (4)

g. **Container closure:**

(b) (4)

h. **Dating period and storage conditions:** The dating period for the daratumumab sc DS will be (b) (4) months when stored at either (b) (4) °C (long term).

C. Drug Substance Hyaluronidase Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 3: Drug Substance (Hyaluronidase) CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Visual Appearance: color (General)	Impact on safety and immunogenicity	May be impacted by cell culture, purification, (b) (4) steps	(b) (4)	N/A
Protein Quantity (General)	Impact on efficacy	DS manufacture (b) (4) step		N/A
Host Cell Proteins (Process Impurity)	Impact on safety and immunogenicity	Cell culture		(b) (4)
DNA (Process Impurity)	Impact on safety and immunogenicity	Cell Culture		
(b) (4)	Impact on safety	Cell culture		N/A
(b) (4)	Impact on safety, immunogenicity, and allergenicity	Cell culture		N/A
(b) (4) (Process Impurity)	Impact on safety	Cell Culture		N/A
(b) (4) (Process impurity)	Impact on safety	Cell culture		N/A
(b) (4) (Process Impurity)	Impact on safety	Cell Culture		N/A

(b) (4) (Process impurity)	Impact on safety	Cell Culture	(b) (4)	N/A
Bioburden (Contaminant)	Safety, Purity and Efficacy due to degradation or modification of product by microbial contamination	Raw materials and the manufacturing process		
Endotoxin (contaminant)	Safety, Purity	Raw materials and the manufacturing process		

a. Description (hyaluronidase, recombinant human):
Recombinant human hyaluronidase (rHuPH20, RPROTFRAG P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20]) is a glycosylated single chain protein with 447 amino acids. The calculated molecular weight of the full-length, reduced polypeptide is 51,106 Da. Glycosylation increases the molecular weight to 60,000-65,000 Da. There are six N-linked and one O-linked glycosylation sites.

Note that rHuPH20 is approved as HYLENEX as a 505(b)(2) (NDA 21-859).

b. Mechanism of action:
rHuPH20 depolymerizes hyaluronan under physiological conditions and acts as a spreading factor in vivo that facilitates the dispersion and absorption of daratumumab by temporarily clearing a path through the connective tissue in the subcutaneous space.

c. Potency Assay:
Enzymatic activity is measured with a turbidimetric assay where an insoluble precipitate is formed when hyaluronic acid binds with a cationic precipitant. rHuPH20 is incubated with hyaluronan substrate for 30 minutes and the undigested hyaluronan is precipitated upon the addition of acidified horse serum. Turbidity is measured at 640 nm and the decrease in turbidity resulting from enzyme activity on the hyaluronan substrate is a measure of the enzyme activity.

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

e. Critical starting materials or intermediates:
(b) (4)

(b) (4)

f. Manufacturing process summary:

(b) (4)

g. Container closure:

(b) (4)

h. Dating period and storage conditions:

(b) (4) months at (b) (4) °C.

D. Drug Product, DARZALEX Faspro, Quality Summary:

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for drug product specific CQAs that derive from the drug product manufacturing process and general drug product attributes. Active pharmaceutical ingredient and drug substance CQAs apply to drug product (see Tables 2 and 3).

Table 4: Drug Product-specific CQA Identification, Risk, and Lifecycle Management (Additional to API CQAs shown in Table 1)

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety, Purity and Efficacy (degradation or modification of the	Contamination introduced throughout DP manufacturing process	(b) (4)	N/A

(b) (4)

	product by contaminating microorganisms)			
Container Closure Integrity (contaminant)	Safety (loss of sterility due breaches in CCI during shelf-life	Container closure breaches during DP shelf-life.		N/A
Endotoxin (contaminant)	Safety, Purity and Immunogenicity	Raw materials and the DP manufacturing process		N/A
Color and clarity of solution (general)	Safety and Efficacy	Formulation, contamination, or degradation		N/A
Subvisible particles	Safety/ Immunogenicity	Manufacturing process		See discussion of PMC and updated stability monitoring below under "Manufacturing Process Summary" and "Novel Approaches"
Polysorbate 20 concentration	Safety and Efficacy (control over degradation)	Formulation		Degradation is seen on stability; limits supported by clinical data and formulation studies
Extractable Volume (general)	Efficacy/Dosing	Manufacturing process		N/A
Leachables (process-related impurities)	Safety	Manufacturing equipment and container closure		Early data is acceptable; sponsor will update AR with remaining timepoints.

