

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761113Orig1s000

PRODUCT QUALITY REVIEW(S)

First Approval for Indication
Recommendation: BLA Approval

BLA Number: 761113
Review Number: 1
Review Date: January 31, 2020

Drug Name/Dosage Form	Sarclisa (isatuximab-irfc) injection (solution)
Strength/Potency	20 mg/mL (100 mg/5 mL or 500 mg/25 mL in a single-dose vial)
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	(b) (4)
Applicant/Sponsor	Sanofi Aventis US LLC

Product Overview

Isatuximab is a chimeric IgG1 monoclonal antibody produced in mammalian (Chinese hamster ovary-CHO) cells. Isatuximab binds to CD38 receptor and triggers several mechanisms leading to the death of CD38 expressing cells. Isatuximab acts through IgG crystallizable fragment (Fc)-dependent mechanisms including: antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). Isatuximab can also trigger cell death by induction of apoptosis via an Fc-independent mechanism. Isatuximab drug product (DP) is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution. Each DP vial contains either 100 mg/5 mL or 500 mg/25 mL of isatuximab at concentration of 20 mg/mL with pH of 6.0. Each mL of solution contains 20 mg isatuximab, 1.46 mg histidine, 2.22 mg histidine hydrochloride monohydrate, 0.2 mg polysorbate 80, 100 mg sucrose and water for injection. The recommended dose for isatuximab is 10 mg/kg administered intravenously every week for 4 weeks followed by every 2 weeks until disease progression or unacceptable toxicity.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance (DS)/Immunogenicity Analysis	Chih-Jung Hsu	OPQ/OBP/DBRR11
DP/Analytical Methods	Pick-Wei Lau	OPQ/OBP/DBRR11
Labeling	Scott Dallas Pick-Wei Lau	OPQ/OBP OPQ/OBP/DBRR11
Facility	Thuy Thanh Nguyen	OPQ/OPMA/DBM
Microbiology	Scott Nichols (DS) Virginia Carroll (DP)	OPQ/OPMA/DBM OPQ/OPMA/DBM
RBPM	Marquita Burnett/Anh-Thy Ly	OPQ/OPRO
Team Lead	Yan Wang Patricia Hughes Peter Qiu	OPQ/OBP/DBRR11 OPQ/OPMA/DBM OPQ/OPMA/DBM
Application Team Lead	Yan Wang	OPQ/OBP/DBRR11

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Saumya Nathan/Kimberly Scott	OND/OHOP/DHP
Cross-disciplinary Team Lead	Nicole Gormley	OND/OHOP/DHP
Medical Officer	Bindu Kanapuru	OND/OHOP/DHP
Pharm/Tox	Shwu-Luan Lee	OND/OHOP/DHOT
Clinical Pharmacology	Amal Ayyoub	OTS/OCP/DCPV
Statistics	Laura Fernandes	OTS/OB/DBV

1. Names:

- Proprietary Name: Sarclisa
- Trade Name: SARCLISA®
- Non-Proprietary Name/USAN: Isatuximab
- CAS Registry Number: 1461640-62-9
- Common Name: Chimeric IgG1 monoclonal antibody
- INN Name: Isatuximab
- OBP systematic name: MAB CHIMERIC (IGG1) ANTI P28907 (CD38_HUMAN) [SAR650984] (parent IND: 103217)
- Other name(s): hu38SB19 and SAR650984 (company code)

Submissions Reviewed:

