

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761097Orig1s000

PRODUCT QUALITY REVIEW(S)

**First Approval for Indication
Priority Review****Recommendation: Approval****BLA 761097
Review**

Date: September 27, 2018
From: Rachel Novak, Ph.D.
Review Chief, DBRR I/OBP/OPQ

Through: Qing (Joanna) Zhou, Ph.D.
Review Chief, DBRR I/OBP/OPQ

Drug Name/Dosage Form	cemiplimab/injection (LIBTAYO)
Strength/Potency	50 mg/mL (250 mg/5mL and 350 mg/ 7mL single-use vial)
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Indication	Treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced cutaneous squamous cell carcinoma (laCSCC) who are not candidates for surgery
Applicant/Sponsor	Regeneron Pharmaceuticals, Inc.
US agent, if applicable	

Product Overview

Cemiplimab is a human IgG4 monoclonal antibody produced in CHO cells. The heavy chains of cemiplimab are engineered with a serine to proline substitution at amino acid residue 225 within the hinge region of the Fc domain to promote stabilization of inter-chain disulfide bonds and to minimize half-antibody formation. Cemiplimab targets the inhibitory checkpoint receptor, human programmed cell death protein 1 (PD-1), expressed on activated T and B cells, natural killer cells and myeloid lineage cells. The binding of PD-1 with its ligand (PD-L1) in the tumor microenvironment triggers immune evasion through the suppression of helper and cytotoxic T cell function. Cemiplimab functions by blocking PD-1/PD-L1 interaction, thus leading to the restoration of immune surveillance. Cemiplimab drug product is manufactured as a sterile, preservative-free, 50 mg/mL solution for infusion in a 250 mg/5 mL or 350 mg/7 mL single-use glass vial. Cemiplimab drug product may be prepared in intravenous infusion bags containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Cemiplimab is proposed as a single agent for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for surgery.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Willie Wilson	DBRR I/OBP/OPQ
Drug Product	Jens Fricke	DBRR I/OBP/OPQ
Immunogenicity	Willie Wilson	DBRR I/OBP/OPQ
Labeling	Scott Dallas	OBP/OPQ
Facility	Ziyang Su	DIA/OPF/OPQ
Microbiology (Drug Substance)	Maxwell Van Tassell	DMA IV/OPF/OPQ
Microbiology (Drug Product)	Aimee Cunningham	DMA IV/OPF/OPQ
Business Process Manager	Anita Brown	RBPMBI/ OPRO/OPQ
Team Lead for OBP	Rachel Novak	DBRR I/OBP/OPQ
Tertiary Reviewer for OBP	Qing (Joanna) Zhou	DBRR I/OBP/OPQ
Microbiology Team Lead	Maria Candau-Chacon	DMA IV/OPF/OPQ
Facilities Team Lead	Peter Qiu	DIA/OPF/OPQ

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Mimi Biable	CDER/OND/OHOP/DOPII
Cross-disciplinary Team Lead	Suzanne Demko	CDER/OND/OHOP/DOPII
Medical Officer	Denise Casey	CDER/OND/OHOP/DOPII
Pharm/Tox	Emily Wearne/Whitney Helms	CDER/OND/OHOP/DHOT
Clinical Pharmacology	Xiling Jiang/Hong Zhao	CDER/OTS/OCP/DCPV
Stats	Mallorie Fiero	CDER/OTS/OB/DBV

a. Names

- i. Proprietary Name: LIBTAYO
- ii. Trade Name: LIBTAYO
- iii. Non-Proprietary/USAN: cemiplimab
- iv. CAS name: 1801342-60-8
- v. INN Name: cemiplimab
- vi. OBP systematic name: MAB HUMAN (IGG4) ANTI Q15116
(PDCD1_HUMAN) [REGN2810]
- vii. Other Names: REGN2810

b. Pharmacologic category: Therapeutic recombinant human monoclonal antibody

Quality Review Team – Signature Page

DISCIPLINE	REVIEWER	SIGNATURE
Microbiology Team Lead	Reyes Candau-Chacon	See electronic signature at the end of review
Facilities Team Lead	Peter Qiu	See electronic signature at the end of review
Application Technical Lead and DS and DP Team Lead	Rachel Novak	See electronic signature at the end of review
Drug Substance and Immunogenicity Primary Reviewer	Willie Wilson	See electronic signature at the end of review
OBP Review Chief; DS, DP and Immunogenicity Tertiary Reviewer	Qing (Joanna) Zhou	See electronic signature at the end of review

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. Submissions Reviewed

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
761097/0002	December 19, 2017	OBP, DMA, DIA
761097/0003	January 30, 2018	OBP, DMA, DIA
761097/0004	February 28, 2018	OBP, DMA
761097/0009	May 3, 2018	DMA, DIA
761097/0011	May 23, 2018	DMA
761097/0012	May 25, 2018	DIA
761097/0016	May 31, 2018	DMA
761097/0017	June 4, 2018	OBP, DMA
761097/0018	June 11, 2018	OBP, DMA
761097/0019	June 18, 2018	OBP
761097/0021	June 25, 2018	OBP, DMA
761097/0025	July 5, 2018	DMA
761097/0027	July 13, 2018	OBP, DMA
761097/0028	July 16, 2018	OBP
761097/0029	July 19, 2018	OBP, DMA
761097/0030	July 24, 2018	OBP
761097/0031	July 24, 2018	OBP, DMA
761097/0032	July 25, 2018	OBP
761097/0035	August 14, 2018	OBP
761097/0037	August 15, 2018	OBP
761097/0039	August 20, 2018	OBP
761097/0040	August 28, 2018	DMA
761097/0041	September 4, 2018	OBP
761097/0043	September 12, 2018	OBP
761097/0044	September 18, 2018	OBP
761097/0047	September 24, 2018	OBP
761097/0048	September 25, 2018	OBP

B. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	V	(b) (4)	(b) (4)	2	Adequate	02/03/2017	(b) (4)
	V		(b) (4)	2	Adequate with Information Request	04/10/2018	(b) (4)
	II		(b) (4)	2	Adequate	01/08/2018	(b) (4)
	III		(b) (4)	3	N/A	N/A	N/A
	III		(b) (4)	3	N/A	N/A	N/A
	V		(b) (4)	3	N/A	N/A	N/A

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

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

C. Other Documents: None**3. CONSULTS: None**

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761097 for cemiplimab manufactured by Regeneron Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of cemiplimab is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

b. Approval action letter language

Under this license, you are approved to manufacture the drug substance (b) (4) at Regeneron Pharmaceuticals, Inc., Rensselaer, NY. The 250 mg/5 mL and 350 mg/7 mL drug product will be manufactured at (b) (4). The drug product will be labelled and packaged at (b) (4).

The dating period for cemiplimab drug product, 250 mg/5mL and 350 mg/7 mL, shall be 18 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product.

(b) (4)

The dating period for cemiplimab drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4)°C.

c. Benefit/Risk Considerations

Cutaneous squamous cell carcinoma is the second most common non-melanoma skin cancer and is characterized by the malignant proliferation of epidermal keratinocytes with invasion of the dermis. Risk factors for CSCC include ultraviolet exposure, advanced age, male sex, light skin and immunosuppression. CSCC is typically managed clinically by surgical intervention with low rates of local recurrence. Less than 5% of CSCC patients cannot be cured surgically and progress to advanced CSCC, collectively referred to as metastatic and locally advanced CSCC. There are currently no approved therapies or widely acceptable standard of care for advanced CSCC. Current systemic therapeutic strategies for advanced CSCC include the off-label use of epidermal growth factor receptor (EGFR) inhibitors (e.g., gefitinib, cetuximab and panitumumab) and cytotoxic chemotherapy (e.g., platinum-based drugs). However, the development of these therapies is limited due to severe toxicities. EGFR inhibitors and cytotoxic chemotherapy also do not provide durable responses or improvement to overall survival compared to no treatment. Due to

the strong link between advanced CSCC and immunosuppression, a PD-1/PD-L1 checkpoint blockade treatment strategy was explored. Cemiplimab targets PD-1 expressed on activated immune cells and restores immunosurveillance by blocking PD-1/PD-L1 interaction in the tumor microenvironment.

The overall control strategy for cemiplimab manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, process monitoring tests, release, and stability testing ensures process consistency, and drug substance (DS), (b) (4) and drug product (DP) that have appropriate quality and are free of adventitious agents.

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

PMC 1: Validate the worst-case capping and crimping parameters using the validated dye ingress container closure integrity test method described in the BLA. Include appropriate positive controls with breaches $\leq 20 \mu\text{m}$ in the validation study.

II. Summary of Quality Assessments

A. COA Identification, Risk and Lifecycle Knowledge Management

(b) (4)

(b) (4) Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to the DS (b) (4) and DP.

