

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761036Orig1s000**

**MICROBIOLOGY / VIROLOGY REVIEW(S)**



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 viral inactivation and neutralization intermediate is manufactured by (b) (4) USA. 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.

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.

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.

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### 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:

(b) (4)

**P 3 2 Batch Formula**

(b) (4)

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(b) (4)

## **P.5 Control of Drug Product**

### **P.5.1 Specifications**

Product quality microbiology specifications for DP release testing include: Sterility, Container Closure Integrity Testing (CCIT) and Endotoxin (LAL) (the limit is (b) (4)).

SATISFACTORY

### **P.5.2 Analytical Procedures**

DP sterility testing is performed using (b) (4) requirements. DP endotoxin testing is performed by USP (b) (4)

(b) (4)

### P.5.3 Validation of Analytical Procedures

#### Method Validation for Sterility Testing of DP

The materials used in the verification of the sterility procedure are listed in Table 1 copied from the submission. The volume that covers half of the content of 20 vials taking into account as the worst case filling volume were used for each culture medium to perform the verification study.

**Table 1: Materials Used During Verification of the Sterility Test**

Test Articles:	Daratumumab DP, 100 mg/vial at [redacted] (b) (4) Daratumumab DP, 400 mg/vial at [redacted] Daratumumab DP, 400 mg/vial at [redacted]
Microorganisms:	<i>Clostridium sporogenes</i> ATCC 11437/NCTC 12935 <i>Pseudomonas aeruginosa</i> ATCC 9027/NCTC 12924 <i>Staphylococcus aureus</i> ATCC 6538/NCTC 10788 <i>Bacillus subtilis</i> ATCC 6633/NCTC 10400 <i>Aspergillus brasiliensis</i> ATCC 16404/NCPF 2275 <i>Candida albicans</i> ATCC 10231/NCPF 3179
Media:	[redacted] (b) (4)
<sup>a</sup> 0.9% sodium chloride	[redacted] (b) (4)

ATCC = American Type Culture Collection (b) (4)  
 NCTC = National Collection of Type Cultures (b) (4)  
 NCPF = National Collection of Pathogenic Fungi (b) (4)  
 [redacted] (b) (4)

The verification of the sterility procedure as suitable for use with DP consisted of product-challenge testing to demonstrate that the components do not interfere with the sterility procedure. (b) (4)

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## 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) sterile filtration (3.2.P.3.4). Clarify, if the bioburden samples are taken (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 maximum endotoxin limit of (b) (4) and the maximum proposed 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 (b) (4) 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 (b) (4) (Section 3.2.P.5.6) the adjustment of the limit appears to be possible. Please readjust the endotoxin limits for both in-process limits (Section P.3.4, Control of Critical Steps and Intermediates) and release specification (Section 3.2.P.5.6) for DP. Alternatively, provide justification for the proposed specification.

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(REVIEWER)  
10/08/2015

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