

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761049Orig1s000

CHEMISTRY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 23, 2017
From: Idara Udoh, MS, Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: BLA761049: Categorical Exclusion

A claim for a categorical exclusion is being made under 21 CFR 25.31 (c). Discussion is present on page 5 of the CMC Integrated Quality Assessment document.

First Approval for Indication Breakthrough Review

Recommendation:
BLA: Approval

BLA 761049 **Review #1** **Review Date February 21 2017**

Drug Name/Dosage Form	Bavencio (avelumab) /Injection for infusion
Strength/Potency	200 mg/10 mL
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Indication	Avelumab is indicated for the treatment of patients with metastatic Merkel Cell Carcinoma (mMCC) whose disease has progressed after at least one previous chemotherapy regimen.
Applicant/Sponsor	EMD Serono, Inc.
US agent, if applicable	N/A

Product Overview

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Arulvathani Arudchandran	OBP/DBRRII
Drug Product	Arulvathani Arudchandran	OBP/DBRRII
Immunogenicity	Arulvathani Arudchandran	OBP/DBRRII
Facilities	Steve Fong	OPF/DIA
Microbiology	DMA-DS: Maria Reyes Candau-Chacon DMA-DP: Lakshmi Narasimhan	OPF/DMA
Regulatory Business Process Manager	Truong Quach	OPQ/OPRO
Team Lead	Joel Welch	OBP/DBRRII
Application Technical Lead	Joel Welch	OBP/DBRRII
Review Chief	Juhong Liu	OBP/DBRRII

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
Regulatory Business Process Manager	Idara Udoh	OHOP/DOP2
Cross-disciplinary Team Lead	Suzanne Demko	OHOP/DOP2
Medical Officer	Denise Casey	OHOP/DOP2
Pharm/Tox	Alexander Putman	OHOP/DTOP
Clinical Pharmacology	Safaa Burns	OTS/OC/DCPV
Statistics	Pallavi Mishra-Kalyani	OB/DBV

a. Names

- i. Proprietary Name: Bavencio
- ii. Trade Name: Bavencio
- iii. Non-Proprietary/USAN: avelumab
- iv. CAS name: 1537032-82-8
- v. Common name: MSB0010718C
- vi. INN Name: avelumab
- vii. Compendial Name: N/A
- viii. OBP systematic name: MAb Human (IgG1 λ) ANTI Q9NZQ7 (PD1L1_HUMAN) [MSB0010718C]

b. Pharmacologic category

Human IgG1 λ monoclonal antibody

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
761049/0.00	July 6, 2016
761049/0.02	September 2, 2016
761049/0.03	September 23, 2016
761049/0.09	November 4, 2016
761049/0.13	November 29, 2016
761049/0.15	December 9, 2016
761049/0.18	December 16, 2016
761049/0.19	December 19, 2016
761049/0.22	December 23, 2016
761049/0.23	December 23, 2016
761049/0.26	January 10, 2017
761049/0.28	January 30, 2017
761049/0.35	February 13, 2017
761049/0.36	February 15, 2017

Quality Review Data Sheet**1. LEGAL BASIS FOR SUBMISSION: 351(a)****2. RELATED/SUPPORTING DOCUMENTS:****A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III	(b) (4)	Glass Vial	N/A	N/A	N/A	Sufficient Detail included in BLA
	Type III		Rubber Stopper	N/A	N/A	N/A	Sufficient Detail included in BLA

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A	N/A	N/A

3. CONSULTS:

DISCIPLINE/TOPIC	DATE REQUESTED	STATUS	RECOMMENDATION	REVIEWER
N/A	N/A	N/A	N/A	N/A

APPEARS THIS WAY ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation

The recommendation from the Office of Pharmaceutical Quality, CDER, is approval of STN 761049 for Bavencio™ (avelumab) manufactured by EMD Serono, Inc. The data submitted in this application support the conclusion that the manufacture of Bavencio™ is well controlled and produces a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

b. Action letter language

- Manufacturing location:
 - Drug substance – Merck Serono SA,
Succursale de Corsier-sur-Vevey
Chemin du Fenil, Zone Industrielle B
1804 Corsier-sur-Vevey
Switzerland
 - Drug product – Merck Serono S.A.
Succursale d'Aubonne
Zone Industrielle de l'Ourietta
CH-1170 Aubonne
Switzerland
- Fill sized and dosage form – 200 mg/10 mL in single dose vial, intravenous Injection
- Dating period:
 - Drug product – 24 months; 2-8 °C
 - Drug substance (b) (4) months; (b) (4) °C
 - Stability option
 - For stability protocols:
 - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
 - Yes
- exempt specified according to 601.2a

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

The sponsor has committed to developing an assay to neutralizing antibodies against avelumab as it was not assessed during clinical development. It is the basis for PMC 1

below. Additionally, during the course of the review, the cut point for the screening assay and confirmatory assay for ADA status was acknowledged by the sponsor to be set higher than appropriate based on their use of normal human serum in lieu of treatment naïve sera. The proposed PMC language below reflects their commitment to provide such a reassessment and is incorporated into the PMC already requested by clinical pharmacology below (PMC 2).

The sponsor has also agreed to conduct media fill runs including the simulation of both maximum sterile hold time and maximum filling time in the same batch on a yearly basis starting from 2017.

PMC 1:

Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against avelumab in the presence of avelumab levels that are expected to be present in samples at the time of patient sampling. Patient samples should be banked for storage until the improved method is available.

PMC 2:

Conduct an assessment of treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses with validated assays (including an updated cutpoint for the screening and confirmatory ADA assay and the neutralizing assay as requested in PMC 1) capable of sensitively detecting ADA responses in the presence of avelumab levels that are expected to be present in the serum at the time of patient sampling. The ADA response be evaluated in at least 300 avelumab -treated patients. The final report will include information on the level of avelumab in each patient's test sample at each sampling point with an appropriate cutpoint.

PMC 3:

Implement the performance at least one media fill run per year which incorporates both the maximum sterile hold time after filtration and the maximum filling time starting from 2017. Submit the information and summary data from the first 2017 media fill as a post marketing commitment in accordance with 21 CFR 601.12.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 is a summary of product-related critical quality attributes that are relevant to both drug substance (DS) and drug product (DP). The table includes the identification of the various attributes along with their risk management. For additional information see the source technical document from the Office of Biotechnology Products and the Product Quality Microbiology Reviews from the Division of Microbiological Assessment.

APPEARS THIS WAY ON ORIGINAL

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

CQA (Type)	Risk	Origin	Control Strategy	Other
High Molecular Weight Impurities (HMW)	Potency and immunogenicity	Originate in (b) (4). May increase during storage of DS and DP. Increase is expected after exposure to heat, low and high pH, and light	(b) (4)	N/A

			(b) (4)	
Low Molecular Weight (LMW) Species (The predominant fragmentation site is at the hinge region, common LMW species include IgG-Fab arm and Fab+Fc arm; half antibody, H chain, L chain)	Potency, PK and immunogenicity	Originate in the (b) (4). LMW can be formed by non-enzymatic fragmentation or cleavage of protein backbone		N/A
Glycosylation (N-Glycan profile) Avelumab is glycosylated at Asn300	This attribute can impact activity, PK and safety. (b) (4) Heterogeneity of afucosylation and mannose glycans are observed.	These modifications occur in the (b) (4). It does not change during DS or DP storage.		N/A

	ADCC has been proposed as as a secondary mechanism of action for avelumab. This mechanism is known to be influenced by levels of afucosylation. High mannose levels have been demonstrated in literature to have a potential impact on PK.		(b) (4)	
Charge Isoforms Most commonly observed charge isoforms of avelumab include (b) (4)	Biological activity and safety	These modifications most likely occur during the (b) (4) Minimal increase is observed during DS and DP manufacture and storage. (b) (4)		N/A
Free-sulfhydryls	This could impact activity,	Free sulfhydryls can form		N/A

	PK, safety, and efficacy	during different stages of manufacturing and storage. The (b) (4) is the most likely source.	(b) (4)
Serine to Asn mis-substitution	This could impact efficacy, immunogenicity PK, and	(b) (4)	N/A

B. Avelumab Drug Substance Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

APPEARS THIS WAY ON ORIGINAL

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Host Cell Proteins (HCP)	Safety and immunogenicity	Process-related impurity from the production cell line	(b) (4)	New method submitted during review demonstrates improved detection capability
Host Cell DNA	Safety	Process related impurity from the production cell line		N/A

			(b) (4)	
(b) (4)	Safety, PK, and immunogenicity	Process related impurity from (b) (4)		N/A
	Safety immunogenicity and	Process related impurity from the (b) (4)		N/A
	Safety immunogenicity and	Process related impurity from the (b) (4)		N/A

			(b) (4)	
(b) (4)	Safety	Process related impurity is (b) (4)		N/A
Bioburden	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contaminant. Bioburden can be introduced by raw materials and throughout the manufacturing process.		N/A
Endotoxin	Safety and Purity	Contaminant. Endotoxin can be introduced by raw materials and throughout the manufacturing process.		N/A

			(b) (4)	
Viruses	Safety	Contaminant. Viruses would most likely be introduced during (b) (4)		N/A
Mycoplasma	Safety	Contaminant. Mycoplasma would most likely be introduced during (b) (4)		N/A
pH	General CQA: Safety and efficacy	General CQA. Formulation		N/A
Protein Concentration	General CQA: Safety and efficacy	Protein concentration of the product (b) (4)		N/A

			(b) (4)	
Appearance: color	General CQA: Safety and efficacy	The color of the DS can be affected by all steps of the manufacturing process, storage conditions and exposure to light.		N/A
Appearance, Clarity/ Opalescence	General CQA: Safety and efficacy	The clarity of the DS can be affected by all steps of the manufacturing process.		N/A
Osmolality	Safety	Osmolality is impacted by formulation. No change is expected on stability.		N/A
(b) (4)	Safety and efficacy	(b) (4)		N/A
Identity	Safety and efficacy	N/A		

			(b) (4)	
Leachables/extractables	Safety and efficacy (indirect effects on stability)	Process-related impurity. Leachables and extractables could potentially be introduced by any product contact equipment, containers and consumables.		N/A

a. Description

Avelumab is a human monoclonal antibody (mAb) of the IgG1 λ isotype that binds PD-L1. It has a molecular weight of approximately 147 kDa.

b. Mechanism of action

PD-L1 molecule is expressed as an immune check point inhibitor on epithelial, vascular, endothelial, immune, and tumor cells. The mechanism of action of avelumab is based on the selective binding to PD-L1 molecules on the surface of tumor cells and blocking the interaction between PD-L1 and PD-1. PD-L1 expression is detected in a broad range of malignancies and PD-L1/PD1 pathway has been identified as playing a major role that allows the tumor to escape elimination by the immune system. Eradicating the binding of PD-L1 to its receptor PD-1 removes the suppressive effects of PD-L1 on anti-tumor CD8+ T-cells. This will result the restoration of cytotoxic T cell response. Antibody dependent cellular cytotoxicity has also been proposed as a secondary mechanism of action.

c. Potency Assay

The biological activity (potency) of avelumab is determined by an *in vitro* cell binding assay. During the assay, avelumab is coated on ELISA plate and the binding ability to human PD-L1 receptor on HEK-293 cells is measured. Different concentrations of avelumab are coated on ELISA plates via Fc portion of the antibody. A fixed number of cells are added and unbound HEK-293 cells are washed out after a certain period. The bound cells are quantified using ATP monitoring system. The concentration of avelumab able to bind 50% of the maximum possible PD-L1 binding capacity (EC_{50}) is calculated. The sponsor reports the potency as relative % to the reference material.

d. Reference material(s)

(b) (4)

Reference standards are suitable for their intended purpose. For additional information, see of the OBP review technical document.

e. Critical starting materials or intermediates

Cell Banks: Avelumab is produced from a recombinant DNA-derived (b) (4) using standard cell culture techniques. (b) (4)

(b) (4)

f. Manufacturing process summary

(b) (4)

g. Container closure

(b) (4)

h. Dating period and storage conditions

The data provided in the BLA support the establishment of a shelf life of (b) (4) months for avelumab drug substance when stored at (b) (4) °C.