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

Table 1: Drug Substance (b) (4) and Drug Product CQA Identification, Risk and Lifecycle Knowledge Management				
CQA	Risk	Origin	Control Strategy	Other notes
PD-1 binding (potency)	Efficacy	Intrinsic to the molecule. Impacted by oxidation, deamidation, aggregation and fragmentation.	(b) (4)	Cemiplimab was shown through cell-based assays not exhibit ADCC or CDC activity.
Identity	Safety and Efficacy	Intrinsic to the molecule.		N/A
High Molecular Weight (HMW) species/Dimers/High Order Structure (product-related impurities)	Efficacy, Pharmacokinetics, and Safety/Immunogenicity Impacts PD-1 binding	Manufacturing process and exposure to heat, deamidation, oxidation, low pH and light stress. Minimal change is expected during DS (b) (4) and DP storage.		N/A

			(b) (4)	
Low Molecular Weight (LMW) Species (product-related impurities)	Efficacy and Pharmacokinetics Impacts PD-1 binding	Manufacturing process and exposure to heat, deamidation, oxidation, light, and low pH stress. Minimal change is expected on stability through expiry.		N/A
Low Molecular Weight (LMW) Species/ Half-antibody	Efficacy Impacts PD-1 binding	Intrinsic to IgG4 molecules. Cemiplimab is engineered with an S225P substitution in the hinge region to promote stabilization of heavy chain disulfide bonds. Minimal half antibodies are expected.		N/A
Heavy chain (b) (4)	Efficacy (PD-1 binding)	The propensity for oxidation during manufacturing and storage is low in the absence of chemical oxidants.		N/A

Light chain (b) (4)	Efficacy	Manufacturing process and exposure to heat, light and low pH stress.	(b) (4)	N/A
Protein Content	Efficacy	Manufacturing process		N/A
pH	Safety and Efficacy	Formulation process		N/A
Osmolality	Safety, Efficacy ((b) (4))	Formulation		N/A
Appearance of Solution (visible particulates, color and clarity)	Safety and Efficacy	Formulation, contamination or degradation		An increased frequency of visible particle formation was observed during DP process validation. See Table 3 for further detail.
Endotoxin	Safety and Purity	Raw materials contamination during manufacturing		N/A

a. Description

Cemiplimab is a human monoclonal immunoglobulin G4 (IgG4 isotype) consisting of two identical heavy chains (HC) and two identical light chains (LC) covalently linked through inter- and intra-chain disulfide bonds. Each HC and LC is composed of 444 and 214 amino acids, respectively. Each HC contains a serine to proline substitution at amino acid residue 225 within the hinge region of the Fc domain to promote stabilization of inter-chain disulfide bonds and to minimize the potential for half-antibody formation. A single N-linked glycosylation site is located in the CH2 domain of each heavy chain at asparagine residue 294. (b) (4)

The extinction coefficient was calculated and confirmed experimentally to be (b) (4) AU x cm² x mg⁻¹ at 280 nm. This value has been used during development and will continue to be used to determine the cemiplimab protein concentration for commercial use.

b. Mechanism of action

PD-1 is an inhibitory checkpoint receptor expressed on activated T and B cells, natural killer (NK) cells, and myeloid lineage cells. PD-1 functions as a pivotal immunomodulator upon binding to programmed death-ligand 1 (PD-L1) which is broadly expressed on activated T and B lymphocytes, myeloid, endothelial, epithelial and within the tumor microenvironment of multiple cancer types. The binding of PD-1/PD-L1 within the tumor microenvironment results in tumor immune evasion through the suppression of CD28 and T cell receptor downstream signaling. Cemiplimab is a human anti-PD-1 antibody that functions by blocking the immune-inhibitory PD-1/PD-L1 signaling pathway and restoring helper and cytotoxic T cell function and the number of effector T cells, thereby rescuing the anti-tumor immune response.

c. Potency Assay

(b) (4) DS and DP potency is controlled using a cell-based luciferase reporter bioassay that measures the ability of cemiplimab to block PD-1/PD-L1 interaction and restore T-cell activation. The bioassay utilizes engineered Jurkat effector T-cells and APC-like HEK293 cells to mimic in vivo TCR/MHC interaction and T-cell activation. The Jurkat cells are engineered to express full-length PD-1 receptor and the AP-1 luciferase reporter. The HEK293 cells are engineered to express PD-L1 and a membrane bound IgE (mIgE) containing anti-CD3 variable domains. Co-culture of the engineered Jurkat and HEK293 cells alone results in suppression of T-cell activation as measured by low AP-1 reporter activity. Cemiplimab potency is determined by incubating the co-culture in the presence of increasing cemiplimab concentrations. The blockade of PD-1/PD-L1 interaction by cemiplimab test articles is measured by the restoration of AP-1 reporter activity. A 4-parameter (4-PL) unconstrained logistic analysis is used to calculate the dose response curve. Potency is reported as a percentage relative to the reference standard.

d. Reference material(s)

(b) (4)

(b) (4)

e. Critical starting materials or intermediates

(b) (4)

f. Manufacturing process summary

(b) (4)

g. Container closure

(b) (4)

h. Dating period and storage conditions

The dating period for the DS is (b) (4) months when stored at (b) (4) C. (b) (4)

C. Drug Product [cemiplimab] Quality Summary

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

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

CQA (Type)	Risk	Origin	Control Strategy	Other
Visible Particles	Safety and Immunogenicity	Through the DP manufacturing process (b) (4)	(b) (4)	(b) (4)
Sterility (contaminant)	Safety (infection), purity and efficacy via degradation or modification of products by contaminating microorganisms	Contaminants could be introduced during manufacturing process or by container closure integrity failure		N/A
Endotoxin	Safety (pyrogenic fever, increased immunogenicity risk) and purity	Contaminants could be introduced during manufacturing or by CCI failure		N/A
Container closure integrity	Safety	May be impacted by storage conditions		N/A
Subvisible Particulate Matter	Safety/ Immunogenicity	Manufacturing process and CCS		N/A

(Product or Process Related Impurities)			(b) (4)	
Volume in Container (general)	Efficacy/Dosing	Manufacturing process		N/A
Leachables (process-related impurities)	Safety	Manufacturing equipment and CCS		N/A

- a. Potency and Strength
Cemiplimab is supplied at 50 mg/mL in a 250 mg/5mL and 350 mg/7 mL glass vials. Potency is defined as the percent activity relative to the current reference standard. The potency assay is the same as described for the DS.
- b. Summary of Product Design
Cemiplimab is supplied as a sterile, preservative-free solution for IV infusion that is presented in a 10-mL single-use glass vial. The drug product formulation consists of 4.8 mM L-Histidine, 5.2 mM L-histidine monohydrochloride monohydrate, 5% (w/v) sucrose, 1.5% (w/v) L-proline, 0.2% (w/v) polysorbate 80, pH 6.0. The extractable volume is 5.0 mL (250 mg vial) and 7.0 mL (350 mg vial).
- c. List of Excipients
Excipients include 4.8 mM L-histidine, 5.2 mM L-histidine monohydrochloride monohydrate, 5% (w/v) sucrose, 1.5% (w/v) L-proline, 0.2% (w/v) polysorbate 80.
- d. Reference material(s)
The same reference material is used for DS (b) (4) and DP.
- e. Manufacturing process summary (b) (4)

f. Container closure

The primary container closure system for cemiplimab DP consists of a 10-mL (b) (4) glass vial (b) (4) 20 mm (b) (4) stopper (b) (4) and a 20 mm aluminum seal cap with (b) (4) flip-off button (b) (4). Appropriate compatibility studies were performed for the container closure system.

The secondary container closure system consists of a (b) (4) cardboard carton which will be used to package one labeled cemiplimab vial and one product information insert.

g. Dating period and storage conditions

The dating period for cemiplimab DP is 18 months when stored at 2-8°C, protected from light.

D. Novel Approaches/Precedents: None**E. Any Special Product Quality Labeling Recommendations**

- Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
- Store in original carton (b) (4)
- Protect from light (b) (4)
- Do not freeze.
- Do not shake.

F. Establishment Information

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE (b) (4)					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Manufacture of cemiplimab DS (b) (4) Manufacture of MCB and WCB; (b) (4) DP release and stability testing; final release site for DP distribution.	Regeneron Pharmaceuticals, Inc. 81 Columbia Turnpike Rensselaer, NY USA 12144-3411	1000514603	Pre-license inspection requested	NAI	Approve
DS in-process testing: in-vitro test for Adventitious Viruses and minute virus of mice PCR assay	Regeneron Pharmaceuticals, Inc. 26 Tech Valley Drive East Greenbush, NY USA 12061	1000514603	Pre-license inspection requested	NAI	Approve
DS in-process testing: in-vitro test for Adventitious Viruses and minute virus of mice PCR assay	(b) (4)	(b) (4)	Acceptable based on profile	N/A	Approve
DS Mycoplasma testing			Acceptable based on profile	N/A	Approve
DS release and stability testing; DP release and stability testing			Acceptable based on profile	N/A	Approve
DS in-process testing			Acceptable based on profile	N/A	Approve
DRUG PRODUCT					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION

Manufacture of DP (b) (4) Endotoxin and Sterility testing.	(b) (4)	Acceptable based on profile	Pre-license inspection waived	Approve
Labeling and packaging of DP.		Acceptable based on profile	N/A	Approve
Final release site for DP distribution. No testing.		Acceptable based on profile	N/A	Approve
DS release and stability testing; DP release and stability testing		Acceptable based on profile	N/A	Approve

G. Facilities

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Regeneron Pharmaceuticals, Inc. (FEI 1000514603) (b) (4) proposed for cemiplimab DS and DP manufacture. All proposed manufacturing and testing facilities are acceptable on the basis of their currently acceptable cGMP compliance status and recent relevant inspectional coverage. BLA 761097 is recommended for approval from a facilities assessment perspective.