- **Potency and Strength:** DARZALEX Faspro is supplied at 1800 mg daratumumab and 30,000 U hyaluronidase/vial. The drug product concentration is 120 mg/mL.

- **Summary of Product Design:**
  DARZALEX Faspro is supplied as a sterile, single dose, preservative-free liquid for subcutaneous injection in a (b) (4) mL vial. The drug product formulation consists of 8 mM histidine, 269 mM sorbitol, 0.9 mg/mL L-methionine, 0.04% polysorbate 20, (b) (4) The deliverable amount is 1800 mg and 30,000 U hyaluronidase.

- **List of Excipients:**
  L-histicine HCl monohydrate, L-histidine, Sorbitol, L-methionine, and polysorbate 20. All excipients are compendial.

- **Reference Standards:**
  Same as the daratumumab and rHuPH20 drug substance RSs.

- **Manufacturing process summary:**
  The DARZALEX Faspro drug product manufacturing includes the following steps:

(b) (4)

- **Container closure:**

(b) (4)

- **Dating period and storage conditions:**

  The shelf life for drug product is 12 months at 5 ± 3°C.

E. Novel Approaches/Precedents:

Due to concern regarding high levels of subvisible particulates (b) (4) µm increase during storage, the sponsor has committed to monitor all DP batches derived from (b) (4) DS on stability for subvisible particles until the impact of additional process improvements has been confirmed.

F. Any Special Product Quality Labeling Recommendations:

None

G. Establishment Information:

(b) (4)

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(b) (4)

Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

1. At-scale Chromatography (b) (4) (3.2.S.2.5 for daratumumab and hyaluronidase sections)
2. At-scale Membrane Lifetime Studies (3.2.S.2.5 for daratumumab and hyaluronidase sections)
3. Ongoing Stability Studies (3.2.S.7.2)
4. Cleaning Protocol for New Product Introduction at (b) (4) (3.2.R, for daratumumab)
5. Comparability Protocol for change of manufacturing equipment (3.2.R, for hyaluronidase)

ii. Outstanding review issues/residual risk:

1. See PMC #1.

iii. Future inspection points to consider:

1. Impurity clearance (b) (4)
2. Microbial control strategy (b) (4)

b. Drug Product

i. Protocols approved:

1. Ongoing stability studies (3.2.P.8.2)
2. Cleaning Protocol for New Product Introduction (3.2.R)

ii. Outstanding review issues/residual risk:

1. See PMC #1

iii. Future inspection points to consider:

1. Subvisible particle testing
2. (b) (4)

Jennifer Swisher

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Rachel Novak

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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Pharmaceutical Manufacturing Assessment
Division of Biotechnology Manufacturing
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Primary Reviewer: Aimee L. Cunningham, Ph.D., M.P.H.
Acting Quality Assessment Lead: Jessica Hankins, Ph.D.
Branch Chief: Patricia Hughes, Ph.D.

BLA:	761145/0
Applicant:	Janssen Biotech, Inc.
US License Number:	1864
Submission Reviewed:	Original BLA
Product:	DARZALEX FASPRO (daratumumab and hyaluronidase [human recombinant])
Indication:	Multiple myeloma
Dosage Form:	Solution for s.c. injection, 1800 mg/15 mL
Manufacturing Sites (DP):	(b) (4)
FDA Receipt Date:	7/12/2019
Action Date:	5/12/2020

Conclusion and Approvability Recommendation

The drug product part of the BLA, as amended, was reviewed from a sterility assurance and product quality microbiology perspective and is recommended for approval.

Product Quality Microbiology Assessment: Drug Product

Janssen has submitted BLA 761145 to license daratumumab and its associated drug substance and drug product manufacturing processes. BLA 761145 was submitted via eCTD on July 17, 2019. This review contains the assessment of the manufacturing process of daratumumab drug product from a microbiological quality perspective. For review of drug substance aspects of this application, please see the review by Dr. Candace Gomez-Broughton.

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0001	7/12/2019	Original BLA
0008	01/06/2020	IR responses
0011	02/14/2020	IR responses

0013	03/02/2020	IR Responses

Letters of authorization (LOAs) to the following drug master files (DMFs) related to product quality microbiology were provided in Module 1. The review status of each DMF is documented below.