C. Drug Product [Bavencio] Quality Summary

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

APPEARS THIS WAY ON ORIGINAL

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility	Safety	Contaminants could be introduced throughout DP manufacturing or through a container closure integrity failure.	(b) (4)	N/A
Endotoxin	Safety, purity and potential immunogenic reactions	Contaminants could be introduced throughout DP manufacturing or		N/A

		due to integrity failure of the container closure.	(b) (4)	
Particulate matter (sub-visible)	Safety and Immunogenicity	Sub-visible particulates could form throughout manufacturing or on storage. Might contain product- and process-related impurities.		N/A
Appearance -Visible particulates	Safety and efficacy	Visible particulate might be affected by the manufacturing process and storage conditions.		N/A
Appearance – Color, Clarity and degree of opalescence	Safety and efficacy	Manufacturing process, formulation, and		N/A

		storage conditions		
pH	Safety and efficacy	pH is impacted by formulation. No change on stability is expected.	(b) (4)	N/A
Osmolality	Safety	Osmolality is impacted by formulation. No change is expected on stability.		N/A
Polysorbate 20	Safety and efficacy	Level of Polysorbate 20 excipient is impacted by formulation. No changes are expected on stability.		N/A
Protein Concentration	Safety and efficacy	Protein concentration is impacted by formulation during DP		N/A

		manufacturing and might be impacted by storage conditions.	(b) (4)	
Identity	Safety and efficacy	General CQA		N/A
Container closure integrity (sterility assurance)	Safety	CQA		N/A
Leachables/extractables	Safety	Process-related leachables and extractables could potentially be introduced by any product contact equipment,		N/A



QUALITY REVIEW



		containers and consumables.	(b) (4)	
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APPEARS THIS WAY ON ORIGINAL

- a. Potency and Strength: Avelumab drug product is a sterilized, clear concentrate solution for intravenous infusion presented at the concentration of 20 mg/mL. Vials are filled with (b) (4) mL of drug product solution in order to allow an extractable volume of 10 mL.
- b. Description/Commercial Image
The avelumab drug product is supplied as a single use clear sterile solution at a concentration of 20 mg/mL in type I glass vials with rubber stoppers and aluminum crimp seals. The DP is filled in vials with (b) (4) mL, allowing an extractable volume of 10 mL.
- c. List of Excipients:
Each single-dose vial contains 200 mg avelumab in 10 mL of solution for a concentration of 20 mg/mL. Each mL of solution contains 20 mg avelumab, D-mannitol (51 mg), glacial acetic acid (0.6 mg), polysorbate 20 (0.5 mg), sodium hydroxide (0.3 mg), and Water for Injection. The pH range of the solution is 5.0 –5.6.
- d. Reference material(s) Same as drug substance
- e. Manufacturing Process; Avelumab drug product is manufactured at Merck SA in Aubonne, Switzerland. (b) (4)
- f. Container Closure: The container closure system for Bavencio drug product includes vial, stopper and seal. The vial is 16 mL nominal capacity colorless type I (b) (4) glass vial (b) (4). The stopper is (b) (4). The crimp is (b) (4). The seal is not in contact with the product.
- g. Expiration Date & Storage Conditions; The stability data in the BLA support a shelf life of 24 months for Bavencio drug product when stored at recommended storage conditions of 2 - 8°C.
- h. List of co-packaged components, if applicable: N/A

Avelumab drug product is a sterile, clear concentrate solution for infusion presented at the concentration of 20 mg/mL. Vials are filled with (b) (4) mL of drug product solution in order to allow an extractable volume of 10 mL.

B. Novel Approaches/Precedents

None

C. Any Special Product Quality Labeling Recommendations

Store in a refrigerator at 2-8°C

Protect from light

Do not freeze

Do not shake

D. Establishment Information

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Drug substance manufacture, in-process testing, & bioburden testing . Master cell bank manufacture and storage.	Merck Serono SA Vevey , Succursale de Corsier-sur Vevey Chemin du Fenil, Zone Industrielle B, Switzerland	FEI 3003131678	Preapproval inspection (PAI) in support of subject BLA was conducted 11/07-15/2016 by CDER OBP, DMA and DIA.	PAI investigators recommended voluntary actions indicated (VAI) for microbial quality issues. Final compliance decision: Approve.	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.
Drug substance release & stability testing. (Also performs drug product release & stability	Merck Serono S.p.A. Guidonia Montecelio, Italy	FEI 3002807252	Latest surveillance inspection conducted 02/16-20/2015 resulted in NAI and approve decision.	No observations issued during most recent inspection conducted 02/20/2015.	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.

testing.)					
DRUG PRODUCT					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Drug product manufacture, in-process testing, packaging, & labelling. Drug Product Release (except cell binding assay and polysorbate 20)	Merck Serono SA Aubonne , Zone Industrielle de l'Ouriettaz, CH-1170 Aubonne, Switzerland	FEI 3002807447	PAI waived due to inspectional history.	Inspections conducted 11/06/2015, 11/12/2013, and 11/16/2012 resulted in VAI conclusions.	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.
Drug product release & stability testing. (Also performs drug substance	Merck Serono S.p.A. Guidonia Montecelio, Italy	FEI 3002807252	Latest surveillance inspection conducted 02/20/2015 resulted in NAI and approve decision.	No observations issued during most recent inspection conducted 02/20/2015.	RECOMMENDED FOR APPROVAL FROM A FACILITIES ASSESSMENT STANDPOINT.



QUALITY REVIEW



release & stability testing.)					
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E. Lifecycle Knowledge Management

a. Drug Substance

- i. Protocols approved: Annual GMP stability protocol and stability protocols for the extension of shelf life. Concurrent validation protocol for (b) (4) protocol. Qualification of new reference standard (primary and secondary) and new WCB.
- ii. Outstanding review issues/residual risk
- iii. Future inspection points to consider: Evaluation of trending program to evaluate (b) (4) batch manufacture

b. Drug Product

- i. Protocols approved: Annual GMP stability protocol and stability protocols for the extension of shelf life.
- ii. Outstanding review issues/residual risk
- iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

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

14.	Other_____				
Regulatory Considerations					
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)			x	
16.	Comparability Protocol(s)			x	
17.	End of Phase II/Pre-NDA Agreements tem)			x	
18.	SPOTS (Special Products On-line Tracking System			x	
19.	USAN Name Assigned		x		
20.	Other_____			x	
Quality Considerations					
21.	Drug Substance Overage			x	
22.	Design Space	Formulation		x	
23.		Process		x	
24.		Analytical Methods		x	
25.		Other		x	
26.	Other QbD Elements				
27.	Real Time Release Testing (RTRT)			x	
28.	Parametric Release in lieu of Sterility Testing			x	

29.	Alternative Microbiological Test Methods		x	
30.	Process Analytical Technology in Commercial Production		x	
31.	Non-compendial Analytical Procedures	Drug Product	x	
32.		Excipients	x	
33.		Drug Substance	x	
34.	Excipients	Human or Animal Origin		x
35.		Novel		x
36.	Nanomaterials		x	
37.	Genotoxic Impurities or Structural Alerts		x	
38.	Continuous Manufacturing		x	
39.	Use of Models for Release		x	
40.	Other _____		x	



Arulvathani
Arudchandran

Digitally signed by Arulvathani Arudchandran
Date: 2/21/2017 09:12:55AM
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Juhong
Liu

Digitally signed by Juhong Liu
Date: 2/21/2017 01:20:19PM
GUID: 508da6da000265f64de5224635a510aa



Joel
Welch

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Lakshmi Rani
Narasimhan

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Date: 2/24/2017 10:27:56AM
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Reyes
Candau-Chacon

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Date: 2/21/2017 08:47:33AM
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Patricia
Hughes Troost

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Date: 2/21/2017 09:54:07AM
GUID: 508da717000297bcbfce0919f8c09594



Steven
Fong

Digitally signed by Steven Fong
Date: 2/21/2017 08:44:23AM
GUID: 508da717000297d4c049faedea31f7c1



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 22,
Silver Spring, MD 20993

Date: February 24, 2016
To: Administrative File, BLA 761049X0
From: Lakshmi Rani Narasimhan, Ph.D., CDER/OPQ/OPF/DMA
Endorsement: Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/ OPQ/OPF/DMA
Subject: Biological License Application (BLA)
US License: 1773
Applicant: EMD Serono, Inc.
Facility: Merck Serono S.A., Succursale d'Aubonne, Zone Industrielle de l'Ourietaz
CH-1170 Aubonne, Switzerland (FEI# 3002807447)
Product: avelumab
Dosage: Sterile, liquid formulation (20mg/mL) in a single use vial for intravenous infusion
Indication: For the treatment of patients with metastatic Merkel Cell Carcinoma (mMCC)
Due Date: May 23, 2017

Recommendation for Approvability: The drug product section of this BLA, as amended, is recommended for approval from a product quality microbiology perspective with the following post-market commitment (PMC):

Implement the performance at least one media fill run per year which incorporates both the maximum sterile hold time after filtration and the maximum filing time starting from 2017. Submit the information and summary data from the first 2017 media fill as a post marketing commitment in accordance with 21 CFR 601.12.

SUMMARY: EMD Serono, Inc. (EMD) has submitted a new biologics license application, BLA 761049 to license the use of avelumab. Drug substance is manufactured by Merck Serono S.A., Corsiersur-Vevey, Switzerland and drug product is manufactured at Merck Serono S.A., Aubonne, Switzerland.

The rolling application was submitted in eCTD format and included Module 1.1.2 - FDA form 356h, Module 1.2 - Cover letter, and 1.14 - Labeling, Module 2 and Module 3 (Sequence# 0003).

INTRODUCTION:

Avelumab drug product (DP) is manufactured by (b) (4) from Avelumab drug substance (DS) at Merck Serono S.A., Aubonne, Switzerland.

This review covers the evaluation of the drug product aspects of the application from a product quality microbiology perspective.

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0002	September 02, 2016	Original
0009	November 04, 2016	Amendment
0018	December 16, 2016	Amendment
0019	December 19, 2016	Amendment
0028	January 30, 2017	Amendment
0035	February 13, 2017	Amendment
0036	February 15, 2017	Amendment

ASSESSMENTS:**3.2.P DRUG PRODUCT**

DP manufacturing process includes (b) (4)

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

DP is a preservative-free, sterile, clear solution presented at the concentration of 20 mg/mL in a single-use vial. In order extract a volume of 10 mL, vials are filled with (b) (4) mL of DP. The composition of DP provided in Table 1 is reproduced below.

Table 1: Composition of Avelumab Drug Product

Raw material	Function	Quality Grade	Fill Weight (mg/vial)
Avelumab	(b) (4)	In-House	200.0 mg
D-Mannitol		Ph. Eur. USP, JP	510.0 mg
Acetic acid glacial*		Ph. Eur., USP, JP	6.0 mg
Polysorbate 20		Ph. Eur., USP, JPE	5.0 mg
Sodium hydroxide*		Ph. Eur., USP, JP	3.0 mg
Water for injection		Ph. Eur., USP, JP	q.s.** 10 mL

USP: US Pharmacopoeia; Ph. Eur.: European Pharmacopoeia; JP: Japanese Pharmacopoeia, JPE: Japanese Pharmaceutical Excipients

* Corresponding to (b) (4)

**q.s.: quantum satis (for as much as required)

An overfill of (b) (4) mL is added to the nominal volume to guarantee an extractable volume of 10 mL

Reviewer's comments: The pH release specification for DP is pH (b) (4)

Satisfactory

3.2.P.2 PHARMACEUTICAL DEVELOPMENT**Microbiological Attributes**

The DP solution is (b) (4)

(b) (4)

FDA question (January 03, 2017):

The microbiological challenge study data does not support twice the label's recommended storage period of (b) (4) for the 0.9% or 0.45% sodium chloride solution diluted drug product. At 15 hour time point, P.aeruginosa and E.coli exhibited significant growth, a

log10 increase of > 0.5 reached 4.0 at 72 hour time point. Lack of growth at twice the post-dilution storage duration (b) (4) was not demonstrated. Please reduce the post-dilution storage period for the 0.9% or 0.45% sodium chloride solution diluted drug product to "not more than 4 hours" at room temperature.

Firm's Response in amendment dated January 30, 2017 in sequence # 0028: The post-dilution storage time of the DP will be reduced to "not more than 4 hours" at room temperature and the labeling will be revised accordingly.

Satisfactory

3.2.P.3.1. MANUFACTURER(S)

FDA questions (November 02, 2016): It is not clear whether all drug product QC, lot release and stability tests are performed at each site where QC, lot release and stability testing is specified in 3.2.P.3.1. Update the BLA with the specific tests that are performed at each of the sites.

Firm's Response in amendment dated November 04, 2016 in sequence # 0009: The following table listing the manufacturing and testing sites for DP is formulated from the revised information provided in the application.