H. Lifecycle Knowledge Management

a. Drug Substance

- i. Protocols approved
 - 1. Annual stability protocols for DS (b) (4)
 - 2. Qualification of future reference standard protocol
 - 3. Qualification of new working cell bank protocol
- ii. Outstanding review issues/residual risk: None
- iii. Future inspection points to consider: None

b. Drug Product

- i. Protocols approved: Annual stability protocol
- ii. Outstanding review issues/residual risk: None
- 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 _____		x	
Regulatory Considerations				

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



Willie
Wilson

Digitally signed by Willie Wilson
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Rachel
Novak

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Zhihao Peter
Qiu

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Qing
Zhou

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Patricia
Hughes Troost

Digitally signed by Patricia Hughes Troost
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Comments: Signing on behalf of Reyes Candau-Chacon



U.S. FOOD & DRUG
ADMINISTRATION

BLA STN 761097

cemiplimab
LIBTAYO

Regeneron Pharmaceuticals, Inc.

CMC Technical Report

Willie Wilson, Ph.D., Chemist
Jens Fricke, Ph.D., Staff Fellow
Rachel Novak, Ph.D., Team Lead

Division of Biotechnology Review and Research I

OBP CMC Review Data Sheet

1. **BLA#:** STN 761097
2. **REVIEW DATE:** September 27, 2018
3. **PRIMARY REVIEW TEAM:**
 - Medical Officer:** Denise Casey, Suzanne Demko
 - Pharm/Tox:** Emily Wearne, Whitney Helms
 - Product Quality Team:** Willie Wilson (Drug Substance Reviewer), Jens Fricke (Drug Product Reviewer), Rachel Novak (ATL)
 - BMT or Facilities:** Maxwell Van Tassell, Aimee Cunningham, Ziyang Su, Reyes Candau-Chacon, Peter Qui
 - Clinical Pharmacology:** Xiling Jiang, Hong Zhao
 - Statistics:** Mallorie Fiero, Pallavi Mishra-Kalyani
 - OBP Labeling:** Scott Dallas
 - Labeling:** Ruth Lidoshore, Barbara Fuller, Stacy Shord
 - OBP RBPM:** Anita Brown
 - RPM:** Mimi Biable
4. **MAJOR GRMP DEADLINES**
 - Filing Meeting:** April 12, 2018
 - Mid-Cycle Meeting:** May 24, 2018
 - Wrap-Up Meeting:** September 20, 2018
 - Primary Review Due:** July 28, 2018
 - Secondary Review Due:** July 31, 2018
 - CDTL Memo Due:** September 30, 2018
 - PDUFA Action Date:** October 28, 2018
5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Filing Review Memo	4-27-18
Information Request 1	5-25-18
Mid-Cycle Communication	7-2-18
Information Request 2	7-6-18
Information Request 3	7-17-18
Information Request 4	7-18-18
Information Request 5	7-19-18
Information Request 6	7-23-18
Information Request 7	8-10-18
Information Request 8	8-8-18
Information Request 9	9-7-18
Late-Cycle Communication	8-8-18
Teleconference with Sponsor (b) (4)	9-6-18

Information Request 10	9-17-18
Information Request 11	9-20-18
Information Request 12	9-24-18

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

Submission	Date Received	Review Completed
STN 761097/2 (Rolling BLA Submission – Module 3.2.S and 3.2.A)	12-19-17	Yes
STN 761097/3 (Rolling BLA Submission – Module 3.2.P, 3.2.A, 3.2.R)	1-30-18	Yes
STN 761097/4 (Complete BLA Original Submission, Module 3.2.P.2, 3.2.P.3.5)	2-28-18	Yes
STN 761097/17 (Sponsor's partial response to IR1)	6-4-18	Yes
STN 761097/18 (Sponsor's partial response to IR1)	6-11-18	Yes
STN 761097/19 (Sponsor's partial response to IR1)	6-18-18	Yes
STN 761097/21 (Updated Module 3.2.P.3)	6-25-18	
STN 761097/27 (Sponsor's response to IR2)	7-13-18	Yes
STN 761097/28 (DP Shipping Validation)	7-16-18	Yes
STN 761097/29 (Sponsor's response to IR3)	7-19-18	Yes
STN 761097/30 (Sponsor's response to IR4)	7-24-18	Yes
STN 761097/31 (Sponsor's response to IR5)	7-24-18	Yes
STN 761097/32 (Sponsor's response to IR6)	7-25-18	Yes
STN 761097/35 (Sponsors' response to IR7)	8-14-18	Yes
STN 761097/37 (Sponsor's partial response to IR8)	8-15-18	Yes
STN 761097/39 (Sponsor's partial response to IR8)	8-20-18	Yes
STN 761097/41 (Correction to Module 3.2.P.3.3)	9-4-18	Yes
STN 761097/43 (Sponsor's response to IR9)	9-12-18	Yes
STN 761097/44 (Sponsor's response to IR10)	9-18-18	Yes
STN 761097/47 (Sponsor's response to IR11)	9-24-18	Yes
STN 761097/48 (Sponsor's response to IR12)	9-25-18	Yes

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

- a. Proprietary Name: Libtayo
- b. Trade Name: Libtayo
- c. Non-Proprietary/USAN: Cemiplimab

- d. CAS name: 1801342-60-8
e. Common name: REGN2810
f. INN Name: Cemiplimab
g. Compendial Name: N/A
h. OBP systematic name: MAB HUMAN (IGG4) ANTI Q15116 (PDCD1_HUMAN) [REGN2810]
i. Other Names: REGN2810
8. **PHARMACOLOGICAL CATEGORY:** Human IgG4 isotype monoclonal antibody against programmed cell death 1 receptor (PD-1)
9. **DOSAGE FORM:** Injection
10. **STRENGTH/POTENCY:**
- The cemiplimab Drug Product is supplied as a 50 mg/mL solution for infusion in a 350 mg/7 mL single-use glass vial.
 - Potency is defined as the percent activity relative to the reference standard using a cell-based bioassay consisting of Jurkat effector T-cells engineered to express PD-1 and AP-1 luciferase, and APC-like HEK293 cell engineered to express PD-L1. The bioassay measures the ability of cemiplimab to block PD-1/PD-L1 interaction via the restoration of luciferase reporter activity.
 - The dating period for cemiplimab drug product is 18 months when stored at 2 – 8°C, protected from light.
11. **ROUTE OF ADMINISTRATION:** Intravenous injection
12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Provided in the BLA	Type III, Sufficient information was provided in the BLA for its intended use.
			Provided in the BLA	Type III, Sufficient information was provided in the BLA for its intended use.
			Provided in the BLA	Type III, Sufficient information was provided in the BLA for its intended use.

(b) (4)		
	Provided in the BLA	Type V, Sufficient information was provided in the BLA for its intended use.
	Provided in the BLA	Type III, Sufficient information was provided in the BLA for its intended use.

13. INSPECTIONAL ACTIVITIES

A pre-license inspection (PLI) for cemiplimab drug substance manufacturing was conducted at Regeneron Pharmaceuticals, Inc., Rensselaer, NY (FEI No. 1000514603) from June 4, 2018 to June 8, 2018 by DMA reviewer (Maxwell Van Tassell), OBP product quality reviewers (Willie Wilson and Jens Fricke) and ORA field inspector (Jay Wong). The PLI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. No Form 483 was issued at the conclusion of the inspection.

The requirement for conducting a PLI for the drug product manufacturing facility (b) (4) was waived based on a facility profile evaluation, which was found to be acceptable.

14. CONSULTS REQUESTED BY OBP: None.

15. QUALITY BY DESIGN ELEMENTS

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

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

Design of Experiments studies were performed as part of process development.

Cemiplimab DP is manufactured (b) (4)

[REDACTED]

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

A review of the immunogenicity assays is provided at the end of the Technical Report. The immunogenicity evaluation is composed of four assays: anti-drug antibody (ADA) screening, ADA confirmatory, ADA titer and neutralizing ADA (NAb) confirmation. The ADA and NAb assays are electrochemiluminescence immunoassays. The drug tolerance limit of the ADA screening (528 – 725 µg/mL cemiplimab in the presence of 500 ng/mL ADA) is acceptable. The NAb assay was determined not to be tolerant to be tolerant to onboard drug levels (DLT ≤ 109 ng/mL cemiplimab in the presence of 300 ng/mL NAb). However, ADA were not detected in the target cutaneous squamous cell carcinoma (CSCC) population during Clinical Study 1423 and 1540.