Submission(s) Reviewed	Document Date (disciplines affected)
STN 761113/SN0001	April 12, 2019 (OBP, OPMA), pre-submission
STN 761113/SN0002	April 30, 2019 (OBP, OPMA), original submission
STN 761113/SN0003 (Response to information request (IR) 1)	May 17, 2019 (OPMA)
STN 761113/SN0004 (Response to IR2)	May 24, 2019 (OPMA)
STN 761113/SN0005 (Response to IR3)	June 7, 2019 (OPMA)
STN 761113/SN0014 (Response to IR4)	October 15, 2019 (OPMA)
STN 761113/SN0019 (Response to IR5)	November 27, 2019 (OBP)
STN 761113/SN0020 (Response to IR6)	December 9, 2019 (OBP)
STN 761113/SN0021 (Amendment of response to IR4)	December 18, 2019 (OPMA)
STN 761113/SN0022 (Response to IR7)	December 20, 2019 (OPMA)
STN 761113/SN0023 (Response to IR8)	December 23, 2019 (OBP)
STN 761113/SN0024 (Response to IR9)	January 2, 2020 (OBP)
STN 761113/SN0026 (Response to IR10)	January 16, 2020 (OPMA)
STN 761113/SN0027 (Response to IR11)	January 17, 2020 (OBP)
STN 761113/SN0028 (Response to IR12)	January 17, 2020 (OBP)
STN 761113/SN0029 (Amendment of response to IR10 and response to IR13)	January 22, 2020 (OPMA, OBP)

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A	N/A
	V		(b) (4)	2	Adequate	N/A	N/A
	III		(b) (4)	3	Adequate	N/A	N/A
	III		(b) (4)	3	Adequate	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 not enough data in the application; therefore, the DMF did not need to be reviewed).

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	103217	Parent IND

3. Consults: None

4. Environmental Assessment:

Sanofi claimed a categorical exclusion from the preparation of an environmental assessment for isatuximab in accordance with 21 CFR 25.31 (c). The claim is because isatuximab is considered "naturally occurring in the environment" and, when exposed to the environment, is not expected to significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. This categorical exclusion claim is also based upon the case that isatuximab is a monoclonal antibody which is considered to be readily metabolized in humans and degraded in the environment. No extraordinary circumstances exist.

The claim of a categorical exclusion is accepted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761113 for Sarclisa (isatuximab) manufactured by Sanofi Aventis US LLC. The data submitted in this application are adequate to support the conclusion that the manufacture of Sarclisa (isatuximab) 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:

Manufacturing location:

- o Drug Substance:
Sanofi Chimie, 94403 Vitry-sur-seine Cedex, France (FEI: 3002808000)
- o Drug Product:
Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main, Germany (FEI: 3003195501)
- Fill size and dosage form: 100 mg/5 mL and 500 mg/25 mL solution
- Dating period:
 - o Drug Product:
 - 36 months at 2-8°C for 100 mg/5 mL
 - 36 months at 2-8°C for 500 mg/25 mL
 - o Drug Substance: (b) (4) months at (b) (4) °C
 - o Stability Option:
 - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
 - For stability protocols: We have approved the stability protocol in your license application for the purpose of extending the expiration dating of your drug substance under 21 CFR 601.12.
- Exempt from lot release in accordance with 21 CFR 601.2a. Isatuximab is a specified product.

C. Benefit/Risk Considerations:

Isatuximab is a chimeric gG1 monoclonal antibody and it specifically targets CD38. CD38 is highly expressed in multiple myeloma cells. Isatuximab acts through IgG Fc-dependent

mechanisms including ADCC, ADPC and CDC. Isatuximab can also trigger cell death by induction of apoptosis via an Fc-independent mechanism. While a few CD38 inhibitors are currently on the market for treatment of multiple myeloma, there is still high unmet medical need for new treatments for multiple myeloma that are more specific and efficacious.

Review of manufacturing has identified that the methodologies used for DS and DP manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. We also recommend approval of the commercial manufacture of isatuximab DS at Sanofi Chimie, Vitry-sur-seine Cedex, France and of isatuximab DP at Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany. The OBP (Office of Biotechnology Products) product quality and immunogenicity assay, OPMA (Office of Pharmaceutical Manufacturing Assessment) facility, microbiological DS and DP, as well as OBP labeling technical assessments are located as separate documents in Panorama.

D. Recommendation on Phase 4 (Post-Marketing) Commitments:

1. Complete a real-time leachables study using the final container closure system with isatuximab drug product for each presentation to identify any potential leachables in final isatuximab drug product at initial, 6, 12, 24 and 36 months under storage condition between 2°C - 8°C.