Name and address of manufacturer	Activities Performed
Merck Serono S.A. Succursale d'Aubonne Zone Industrielle de l'Ouriettaz CH-1170 Aubonne Switzerland	• All manufacturing operations for the drug product ▪ All QC lot release testing except the cell binding assay and the RP-HPLC-ELSD method ▪ Labeling and secondary packaging ▪ Release of DP
Merck Serono S.p.A. Via Luigi Einaudi, 11 00012 Guidonia Montecelio (Roma) Italy	▪ All QC lot release testing including the cell binding assay and the RP-HPLC-ELSD method ▪ Stability Testing
Merck Serono S.A. Centre Industriel CH-1267 Coinsins Switzerland	▪ Labeling and secondary packaging
(b) (4)	▪ Labeling and secondary packaging

Satisfactory

3.2.P.3.2. BATCH FORMULA

(b) (4)

3.2.P.3.3. DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

(b) (4)

(b) (4)

Satisfactory

3.2.P.8 STABILITY

DP lots were evaluated at the following storage conditions, long-term storage at $5\pm 3^{\circ}\text{C}$, accelerated, $25\pm 2^{\circ}\text{C}$ and $60\pm 5\%$ RH and stressed, $40\pm 2^{\circ}\text{C}$ and $75\pm 5\%$ RH. Based on these data, a 24-month shelf life is proposed for DP at the recommended temperature of $5\pm 3^{\circ}\text{C}$ when protected from light. Sterility, endotoxin and were tested initially and annually until expiry for the primary lots in long-term storage at $5\pm 3^{\circ}\text{C}$. Additionally, CCIT was implemented initially and annually until expiry starting the PV batches in the long term stability protocol. All batches met the acceptance criteria for sterility, endotoxin for the tested time points. PV batches passed the CCIT performed by HVLD method for the initial time point and the test results for the other time points are not yet available.

Post-Approval Annual Stability Protocol and Commitment

One batch of DP per year will be placed at long-term storage storage conditions. In the post approval stability program microbiological tests (endotoxin, sterility, and CCI) are performed annually until expiry.

CCI validation report, Report 38401 and SOP are included in this section.

(b) (4)

(b) (4)

Conclusion

- I. The drug product section of this BLA, as amended, is recommended for approval from a product quality microbiology perspective with the following post-market commitments (PMC):
 - Implement the performance at least one media fill run per year which incorporates both the maximum sterile hold time after filtration and the maximum filling time starting from 2017. Submit the information and summary data from the first 2017 media fill as a post marketing commitment in accordance with 21 CFR 601.12.
- II. Product quality aspects other than microbiology are deferred to the OBP reviewer.
- III. See Panorama for the compliance status of the drug product manufacturing site.

The following information requests sent out during the review cycle were satisfactorily addressed by the Sponsor

November 02, 2016

1. Labeling

Avelumab drug product does not contain a preservative. The proposed labeling claims that drug product diluted in 0.9% or 0.45% sodium chloride solution may be stored refrigerated at 2-8°C (36-46°F) (b) (4) for up to 24 hours. Please submit microbiological studies to support the 24 hour storage time at 2- 8°C (b) (4)

(b) (4) Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions for twice the recommended storage period, and use the label-recommended diluent. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of this data, the product labeling should recommend that the post-dilution storage period is not more than 4 hours at 2-8°C or at room temperature.

2. Container closure integrity test

Microbial immersion:

- a. Please clarify and confirm if the vials used for qualification of microbial immersion CCI test methods are the same as the commercial vials described in 3.2.P.7.
- b. The microbial immersion CCI test method was not qualified using worst case pressure or vacuum challenge and a compromised positive control. Compromised positive-control vials with known breach sizes should be included and exposed to the same worst case conditions as the test vials to assess the efficiency of the CCI test method.

Capping Force

- c. Please provide CCI test results obtained using with worst-case crimping process parameters to qualify the container closure system for avelumab drug product.

3. Manufacturer(s)

It is not clear whether all drug product QC, lot release and stability tests are performed at each site where QC, lot release and stability testing is specified in 3.2.P.3.1. Update the BLA with the specific tests that are being performed at each of the sites.

4. Drug product manufacturing process

(b) (4)

(b) (4)

January 13, 2017

FDA comments on the response submitted in amendment dated November 04, 2016

1. Labeling

The microbiological challenge study data does not support twice the label's recommended storage period of (b) (4) for the 0.9% or 0.45% sodium chloride solution diluted drug product. At 15 hour time point, *P.aeruginosa* and *E.coli* exhibited significant growth, a log₁₀ increase of > 0.5 reached 4.0 at 72 hour time point. Lack of growth at twice the post-dilution storage duration (b) (4) was not demonstrated. Please reduce the post-dilution storage period for the 0.9% or 0.45% sodium chloride solution diluted drug product to "not more than 4 hours" at room temperature.

2. Drug product manufacturing process

- a. Submit the protocol for (b) (4) process step.

- b. Clarify and confirm that (b) (4) in the event of bioburden action limits are exceeded. In addition, indicate if additional bioburden samples will be taken (b) (4).

(b) (4)



(b) (4)



February 07, 2017

FDA comments on the response submitted in amendment dated January 30, 2017:

Process Validation

(b) (4)



(b) (4)

Validation of Analytical procedures

Clarify if sterility and endotoxin testing of the avelumab drug product is performed at Merck Serono S.p.A., Guidonia Montecelio (Roma), Italy site and submit the method qualification/verification data to support the performance of these tests at this site.

February 14, 2017**FDA comments on the response submitted in amendment dated February 13, 2017:**

(b) (4)



**Lakshmi Rani
Narasimhan**

Digitally signed by Lakshmi Rani Narasimhan

Date: 2/24/2017 10:19:43AM

GUID: 508da7160002976791592556d218b997



**Patricia
Hughes Troost**

Digitally signed by Patricia Hughes Troost

Date: 2/24/2017 10:23:20AM

GUID: 508da717000297bcbf0e0919f8c095694



**U.S. FOOD & DRUG
ADMINISTRATION**

BLA STN 761049

Bavencio (Avelumab)

**Manufacturer
MERCK SERONO SA**

**Reviewer
Arulvathani Arudchandran, Ph.D.**

**TL
Joel Welch, Ph.D.**

**Office of Biotechnology Products
Division of Biotechnology Review and Research II**

OBP CMC Review Data Sheet

1. **BLA#:** STN 761049
2. **REVIEW DATE:** February 17 2017
3. **PRIMARY REVIEW TEAM:**
- | | |
|-------------------------------|---|
| Medical Officer: | Denise Casey |
| Pharm/Tox: | Alexander Putman |
| Product Quality Team: | Arulvathani Arudchandran
Reyes Candauchaon
Lakshmi Narasimhan |
| Facilities: | Steven Fong |
| Clinical Pharmacology: | Safaa Burns and Fourie Zirkelbach, Jeanne |
| Statistics: | Pallavi Mishra-Kalyani |
| OBP Labeling: | Jibril Abdus-Samad |
| Product quality RBPM: | Truong Quach |
| RBPM: | Idara Udoh |

4. **MAJOR GRMP DEADLINES**
- | | |
|------------------------------|-------------------|
| Filing Meeting: | November 8 2016 |
| Mid-Cycle Meeting: | December 8 2016 |
| Late-Cycle Meeting: | February 27, 2017 |
| Primary Review Due: | February 23 2017 |
| Secondary Review Due: | February 24 2017 |
| ATL Memo Due: | March 15 2017 |
| PDUFA Action Date: | March 23 2017 |

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

Communication/Document	Date
Planning meeting with DOP2	October 17 2016
Application orientation meeting with sponsor	October 18 2016
Mid-Cycle meeting DOP2	December 8 2016
Mid-Cycle communication – Sponsor /T-con	January 5 2016
Labeling meeting with DOP2	January 9 2017
Labeling meeting with DOP2	January 17 2017
Team meeting with DOP2	February 7 2017
Late cycle meeting with DOP 2	February 27 2017

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

Submission	Date Received	Review Completed (Yes/No)
Module 3 Quality ; as part of the rolling submission #0002	Sep.2 2016	Yes

Immunogenicity assay validation (Module 5.3.1.4), Module 2, Module 1- #0003	Sep 23 2016	Yes
Quality response to IR # 0009	Nov 04 2016	Yes
Quality response to IR #0013	Nov 29 2016	Yes
Quality response to IR #0015	Dec.9 2016	Yes
Stability update , shipment validation- #0018	Dec.16 2016	Yes
Quality response to IR # 0022	Dec.23 2016	Yes
Quality response to IR #0026	Jan 10 2017	Yes
Quality response to IR #0032	Feb 6 2017	Yes
Quality response to IR #0036	Feb 15 2017	Yes

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

- a. **Proprietary Name:** Bavencio
- b. **Trade Name:** Bavencio
- c. **Non-Proprietary/USAN:** Avelumab
- d. **CAS name:** 1537032-82-8
- e. **Common name:** MSB0010718C
- f. **INN Name:** Avelumab
- g. **Compndial Name:** None
- h. **OBP systematic name:** MAb Human (IgG1) ANTI Q9NZQ7 (PD1L1_HUMAN) [MSB0010718C]
- i. **Other Names:** None

8. **PHARMACOLOGICAL CATEGORY:** Therapeutic recombinant humanized monoclonal IgG1 antibody.
- a. **PRODUCT:** Anti-PD-L1 antibody ((MSB0010718C)
 - b. **DOSAGE FORM:** Injection for intravenous infusion, 10 mg/kg, once every two weeks.
 - c. **STRENGTH/POTENCY:** 200 mg/10 mL
 - d. **ROUTE OF ADMINISTRATION:** Intravenous infusion

9. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Type	COMMENTS (STATUS)
	(b) (4)	Glass vial	Type III	Sufficient detail included in BLA
		Rubber Stopper	Type III	Sufficient detail included in BLA

10. **INSPECTIONAL ACTIVITIES-** Merk Serono S.A., Corsier-sur-Vecvey, Switzerland, FEI # 3003131678, start date 11/7/2016, end date- 11/15/2016.

The pre-license inspection covered the manufacturing operations for avelumab DS under BLA

STN 761049; conducted by reviewers from OBP, DMA, and DIA. The PLI covered quality assessment procedures, manufacturing process, facilities and equipment, material management, data entry, contamination prevention, laboratory controls, and training programs. Assessment was made in accordance with ICH Q7A. A four-item 483 was issued; all four issues are related with bio burden assessment and control. A waiver for the inspection of the DP facility was issued.

11. **CONSULTS REQUESTED BY OBP- N/A**

12. **QUALITY BY DESIGN ELEMENTS –**

The following was submitted in the identification of QbD elements (check all that apply):

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

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The data submitted in BLA 761049 support the conclusion that the manufacturing process of Bavencio (avelumab) is well controlled and leads to a product that is pure and potent. From the product quality perspective, I recommend Bavencio (avelumab) be approved for human use under conditions specified in the package insert.

II. List Of Deficiencies To Be Communicated- None

III. List Of Post-Marketing Commitments/Requirement

PMC:

- a. Conduct an assessment of treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses with validated assays (including an updated cutpoint for the screening and confirmatory ADA assay and the neutralizing assay as requested in PMC b) capable of sensitively detecting ADA responses in the presence of avelumab levels that are expected to be present in the serum at the time of patient sampling. The ADA response be evaluated in at least 300 avelumab -treated patients. The final report will include information on the level of avelumab in each patient's test sample at each sampling point with an appropriate cutpoint.

- b. Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against avelumab in the presence of avelumab levels that are expected to be present in samples at the time of patient sampling. Patient samples should be banked for storage until the improved method is available.

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment or Claim Of Categorical Exclusion

A claim for a categorical exclusion is being made under 21 CFR 25.31 (c). This application is for marketing approval of a biologic product comprised of substances that occur naturally in the environment and approval of this action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. To the sponsor's knowledge, no extraordinary circumstances, as described in 21 CFR 25.21, exist that would result in significant impact to the environment from the discharge of this substance. This waiver is appropriate and found acceptable.

V. Primary Container Labeling Review

The primary and secondary container closure labeling review is performed in a separate review by Jibril Abdus Samad, OBP.

VI. Review Of Common Technical Document-Quality Module 3.2 – Refer below

VII. Review Of Immunogenicity Assays – Module 5.3.1.4 – Refer below

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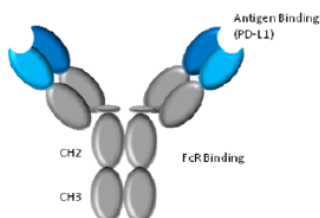
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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT**S. DRUG SUBSTANCE****3.2.S.1 General Information****3.2. S.1.2 Structure**Primary structure:

Avelumab (MSB0010718C) is a human immunoglobulin G1 (IgG1 λ) monoclonal antibody directed against the programmed death ligand-1 (PD-L1) molecules. PD-L1 molecules are expressed on surfaces of tumor cells and immune cells that are found in the tumor micro-environment. The recombinant antibody is produced in (b) (4) and contains two heavy chains (450 amino acid residues each) and two light chains (216 amino acid residues each) with antigen (PD-L1) binding and FcR binding regions. The schematic diagram of the antibody is given below, presented in the submission.

Structure of Avelumab

Amino acid sequence:

The amino acid sequences of the light chain and heavy chain with intra-chain disulfide bonds are indicated below, directly obtained from the submission.