Willie
Wilson

Digitally signed by Willie Wilson
Date: 9/27/2018 08:22:02AM
GUID: 542e18bc000444f367cd79bb56beba7a



Jens
Fricke

Digitally signed by Jens Fricke
Date: 9/27/2018 10:16:56AM
GUID: 57d6a75701b1361db26ba4f78c02a5a9



Rachel
Novak

Digitally signed by Rachel Novak
Date: 9/27/2018 08:47:03AM
GUID: 52e163f70002ba9e745b4e39384c76d7



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

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date of review:	September 27, 2018
Reviewer:	Scott Dallas, RPh Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Willie Wilson, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research I
Application:	761097
Applicant:	Regeneron Pharmaceuticals, Inc.
Submission Dates:	February 28 (original), June 18, September 10, September 18 and September 26, 2018
Product:	Libtayo (cemiplimab)
Dosage form(s):	injection
Strength and Container-Closure:	250 mg/5 mL (50 mg/mL) and 350 mg/7 mL (50 mg/mL) solution in a single-dose vial
Indication, dose, route, and frequency of administration:	indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for surgery. Dosage: Administer 350 mg (every 3 weeks) as an intravenous infusion over 30 minutes until symptomatic disease progression or unacceptable toxicity. (b) (4)
Background and Summary Description:	The Applicant submitted an original BLA application for consideration of approval and references IND 127100 and IND 123950.
Recommendations:	The prescribing information, container labels, and carton labeling are acceptable from a quality labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

DISCUSSION and CONCLUSION

During the review of the application [REDACTED] (b) (4)

On September 26, 2018 the applicant provided updated labeling to include the suffix "rwl" as part of the proper name.

We evaluated the proposed labels and labeling for compliance to the applicable requirements in the Code of Federal Regulations, United States Pharmacopeia (USP) nomenclature and labeling standards, and CDER labeling practices and guidances to help ensure consistent labeling across products.

The prescribing information, medication guide, container labels, and carton labeling were reviewed and found to be acceptable with relevant regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100), USP standards, and CDER labeling practices and guidances.

The labels and labeling submitted on September 26, 2018 are acceptable (see Appendix C) from a OBP quality labeling perspective.

APPENDICES

Appendix A: Proposed Labels and Labeling

- Prescribing Information and Medication Guide (submitted on February 28, 2018 <\\cdsesub1\evsprod\bla761097\0004\m1\us\114-labeling\114a-draft-label\proposed-uspi.docx>)
- Container Labels 250 mg/5 mL (submitted on February 28, 2018)



Appendix B: Evaluation Tables
Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Regulations, Guidance and CDER Best Labeling Practices	Conforms
<u>Proper Name</u> (21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10) <i>for container of a product capable of bearing a full label</i>	☐ No ☒ Yes ☐ N/A
<u>Manufacturer name, address, and license number</u> (21 CFR 610.60) <i>for container of a product capable of bearing a full label</i> Comment/Recommendation: Relocate the U.S. License No. 1760 to appear directly below the Manufactured by address. Applicant's response dated June 18, 2018: The Sponsor accepts the Agency's comment and relocated the U.S. License No. 1760 to appear directly below the Manufactured by address.	☐ No ☒ Yes ☐ N/A
<u>Lot number or other lot identification</u> (21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100) Comment/Recommendation: Per section 3.2.P.7 SECONDARY PACKAGING COMPONENTS One labeled cemiplimab vial and one product information physician insert are loaded into a (b) (4) cardboard carton. The lot number and expiration date are applied to the vial label and carton. However, DMEPA is including a comment to identify the exact location and format of this information.	☐ No ☒ Yes ☐ N/A
<u>Expiration date</u> (21 CFR 610.60, 21 CFR 201.17)	☐ No ☒ Yes ☐ N/A

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Comment/Recommendation:

Per section 3.2.P.7

SECONDARY PACKAGING COMPONENTS

One labeled cemiplimab vial and one product information physician insert are loaded into a (b) (4) cardboard carton. The lot number and expiration date are applied to the vial label and carton.

However, DMEPA is including a comment to identify the exact location and format of this information.

Multiple dose containers (recommended individual dose)

21 CFR 610.60

- ☐ No
☐ Yes
☒ N/A

Statement: "Rx only"

21 CFR 610.60

21 CFR 201.100

- ☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Please debold the "Rx only" statement to allow for the prominence of other important information on the principal display panel.

CDER recommendation to promote consistency across labeling.

Applicant's response dated June 18, 2018:

The Sponsor acknowledges the Agency's comment and debolded the "Rx only".

Medication Guide

21 CFR 610.60

21 CFR 208.24

- ☒ No
☐ Yes
☐ N/A

Comment/Recommendation:

Medication Guide statement is on the carton labeling, because the vial label is too small.

No Package for container

21 CFR 610.60

- ☒ No
☐ Yes
☐ N/A

Comment/Recommendation:

The vial is placed in a carton.

Partial label

21 CFR 610.60

21 CFR 201.10

- ☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Label does not contain the Medication Guide statement

No container label

21 CFR 610.60

- ☐ No
☐ Yes
☒ N/A

<u>Ferrule and cap overseal</u>	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: Please confirm there is no text on the ferrule and cap overseal of the vial to comply with a revised United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals). <u>Applicant's response dated June 18, 2018:</u> The Sponsor confirms there is no text on the ferrule and cap overseal of the vials.	
<u>Visual inspection</u> 21 CFR 610.60	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: Per section 3.2.P.7 Container Closure System an image indicates that there is space to visually inspect the product when the label has been affixed to the vial.	
<u>NDC numbers</u> 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: DMEPA is providing a comment (b) (4) _____ _____ _____ <u>Applicant's response dated June 18, 2018:</u> The Sponsor acknowledges the Agency's comments and revised the NDC number for the 350 mg/7mL strength to 61755-008-01, (b) (4) _____	
<u>Route of administration</u> 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: However DMEPA is providing a comment to revise the statement (b) (4) to "For intravenous infusion after dilution."	
<u>Preparation instructions</u> 21 CFR 201.5	☐ No ☐ Yes ☒ N/A
<u>Package type term</u> 21 CFR 201.5	☐ No ☒ Yes ☐ N/A

Comment/Recommendation:

Revise the package type term for this injection product from (b) (4) to "single-dose" vial throughout the prescribing information and on all container labels and carton labeling.

The Agency recommends consistent use of the appropriate package type terms and discard statements. The appropriate package-type term for this injection product is "single-dose". A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose. Refer to FDA's Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple -Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2015

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

Applicant's response dated June 18, 2018:

The Sponsor acknowledges the Agency's comments and revised the package type term for this injection product from (b) (4) to "Single-Dose Vial" throughout the container labels and cartons.

Drugs Misleading statements 21 CFR 201.6	☒ No ☐ Yes ☐ N/A
Strength 21 CFR 201.10 21CFR 201.100	☐ No ☒ Yes ☐ N/A
Drugs Prominence of required label statements 21 CFR 201.15 Comment/Recommendation:	☐ No ☒ Yes ☐ N/A
Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A

<u>Bar code label requirements</u> 21 CFR 201.25 21CFR 610.67	☐ No ☒ Yes ☐ N/A
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u> 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
<u>Net quantity</u> 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
Comment/ Recommendation: (b) (4) The net quantity (b) (4) is conveyed in the statement of Single-Dose Vial. Applicant's response dated June 18, 2018: The Sponsor accepts the Agency's comment (b) (4) 	
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
<u>Inactive ingredients</u> 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
<u>Storage requirements</u>	☐ No ☐ Yes ☒ N/A
<u>Dispensing container</u> 21 CFR 201.100	☐ No ☐ Yes ☒ N/A

Package Label⁵ Evaluation

<u>Regulations, Guidance and CDER Best Labeling Practices</u>	<u>Conforms</u>
<u>Proper name</u> (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10)	☐ No ☒ Yes ☐ N/A
Comment/ Recommendation:	
<u>Manufacturer name, address, and license number</u> 21 CFR 610.61	☐ No ☒ Yes

⁵ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Comment/Recommendation: Relocate the U.S. License No. 1760 to appear directly below the Manufactured by address. <u>Applicant's response dated June 18, 2018:</u> The Sponsor accepts the Agency's comment and relocated the U.S. License No. 1760 to appear directly below the Manufactured by address.	☐ N/A
<u>Lot number or other lot identification</u> 21 CFR 610.61 Comment/Recommendation: Ensure lot number appears on the label per 21 CFR 610.61(c). DMEPA has also provided a comment. <u>Applicant's response dated June 18, 2018:</u> Lot number appears on the carton labeling.	☐ No ☒ Yes ☐ N/A
<u>Expiration date</u> 21 CFR 610.61 21 CFR 201.17 Comment/Recommendation: Ensure the expiration date appears on the label per 21 CFR 610.61(d). DMEPA has also provided a comment. <u>Applicant's response dated June 18, 2018:</u> Expiration date appears on the carton labeling.	☐ No ☒ Yes ☐ N/A
<u>Preservative</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
<u>Number of containers</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
<u>Strength/volume</u> 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	☐ No ☒ Yes ☐ N/A

<u>Storage temperature/requirements</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
<u>Handling: "Do Not Shake", "Do not Freeze" or equivalent</u> (21 CFR 610.61)	☐ No ☒ Yes ☐ N/A
<u>Multiple dose containers (recommended individual dose)</u> 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
<u>Route of administration</u> 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
<u>Known sensitizing substances</u> 21CFR 610.61	☐ No ☐ Yes ☒ N/A
<u>Inactive ingredients</u> 21 CFR 610.61 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
<u>Source of the product</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
<u>Minimum potency of product</u> 21 CFR 610.61 Dr. Jens Fricke, confirmed there is no compendial standard.	☐ No ☒ Yes ☐ N/A
<u>Rx only</u> 21CFR 610.61 21 CFR 201.100 Comment/Recommendation: Please debold the "Rx only" statement to allow for the prominence of other important information on the principal display panel. A CDER recommendation to promote consistency in labeling. <u>Applicant's response dated June 18, 2018:</u> The Sponsor acknowledges the Agency's comment and debolded the "Rx only".	☒ No ☐ Yes ☐ N/A
<u>Divided manufacturing</u> 21 CFR 610.63	☐ No ☐ Yes ☒ N/A
<u>Distributor</u> 21 CFR 610.64	☐ No ☒ Yes ☐ N/A
<u>Bar code</u>	☐ No