Final Report Submission:

09/2021

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management for Isatuximab

Table 1: Active Pharmaceutical Ingredient CQA (critical quality attribute) Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
ADCC (potency)	Efficacy	Intrinsic to the molecule, impacted by (b) (4) (b) (4)	(b) (4)	(b) (4)
CDC (potency)	Efficacy	Intrinsic to the molecule, impacted by (b) (4) (b) (4)	(b) (4)	(b) (4)
Binding to CD38 (Potency)	Efficacy	Intrinsic to the molecule, impacted by (b) (4)	(b) (4)	(b) (4)

		(b) (4)	(b) (4)
ADCP	Efficacy	Intrinsic to the molecule	
Identity	Efficacy and Safety	Intrinsic to the molecule	
High Molecular Weight (HMW) species/Aggregates (Product related impurity)	Efficacy, Pharmacokinetics (PK), and Safety (Immunogenicity)	Manufacturing process, storage and exposure to heat, (b) (4) stress, and light	
LMW species/Fragments (Product related impurity)	Efficacy	Manufacturing process, and exposure to low pH, heat and light	
Heavy chain (b) (4)	Efficacy and PK	Manufacturing process and exposure to heat,	

		(b) (4) stress and light Minimal change is expected on stability	(b) (4)
(b) (4)	PK	(b) (4)	
(b) (4)	Efficacy and Safety	Introduced during manufacturing process	
Charge variant profile (Acidic variants)	Efficacy, PK/ Pharmacody namics (PD)	Manufacturing process and exposure to low pH, heat, and light	
Charge variant profile (Basic variants)	Efficacy	Manufacturing process	

B. Drug Substance (Isatuximab) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
(b) (4)	Efficacy (Product (b) (4) and Stability	Formulation component		(b) (4)

			(b) (4)	(b) (4)
Quantity	Efficacy	Manufacturing process		N/A
pH (General)	Efficacy and Stability	Formulation components and stability		N/A
Osmolality (General)	Stability	Composition of the DS		N/A
Appearance (includes clarity, degree of opalescence and color of solution) (General)	Stability	Formulation components and stability		N/A
Host Cell DNA (Process related impurity)	Safety	(b) (4)	(b) (4)	
Host Cell Protein (Process related impurity)	Immunogenicity	(b) (4)		
(b) (4) (Process related impurity)	Safety	(b) (4)		
Adventitious viruses, endogenous virus (Process related impurity)	Safety	(b) (4)		
Mycoplasma (Process related impurity)	Safety	(b) (4)		

Endotoxin (contaminant)	Safety and Purity	Raw materials and manufacturing process	(b) (4)	N/A
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials and manufacturing process		N/A
Leachables (Process-related impurity)	Safety and Stability	from manufacturing contact material and the DS container closure system (CCS)		Risk for leachables from CCS is low (b) (4)
(b) (4)	Safety	(b) (4)		Levels are below toxicological concern based on the risk assessment
(b) (4)	efficacy	(b) (4)		(b) (4)

- **Description:**
Isatuximab is a chimeric immunoglobulin G1 (IgG1) monoclonal antibody (mAb) against CD38 antigen. Isatuximab is produced from a mammalian cell line (CHO) using a fed-batch production process. Isatuximab is composed of two identical immunoglobulin kappa light chains and two identical immunoglobulin gamma heavy chains. The heavy chain N-terminal glutamine residue is fully converted to pyroglutamate. The majority of the heavy chain C-terminal K450 is clipped. Isatuximab contains 32 cysteines leading to 16 disulfide bonds and two glycosylation sites located on Asparagine N300 of heavy chain. The glycosylated isatuximab has an overall molecular weight of approximately 148 kDa.
- **Mechanism of Action (MoA):**
Isatuximab binds to a discontinuous epitope which includes amino acids located opposite to the catalytic site of CD38 expressed on the surface of hematopoietic and tumor cells, including multiple myeloma cells. Binding of isatuximab to CD38 expressing cells can result in cell killing via multiple mechanisms, that include direct cell killing, lysis upon activation of the human complement (CDC), lysis mediated by natural killer cells (ADCC), or macrophages (ADCP) and apoptosis of CD38 expressing tumor cells.
- **Potency Assays:**
 - A cell-based assay is used to determine the CDC bioactivity on target cells expression the CD38 antigen. Specifically, T cell leukemia DND-41 cells are incubated with isatuximab containing solutions. Isatuximab binds specifically to CD38 expressed on the surface of the DND-41 target cells. Then, human complement is added, and the reaction cascade of the classical complement