Figure 2: Primary Amino Acid Sequence of the Lambda Light Chain

```
QSALTQPASV SGSPGQSITI SCTGTSSDVG GYNYVSWYQQ HPGKAPKLMI
YDVSNRPSGV SNRFGSKSG NTASLTISGL QAEDEADYYC SSYTSSSTRV
FGTGTQVTVL GQPKANPTVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV
AWKADGSPVK AGVETTKPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT
HEGSTVEKTV APTECS
```

Figure 3: Primary Amino Acid Sequence of the Heavy Chain

```
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYIMMWVRQA PGKGLEWVSS
IYPSGGITFY ADTVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARIK
LGTVTVDYV GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK
DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSVVT VPSSSLGTQT
YICNVNHHKPS NTKVDKKVEP KSCDKHTTCP PCPAPPELLGG FSVFLFPPKP
KDTLMISRTP EVTCVVDVVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
STYRVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ
VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTPPV
LDSGDSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
```

VL region: 1~110, VH region: 1~120

Intra-chain disulfide bond positions: Cys138-Cys197; Cys22-Cys96; Cys147-Cys203; Cys264-Cys324; Cys370-Cys428; Cys22-Cys90.

Reviewer comment:

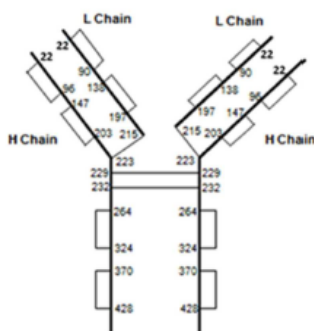
*The most aligned light chain V-region gene is human IGLV2-14*01 and the most aligned heavy chain V-region is IGHV3-23*01. The homology of the heavy and light chains of avelumab to human VH and VL regions is greater than 90% indicating its identity as a fully human monoclonal antibody.*

The sponsor provided data from the liquid chromatography- mass spectrometry (LC-MS) analysis (characterization section, S.3.1) and confirmed the formation of the six intra-chain disulfide bonds.

Higher order structure:

The schematic diagram of the higher order structure indicated below is directly obtained from the submission.

Higher Order Structure of Avelumab



Reviewer comment:

In addition to the six intra-chain disulfide bonds, three different inter-chain disulfide bonds are identified. Two are between the heavy chains (Cys229-Cys229; Cys232- Cys232) and one connects the heavy and the light chain (Cys215-Cys223).

3.2.S.1.3 General Properties

The recombinant heterodimer human monoclonal antibody drug substance (DS) is a clear solution with the pI value ranges from 8.5 to 9.3. The calculated molecular weight is 22,806 Da for the light chain subunit and 49,126 Da for the heavy chain subunit. The calculated molecular weight of the intact avelumab molecule is 144 Da and 147Da with glycosylation.

Mechanism of action:

PD-L1 molecule is expressed as an immune check point inhibitor on epithelial, vascular, endothelial, immune, and tumor cells. The mechanism of action of avelumab is based on the selective binding to PD-L1 molecules on the surface of tumor cells and blocking the interaction between PD-L1 and PD-1. PD-L1 expression is expressed in a broad range of malignancies and PD-L1/PD1 pathway has been identified as playing a major role that allows the tumor to escape elimination by the immune system. Eradicating the binding of PD-L1 to its receptor PD-1

removes the suppressive effects of PD-L1 on anti-tumor CD8+ T-cells. This will result the restoration of cytotoxic T cell response.

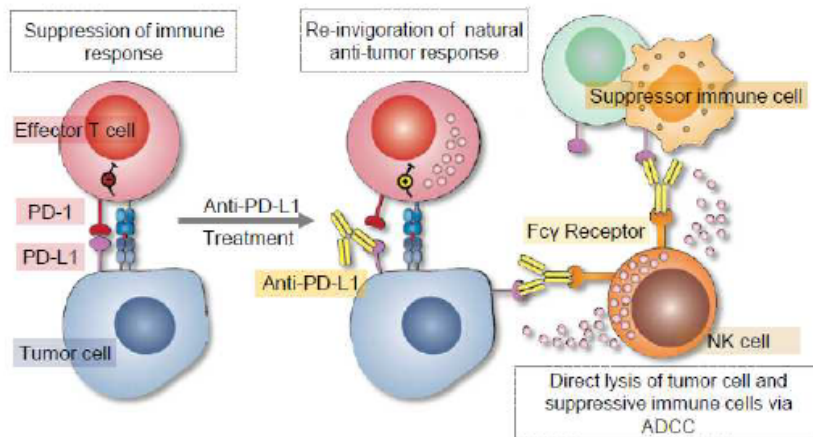
A secondary mechanism of action for avelumab is also proposed through the induction of antibody dependent cytotoxicity, ADCC. To support the evaluation of the mechanism(s) of action, *in vitro* binding studies were performed using various human cancer cell lines and evaluated by flow cytometry. Both ADCC and CDC were also assessed using *in vitro* assays. Additionally, mice were inoculated with tumor cells that were depleted of CD8+ T cells and demonstrated the criticality of these cytotoxic T cells for function. To evaluate the contribution of ADCC activity, a deglycosylated version of avelumab was evaluated in several studies. A measurable reduction in anti-tumor activity was observed when the non-glycosylated version was evaluated in the same MC38 cell line, used in the CD8 depletion study. Additionally, when NK cells were systemically depleted prior to treatment with avelumab, a reduction in anti-tumor effect was also observed. However, recent literature (*Clinical & Translational Immunology* (2016) 5, e83; doi:10.1038/cti.2016.27) suggests that “avelumab did not induce lysis of activated human immune cells that express elevated levels of PD-L1, but instead significantly increased antigen-specific immune activation”. Thus, it remains unclear to what degree, if any, ADCC contributes to the activity of avelumab.

The biological activity (potency) of avelumab is determined by an *in vitro* cell binding assay. During the assay, avelumab is coated on ELISA plate and the binding ability to human PD-L1 receptor on HEK-293 cells is measured. Different concentrations of avelumab are coated on ELISA plates via Fc portion of the antibody. A fixed number of cells are added and unbound HEK-293 cells are washed out after a certain period. The bound cells are quantified using ATP monitoring system. The concentration of avelumab able to bind 50% of the maximum possible PD-L1 binding capacity (EC_{50}) is calculated. The sponsor reports the potency as relative % to the reference material.

Reviewer Comment:

A test for glycosylation, sufficient to control ADCC activity is proposed and the control strategy designed under the presumption that ADCC may play a role.

A schematic figure reproduced directly from the submission describes the potential mechanisms of action.

Figure 3: Avelumab Mechanism of Action

Avelumab is generated as an anti-PD-L1 treatment for patients with metastatic Merkel cell carcinoma whose disease has progressed after at least one previous chemotherapy regimen.

3.2.S.2 Manufacture

(b) (4)

In addition, the sponsor provided data from the photo stability testing studies to support the use of secondary container closure system. In this study, DP vials were kept in dark, exposed to light with and without the secondary container closure system for 6 days. Following exposure, physicochemical parameters were assessed. Data from the study demonstrated that comparable values were obtained for the sample that was kept in the secondary package to that of the unexposed one (Table 6), not copied here.

Reviewer comment:

The sponsor performed the experiments as per ICH Q1B, and provided data to support the suitability of the secondary container closure system. Overall information provided is found acceptable to support the suitability of the secondary container closure system.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

Avelumab DP batches were manufactured through two different processes, process A and process B at Merck Serono Aubonne, Switzerland. The composition of the batches used in the primary stability studies (process B) and in the supportive stability studies (process A) are indicated below.

Table 3: Comparison of Dose Presentation

	Primary Stability Batches	Supportive Stability Batches
Avelumab Content	200 mg / vial	(b) (4)
Formulation	mannitol, sodium acetate buffer and polysorbate 20	
Filling Volume	10 mL	
Container	16 mL Type I glass vial	
Manufacturing Process	Process B	
Manufacturing Facility	MSA (b) (4)	

MSA= Merck Serono Aubonne

Eleven batches from process B and three batches from process A were used in the stability studies and the following table lists the data availability to support the stability of avelumab from process B. The sponsor provided 24-month stability data for the primary batches manufactured through process-B and three month stability data for the process validation batches at the recommended long-term storage conditions. In addition, three month stability data were provided for all batches under stress and accelerated conditions.

Reviewer Comment:

Shelf life is established exclusively based on real time Process B stability data. Additionally, Process B validation batches were considered to have equivalent stability criteria to the primary stability lots.

Table 1: Primary and Process Validation Stability Study Batches

Batch Number	Filling Volume (mL/vial)	Date of Manufacture	Batch Size (vials)	Use of Batch	Available Stability Data	
PD1E001	10	04 Sep 2014	(b) (4)	Stability; Comparability; Clinical Trials	Long-term	5 ± 3 °C up to 24 months
					Accelerated	25 ± 2 °C up to 6 months
					Stressed	40 ± 2 °C up to 3 months
PD1E002	10	08 Sep 2014		Stability; Comparability; Clinical Trials	Long-term	5 ± 3 °C up to 24 months
					Accelerated	25 ± 2 °C up to 6 months
					Stressed	40 ± 2 °C up to 3 months
PD1E003	10	10 Sep 2014		Stability; Comparability; Clinical Trials	Long-term	5 ± 3 °C up to 24 months
					Accelerated	25 ± 2 °C up to 6 months
					Stressed	40 ± 2 °C up to 3 months
PD1F004	10	22 Jun 2015		Stability, Clinical Trials	Long-term	5 ± 3 °C up to 12 months
					Long-term	5 ± 3 °C up to 12 months in inverted position
					Accelerated	25 ± 2 °C up to 6 months
					Stressed	40 ± 2 °C up to 3 months in inverted position
PD1F005	10	24 Jun 2015		Stability, Clinical Trials	Long-term	5 ± 3 °C up to 12 months
					Accelerated	25 ± 2 °C up to 6 months
PD1F006	10	08 Jul 2015		Stability Clinical Trials	Long-term	5 ± 3 °C up to 12 months
					Accelerated	25 ± 2 °C up to 6 months
PD1G006 /1	10	09 Mar. 2016		Process validation	Long-term	5 ± 3 °C up to 3 months
					Accelerated	25 ± 2 °C up to 3 months
					Stressed	40 ± 2 °C up to 3 months
PD1G007	10	11 Mar. 2016		Process validation	Long-term	5 ± 3 °C up to 3 months
					Accelerated	25 ± 2 °C up to 3 months
PD1G008	10	14 Mar. 2016		Process validation	Long-term	5 ± 3 °C up to 3 months
					Accelerated	25 ± 2 °C up to 3 months
PD1G009	10	31 Mar. 2016		Process validation	Long-term	5 ± 3 °C up to 3 months
					Accelerated	25 ± 2 °C up to 3 months
PD1G010	10	29 Mar 2016		Process validation	Long-term	5 ± 3 °C up to 3 months
					Accelerated	25 ± 2 °C up to 3 months
					Photostability	25 ± 2 °C, simulated daylight conditions

Shelf life:

The sponsor proposed a shelf-life of 24 months at the recommended storage temperature of 5 ± 3°C. The drug product should be protected from light during the storage period and after the dilution it could be exposed to light up to 24 hours prior to administration.

Stability protocol:

Table 5: Long Term Stability Protocol – Primary Stability Batches

Quality Attribute	Time points (Months)											
	0	3	6	9	12	18	24	30	36	48	60	
Appearance – visible particles	x	x	x	x	x	x	x	x	x	x	x	
Clarity and degree of opalescence	x	x	x	x	x	x	x	x	x	x	x	
Degree of coloration	x	x	x	x	x	x	x	x	x	x	x	
pH	x	x	x	x	x	x	x	x	x	x	x	
Osmolality	x	x	x	x	x	x	x	x	x	x	x	
Particulate contamination: sub-visible particles	x	x	x	x	x	x	x	x	x	x	x	
Extractable volume	x	x	x	x	x	x	x	x	x	x	x	
Charge Variants	x	x	x	x	x	x	x	x	x	x	x	
Charge variants pI range*	x	x	x	-	-	-	-	-	-	-	-	
CPI of clusters	x	x	x	x	x	x	x	x	x	x	x	
Protein content	x	x	x	x	x	x	x	x	x	x	x	
Polysorbate 20 content***	x	x	x	x	x	x	x	x	x	x	x	
Polysorbate 20 Identity***	x	x	x	x	x	x	x	x	x	x	x	
Mannitol Concentration***	x	x	x	x	x	x	x	x	x	x	x	
Mannitol Identity***	x	x	x	x	x	x	x	x	x	x	x	
Biological activity	x	x	x	x	x	x	x	x	x	x	x	
ADCC***	x	x	x	x	x	x	x	x	x	x	x	
High molecular weight (HMW) species	x	x	x	x	x	x	x	x	x	x	x	
Identification by SE-HPLC	x	x	x	x	x	x	x	x	x	x	x	
Intact Monomer Calculation by SE-HPLC/ CE-SDS	x	x	x	x	x	x	x	x	x	x	x	
Low molecular weight (LMW) species by CE-SDS*	x	x	x	x	x	x	x	x	x	x	x	
Electrophoretic purity by CE-SDS	x	x	x	x	x	x	x	x	x	x	x	
Glycosylation***	x	x	x	-	x	-	x	-	x	x	x	
Deamidation **	x	x	x	x	x	x	x	x	x	x	x	
Oxidation**	x	x	x	x	x	x	x	x	x	x	x	
Sterility	x	-	-	-	x	-	x	-	x	x	x	
Bacterial endotoxin	x	-	-	-	x	-	x	-	x	x	x	
CCIT****	x				x		x		x	x	x	

* PD1E001, PD1E002, PD1E003, (2014 campaign) only

**Oxidation and deamidation performed on 2014 campaign batches starting the 18-mo time point only

*** Glycosylation, ADCC, mannitol and polysorbate were not performed on the 2014 campaign batches.

****CCIT implemented starting the PV batches

Stability protocols proposed for monitoring stability at long-term conditions is followed for the monitoring the stability under the accelerated conditions; the duration is for 6 month for accelerated stability monitoring protocol.