21 CFR 610.67 21 CFR 201.25	☒ Yes ☐ N/A
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u> 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
<u>NDC numbers</u> 21 CFR 201.2 21 CFR 207.35 Comment/ Recommendation: Applicant's response dated June 18, 2018: The Sponsor acknowledges the Agency's comments and revised the NDC number for the 350 mg/7mL strength to 61755-008-01, (b) (4) -	☐ No ☒ Yes ☐ N/A
<u>Preparation instructions</u> 21 CFR 201.5	☐ No ☐ Yes ☒ N/A
<u>Package type term</u> 21 CFR 201.5 Comment/ Recommendation: Revise the package type term for this injection product from (b) (4) to "single-dose" vial throughout the prescribing information and on all container labels and carton labeling. The Agency recommends consistent use of the appropriate package type terms and discard statements. The appropriate package-type term for this injection product is "single-dose". A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose. Refer to FDA's Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple -Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2015 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf Applicant's response dated June 18, 2018: The Sponsor acknowledges the Agency's comments and revised the package type term for this injection product from (b) (4) to "Single-Dose Vial" throughout the container labels and cartons.	☐ No ☒ Yes ☐ N/A

<u>Drugs</u> <u>Misleading statements</u> 21 CFR 201.6	☐ No ☒ Yes ☐ N/A
<u>Drugs</u> <u>Prominence of required label statements</u> 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
<u>Spanish-language (Drugs)</u> 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u> 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
<u>Phenylalanine as a component of aspartame</u> 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
<u>Sulfites; required warning statements</u> 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
<u>Net quantity</u> 21 CFR 201.51 21 CFR 610.61(f) Comment/ Recommendation: <u>Applicant's response dated June 18, 2018:</u> The Sponsor accepts the Agency's comment and revised the "Carton Statement" from (b) (4) Package Insert, and Medication Guide" to "Single-Dose Vial, Prescribing Information, and Medication Guide" to display the appropriate packaging type term and maintain consistency with PI. <u>FDA evaluation:</u> The comment to the applicant was only directed to the container label, but the applicant applied the comment to both the container and carton labeling. Per 21 CFR 610.61(f) the number of containers is only required if more than one. Therefore the net quantity statement is acceptable. Also the overfill volume is acceptable, based upon a response in amendment 30 dated July 24, 2018	☐ No ☒ Yes ☐ N/A
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
<u>Dispensing container</u> 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
<u>Medication Guide</u> 21 CFR 610.60 21 CFR 208.24	☐ No ☒ Yes ☐ N/A
<u>Other</u>	☐ No

Comment/Recommendation:

☐ Yes
☒ N/A

Prescribing Information and Medication Guide Evaluation

Regulations	Conforms
PRESCRIBING INFORMATION	
Highlights of prescribing information	
<u>PRODUCT TITLE</u> 21 CFR 201.57(a)(2)	☐ No ☒ Yes ☐ N/A
<u>DOSAGE AND ADMINISTRATION</u> 21 CFR 201.57(a)(7)	☐ No ☒ Yes ☐ N/A
<u>DOSAGE FORMS AND STRENGTHS</u> 21 CFR 201.57(a)(8)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: Revise the package type term for this injection product from (b) (4) to "single-dose" vial throughout the prescribing information and on all container labels and carton labeling. The Agency recommends consistent use of the appropriate package type terms and discard statements. The appropriate package-type term for this injection product is "single-dose". A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose. Refer to FDA's Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple -Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2015 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf	
Full Prescribing Information	
<u>2 DOSAGE AND ADMINISTRATION</u> 21 CFR 201.57(c)(3)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: Insert as the 2 nd bullet in section 2.3 Include statement for parenteral products: "Parenteral drug products should be inspected	

visually for particulate matter and discoloration prior to administration, whenever solution and container permit” per 21 CFR 201.57 (c)(3)(iv).

3 DOSAGE FORMS AND STRENGTHS

21 CFR 201.57(c)(4)

clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles

☐ No
☒ Yes
☐ N/A

6.2 IMMUNOGENICITY

Draft Guidance for Industry: Labeling for Biosimilar Products

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:

To Applicant: Revise the first paragraph to be consistent with FDA guidance.

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf>

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cemiplimab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

11 DESCRIPTION

(21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q))

☐ No
☐ Yes
☐ N/A

Comment/Recommendation:

(b) (4)

Each (b) (4) vial (b) (4) contains 350 mg of cemiplimab (b) (4) Each mL contains cemiplimab 50 mg, L-histidine (0.74 mg), L-histidine monohydrochloride monohydrate (1.1 mg), sucrose (50 mg), L-proline (15 mg), Polysorbate 80 (2 mg), and Water for Injection, USP.

On May 21, 2018 Dr. Jens Fricke was able to confirm the inactive ingredients and quantities per

mL are correct.

On September 6, 2018 it was decided the Description section will only reference the 350 mg/vial.

16 HOW SUPPLIED/ STORAGE AND HANDLING

21 CFR 201.57(c)(17)

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

LIBTAYO (cemiplimab) Injection is a clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles (b) (4) supplied in a carton (b) (4) containing 1 single-dose vial (b) (4):

- 250 mg/5 mL (50 mg/mL) (NDC 61755-007-01)
- 350 mg/7 mL (50 mg/mL)(NDC 61755 (b) (4))

(b) (4)

MANUFACTURER INFORMATION

For BLAs: 21 CFR 610.61, 21 CFR 610.64

For NDAs: 21 CFR 201.1

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Relocate the U.S. License No. 1760 to appear directly below the Manufactured by address.

The sponsor relocated the license number.

MEDICATION GUIDE

TITLE (NAMES AND DOSAGE FORM)

☐ No
☒ Yes
☐ N/A

STORAGE AND HANDLING

☐ No
☐ Yes
☒ N/A

INGREDIENTS

☐ No
☒ Yes
☐ N/A

MANUFACTURER INFORMATION

For BLAs: 21 CFR 610.61, 21 CFR 610.64

For NDAs: 21 CFR 201.1

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Relocate the U.S. License No. 1760 to appear directly below the Manufactured by address.

The sponsor relocated the license number.

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on September 26, 2018)
<\\cdsesub1\evsprod\bla761097\0049\m1\us\114-labeling\114a-draft-label\proposed-uspi-tc.pdf>
- Medication Guide (submitted on September 26, 2018)
<\\cdsesub1\evsprod\bla761097\0049\m1\us\114-labeling\114a-draft-label\proposed-medication-guide.docx>
- Container Labels (submitted on September 26, 2018)





Scott
Dallas

Digitally signed by Scott Dallas

Date: 9/27/2018 05:38:40AM

GUID: 508da712000294048aa136a18a6af06a



Willie
Wilson

Digitally signed by Willie Wilson

Date: 9/27/2018 07:59:22AM

GUID: 542e18bc000444f367cd79bb56beba7a



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

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date of review:	September 18, 2018
Reviewer:	Scott Dallas, RPh Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Jens Fricke, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research I
Application:	761097
Applicant:	Regeneron Pharmaceuticals, Inc.
Submission Dates:	February 28 (original), June 18, September 10 and September 18, 2018
Product:	Libtayo (cemiplimab)
Dosage form(s):	injection
Strength and Container-Closure:	250 mg/5 mL (50 mg/mL) and 350 mg/7 mL (50 mg/mL) solution in a single-dose vial
Indication, dose, route, and frequency of administration:	Indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for (b) (4) Dosage: Administer 350 mg (every 3 weeks) as an intravenous infusion over 30 minutes until symptomatic disease progression or unacceptable toxicity. (b) (4)
Background and Summary Description:	The Applicant submitted an original BLA application for consideration of approval and references IND 127100 and IND 123950.
Recommendations:	The prescribing information, container labels, and carton labeling are acceptable from a quality labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

DISCUSSION and CONCLUSION

During the review of the application

(b) (4)

(b) (4)

We evaluated the proposed labels and labeling for compliance to the applicable requirements in the Code of Federal Regulations, United States Pharmacopeia (USP) nomenclature and labeling standards, and CDER labeling practices and guidances to help ensure consistent labeling across products.

The prescribing information, container labels, and carton labeling were reviewed and found to be acceptable with relevant regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100), USP standards, and CDER labeling practices and guidances.

The labels and labeling submitted on June 18 and September 18, 2018 are acceptable (see Appendix C) from a OBP quality labeling perspective.