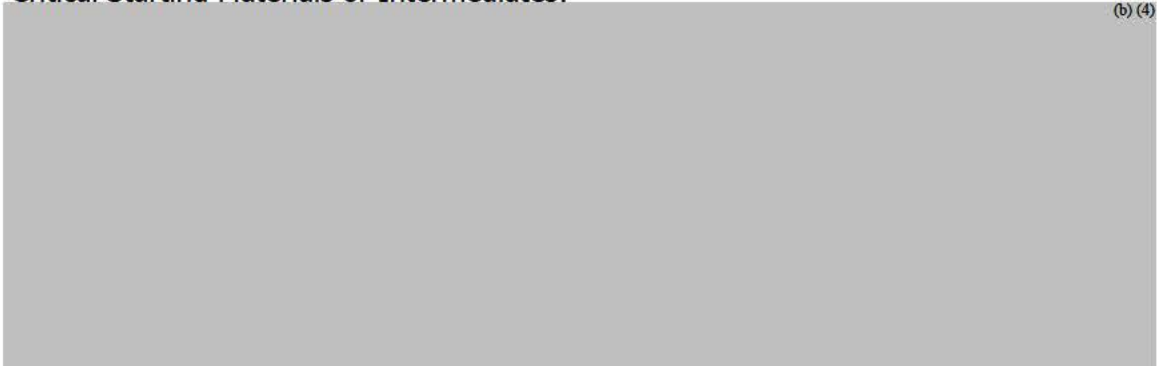
pathway is initiated through the bound antibodies, which induces lysis of the target cells. The metabolic activity of the remaining living cells is determined by addition of a water-soluble tetrazolium salt, which is reduced by viable cells to a formazan dye. Therefore, the absorbance measured at 450 nm for formazan dyes is proportional to the number of living cells. This enables the determination of dose-response curves and of the half maximal effective concentration (EC₅₀) for reference standard and sample. The CDC bioactivity of isatuximab samples is determined in relative percentage to that of the reference standard.

- A cell-based assay is used to determine the ADCC bioactivity on target cells expression the CD38 antigen. Specifically, DND-41 cells are incubated with isatuximab containing solutions. Isatuximab binds specifically to CD38 expressed on the surface of the DND-41 target cells. Then human jurkat cells stably expressed CD16 (FcγRIIIa) served as FcγRIIIa positive effector cells are added. Effector cells recognize the Fc region of the isatuximab antibody through interaction between the Fc region and the CD16 receptor. The molecular interaction between CD38 antigen, isatuximab and CD16 receptor induces a specific intracellular signaling that activates the NFAT pathway in the effector cells, which controls the expression of the luciferase reporter gene. This allows the induction of a luminescence signal upon addition of the luciferase substrate. The luminescence intensity measured is therefore proportional to the quantity of ADCC signal for any isatuximab concentration applied. This enables the determination of dose-response curves and of the EC₅₀ for reference standard and sample. The ADCC bioactivity of isatuximab samples is determined in relative percentage to that of the reference standard.
- An ELISA based CD38 binding assay is used to determine the relative binding activity of the isatuximab to the purified recombinant human CD38 antigen. Specifically, the CD38 antigen is first coated into a 96-well plate. After saturation, the plate is incubated with different dilutions of isatuximab. The antibody/antigen interaction is revealed with a secondary antibody targeting human IgG conjugated to horse radish peroxidase (HRP). After incubation with tetramethylbenzidine (TMB) substrate the colorimetric signal reveals the binding of isatuximab to the CD38 antigen. The absorbance measured is proportional to the quantity of isatuximab antibodies bound to the antigen. This allows the determination of dose-response curves for the reference and for the sample. The simultaneous comparative analysis of the sample and the reference standard curves determines the relative sample binding activity to the CD38 antigen.
- Reference Materials:
A two-tiered reference material system is in place. The current primary reference standard (b) (4) and working reference standard (b) (4) were derived from the same DS batch – C1061340 manufactured using (b) (4). (b) (4) DS batch C1061340 was used in the pivotal phase 3 clinical study. Therefore, the current primary and working reference standards are representative of the clinical and manufacturing experiences. A protocol is provided for the qualification of future working reference standards. The protocol contains adequate testing and

acceptance criteria (AC). The procedures (i.e., requalification) to monitor the potential changes and stability of the primary and working reference standards are appropriate.