Photo stability protocol:

The sponsor stated that photo stability testing was performed as per ICH Q 1B (option2). Vials were kept horizontally and were exposed to light conditions of 1.2 million lux hours and an integrated near ultraviolet energy of 200 watt h/m² in a light chamber set at 25°C for 6 days. Data were obtained from non-exposed, exposed, and dark control samples.

Reviewer comment:

All stability protocols are found acceptable, additional tests were included in the stability protocol that was generated to assess the stability of the DP batches from process B compared to the protocol generated for Process A DP stability monitoring. Criteria associated with ongoing stability programs have been revised to reflect proposed commercial criteria.

The sponsor followed a statistical analysis approach (as per ICH Q1E) to evaluate the data obtained for the stability indicating parameters, such as biological activity, protein content, LMW, HMW, oxidation, deamidation, and charge variants. The stability comparison between primary batches (process B) and the supportive batches (process A) was performed using a homogeneity of slopes approach. The sponsor started monitoring deamidation and oxidation from 2015 and therefore no comparison was made between process B and process A DP batches for these attributes.

In-use stability:

The sponsor notes that (b) (4).

However, the stability of the diluted DP under light exposure was demonstrated for up to 24 hours, review could be found under section 3.2.P.2.6-pharmaceutical development compatibility.

3.2.P.8.2 Post-Approval Stability Commitment

The sponsor stated the post-approval commitment as follows “One commercial avelumab Drug Product batch will be added to the stability program annually, if commercial production occurs during the calendar year. The studies will be performed in the avelumab Drug Product primary packaging. The Drug Product will be tested until end of shelf life following the protocol outlined in the table below”.

Table 1: Post-Approval Stability Commitment

Test	Time Point				
	0	6	12	24	36
Appearance	X	X	X	X	X
pH	X	-	X	X	X
Degree of coloration	X	-	X	X	X
Clarity and degree of opalescence	X	-	X	X	X
Extractable volume	X	-	X	X	X
Osmolality	X	-	X	X	X
Particulate contamination: sub-visible particles	X	-	X	X	X
Charge variants by ICE	X	X	X	X	X
Protein content by O.D.	X	X	X	X	X
Polysorbate 20 content	X	X	X	X	X
Biological activity	X	-	X	X	X
LMW species by CE-SDS under non-reduced conditions	X	X	X	X	X
Electrophoretic purity by CE-SDS under reduced conditions	X	X	X	X	X
Oxidation	X	X	X	X	X
Deamidation	X	X	X	X	X

Table 1: Post-Approval Stability Commitment (Cont.)

Test	Time Point				
	0	6	12	24	36
Container Closure Integrity	X	-	X	X	X
Bacterial endotoxins	X	X	X	X	X
Sterility	X	X	X	X	X

Reviewer comment:

The information provided for the post-approval stability commitment was not adequate and was revised to include an assessment of high molecular weight species. The sponsor stated that all analytical procedures are same as the ones used to analyze the DP at release and stability. Additionally, the sponsor developed a new container closure integrity testing method for the post-approval stability program and the review for the validation of this method is referred to DMA.

As a response to IR (1/10/2017), the sponsor included the test with appropriate acceptance criterion to monitor HMW species in the post approval stability protocol.

3.2.P.8.3 Stability Data

Long-term storage conditions:

The sponsor provided stability data for three process B batches (24 months) and for three process validation batches (3 months) at the long-term storage conditions. All critical product quality attributes were monitored as specified in the stability protocol.

Reviewer comment:

Tests of appearance (Color, Clarity/Opalescence, visible particle), pH, osmolality, sub-visible particles, Extractable volume, Identification (SE-HPLC, and iCE), Charge Variant Profile, Protein Content, Potency, Aggregates, LMW Species (NRCE-SDS), Electrophoretic Purity (RCE-SDS), and ADCC remain unchanged throughout shelf life.

Tests for ADCC, Polysorbate 20, Deamidation, and Oxidation were introduced later in development and lack the full data set for the primary stability program. However, their results are similar to release tests associated with PV batches and are sufficient to presume them to be stable throughout the shelf life, as they were incorporated and tested at the 18 and 24 month timepoint for the primary batches. Up to 12 months for the PV batches is available as well. No change was observed.

The sponsor revised all acceptance criteria in the stability data table according to the ones stated in the stability specifications (response-1/10/2017). In addition, the sponsor commits to test leachables on aged DS and DP materials prior to extending the DS and DP shelf-life (response- 1/10/2017).

Review of SVP less than 10 microns is described in section 3.2.P.5.4.

Accelerated condition:

Data is provided (12/16/2016) for three process validation batches that were assessed at 25°C ± 2°C and RH 60% ± 5%. Six months of data is provided for the primary stability program.

Reviewer comment:

No change is observed for appearance (Color, Clarity/Opalescence, visible particle), pH, osmolality, sub-visible particles, Extractable volume, Identification (SE-HPLC, and iCE), and Protein Content.

Approximately 7% increase in acidic variants, a 15% increase in potency, a 1% increase in LMW by CE-SDS, a 0.5% decrease in purity by rCE-SDS is observed over 6 months.

Stress condition:

Three months of data is provided for the primary program and were stored at 40°C ± 2°C and RH 75% ± 5%.

Reviewer comment:

No change is observed for appearance (Color, Clarity/Opaescence, visible particle), pH, osmolality, sub-visible particles, Extractable volume, Identification (SE-HPLC, and iCE), and Protein Content.

Approximately 20-25% increase in acidic variants, a 10% decrease in basic variants, a 20% increase in potency, a 4% increase in fragments by nr CE-SDS, and a 4.0% decrease in purity by rCE-SDS is observed. ADCC was not assessed.

A response to IR was provided on December 9, 2016 by the sponsor to address which critical quality attribute(s) change on stability under accelerated and stress conditions is responsible for the increase in potency or decrease in ADCC that is observed. Their response is summarized in section 3.2.S.3.1.9 Biological characterization. Briefly, they attribute it to either deamidation or oxidation but could not provide additional specific information. Specifications control for deamidation and oxidation at release and on stability for both DS and DP.

Photo stability:

Table 1: Photostability Data of Avelumab Drug Product (Cont.)

Tests Acceptance criteria	Time Zero	After Exposure	Dark Control
Protein content by O.D. (b) (4)	21.6	21.4	21.9
Mannitol concentration HILIC-HPLC (b) (4)	48.4	49.3	49.2
Polysorbate 20 concentration RP-HPLC / ELSD (b) (4)	0.46	0.45	0.46
Biological Activity Binding Assay (b) (4)	106	105	106
ADCC Reporter assay (b) (4)	110	90	104
HMW species SE-HPLC NMT (b) (4)	0.7	1.2	0.7
LMW species CE-SDS on Non-Reducing Conditions NMT (b) (4)	3.7	12.5	3.6
Electrophoretic Purity (by CE-SDS) CE-SDS on Reducing Conditions NLT	98.5	94.5	98.4
Intact Monomer Calculation SE-HPLC / CE-SDS Calculation NLT (b) (4)	95.6	86.3	95.7
Deamidation IEX-HPLC NMT (b) (4)	14.3	16.4	14.4
Oxidation Peptide Mapping RP-UPLC NMT (b) (4)	2.3	23.0	2.4

NMT: not more than; NLT: not less than

Reviewer comment:

Data obtained at day 6 after the exposure to light indicated that the product had undergone high oxidation. The light exposure conditions employed in the experiment are very severe and

therefore, obtaining a higher rate of oxidation is not a concern. Protection from light will be included on all labeling and thus, is considered sufficient.

Statistical analysis:

The sponsor performed linear regression analysis for all critical product quality attributes that potentially change on of the DP batches stored under the proposed long-term storage conditions:

(b) (4)

Reviewer comment:

Statistical analysis indicated that the trend for critical product quality attributes would remain within the specification limits for up to 36 months as indicated in the above graphs. A shelf-life of 24 –month period is warranted for DP batches as per sponsor’s claim of the shelf life at the recommended long-term storage condition, at 5 ± 3 °C.

3.2.A Appendices Table of Contents

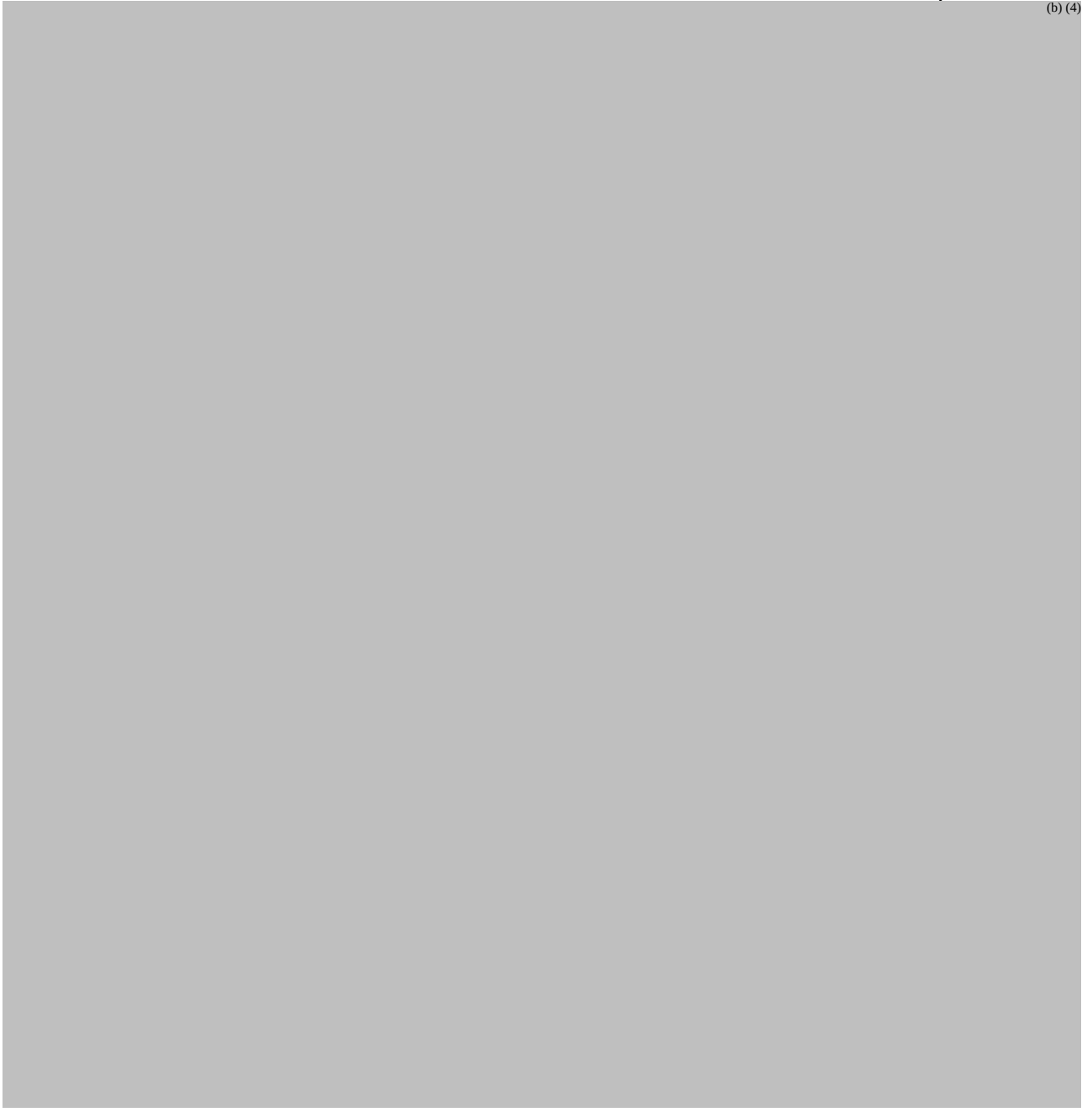
3.2.A.1 Facilities and Equipment- Referred to the facility reviewer

3.2.A.2 Adventitious Agents Safety Evaluation

Raw material / cell line safety:

All raw materials used in the manufacture of avelumab are free of animal derived components.