APPENDICES

Appendix A: Proposed Labels and Labeling

- Prescribing Information and Medication Guide (submitted on February 28, 2018 <\\cdsesub1\evsprod\bla761097\0004\m1\us\114-labeling\114a-draft-label\proposed-uspi.docx>)
- Container Labels 250 mg/5 mL (submitted on February 28, 2018)

(b) (4)

Appendix B: Evaluation Tables
Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Regulations, Guidance and CDER Best Labeling Practices	Conforms
Proper Name (21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10) <i>for container of a product capable of bearing a full label</i>	☐ No ☒ Yes ☐ N/A
Manufacturer name, address, and license number (21 CFR 610.60) <i>for container of a product capable of bearing a full label</i> Comment/Recommendation: Relocate the U.S. License No. 1760 to appear directly below the Manufactured by address. <u>Applicant's response dated June 18, 2018:</u> The Sponsor accepts the Agency's comment and relocated the U.S. License No. 1760 to appear directly below the Manufactured by address.	☐ No ☒ Yes ☐ N/A
Lot number or other lot identification (21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100) Comment/Recommendation: Per section 3.2.P.7 SECONDARY PACKAGING COMPONENTS One labeled cemiplimab vial and one product information physician insert are loaded into a (b) (4) cardboard carton. The lot number and expiration date are applied to the vial label and carton. However, DMEPA is including a comment to identify the exact location and format of this information.	☐ No ☒ Yes ☐ N/A
Expiration date (21 CFR 610.60, 21 CFR 201.17)	☐ No ☒ Yes ☐ N/A

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Comment/Recommendation:

Per section 3.2.P.7

SECONDARY PACKAGING COMPONENTS

One labeled cemiplimab vial and one product information physician insert are loaded into a (b) (4) cardboard carton. The lot number and expiration date are applied to the vial label and carton.

However, DMEPA is including a comment to identify the exact location and format of this information.

Multiple dose containers (recommended individual dose)

21 CFR 610.60

- ☐ No
☐ Yes
☒ N/A

Statement: "Rx only"

21 CFR 610.60

21 CFR 201.100

- ☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Please debold the "Rx only" statement to allow for the prominence of other important information on the principal display panel.

CDER recommendation to promote consistency across labeling.

Applicant's response dated June 18, 2018:

The Sponsor acknowledges the Agency's comment and debolded the "Rx only".

Medication Guide

21 CFR 610.60

21 CFR 208.24

- ☒ No
☐ Yes
☐ N/A

Comment/Recommendation:

Medication Guide statement is on the carton labeling, because the vial label is too small.

No Package for container

21 CFR 610.60

- ☒ No
☐ Yes
☐ N/A

Comment/Recommendation:

The vial is placed in a carton.

Partial label

21 CFR 610.60

21 CFR 201.10

- ☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Label does not contain the Medication Guide statement

No container label

21 CFR 610.60

- ☐ No
☐ Yes
☒ N/A

Ferrule and cap overseal

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Please confirm there is no text on the ferrule and cap overseal of the vial to comply with a revised United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals).

Applicant's response dated June 18, 2018:

The Sponsor confirms there is no text on the ferrule and cap overseal of the vials.

Visual inspection

21 CFR 610.60

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Per section 3.2.P.7 Container Closure System an image indicates that there is space to visually inspect the product when the label has been affixed to the vial.

NDC numbers

21 CFR 201.2

21 CFR 207.35

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

DMEPA is providing a comment

(b) (4)

(b) (4)

Applicant's response dated June 18, 2018:

The Sponsor acknowledges the Agency's comments and revised the NDC number for the 350 mg/7mL strength to 61755-008-01, (b) (4)

Route of administration

21 CFR 201.5

21 CFR 201.100

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

However DMEPA is providing a comment to revise the statement (b) (4) to "For intravenous infusion after dilution."

Preparation instructions

21 CFR 201.5

☐ No
☐ Yes
☒ N/A

Package type term

21 CFR 201.5

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Revise the package type term for this injection product from '(b) (4)' to "single-dose" vial throughout the prescribing information and on all container labels and carton labeling.

The Agency recommends consistent use of the appropriate package type terms and discard statements. The appropriate package-type term for this injection product is "single-dose". A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose. Refer to FDA's Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple -Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2015

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

Applicant's response dated June 18, 2018:

The Sponsor acknowledges the Agency's comments and revised the package type term for this injection product from '(b) (4)' to "Single-Dose Vial" throughout the container labels and cartons.

<u>Drugs</u> <u>Misleading statements</u> 21 CFR 201.6	☒ No ☐ Yes ☐ N/A
<u>Strength</u> 21 CFR 201.10 21CFR 201.100	☐ No ☒ Yes ☐ N/A
<u>Drugs</u> <u>Prominence of required label statements</u> 21 CFR 201.15 Comment/Recommendation:	☐ No ☒ Yes ☐ N/A
<u>Spanish-language (Drugs)</u> 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u> 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
<u>Phenylalanine as a component of aspartame</u> 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
<u>Sulfites; required warning statements</u> 21 CFR 201.22	☐ No ☐ Yes ☒ N/A

<u>Bar code label requirements</u> 21 CFR 201.25 21CFR 610.67	☐ No ☒ Yes ☐ N/A
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u> 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
<u>Net quantity</u> 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: (b) (4) The net quantity is conveyed in the statement of Single-Dose Vial.	
<u>Applicant's response dated June 18, 2018:</u> The Sponsor accepts the Agency's comment and deleted the reference to the number 1 as a net quantity.	
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
<u>Inactive ingredients</u> 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
<u>Storage requirements</u>	☐ No ☐ Yes ☒ N/A
<u>Dispensing container</u> 21 CFR 201.100	☐ No ☐ Yes ☒ N/A

Package Label⁵ Evaluation

Regulations, Guidance and CDER Best Labeling Practices		Conforms
<u>Proper name</u> (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10)		☐ No ☒ Yes ☐ N/A
Comment/Recommendation:		
<u>Manufacturer name, address, and license number</u> 21 CFR 610.61		☐ No ☒ Yes

⁵ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

☐ N/A	
Comment/Recommendation: Relocate the U.S. License No. 1760 to appear directly below the Manufactured by address. <u>Applicant's response dated June 18, 2018:</u> The Sponsor accepts the Agency's comment and relocated the U.S. License No. 1760 to appear directly below the Manufactured by address.	
<u>Lot number or other lot identification</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: Ensure lot number appears on the label per 21 CFR 610.61(c). DMEPA has also provided a comment. <u>Applicant's response dated June 18, 2018:</u> Lot number appears on the carton labeling.	
<u>Expiration date</u> 21 CFR 610.61 21 CFR 201.17	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: Ensure the expiration date appears on the label per 21 CFR 610.61(d). DMEPA has also provided a comment. <u>Applicant's response dated June 18, 2018:</u> Expiration date appears on the carton labeling.	
<u>Preservative</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
<u>Number of containers</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
<u>Strength/volume</u> 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	☐ No ☒ Yes ☐ N/A

<u>Storage temperature / requirements</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
<u>Handling: "Do Not Shake", "Do not Freeze" or equivalent</u> (21 CFR 610.61)	☐ No ☒ Yes ☐ N/A
<u>Multiple dose containers (recommended individual dose)</u> 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
<u>Route of administration</u> 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
<u>Known sensitizing substances</u> 21CFR 610.61	☐ No ☐ Yes ☒ N/A
<u>Inactive ingredients</u> 21 CFR 610.61 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
<u>Source of the product</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
<u>Minimum potency of product</u> 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Dr. Jens Fricke, confirmed there is no compendial standard.	
<u>Rx only</u> 21CFR 610.61 21 CFR 201.100 Comment/Recommendation: Please debold the "Rx only" statement to allow for the prominence of other important information on the principal display panel. A CDER recommendation to promote consistency in labeling. <u>Applicant's response dated June 18, 2018:</u> The Sponsor acknowledges the Agency's comment and debolded the "Rx only".	☒ No ☐ Yes ☐ N/A
<u>Divided manufacturing</u> 21 CFR 610.63	☐ No ☐ Yes ☒ N/A
<u>Distributor</u> 21 CFR 610.64	☐ No ☒ Yes ☐ N/A
<u>Bar code</u>	☐ No

21 CFR 610.67 21 CFR 201.25	☒ Yes ☐ N/A
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u> 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
<u>NDC numbers</u> 21 CFR 201.2 21 CFR 207.35 Comment/Recommendation: 	☐ No ☒ Yes ☐ N/A
<u>Applicant's response dated June 18, 2018:</u> The Sponsor acknowledges the Agency's comments and revised the NDC number for the 350 mg/7mL strength to 61755-008-01, (b) (4)	
<u>Preparation instructions</u> 21 CFR 201.5	☐ No ☐ Yes ☒ N/A
<u>Package type term</u> 21 CFR 201.5 Comment/Recommendation: Revise the package type term for this injection product from " (b) (4)" to "single-dose" vial throughout the prescribing information and on all container labels and carton labeling. The Agency recommends consistent use of the appropriate package type terms and discard statements. The appropriate package-type term for this injection product is "single-dose". A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose. Refer to FDA's Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple -Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2015 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf	☐ No ☒ Yes ☐ N/A
<u>Applicant's response dated June 18, 2018:</u> The Sponsor acknowledges the Agency's comments and revised the package type term for this injection product from " (b) (4)" to "Single-Dose Vial" throughout the container labels and cartons.	