DMF #	Content	Date Reviewed	Finding	Document Name
[redacted] (b) (4)		03/04/2019	Adequate	D18370M15R01

Module 1

1.14 Labeling

Darzalex Faspro is to be administered subcutaneously (s.c.) into the abdomen (rotating injection sites) over 3-5 minutes, with a recommended dosage of 1800 mg daratumumab / 30000 units human recombinant hyaluronidase. Initial dosing is weekly, moving to every 2-3 weeks depending on the indication, then every 4 weeks. Vials are stored refrigerated until use and must be equilibrated to ambient temperature prior to administration; temperature equilibration of the unpunctured vial at ambient temperature and light cannot exceed 24 hrs. The dosing syringe is prepared under controlled and validated aseptic conditions, with the needle or infusion set attached immediately prior to use to avoid needle clogging. The prepared syringe can be stored for up to 4 hours at ambient temperature and light before use.

Reviewer's Comment: *No study is required to support the 4 hour hold at ambient temperature, and the room temperature hold of unopened vial to equilibrate temperature is also adequate as the vial is not compromised.*

SATISFACTORY

Module 3.2

P.1 Description and Composition of the Drug Product

Daratumumab is supplied as a sterile 120 mg/mL solution for subcutaneous injection, containing 1800 mg daratumumab and 30,000 units of recombinant human hyaluronidase. The fill volume is 15 mL, with an excess volume of [redacted] (b) (4) mL. The drug product contains no preservatives and is intended for single use. Primary packaging is a [redacted] (b) (4) glass vial with elastomeric closure, aluminum seal, and flip-off cap. DP composition is outlined below (table adapted from submission).

Component	Concentration	Quantity per Vial
Daratumumab	120 mg/mL	1800 mg
rHuPH20	2000 U/mL (20 µg/mL)	30000 U (300 µg)
L-histidine	8 mM	4.9 mg
L-histidine HCl monohydrate		18.4 mg
Sorbitol	269 mM	735.1 mg
L-methionine	0.9 mg/mL	13.5 mg
Polysorbate 20	0.4 mg/mL	6 mg
WFI	q.s.	q.s.

SATISFACTORY

P.2 Pharmaceutical Development

(b) (4)

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Hughes Troost

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BLA STN 761145
Product Daratumumab SC (with hyaluronidase)
Manufacturer Janssen Biotech, Inc.

OBP CMC Review Data Sheet

1. BLA#: 761145
2. Review Date: 4/2/2020
3. Primary Review Team:
    a. Medical Officer: Andrea Baines and Bindu Kanapuru (TL)
    b. Pharm/Tox: Emily Place and Christopher Sheth (TL)
    c. Product Quality Team: Deborah Schmiel and Jennifer Swisher (TL)
        Hyaluronidase: Shen Luo and Serge Beaucage (TL)
        Microbiology: Ziyang Su, Amy Devlin, and Candace Gomez-Broughton (TL)
    d. Facilities: Li Zhong and Peter Qiu (TL)
    e. Clinical Pharmacology: Yibo Wang and Hong Zhao (TL)
    f. Statistics: Haiyan Chen and Yute Wu (TL)
    g. OBP Labeling: Vicky Borders-Hemphill
    h. RBPM: Andrew Shiber

4. Major GRMP Deadlines:
    a. Filing Meeting 8/13/2019
    b. Mid-cycle meeting 12/10/2019
    c. Wrap-up meeting 3/31/2019
    d. Primary review due 4/3/2019
    e. Secondary review due 4/12/2019
    f. PDUFA action date 5/12/2019

5. Communications with Sponsor and OND:

Communication/Document:	Date:
CMC Pre-BLA Meeting	1/24/2019
Information Request #1	9/16/2019
Filing Letter	9/10/2019
Information Request #2	1/23/2020
Information Request #6	3/9/2020
Information Request #8	3/30/2020
Information Request #9	4/3/2020
Teleconference	4/7/2020

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
761145 Original BLA submission	7/12/2019	Yes
761145/5 (Response to IR#1)	9/27/2019	Yes
761145/10 (Response to IR#2)	2/4/2020	Yes
761145/11 (Stability update)	2/14/2020	Yes
761145/17 (Response to IR#6)	3/16/2020	Yes
761145/22 (Response to IR#8)	4/2/2020	Yes