(b) (4)



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Reviewer comment:

Overall, the qualification of small scale models used in the viral clearance studies, the experimental designs, and the assessment are found appropriate and acceptable, indicating that there is a minimal risk due to adventitious agent transmission during the administration of the avelumab DP.

3.2.A.3 Novel Excipients -None

3.2.R Regional Information (U.S.A.)**3.2.R.1 Executed Batch Records**

Review is done during the pre-licensed inspection- Nov.7 2016- Nov.15 2016 . Refer to the EIR report.

3.2.R.2 Method Validation Package

None

3.2.R.3 Comparability Protocols –N/A

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Immunogenicity:

Treatment related ADA:

Treatment –related anti-drug antibody (ADA) formation was monitored in both EMR100070-003 and EMR100070-001 clinical studies that were conducted for the treatment of patients with solid tumors. Samples were analyzed prior to dosing, every two weeks throughout the study, and at end of treatment visit. Figure 12.9.2.2 indicates the onset of the positive treatment related ADA formation in both clinical trials #001(90 weeks) and #003 (60 weeks). Of the 88 subjects tested in EMR 100070-003, baseline assessment was performed for 85 subjects and found that none of the subjects had baseline positive for ADA.

Reviewer Comment:

The lack of positive pre-existing samples likely reflects a cutpoint set too high due to the use of (b) (4). This is described in the sponsors December 23 2016 response, and a PMC is proposed to provide updated immunogenicity data that will reflect an updated cutpoint.

Post-baseline assessment was done for 82 subjects, and 3 of them have positive ADA results (3.85%). No clear relationship was obtained between the duration of the immunogenicity response and the titer levels, as per the data presented in module 2.7.2.4.1. Similar incidence (3.5%) of ADA formation was observed for both EMR100070-001 and EMR100070-003 studies.

Table 25 Immunogenicity Incidence for Subjects Treated with 10 mg/kg Avelumab for Individual Studies and Integrated Safety Summary

Indication	Solid Organ Tumor		mMCC	Integrated Safety Summary
Studies	EMR100070-001 expansion	EMR100070-002 expansion	EMR100070-003	EMR100070-001 EMR100070-003
Ever positive n/N0 (%)	53/1385 (3.8%)	2/34 (5.9%)	3/88 (3.4%)	56/1484 (3.8%)
Pre-existing n/N1 (%)	7/1218 (0.6%)	0/34	0/85	7/1315 (0.5%)
Treatment boosted n/N2 (%)	0/1132	0/31	0/79	0/1221
Treatment-emergent n/N3 (%)	46/1291 (3.6%)	2/31 (6.5%)	3/82 (3.8%)	49/1383 (3.5%)
Transient n/N3 (%)	16/1291 (1.2%)	0/31	1/82 (1.3%)	16/1383 (1.2%)
Persistent n/N3 (%)	30/1291 (2.3%)	2/31 (6.5%)	2/82 (2.5%)	33/1383 (2.4%) ^a

Source: Study EMR100070-001 CSR, Table 70; Study EMR100070-002 CSR, Table 61; Study EMR100070-003 CSR, Table 49; Module 5.3.5.3 SCS Table 12.9.2.1.1.

N0 = The number of subjects with at least 1 valid result.

N1 = The number of subjects with valid baseline result.

N2 = The number of subjects with valid baseline and at least 1 valid post-baseline result.

N3 = The number of subjects with at least 1 valid post-baseline result and without positive baseline results (including missing, NR).

a One subject was characterized as transient for Study 100070-003 and persistent for the SCS based on slightly different calculations for duration. The SCS calculated duration of 16 weeks including the date of first and last ADA-positive result. The CSR, calculated duration of 15.9 weeks as the difference between the first and last ADA-positive result.

Comparison of immunogenicity for process A and process B materials:

The sponsor compared the incidence of ADA formation for subjects received 10 mg/ml of avelumab for every two weeks. Of the total subjects (#1484) tested, 734 received process A

material and 551 received process B material. Subjects with at least one valid ADA result is accounted for the treatment-related ADA incidence.

Table 9 Immunogenicity Incidence by Drug Manufacturing Process

Process	Process A only	Process B only	All Subjects
Ever positive n/N0 (%)	27/734 (3.7%)	22/551 (4.0%)	56/1484 (3.8%)
Pre-existing n/N1 (%)	4/666 (0.6%)	3/484 (0.6%)	7/1315 (0.5%)
Treatment-boosted n/N2 (%)	0/619	0/437	0/1221
Treatment Emergent n/N3 (%)	23/683 (3.4%)	19/501 (3.8%)	49/1383 (3.5%)
Transient n/N3 (%)	11/683 (1.6%)	1/501 (0.2%)	16/1383 (1.2%)
Persistent n/N3 (%)	12/683 (1.8%)	18/501 (3.6%)	33/1383 (2.4%)

Source: Module 5.3.5.3 SCS Section 12.9.2.1

N0 = The number of subjects with at least 1 valid result at any time point.

N1 = The number of subjects with valid baseline result.

N2 = The number of subjects with valid baseline and at least 1 valid post-baseline result.

N3 = The number of subjects with at least 1 valid post-baseline result and without positive baseline results (including missing, NR).

Reviewer comment:

Information provided in Table 9 demonstrated that comparable immunogenicity incidence occurred when subjects received either process A or process B material. In addition, the method that the sponsor used to categorize the subjects based on ADA results in Table 8 (not copied in the review) is found adequate.

Neutralizing antibody:

The sponsor is currently developing the neutralizing antibody assay (NAb) by utilizing a (b) (4) assay and therefore, no information is available for evaluation to assess the incidence of NAb, a PMC is proposed for this assay.

Reviewer comment:

The reported incidence of immunogenicity is low across the clinical studies (3.8%). In addition, limited impact on PK, efficacy, and safety are reported upon discussion with clinical pharmacology colleagues. Therefore, we agree that not having the neutralizing antibody assessment during the BLA review cycle does not preclude the approval of the BLA. The sponsor could submit the assay validation along with the data for the presence of NAb (if any) as a PMC.

PMC:

Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against avelumab in the presence of avelumab levels that are expected to be present in samples at the time of patient sampling. Patient samples should be banked for storage until the improved method is available.

Detection of binding antibody against avelumab:

Method- TLIAM-13170: “Analytical Method Using Acid Dissociation for the Detection of Antibodies to Anti-PDL1 Antibodies in Human Serum by Meso-Scale Discovery (MSD) and Electrochemiluminescence (ECL)” was used to assess ADA data in this BLA and labeling.

The ADA detection assay is a step wise ECL assay, developed and validated at

(b) (4)

(b) (4)

Reviewer comment:

The sponsor proposed to test all samples that are identified positive from screening assay for neutralization. This approach is found suitable for the assessment of immunogenicity.

Assay validation:

Acceptance criteria used in the assay validation exercise is provided in the Table below:

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Reviewer comment:

The newly developed assay for the ongoing Phase III trials was validated with the data obtained from 53 runs. The assay is found more suitable to detect ADA incidence compared to the assay used to assess the immunogenicity for BLA 761049; treatment naïve patient samples were used in the assay, the inter-assay precision is significantly lower, the screening cut point factor and confirmation cut point factor are lower compared to the initial ones (b) (4)

Overall, the sponsor currently has a better assay in place and committed to report the incidence of ADA once more data are obtained from the ongoing trial. In addition, the sponsor is re-assessing all samples using the cut point obtained from the treatment naïve patient samples.

ADA data from the re-analysis: (Response 1/10/17)

The sponsor stated that 545 samples be analyzed from study #003 (MCC) and 9482 samples be analyzed from study #001(multiple indications) based on the cut point obtained from the treatment naïve patient samples. In addition, newly identified positive samples will be tested in the confirmatory assay. Further the sponsor proposed to test all positive samples in the neutralizing assay.

Reviewer comment:

A PMC is proposed (draft language below) to generate additional immunogenicity data. In addition, re-evaluation of the data from the confirmation assay is also requested. (b) (4)

Of note, this PMC is generated with the clinical pharmacology team:

PMC:

Conduct an assessment of treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses with validated assays (including an updated cutpoint for the screening and confirmatory ADA assay and the neutralizing assay as requested in PMC 1) capable of sensitively detecting ADA responses in the presence of avelumab levels that are expected to be present in the serum at the time of patient sampling. The ADA response be evaluated in at least 300 avelumab -treated patients. The final report will include information on the level of avelumab in each patient's test sample at each sampling point with an appropriate cutpoint.



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

Date: 02/07/2017

From: Steven Fong, Ph.D., Microbiologist, OPQ/OPF/DIA Branch 1
Arulvathani Arudchandran, Ph.D., Microbiologist OPQ/OBP/DBRRII
Lakshmi Narasimhan, Ph.D., Microbiologist, OPQ/OPF/DMA Branch IV

To: STN File 761049/0

Through: Zhihao (Peter) Qiu, Ph.D., Branch Chief, OPQ/OPF/DIA Branch 1

Subject: Inspection waiver memo for manufacture of Bavencio DP at the Merck Serono SA Aubonne facility in Succursale d'Aubonne, Switzerland.

Applicant: EMD Serono, Inc.

Facility: Merck Serono SA Aubonne (MS-Aubonne)
Zone Industrielle de l'Ourietaz
CH-1170 Succursale d'Aubonne
Switzerland
FEI #3002807447

Product: Bavencio (Avelumab, Anti-PDL-1)

Dosage: 20 mg/mL solution for infusion

Indication: Treatment of metastatic Merkel cell carcinoma.

Waiver Recommendation

Bavencio DP will be manufactured in Building (b) (4), at Merck Serono SA Aubonne, Succursale d'Aubonne, Switzerland (MS-Aubonne, FEI 3002807447). The proposed commercial manufacturing scheme is similar to the approved processes for other (b) (4) products at MS-Aubonne, including (b) (4)

The most recent inspection of MS-Aubonne was conducted 10/29/2015 – 11/06/2015 by the IOG. At the conclusion of the inspection a one item Form FDA 483 was issued that cited deficiencies in environmental monitoring procedures. The firm's response was determined to be adequate and the inspection was classified VAI for profiles BMI, SVL and SVS. Based on the firm's compliance history, its current acceptable status for profile SVS, and the fact that the proposed (b) (4) manufacturing procedure for Bavencio DP is similar to that for other FDA approved, sterile products produced at MS-Aubonne, we recommend that inspection of this facility be waived for BLA 761049/0.

Summary

BLA 761049/0 was submitted by EMD Serono, Inc. to provide information and data to support manufacture of Bavencio DS at Merck-Serono Vevey in Corsier-Sur-Vevey, Switzerland (FEI 3003131678), and Bavencio DP at MS-Aubonne (FEI #3002807447). The current waiver recommendation is in regards to Bavencio DP manufacture at MS-Aubonne.

Facility Information

(b) (4)

Evaluation of criteria that may warrant inspection

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

(b) (4)

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

As noted above under "Waiver Recommendation", at the conclusion of the 10/29/2015 – 11/06/2015 inspection a Form FDA 483 was issued citing one (b) (4) manufacturing GMP deficiency. The Agency determined that this deficiency was adequately addressed by the firm, and the inspection was classified VAI. The inspection included an assessment of the Suite (b) (4) area proposed for Bavencio DP manufacture.

3. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include*

areas that are currently dedicated areas that have not been approved as multi-product facilities / buildings / areas.

As noted above in the response to item 1, the Suite (b) (4) proposed for Bavencio DP manufacture has previously been approved for multi-product, (b) (4) manufacture of several U.S.-distributed products.

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



Steven Fong -S

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Steven Fong, Ph.D., Microbiologist, OPF/DIA Branch 1:

Lakshmi Narasimhan -S

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Lakshmi Narasimhan, Ph.D., Microbiologist, OPF/DMA Branch IV:

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Arulvathani Arudchandran, Ph.D., Microbiologist, OBP/DBRRII:

Joel T. Welch -A

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Date: 2017.02.10 15:23:33 -05'00'

Joel Welch, Ph.D., ATL, OBP/DBRRII:

Patricia F.

Digitally signed by Patricia F. Hughestroost -S
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Date: 2017.02.10 09:22:20 -05'00'

Hughestroost -S

Patricia Hughes, Ph.D., Branch Chief (Acting), OPF/DMA Branch IV:

Zhihao Qiu -S

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Date: 2017.02.10 09:09:49 -05'00'

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

David Frucht, MD, Chief Medical Officer, OBP/DBRRII

David M. Frucht -S

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Date: 2017.02.15 09:51:20 -05'00'



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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

Date: 02/15/2017
To: Administrative File, STN 761049/0
From: Steven Fong, Ph.D., Quality Assessment Lead, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: 1773
Applicant: EMD Serono, Inc.
Mfg Facility: Drug Substance: Merck Serono Vevey, Corsier-Sur-Vevey, Switzerland
FEI #3003131678
Drug Product: Merck Serono Aubonne, Succursale d'Aubonne, Switzerland
FEI #3002807447
Product: Avelumab (MSB0010718C)
Dosage: 20 mg/mL Solution for Infusion.
Indication: Metastatic Merkel Cell Carcinoma (mMCC)
Due Date: 05/23/2017

RECOMMENDATION: The BLA is recommended for approval from a facilities assessment standpoint.