<u>Drugs</u> <u>Misleading statements</u> 21 CFR 201.6	☐ No ☒ Yes ☐ N/A
<u>Drugs</u> <u>Prominence of required label statements</u> 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
<u>Spanish-language (Drugs)</u> 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u> 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
<u>Phenylalanine as a component of aspartame</u> 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
<u>Sulfites; required warning statements</u> 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
<u>Net quantity</u> 21 CFR 201.51 21 CFR 610.61(f) Comment/ Recommendation: <u>Applicant's response dated June 18, 2018:</u> The Sponsor accepts the Agency's comment and revised the "Carton Statement" from (b) (4), Package Insert, and Medication Guide" to "Single-Dose Vial, Prescribing Information, and Medication Guide" to display the appropriate packaging type term and maintain consistency with PI. <u>FDA evaluation:</u> The comment to the applicant was only directed to the container label, but the applicant applied the comment to both the container and carton labeling. Per 21 CFR 610.61(f) the number of containers is only required if more than one. Therefore the net quantity statement is acceptable. Also the overfill volume is acceptable, based upon a response in amendment 30 dated July 24, 2018	☐ No ☒ Yes ☐ N/A
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
<u>Dispensing container</u> 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
<u>Medication Guide</u> 21 CFR 610.60 21 CFR 208.24	☐ No ☒ Yes ☐ N/A
<u>Other</u>	☐ No

Comment/Recommendation:

☐ Yes
☒ N/A

Prescribing Information and Patient Labeling Evaluation

Regulations	Conforms
PRESCRIBING INFORMATION	
Highlights of prescribing information	
PRODUCT TITLE 21 CFR 201.57(a)(2)	☐ No ☒ Yes ☐ N/A
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	☐ No ☒ Yes ☐ N/A
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: Revise the package type term for this injection product from "(b) (4)" to "single-dose" vial throughout the prescribing information and on all container labels and carton labeling. The Agency recommends consistent use of the appropriate package type terms and discard statements. The appropriate package-type term for this injection product is "single-dose". A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose. Refer to FDA's Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple -Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2015 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf	
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: Insert as the 2 nd bullet in section 2.3 Include statement for parenteral products: "Parenteral drug products should be inspected	

visually for particulate matter and discoloration prior to administration, whenever solution and container permit" per 21 CFR 201.57 (c)(3)(iv).

3 DOSAGE FORMS AND STRENGTHS

21 CFR 201.57(c)(4)

clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles

☐ No
☒ Yes
☐ N/A

6.2 IMMUNOGENICITY

Draft Guidance for Industry: Labeling for Biosimilar Products

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:

To Applicant: Revise the first paragraph to be consistent with FDA guidance.

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf>

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cemiplimab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

11 DESCRIPTION

(21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q))

☐ No
☐ Yes
☐ N/A

Comment/Recommendation:

(b) (4)

Each (b) (4) vial (b) (4) contains 350 mg of cemiplimab (b) (4) Each mL contains cemiplimab 50 mg, L-histidine (0.74 mg), L-histidine monohydrochloride monohydrate (1.1 mg), sucrose (50 mg), L-proline (15 mg), Polysorbate 80 (2 mg), and Water for Injection, USP.

On May 21, 2018 Dr. Jens Fricke was able to confirm the inactive ingredients and quantities per

mL are correct.

(b) (4)

16 HOW SUPPLIED/ STORAGE AND HANDLING

21 CFR 201.57(c)(17)

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

LIBTAYO (cemiplimab) Injection is a clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles (b) (4) supplied in a carton (b) (4) containing 1 single-dose vial (b) (4):

- 250 mg/5 mL (50 mg/mL) (NDC 61755-007-01)
- 350 mg/7 mL (50 mg/mL) (NDC 61755 (b) (4))

(b) (4)

MANUFACTURER INFORMATION

For BLAs: 21 CFR 610.61, 21 CFR 610.64

For NDAs: 21 CFR 201.1

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Relocate the U.S. License No. 1760 to appear directly below the Manufactured by address.

The sponsor relocated the license number.

MEDICATION GUIDE

TITLE (NAMES AND DOSAGE FORM)

☐ No
☒ Yes
☐ N/A

STORAGE AND HANDLING

☐ No
☐ Yes
☒ N/A

INGREDIENTS

☐ No
☒ Yes
☐ N/A

MANUFACTURER INFORMATION

For BLAs: 21 CFR 610.61, 21 CFR 610.64

For NDAs: 21 CFR 201.1

☐ No
☒ Yes
☐ N/A

Comment/Recommendation:

Relocate the U.S. License No. 1760 to appear directly below the Manufactured by address.

The sponsor relocated the license number.



Scott
Dallas

Digitally signed by Scott Dallas
Date: 9/26/2018 09:42:09AM
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Jens
Fricke

Digitally signed by Jens Fricke
Date: 9/26/2018 09:33:49AM
GUID: 57d6a75701b1361db26ba4f78c02a5a9



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: 7/26/2018
To: Administrative File, STN 761097/0
From: Ziyang Su, Ph.D., Chemist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: 1760
Applicant: Regeneron Pharmaceuticals, Inc.
Mfg. Facility: Drug Substance *Regeneron Pharmaceuticals, Inc., Rensselaer, NY, USA*
FEI 1000514603
Drug Product (b) (4)
Product: Cemiplimab, Solution for infusion
Dosage: 50 mg/mL (250 mg/5 mL and 350 mg/7 mL), supplied in 10 mL glass vials
Indication: Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (laCSCC or mCSCC)
Due Date: 7/27/2018

RECOMMENDATION:

Approval: This submission is recommended for approval from a facilities assessment perspective.

SUMMARY

BLA STN 761097/0 was submitted by Regeneron Pharmaceuticals, Inc., which provided information and data to support the manufacture of cemiplimab, solution for injection. Cemiplimab is a recombinant human IgG4 isotype monoclonal antibody that binds specifically to programmed cell death 1 receptor (PD-1) blocking the interaction with its ligands, PD-L1 and PD-L2. It consists of two disulfide-bonded human heavy chains, each covalently linked through a disulfide bond to a human kappa light chain. Cemiplimab is produced (b) (4) with recombinant Chinese hamster ovary (CHO) cells that have been engineered to express cemiplimab heavy and light chains. Cemiplimab drug product, 250 mg/5 mL and 350 mg/7 mL, is a clear to slightly opalescent, colorless to pale yellow, (b) (4) sterile solution. Cemiplimab DP is provided in a 10 mL glass vial with a 20 mm finish made of clear (b) (4) glass, equipped with a 20 mm gray (b) (4) stopper, and a 20 mm seal cap with a flip-off button.

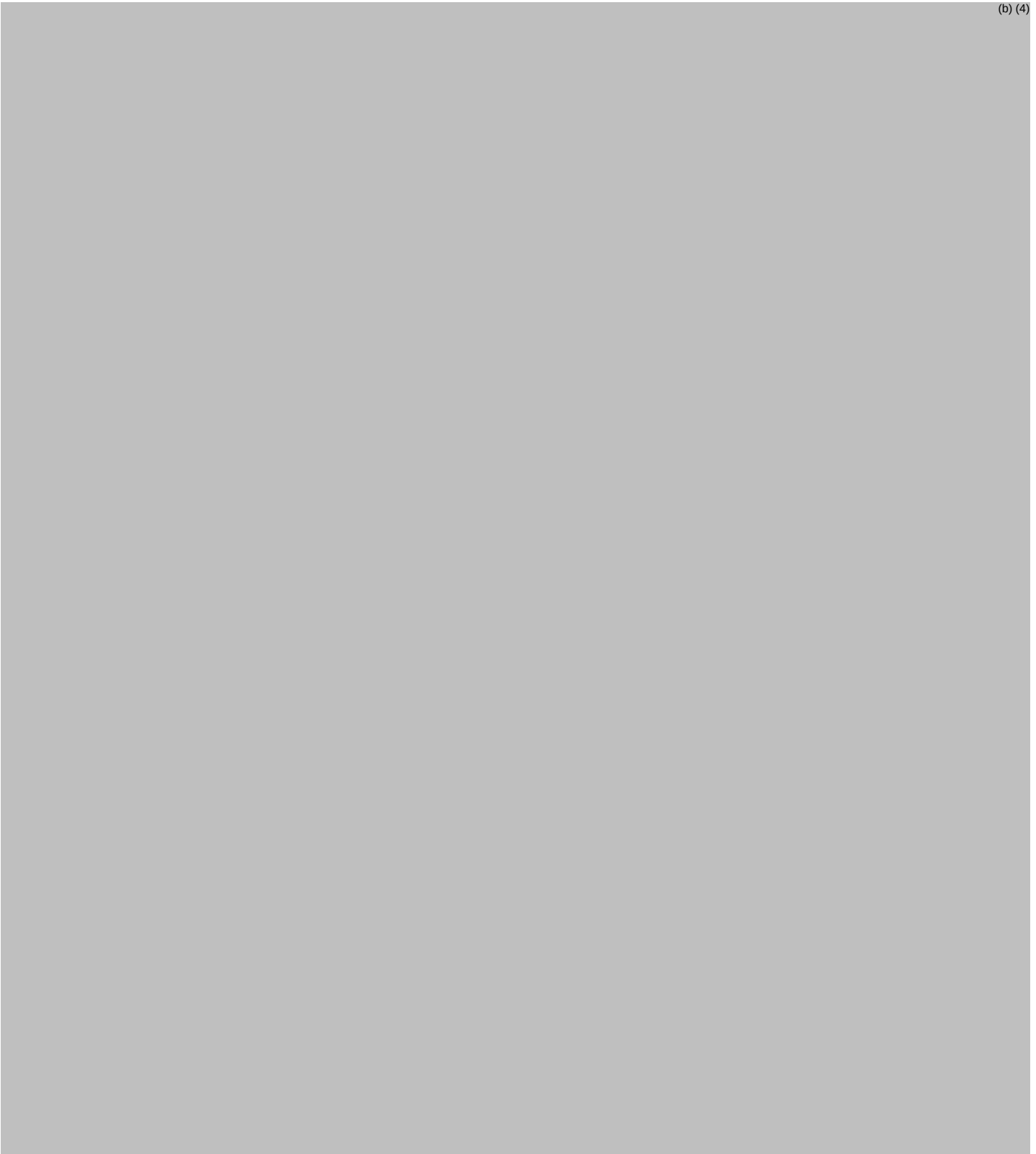
The subject BLA proposes commercial manufacture of Cemiplimab DS and DP at Regeneron Pharmaceuticals, Inc., Rensselaer, NY (FEI 1000514603) (b) (4) respectively. Cell banking and testing operations will occur at Regeneron

BLA 761097 Cemiplimab DS and DP Manufacture

Pharmaceuticals, Inc., Rensselaer, NY. Refer to the following Sections 3.2.S.2.1 and 3.2.P.3.1 for details of the DS and DP testing facilities.