- Critical Starting Materials or Intermediates:

(b) (4)

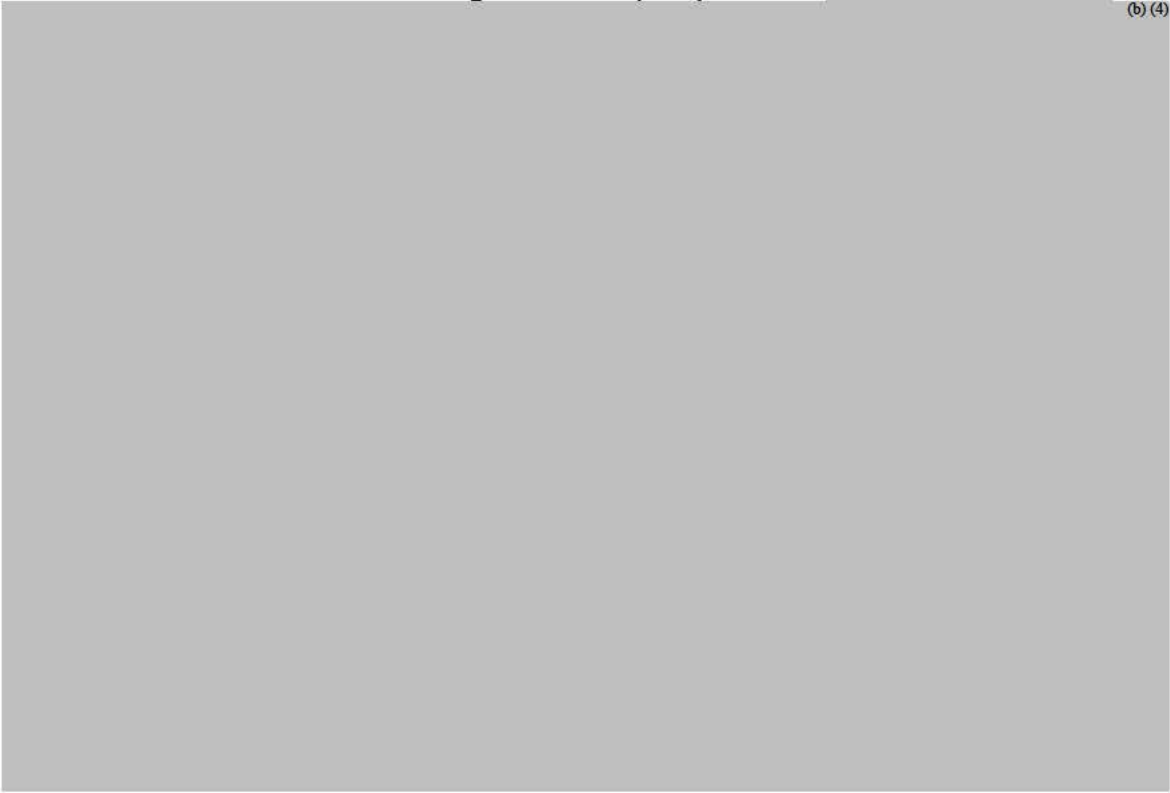


- Manufacturing Process Summary:

The manufacture of formulated drug substance (FDS) includes

(b) (4)

(b) (4)



(b) (4)

(b) (4)

- Container Closure System:
Isatuximab bulk FDS is stored (b) (4)
(b) (4) The CCS is suitable for isatuximab,
based on stability data and maintenance of closure integrity.
- Dating Period and Storage Conditions:
The dating period for the FDS is (b) (4) months when stored at (b) (4) °C. Upon the Agency's
request, Sanofi agreed to add monitoring of stability of isatuximab FDS (b) (4)
(b) (4) in the annual post-approval stability
protocol.