7. Drug Product Name/Code/Type:
    a. Proprietary Name: DARZALEX FASPRO
    b. Trade Name: DARZALEX FASPRO

c. Non-Proprietary Name/USAN: daratumumab and hyaluronidase
d. CAS Name: 945721-28-8 and 757971-58-7
e. Common Name: Daratumumab hyaluronidase-fihj
h. OBP systematic name: COMBINATION: MAB HUMAN (IGG1) ANTI P28907 (CD38_HUMAN)[HuMaxCD38] AND RPROTFRAG P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20]
i. Other names: HuMax-CD38, JNJ-54767414, α-CD38 monoclonal antibody

8. Pharmacological Category: Therapeutic recombinant chimeric monoclonal antibody (IgG1, kappa, anti-CD37) and recombinant human hyaluronidase as a dispersing agent
9. Dosage Form: 120 mg/ml daratumumab solution for subcutaneous injection
10. Strength/Potency:
    (i): The concentration/strength of the Drug Product: 120 mg/ml daratumumab with 2,000 Units/ml rHuPH20, supplied at 1800 mg daratumumab and 30,000 U hyaluronidase/vial
    (ii): Type of potency assay(s): CDC, ADCC, and hyaluronidase activity

11. Route of Administration: subcutaneous

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
		(b) (4)	Yes	Not reviewed, because information provided in the BLA is sufficient.
			Yes	Not reviewed, because information provided in the BLA is sufficient.
			Yes	Not reviewed, because information provided in the BLA is sufficient.
			Yes	Not reviewed, because information provided in the BLA is sufficient.
			Yes	Not reviewed, because information provided in the BLA is sufficient.
			Yes	Not reviewed, because information provided in the BLA is sufficient.
			Yes	Not reviewed, because information provided in the BLA is sufficient.
			Yes	Not reviewed, because information provided in the BLA is sufficient.
			Yes	Not reviewed, because information provided in the BLA is sufficient.
			Yes	Not reviewed, because information provided in the BLA is sufficient.

13. Inspectional Activities:
A Pre-license inspection (PLI) of (b) (4) was conducted by CDER/OPF and CDER/OBP from (b) (4) to support review of daratumumab SC drug substance manufacture under BLA 761145/0. The inspection covered the facilities, utilities, equipment, processes, and procedures with respect to product quality, compliance to commitments in the BLA, and compliance to cGMPs in accordance with ICH Q7. A 5-item FDA-483 was issued at the conclusion of the inspection, which was classified as VAI.

14. Consults Requested by OBP: None.
15. Quality by Design Elements:
The following was submitted in the identification of QbD elements (check any that apply):

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

16. Precedents: None.

17. Administrative:

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation
I recommend approval of this 351(a) BLA application for DARZALEX FASPRO (Daratumumab SC) for subcutaneous administration of Daratumumab from the Product Quality perspective.

II. List of Deficiencies to be Communicated None.

III. List of Post-Marketing Commitments/Requirements
To ensure the continued ability to meet compendial expectations during the shelf life and the manufacture of drug product with critical product quality attributes to assure efficacy and patient safety, implement modifications to the daratumumab SC drug substance manufacturing process and controls and submit supplements under BLA 761145. Compare real-time and accelerated drug product stability data between material produced by the current manufacturing process and the improved process, with analysis. Provide the statistical plans used to evaluate the data, as well as validation and supportive data for any process updates and manufacturing control strategy updates in the final report.

IV. Review of Common Technical Document- Quality Module 1
A. Environmental Assessment of Claim of Categorical Exclusion
"Janssen Research & Development, division of Janssen Pharmaceutica NV, Beerse, Belgium (on behalf of Janssen Biotech, Inc, Horsham, PA), certifies that the Biological License Application for daratumumab subcutaneous (SC) meets the criteria for a categorical exclusion defined in the regulations (21 CFR 25.31[c]), and that to the knowledge of Janssen R&D, no extraordinary circumstances exist. Thus, no environmental assessment needs to be performed."

The categorical exclusion claim is acceptable as Daratumumab will degrade naturally.

V. Primary Container Labeling Review
The primary container labeling review was performed by Vicky Borders-Hemphill, under separate cover, with secondary review by Deborah Schmiel.

VI. Review of Common Technical Document- Quality Module 3.2
Module 2.3 of the submission contains a synopsis of the information contained in Quality Module 3.

VII. Review of Immunogenicity Assays- Module 5.3.1.4
The methods to detect and quantitate anti-daratumumab antibodies and anti-daratumumab neutralizing antibodies have been reviewed in previous submissions to BLA 761136 in both the original license application and supplements 13, 20, and a PMC (6/8/2017).