ASSESSMENT

(b) (4)



CONCLUSION

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Regeneron Pharmaceuticals, Inc. (FEI 1000514603) and (b) (4) proposed for cemiplimab DS and DP manufacture. All proposed manufacturing and testing facilities are acceptable on the basis of their currently acceptable cGMP compliance status and recent relevant inspectional coverage.

BLA 761097 is recommended for approval from a facilities assessment perspective.

Ziyang Su -
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Ziyang Su, Ph.D.
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OPF Division of Inspectional Assessment
Branch 1

Zhihao
Qiu -S

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

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

Date: 6/25/2018

From: Ziyang Su, Ph.D., Chemist, CDER/OPQ/OPF/DIA

To: BLA File, STN 761097/0

Through: Thuy T. Nguyen, QAL, OPQ/OPF/DIA Branch 1

Subject: Inspection waiver memo for manufacture of cemiplimab drug product at
(b) (4)

Applicant: Regeneron Pharmaceuticals, Inc.

Facility: (b) (4)

Product: Cemiplimab, Solution for Infusion

Dosage: Solution for Injection, 50 mg/mL (250 mg/5 mL and 350 mg/7 mL), supplied in 10 mL glass vials

Indication: Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (laCSCC or mCSCC)

Waiver Recommendation

Cemiplimab DP will be manufactured at the (b) (4)
(b) (4) The proposed (b) (4) for
cemiplimab DP is similar to that of the licensed processes for (b) (4)

(b) (4) The facility was recently inspected by the FDA in (b) (4)
(b) (4) The two inspections conducted in (b) (4)
provided pre-license coverage for drug substance manufacturing (profile class CBI). Both
inspections were classified VAI. The (b) (4) inspection conducted by ORA is a relevant
inspection covering (b) (4). It provided cGMP and pre-approval coverage (b) (4)
(b) (4) Profile class SVS was updated
acceptable. The inspection was classified VAI, and the facility was found to be in compliance
with cGMPs.

Based on the firm's compliance history, current acceptable GMP status, and the (b) (4)
manufacture of several other licensed and approved sterile liquid products (b) (4)
(b) (4) we recommend that a

pre-license inspection of the [REDACTED] (b) (4)
be waived for STN 761097/0.

Summary

BLA 761097/0 proposes the manufacture of cemiplimab drug substance at Regeneron Pharmaceuticals, Inc., Rensselaer, New York (FEI 1000514603), and cemiplimab drug product at [REDACTED] (b) (4). This waiver recommendation is in regard to cemiplimab DP manufacture [REDACTED] (b) (4).

Facility Information

Cemiplimab commercial drug product (250 mg/5.0 mL and 350 mg/7.0 mL solutions for injection) [REDACTED] (b) (4)

[REDACTED] (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.*

[REDACTED] (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 briefly discussed in “Waiver Recommendation”, the two most recent inspections completed in [REDACTED] (b) (4)

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.*

The same manufacturing areas and similar equipment

(b) (4)

are proposed for cemiplimab 50 mg/mL solutions for injection.

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

The proposed manufacturing scheme for cemiplimab DP is similar to the currently licensed products

(b) (4)

Signed:

Ziyang Su, Ph.D., OPF/DIA Reviewer

Ziyang Su -S

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Willie Wilson, Ph.D., OPQ/OBP Reviewer

Willie Wilson III -S

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Rachel Novak, Ph.D., OPQ/OBP ATINovak -S

Rachel L. Novak -S

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Aimee Cunningham, Ph.D., OPF/DMA Reviewer

Aimee L. Cunningham -S

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Patricia Hughes, Ph.D., OPF/DMA Branch Chief

Patricia F. Hughestroost -S

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Thuy T. Nguyen, OPF/DIA QAL

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

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, STN 761097/0
From: Maxwell Van Tassell, Ph.D., DMA Branch IV
Through: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead, DMA Branch IV
Subject: Review of Original 351(a) BLA Submission for Cemiplimab
US License: 1760
Applicant: Regeneron Pharmaceuticals, Inc.
Product: Cemiplimab
Indication: Treatment of cutaneous squamous cell carcinoma
Dosage: Solution for infusion, 50 mg/mL
Facilities: Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike, Rensselaer, NY 12144, USA
(FEI: 1000514603)
Receipt Date: 02/28/2018
Action Date: 10/28/2018

Recommendation for Approvability: The drug substance part of this BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval.

Review Addendum

Qualification of the bioburden test method

In Section 1.11.1 *Response to Request for Information dated 28Jul2018*, dated 07-05-2018 (eCTD 0025), the applicant indicated in response to Question 2 that they would qualify (b) (4)

. The interim review of the drug substance product quality microbiology recommended approvability, noting that the additional method suitability data would be reviewed upon submission.

In eCTD SN0040 (8/28/18), the applicant provided reports AV-SR-023691 and AV-SR-023689 to support the suitability of the microbial enumeration method (b) (4)

If test plates exhibit no growth during routine testing, the result will be reported as < 1 CFU/10 mL for TAMC and TYMC.

Reviewer Comment

The revised method reflects undiluted sample volumes of 10 mL, accurately justifying the reporting of results with a limit of detection of < 1 CFU/10 mL and providing greater sensitivity to the bioburden method for this process intermediate samples.

SATISFACTORY

Conclusions

- I. The drug substance section of this BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval.
- II. Product quality aspects other than microbiology should be reviewed by OBP.
- III. See Panorama for compliance status of manufacturing facilities.

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PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, **STN 761097/0**
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Indication: Treatment of cutaneous squamous cell carcinoma
Dosage: Solution for infusion, 50 mg/mL
Facilities: Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike, Rensselaer, NY 12144, USA
(FEI: 1000514603)
Receipt Date: 02/28/2018
Action Date: 10/28/2018

Recommendation for Approvability: STN 761097/0 was reviewed from a product quality microbiology perspective and is recommended for approval. Bioburden qualification of in-process samples will be submitted to the BLA in August 2018 and reviewed in an addendum to this memo.

Review Summary

Regeneron Pharmaceuticals, Inc. has submitted 351(a) BLA 761097 to obtain approval of cemiplimab, a recombinant human IgG4 monoclonal antibody for the treatment of cutaneous squamous cell carcinoma.

BLA 761097 was submitted in eCTD as a rolling submission. The fourth and final part of the initial submission was submitted on February 28, 2018. This review contains the assessment of the microbial quality attributes of the cemiplimab drug substance from a microbiological quality perspective. For microbiology review of Drug Product (DP) aspects of the application, please see the review by Aimee Cunningham, PhD.

Drug Substance Quality Microbiology Information Reviewed

Sequence number	Date	Description
eCTD 0002	12/19/2018	Original 351(a) BLA: Quality Information – Rolling Submission, Part 2 of 4
eCTD 0011	05/23/2018	Response to Information Request
eCTD 0018	06/11/2018	Response to Information Request
eCTD 0025	07/05/2018	Response to Information Request
eCTD 0027	07/15/2018	Response to Information Request

Review Assessment**3.2.S DRUG SUBSTANCE****3.2.S.1 GENERAL INFORMATION**

Cemiplimab is a recombinant human monoclonal antibody produced in genetically engineered Chinese Hamster Ovary (CHO) cell line. Cemiplimab is an IgG4 isotype engineered to bind specifically to cell death 1 receptor to block interaction with its ligands and antagonize inhibitory signaling in T cells. The protein is a heterotetramer of approximately 146 kDa comprised of two heavy chains modified to stabilize disulfide-bond linkage together, each linked by disulfide bond to a human kappa light chain.

3.2.S.2 MANUFACTURE**3.2.S.2.1 Manufacturer(s)**

(b) (4)

Conclusion

- I. The drug substance section of this BLA, as amended, was reviewed from a product quality microbiology 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 the appropriate division.
- III. A pre-license inspection was conducted at Regeneron Pharmaceuticals, Inc. in Rensselaer, NY from June 4th-8th by OPF/DMA, OBP, and ORA. No Form FDA 483 was issued. Refer to Panorama for compliance status of the facilities.