C. Drug Product (Isatuximab) 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.

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

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process	(b) (4)	N/A
Endotoxin (contaminant)	Safety, Purity, and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing process		N/A
Container closure integrity (contaminant)	Safety (failure in closure integrity may lead to contamination and loss of sterility or evaporation/leakage impacting concentration or content)	Container closure breaches during storage		N/A
Quantity	Efficacy	Manufacturing process		N/A
Appearance (visible particles) (Product and process related impurities)	Safety and Immunogenicity	Manufacturing material and CCS		N/A

Clarity and degree of opalescence	Stability	Formulation components and stability	(b) (4)	N/A
Color	Stability	Formulation components and stability		N/A
Particulate matter for subvisible particles (Product or process related impurities)	Safety and Immunogenicity	Manufacturing process and CCS, subvisible particles could be product or foreign particles		N/A
Polysorbate 80 Concentration	Efficacy (Product (b) (4) and Stability	Formulation component		N/A
pH (General)	Efficacy and Stability	Formulation components and stability		N/A
Extractable volume (General)	Efficacy/Dosing	Fill process		N/A
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS		PMC to complete a real time, real condition leachables study at initial, 6, 12, 24 and 36 months shelf life

- Potency and Strength:**
 Isatuximab is supplied as 20 mg/mL solution in two strengths (i.e., 100 mg/5 mL and 500 mg/25 mL). Potency is defined as the percent activity relative to the current isatuximab working reference standard. The potency assays are the same as described in the DS section of this memo.
- Summary of Product Design:**
 Isatuximab is supplied as a sterile, single-dose, preservative-free solution for intravenously infusion in two strengths. For the 500 mg/25 mL strength, each vial is filled with a target fill volume of (b) (4) mL. For the 100 mg/5 mL strength, each vial is filled with a target fill volume of (b) (4) mL.
- List of Excipients:**
 (b) (4) mM histidine, (b) (4) % (w/v) sucrose, (b) (4) % (w/v) polysorbate 80, water for injection, pH 6.0.
- Reference Materials:**
 The same reference standards are used for FDS and DP.
- Manufacturing Process Summary:**
 The manufacturing process for isatuximab DP includes the following steps: (b) (4)

(b) (4)

- **Container Closure System:**
The primary CCS for isatuximab DP consists of a colorless (b) (4) glass vial (a 6 mL vial for 100 mg/5 mL and a 30 mL vial for 500 mg/25 mL) closed with a (b) (4) rubber stopper (b) (4).
The rubber stopper is crimped to the vial with an aluminum seal with plastic flip-off cover.
- **Dating Period and Storage Conditions:**
The dating period for the 500 mg/25 mL strength DP is 36 months when stored at 2-8°C. The dating period for the 100 mg/5 mL strength DP is 36 months when stored at 2-8°C.
- **List of Co-Package Components (if applicable):** None

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Store in a refrigerator at 2°C to 8°C in the original carton
- Protect from light
- Do not freeze
- Do not shake

F. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of isatuximab FDS, WCB storage, release and stability testing of FDS and DP	Sanofi Chimie 9 quai Jules Guesde, BP 35, Vitry-sur-seine Cedex, France, 94403	3002808000	Pre-license inspection requested	VAI	Approve
Manufacture of WCB, storage of MCB and WCB	sanofi-aventis recherche & développement 13, quai Jules Guesde, Vitry-sur-Seine, France, 94400	3004883328	Acceptable based on file review	N/A	Approve
Release testing of FDS and DP,	Quality assistance	(b) (4)	Acceptable based on file review	N/A	Approve