Description of Drug Substance and Drug Product

DARZALEX® (daratumumab) was approved under BLA 761036 on 11/21/2015 as a monotherapy at 16 mg/kg by intravenous administration for the treatment of patients with multiple myeloma who had received multiple prior lines of therapy. This application is for a daratumumab formulation that is administered subcutaneously (SC) using a co-formulated recombinant human hyaluronidase PH20 enzyme (rHuPH20) that acts transiently in the subcutaneous space to increase tissue dispersion and adsorption of the daratumumab. The sequence of daratumumab in the SC formulation is identical to the original IV formulation (b) (4) and the drug substances are manufactured using the same CHO cell line. The manufacturing process for daratumumab SC has been modified from the original BLA to manufacture a more concentrated drug and the manufacturing process includes modifications that increase the efficiency and capacity of the process.

S. Drug Substance
3.2.S.1.2 Structure
Daratumumab is a recombinant human IgG1κ monoclonal antibody specific for extracellular domain of CD38, a transmembrane glycoprotein that functions as a receptor and ectoenzyme. CD38 is highly expressed on multiple myeloma cells in addition to activated T and B cells. The primary sequence of the L and H chains appear below with complementarity determining regions (CDR) underlined, disulfide bonds in red font, and the N-glycosylation site Asn302 in bold text.

Figure 1: The Amino Acid Sequences of Daratumumab Heavy and Light Chains

The glutamic acid (E) at position 1 of the LC and the glutamic acid (E) at position 1 of the HC constitute the N termini of the secreted protein. Although the heavy chain C-terminal lysine residue is depicted, daratumumab is produced as predominantly the des-lys form.

Heavy Chain

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EVQLLESGGG  LVQPGGSLRL  SCAVSGFTFN  SFAMSWVRQA  PGKGLEWVSA  ISGSGGGTYY     60
                        HC 22-96
ADSVKGRFTI  SRDNSKNTLY  LQMNSLRAED  TAVYFCAKDK  ILWFGEPVFD  YWGQGTLVTV    120

SSASTKGPSV  FPLAPSSKST  SGGTAALGCL  VKDYFPEPVT  VSWNSGALTS  GVHTFPAVLQ    180
                        HC 149-205
SSGLYSLSSV  VTVPSSSLGT  QTYICNVNHK  PSNTKVDKRV  EPKSCDKTHT  CPPCPAPELL    240
                                                HC 225 - LC 214  HC2 HC2
GGPSVFLFPP  KPKDTLMISR  TPEVTCVVVD  VSHEDPEVKF  NWYVDGVEVH  NAKTKPREEQ    300
N-Glycan                        HC 266-326
YNSTYRVVSV  LTVLHQDWLN  GKEYKCKVSN  KALPAPIEKT  ISKAKGQPRE  PQVYTLPPSR    360

EEMTKNQVSL  TCLVKGFYPS  DIAVEWESNG  QPENNYKTTP  PVLDSDGSFF  LYSKLTVDKS    420
            HC 372-430
RWQQGNVFSC  SVMHEALHNH  YTQKSLSLSP  GK                                   452
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Light Chain

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EIVLTQSPAT  LSLSPGERAT  LSCRASQSVS  SYLAWYQQKP  GQAPRLLIYD  ASNRATGIPA     60
                        LC 23-88
RFSGSGSGTD  FTLTISSLEP  EDFAVYYCQQ  RSNWPPTFGQ  GTKVEIKRTV  AAPSVFIFPP    120

SDEQLKSGTA  SVVCLLNNFY  PREAKVQWKV  DNALQSGNSQ  ESVTEQDSKD  STYSLSSTLT    180
            LC 134-194
LSKADYEKHK  VYACEVTHQG  LSSPVTKSFN  RGEC                                  214
                                    LC 214 - HC 225
```

The N-linked glycans are biantennary structures typical for an IgG1 expressed in CHO cells. The molecular masses of the main forms of daratumumab range from 148,026 to 148,351 Da correspond to the intact 2H and 2L chain IgG form with combinations of G0F, G1F, and G2F glycoforms (2 per molecule).

Reviewer Comment: *The primary sequence and characteristics described are identical to the original daratumumab application (BLA 761036).*

3.2.S.1.3 General Properties
3.2.S.2 Manufacture
3.2.S.2.1 Manufacturer(s)
The daratumumab SC drug substance (DS) is manufactured at:

(b) (4)

Reviewer comment

(b) (4)

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Deborah Schmiel

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Jennifer Swisher

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/s/

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