SUMMARY

The subject BLA proposes manufacture and testing of Avelumab DS and DP, respectively, at Merck Serono, Sorsier-Sur-Vevey, Switzerland (FEI #3003131678) and Merck Serono Succursale d'Aubonne, Switzerland (FEI 3002807447). Additional testing operations will be conducted at Merck Serono S.p.A. Guidonia Montecelio (FEI 3002807252).

Avelumab, also referred to as Anti PD-1, is an IgG1 mAb expressed in (b) (4) that is proposed as a treatment for metastatic Merkel Cell Carcinoma. The DP is filled in (b) (4) mL volumes into 16 mL vials that are closed with rubber stoppers and sealed with aluminum crimp seals. The formulation consists of 200 mg/mL Avelumab DS, 510 mg/mL D-Mannitol, 6 mg/mL Glacial Acetic Acid, 5 mg/mL Polysorbate 20, and 3 mg/mL Sodium Hydroxide.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

3.2.S.2.1 DS Manufacturers.

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

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

Site Name	Address	FEI Number	Responsibilities
Merck Serono SA (MS-Vevey)	Succursale de Corsier-sur Vevey Chemin du Fenil, Zone Industrielle B 1804 Corsier-sur-Vevey Switzerland	3003131678	DS manufacture. DS analytic testing. DS release testing. Master and working cell bank manufacture and storage.
Merck Serono S.p.A. Guidonia Montecelio (MS-Guidonia)	Via Luigi Einaudi, 11 00012, Guidonia Montecilio (RM) Italy	3002807252	DS stability testing. (Also performs DP stability testing. Refer to Table 5 below.)
(b) (4)			Cell bank storage. <i>Facilities evaluation not necessary.</i>

Reviewer Comment 1: The facilities for manufacture of Avelumab DS manufacture and testing were adequately described. Facilities evaluation is not necessary for the (b) (4) site proposed for cell bank storage.

Prior Inspection History for DS Manufacturing and Testing Sites

- Merck-Serono Vevey, Succursale de Corsier-sur Vevey, Chemin du Fenil, Zone Industrielle B, 1804 Corsier-sur-Vevey, Switzerland (MS-Vevey, FEI 3003131678).
Responsibility: Avelumab DS manufacture, analytic testing, release testing, master cell bank manufacture, working cell bank manufacture and storage.
- CGMP Surveillance Inspection Conducted 02/01-05/2016 by the IOG. Inspection was conducted as part of the 2016 IOG workplan. Training, quality, facilities/equipment, materials, production, and laboratory controls were covered for profile CBI, and a follow-up was conducted to confirm that the deficiencies cited in the previous 10/29/2012 – 11/06/2012 inspection had been adequately addressed. The inspection included an assessment (b) (4) manufacture. At the conclusion of the inspection a 5-item FDA Form 483 was issued citing: (1) failure to establish controls to prevent deletion, alteration and/or modification of data generated in the QC labs; (2) failure to conduct a daily verification of the analytical balance as required by written procedure; (3) inadequate procedures for preventing microbiological contamination of DPs purporting to be sterile; (4) inadequate inspection of equipment as described in written programs designed to assure proper performance; and (5) failure of the quality unit to include an identification test for acceptance/release of (b) (4). The firm's responses were determined to be adequate and the inspection was classified VAI.
- Warning Letter Follow-up Inspection Conducted 10/29/2012-11/06/2012 by the IOG. The inspection was conducted to assess the firm's response to Warning Letter 320-12-06 dated 12/15/2011, which stated that a change in the suite used for (b) (4)

BLA 761049. Avelumab DS and DP Manufacture

manufacture was not reported to the FDA through supplement, CBE-30, or annual report. Training, quality, facilities/equipment, materials, manufacturing/design operations, and laboratory systems were assessed for (b) (4) manufacturing operations in the previously unreported suite. At the conclusion of the inspection a one-item Form FDA 483 was issued citing failure of the Quality Unit to establish procedures, processes, resources, and activities as necessary to ensure that (b) (4) meets quality and purity specifications. The citation included inadequate follow-up investigations for EM deviations, inadequate justification for changing process bioburden alert and action limits for microbial control, inadequate physical and procedural controls for protection of raw materials being sampled on a table exposed to the unclassified warehouse, and inadequate cleaning validation for media hold tanks. The firm was determined to have adequately addressed the Warning Letter and the Form FDA 483 observation. Final inspection classification: VAI.

- Merck Serono S.p.A., Via Luigi Einaudi, 11, 00012, Guidonia Montecilio, Italy (MS-Guidonia, FEI 3002807252). Responsibility: Avelumab DS and DP stability testing.
- CGMP Surveillance Inspection Conducted 02/16-20/2015 by the IOG. Inspection was conducted as part of the 2016 IOG workplan. Training, quality, and laboratory controls were assessed for profile CTL. No FDA Form 483 was issued. Final inspection classification: NAI.
 - Warning Letter Follow-up and CGMP Surveillance Inspection Conducted 03/11-14/2013 by the IOG. The follow-up portion was conducted in reference to Warning Letter 320-12-06 dated 12/15/2011, which cited deficiencies regarding the reference standards for (b) (4) control samples, timely investigations for OOS results, the software used for laboratory testing of (b) (4) quality, and the lack of validation testing for disinfectant effectiveness. The surveillance portion was conducted as part of the 2013 IOG work plan. Laboratory operations were assessed for US biotechnology products tested at the site. At the conclusion of the inspection a nine-item Form FDA 483 was issued citing: (1) inadequate procedures for reporting of sterility test results; (2) inadequate sampling methods for environmental monitoring; (3) inadequate procedures for conducting the gel clot method for endotoxin testing; (4) inadequate procedures for microorganism identification testing; (5) inadequate procedures for media growth promotion testing; (6) improper blockage of the (b) (4); (7) inadequate procedures for oligosaccharide profile testing and equipment revalidation; (8) inadequate Excel spreadsheet security safeguards; and (9) inadequate display of the maximum calibrate range on scales used by laboratory analysts. The firm was determined to have adequately addressed the Warning Letter and the Form FDA 483 observation. Final inspection classification: VAI.
 - CGMP Surveillance Inspection Conducted 06/27/2011- 07/01/2011 by the IOG. Inspection was conducted as part of the 2011 IOG work plan. Laboratory operations were assessed for US biotechnology products tested at the site. At the conclusion of the inspection an eight-item Form FDA 483 was issued citing: (1) deficiencies in the reference standard used for (b) (4) manufacture; (2) deficiencies in the change control procedure used for handling of (b) (4) control samples; (3) deficiencies in the procedure for qualification of the control sample for dimer and aggregate testing; (4) non-timely completion of investigations into OOS test results; (5) inadequate

BLA 761049. Avelumab DS and DP Manufacture

documentation demonstrating that the PCN Columbo software can accurately calculate results; (6) inadequate documentation of the incubation time used for the in vitro (b) (4) assay for the (b) (4) activity test; (7) inadequate qualification of cleaning disinfectant effectiveness testing; and (8) absence of a time frame for closure of deviations. The firm was determined to have not adequately addressed the deficiencies and a Warning Letter, 320-12-06, was issued 12/15/2011. Final inspection classification: OAI.

• Current Prior Approval Inspection Decisions

- MS-Vevey (FEI 3003131678). *Avelumab DS manufacture, analytic testing, release testing, master cell bank manufacture, working cell bank manufacture and storage*. A PAI in support of the subject BLA was conducted 11/07-15/2016 by CDER OBP, DMA and DIA. Quality, facilities/ equipment, materials, production, laboratory controls, and packaging/labeling systems were covered for profile CBI. The inspection resulted in issuance of a four-item Form FDA 483 citing (1) persistent bioburden excursions in the (b) (4); (2) inadequate investigations for bioburden excursions in the (b) (4) used for purification; (3) inadequate procedures for bioburden sampling; and (4) inadequate validation of storage periods for cell culture solutions. The firm's responses were determined to be adequate and the inspection was classified VAI.
- MS-Guidonia, (FEI 3002807252). *Avelumab DS stability testing*. Facility approved based on profile.

Reviewer Comment 2: *The sites proposed for Avelumab DS manufacture and testing are adequate from the standpoint of inspectional assessment. As noted a PAI was conducted 11/07-15/2016 in support of the subject BLA for the MS-Vevey site proposed for DS manufacture. The inspection resulted in a VAI conclusion.*

• 3.2.S.2.2. Overview of Avelumab DS Manufacturing Operations Conducted at MS-Vevey. (b) (4)

(b) (4)

• 3.2.A.1.1 – 3.2.A.1.5. MS-Vevey Design and Site Plan, and Avelumb DS Manufacturing Areas.

(b) (4)

DRUG PRODUCT FACILITIES

- **DP Manufacturers.**

The sites proposed for Avelumab DP manufacture, testing, packaging, and labeling are presented below in Table 5.

TABLE 5. Sites Proposed for Avelumab DP Manufacture and Testing

Site Name	Address	FEI Number	Responsibilities
Merck Serono SA Aubonne (MS-Aubonne)	Zone Industrielle de l'Ouriettaz CH-1170 Aubonne, Switzerland	3002807447	DP manufacture. DP IPC, release, and stability testing. DP primary packaging and labeling. DP secondary packaging.
Merck Serono S.p.A. Guidonia Montecelio (MS-Guidonia)	Via Luigi Einaudi, 11 00012, Guidonia Montecilio (RM) Italy	3002807252	DP stability testing. (Also conducts DS stability testing; refer to Table 1 above.)
Merck Serono S.A. Coinsins	Centre Industriel CH1267 Coinsins, Switzerland	3002807447	DP secondary packaging. <i>Facilities evaluation not necessary.</i>

(b) (4)

DP secondary packaging.
Facilities evaluation not necessary.

• **Prior Inspection History for DP Manufacturing and Testing Sites**

- Merck Serono SA Aubonne, Zone Industrielle de l'Ourietaz CH-1170 Aubonne, Switzerland (FEI 3002807447). *Responsibility: DP manufacture, testing, packaging/labeling.*
 - Inspection Conducted 10/29/2015 – 11/06/2015 by IOG. Surveillance inspection conducted as part of the 2015 IOG workplan. Quality, facilities/equipment, materials, production, laboratory controls, and packaging/labeling were covered for profiles BMI, SVL, and SVS. The inspection included an assessment (b) (4) manufacture, and an assessment of DP manufacture in the area, Suite (b) (4), proposed for Avelumab DP production in the subject BLA. At the conclusion of the inspection a one-item FDA Form 483 was issued citing deficiencies in environmental monitoring. The firm's responses were determined to be adequate and the inspection was classified VAI.
 - Inspection Conducted 11/04-12/2013 by IOG. Surveillance inspection conducted as part of the 2013 IOG workplan. Facilities/equipment, materials, production, and laboratory controls were covered for profiles BMI, SVL, and SVS. At the conclusion of the inspection a three-item FDA Form 483 was issued citing deficiencies in investigations of deviations, written procedures for production and process controls, and laboratory controls. The firm's responses were determined to be adequate and the inspection was classified VAI.
- MS-Guidonia, (FEI 3002807252). *Avelumab DP stability testing.* This firm also conducts DS stability testing. Please see the compliance history of this firm presented above under *DS Facilities*.

• **Current Prior Approval Inspection Decisions**

- MS-Aubonne (FEI 3002807447). *DP Manufacturing and Testing Site.* A PAI for this site was waived for the subject BLA on 02/15/2017. Facility approved based on profile.
- MS-Guidonia, (FEI 3002807252). *Avelumab DP stability testing.* Facility approved based on profile.

Reviewer Comment 11. *The sites proposed for Avelumab DP manufacture and testing are adequate from the standpoint of inspectional assessment.*

• **3.2.P.3.3. Overview of Avelumab DP Manufacturing Operations Conducted at MS-Aubonne.**

(b) (4)

BLA 761049. Avelumab DS and DP Manufacture

Reviewer Comment 20: *The description of other products manufactured at MS-Aubonne is acceptable. None of the listed products is toxic or potent.*

CONCLUSION

Adequate descriptions were provided for the MS-Vevey (FEI 3003131678) and MS-Aubonne (FEI 3002807447) facilities proposed for Avelumab DS and DP manufacture. The descriptions were verified by inspection. These manufacturing sites, the proposed testing facility, MS-Guidonia (FEI 3002807252), and the proposed cell bank storage facility, (b) (4), are currently in a state of compliance. The subject BLA is recommended for approval from the standpoint of facilities assessment.

Steven E. Fong, M.S., Ph.D.
Microbiologist
OPF Division of Inspectional Assessment
Branch 1

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



Steven
Fong

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Zhihao Peter
Qiu

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Date: 2/15/2017 10:04:00AM
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Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: January 31, 2016
To: Administrative File, STN 761049/0
From: Reyes Candau-Chacon, Ph.D., Reviewer, OPQ/OPF/DMA/BIV
Through: Patricia Hughes, Ph.D., Acting Branch Chief, OPQ/OPF/DMA/BIV
Subject: New Biologic License Application (BLA)
US License: 1773
Applicant: EMD Serono, Inc.
Facilities: MERCK SERONO SA, Succursale de Corsier-sur-Vevey, Chemin du Fenil, Zone Industrielle B, 1804 Corsier-sur-Vevey, Switzerland (FEI # 3003131678)
Product: BAVENCIO (Avelumab, MSB0010718C)
Dosage: Single-Use Vial containing 200 mg/10 mL (20 mg/mL) solution to be diluted prior to Intravenous Infusion
Indication: Treatment of patients with metastatic Merkel Cell Carcinoma (mMCC) whose disease has progressed after at least one previous chemotherapy regimen.
Due date: May 23, 2017

Recommendation for Approvability: BLA 761049 is recommended for approval from a microbial control and microbiology product quality perspective.

Review Summary

EMD Serono, Inc. has submitted BLA 761049 to license avelumab and the associated drug substance and drug product manufacturing processes.

BLA 761049 was submitted in eCTD as a rolling BLA; the original application was submitted on July 6, 2016 and contained modules 1 and 4; module 3 was submitted on September 2, 2016 in amendment 0002, and the rest of the modules were submitted on September 9, 2016 in amendment 0003. This review contains the assessment of the manufacturing process of avelumab bulk drug substance from a microbiological quality perspective. For review of drug product aspects of the application, please see the review by Dr. Lakshmi Narasimhan.

Amendments Reviewed for Drug Substance Quality

Information Request date	Question numbers	Amendment sequence	Amendment date
November 29, 2016	1 to 16	0019	December 19, 2016

Review Narrative

S DRUG SUBSTANCE

S.1 General Information

Avelumab is a recombinant fully human monoclonal antibody that specifically binds to the PD-L1 cell surface molecule and blocks its interaction with receptors PD-1 and B7.1.

Avelumab is based on the human immunoglobulin G1; the recombinant antibody is produced in (b) (4) and has two heavy chains with 450 aminoacids and two light chains with 213 aminoacids.

S.2 Manufacture

S.2.1 Manufacturer(s)

The following facilities are used for the manufacture, release testing, and stability testing of avelumab drug substance:

- MERCK SERONO SA, Succursale de Corsier-sur-Vevey, Chemin du Fenil, Zone Industrielle B, 1804 Corsier-sur-Vevey, SWITZERLAND; DS manufacture, DS in-process and release testing and cell bank storage FEI 3003131678
- MERCK SERONO S.P.A., Via Luigi Einaudi, 11, 00012, Guidonia Montecilio (RM), ITALY: DS release and stability testing FEI 3002807252

Reviewer comments:

A pre-license inspection of Merck-Serono, Vevey was conducted from November 7, 2016 to November 15, 2016. A 4-observation FDA 483 form was issued and the initial classification of the facility was VAI. Refer to Panorama for the updated status of the relevant facilities.

S.2.2 Description of the Manufacturing Process and Process Controls

S.2.2.1 Batches and Scale Definition

(b) (4)

SATISFACTORY

SATISFACTORY

S.7 Stability

S.7 .1 Stability Summary and Conclusions

The proposed shelf-life of avelumab drug substance is (b) (4) months at (b) (4) °C. The stability program includes bioburden and endotoxin tested annually for the long term stability protocol, at 6 months for accelerated conditions, and at 3 months for stressed conditions.

S.7 .2 Post-Approval Stability Protocol and Stability Commitment

One commercial batch is added to stability program annually if production occurs during the calendar year. Endotoxin samples tested at 6, 12, 24, and 36 months will be part of the program.

S.7 .3 Stability Data

All bioburden and endotoxin results are below the limit of detection, with the exception of one of the accelerated stability batches, which showed 0.06 EU/mg (below AC of (b) (4) EU/mg) at release.

Reviewer Comments:

Microbial quality results of stability samples are not necessarily representative of microbial quality of drug substance stored in different containers. BDS stability is not required from a microbial quality point of view and is deferred to OBP. All bioburden and endotoxin results taken during stability are within specifications.

SATISFACTORY

cGMP Status

Refer to Panorama for cGMP status of the relevant facilities.

Conclusion

- I. The drug substance part of BLA 761049 was reviewed from a microbial control and microbiology product quality perspective and is recommended for approval.
- II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by an OBP reviewer.
- III. A pre-license inspection of MERCK SERONO SA. Was conducted between November 7 and 15, 2016 by OPQ/OPF/DMA (Reyes Candau-Chacon and Scott Nichols), OPQ/OPF/DIA (Steve Fong), and OBP (William Hallet and Arulvathani Arudchandran)

APPEARS THIS WAY ON ORIGINAL

STN 761049/0, EMD Serono, Inc., Avelumab

FDA Information Request for STN 761049/0 Microbial Quality – Drug Substance (11/29/2016)

Manufacture - Description of the Manufacturing Process and Process Controls

(b) (4)





Patricia
Hughes Troost

Digitally signed by Patricia Hughes Troost
Date: 2/02/2017 06:59:50AM
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OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 761049

Submission Type: 351(a)

**Established/Proper Name:
Avelumab**

Applicant: Merk Serono

Letter Date: 9/23/2016

**Dosage Form: Vials-solution for
intravenous injection-10 mg/kg
body weight**

**Chemical Type: Monoclonal
antibody**

Stamp Date: 9/23/2016

Strength: 20mg/mL

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	Yes		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Fileable
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?		No	

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	X	☐	
2.	Botanical ¹	☐	X	
3.	Naturally-derived Product	☐	X	
4.	Narrow Therapeutic Index Drug	☐	X	
5.	PET Drug	☐	X	
6.	PEPFAR Drug	☐	X	
7.	Sterile Drug Product	X	☐	
8.	Transdermal ¹	☐	X	
9.	Pediatric form/dose ¹	☐	X	
10.	Locally acting drug ¹	☐	X	
11.	Lyophilized product ¹	☐	X	
12.	First generic ¹	☐	X	
13.	Solid dispersion product ¹	☐	X	
14.	Oral disintegrating tablet ¹	☐	X	
15.	Modified release product ¹	☐	X	
16.	Liposome product ¹	☐	X	
17.	Biosimilar product ¹	☐	X	
18.	Combination Product	☐	X	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
19.	Other	X	☐	Recombinant humanized monoclonal antibody
Regulatory Considerations				
20.	USAN Name Assigned	X	☐	Avelumab
21.	End of Phase II/Pre-BLA Agreements	X	☐	Stability data will be updated
22.	SPOTS (Special Products On-line Tracking System)	☐	X	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	☐	X	
24.	Comparability Protocol(s) ²	☐	X	
25.	Other	☐	X	
Quality Considerations				
26.	Drug Substance Overage	☐	X	
27.	Design Space	Formulation	☐	X
28.		Process	☐	X
29.		Analytical Methods	☐	X
30.		Other	☐	X
31.	Real Time Release Testing (RTRT)		☐	X
32.	Parametric Release in lieu of Sterility Testing		☐	X
33.	Alternative Microbiological Test Methods		☐	X
34.	Process Analytical Technology ¹		☐	X
35.	Non-compendial Analytical	Drug Product	X	☐
36.	Procedures and/or	Excipients	☐	X
37.	specifications	Microbial	☐	X
38.	Unique analytical methodology ¹		☐	X
39.	Excipients of Human or Animal Origin		☐	X
40.	Novel Excipients		☐	X
41.	Nanomaterials ¹		☐	X
42.	Hold Times Exceeding 30 Days		☐	X
43.	Genotoxic Impurities or Structural Alerts		☐	X
44.	Continuous Manufacturing		☐	X
45.	Other unique manufacturing process ¹		☐	X
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	X
47.	New delivery system or dosage form ¹		☐	X
48.	Novel BE study designs		☐	X
49.	New product design ¹		☐	X
50.	Other Labeling	☐	X	Microbiological data to support the proposed labeling claim of storing the diluted drug product (in 0.9% or 0.45% sodium chloride solution) at 2- 8°C (36- 46°F) (b) (4) for up to 24 hours will be requested.

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
1.	Has an environmental assessment report or categorical exclusion been provided?	X	☐	☐	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ Drug Substance ☐ Drug Product ☐ Appendices ☐ Facilities and Equipment ☐ Adventitious Agents Safety Evaluation ☐ Novel Excipients ☐ Regional Information ☐ Executed Batch Records ☐ Method Validation Package ☐ Comparability Protocols	X	☐	☐	
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ☐ Name of facility, ☐ Full address of facility including street, city, state, country ☐ FEI number for facility (if previously registered with FDA) ☐ Full name and title, telephone, fax number and email for on-site contact person. ☐ Is the manufacturing responsibility and function identified for each facility, and ☐ DMF number (if applicable)	X	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ☐ Is a manufacturing schedule provided? ☐ Is the schedule feasible to conduct an inspection within the review cycle?	X	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of	☐	☐	X	<u>Drug Product</u> Letter of Authorization (LOA) which

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

C. FILING CONSIDERATIONS				
	Authorization provided?			references (b) (4) washing validation data for the (b) (4) vial stopper in a CDER DMF will be requested.
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ general information ☐ manufacture ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only ☐ characterization of drug substance ☐ control of drug substance ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ☐ reference standards or materials ☐ container closure system ☐ stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment	X	☐	☐
DRUG PRODUCT INFORMATION				
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ Description and Composition of the Drug Product ☐ Pharmaceutical Development ○ Includes descriptions of changes in the manufacturing process from material used	X	☐	☐

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS				
- in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development ❑ Manufacture ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System ○ Include data outlined in container closure guidance document ❑ Stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				Information and summary data from three recent requalification runs of (b) (4) process of the filling machine will be requested. Details of in process bioburden testing and method qualification summary data from 3 formulated bulk drug product lots will be requested.
BIOPHARMACEUTICS				

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FILING REVIEW

C. FILING CONSIDERATIONS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: - Does the application contain the complete BA/BE data? - Are the PK files in the correct format? - Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	X	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	X	☐	☐	For CMC, data provided to demonstrate the comparability of product qualities for the two different formulations.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☐	X	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	X	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	X	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	X	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	X	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	X	☐	☐	These will be reviewed during inspection, presented in foreign language
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ☐ facilities and equipment - manufacturing flow; adjacent areas - other products in facility - equipment dedication, preparation, sterilization and storage - procedures and design features to prevent contamination and cross-contamination ☐ adventitious agents safety evaluation (viral and non-viral) e.g.: - avoidance and control procedures - cell line qualification - other materials of biological origin - viral testing of unprocessed bulk - viral clearance studies - testing at appropriate stages of production	X	☐	☐	

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C. FILING CONSIDERATIONS					
	☐ novel excipients				
17.	Are the following information available for Biotech Products: ☐ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: - o LAL instead of rabbit pyrogen - o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples	X			Results for Rabbit pyrogen test conducted with three batches of drug product are provided. LAL test will be used for routine DP release.

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Arulvathani Arudchandran, Ph.D. Product Quality Reviewer, DBRRII, Office of Biotechnology Product

Joel Welch, Ph.D., Product Quality Team Leader, DBRRII, Office of Biotechnology Product

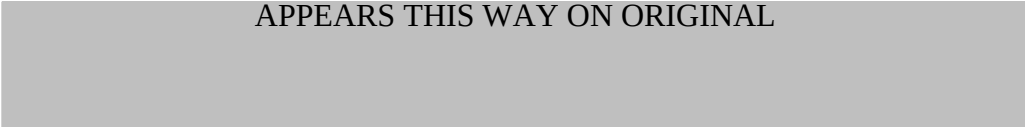
Lakshmi Narasimhan, Ph.D., DMA, Office of Process and Facilities

Maria Candauchacon, Ph.D., DMA, Office of Process and Facilities

Steven, Fong, Ph.D., DIA, Office of Process and Facilities

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

APPEARS THIS WAY ON ORIGINAL





Arulvathani
Arudchandran

Digitally signed by Arulvathani Arudchandran
Date: 10/31/2016 12:52:43PM
GUID: 508da6d9000264bd2c1522e8421907fa



Joel
Welch

Digitally signed by Joel Welch
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GUID: 508da8dc0002673d83d264d81364d6cf



Lakshmi Rani
Narasimhan

Digitally signed by Lakshmi Rani Narasimhan
Date: 10/31/2016 02:59:06PM
GUID: 508da7160002976791592556d218b997



Reyes
Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 10/31/2016 02:12:26PM
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Patricia
Hughes Troost

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GUID: 508da717000297bcbfce0919f8c09594



Steven
Fong

Digitally signed by Steven Fong
Date: 10/31/2016 01:12:18PM
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