stability testing of FDS and DP	(b) (4)				
(b) (4) WCB testing		Acceptable based on file review	N/A	Approve	
(b) (4) WCB testing		Acceptable based on file review	N/A	Approve	
WCB testing: sterility and fertility tests		Acceptable based on file review	N/A	Approve	
WCB testing		Acceptable based on file review	N/A	Approve	
WCB testing		Acceptable based on file review	N/A	Approve	
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of DP, release testing of FDS and DP, stability testing of FDS and DP, labeling and packaging and release of DP	Sanofi-Aventis Deutschland GmbH Sanofi-Aventis Deutschland GmbH, Brüningstr. 50, Frankfurt am Main, Germany, 65926	3003195501	Acceptable based on file review	N/A	Approve
Labeling and packaging, release of DP	Genzyme Corporation 11 Forbes Road, Northborough, MA, USA. 1532	3009389940	Acceptable based on file review	N/A	Approve

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Sanofi Chimie (FEI: 3002808000) and Sanofi-Aventis Deutschland GmbH (FEI: 3003195501), proposed for isatuximab DS and DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their

currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.S.2.3	Preparation of a new WCB	(b) (4)	The full-scale qualification data confirming the suitability of the new WCB for use in routine manufacturing will be submitted in the Annual Report.
3.2.S.2.5	Concurrence validation protocol (b) (4)	The verification testing under commercial scale (b) (4)	Results will be reported in Annual Report following study completion
3.2.S.2.5	Concurrence validation protocol (b) (4)	The verification testing under commercial scale (b) (4)	Results will be reported in Annual Report following study completion
3.2.S.2.5	Concurrence validation protocol (b) (4)	The verification testing under commercial scale (b) (4)	Results will be reported in Annual Report following study completion
3.2.S.2.5	Concurrence validation protocol (b) (4)	The verification testing under commercial scale (b) (4)	Results will be reported in Annual Report following study completion
3.2.S.5	Qualification protocol for future isatuximab working reference standards	The procedure and AC to qualify future working reference standards	Results will be reported in Annual Report following study completion
3.2.S.7.2	Annual stability protocol for DS (b) (4)	(b) (4) 3.2.S.7.3 Stability Data and 3.2.S.4.1 Specification, respectively	Stability updates will be provided annually as part of the Annual Report

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
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3.2.P.8.2	Annual stability protocol for DP	At 5°C ± 3°C, at least one bath per year for each strength at initial, 1, 3, 6, 9, 12, 18, 24 and 36 months, according to the tests and AC listed in 3.2.P.8.3 Stability Data and 3.2.P.5.1 Specification, respectively	Stability updates will be provided annually as part of the Annual Report
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- 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 source		X	
9.	Transgenic Plant source		X	
10.	New Molecular Entity	X		
11.	PEPFAR drug		X	
12.	PET drug		X	
13.	Sterile Drug Product	X		
14.	Other: [fill in information]			X
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]		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 assigned name	X		
20.	Other [fill in]			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 {fill-in}			X

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/s/

YAN WANG
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XIANGHONG JING
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**U.S. FOOD & DRUG
ADMINISTRATION**

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	February 7, 2020
Assessor:	Scott Dallas, RPh, Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Pick-Wei Lau, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research II
Application:	BLA 761113
Applicant:	Sanofi Aventis U.S. LLC
Submission Dates:	April 30, July 11, November 15, November 26, December 23, 2019 and January 16 and February 3, 2020
Product:	Sarclisa (isatuximab-irfc)
Dosage form:	injection
Strength and Container-Closure:	100 mg/5 mL (20 mg/mL) and 500 mg/25 mL (20 mg/mL) in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application seeking approval of BLA 761113, isatuximab, (b) (4) [REDACTED] [REDACTED] [REDACTED]
Recommendations:	The prescribing information, patient labeling, container labels and carton labeling are acceptable from an OBP labeling perspective.

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

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

CONCLUSION

The draft prescribing information and draft patient labeling submitted on February 3, 2020 and the container labels and carton labeling submitted on November 26, 2019 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Patient Labeling (submitted on July 11, 2019)
<\\cdsesub1\evsprod\bla761113\0010\m1\us\annotatedpi.doc>
- Container Labels (submitted on April 30, 2019)
100 mg/5 mL (20 mg/mL)



500 mg/25 mL (20 mg/mL)

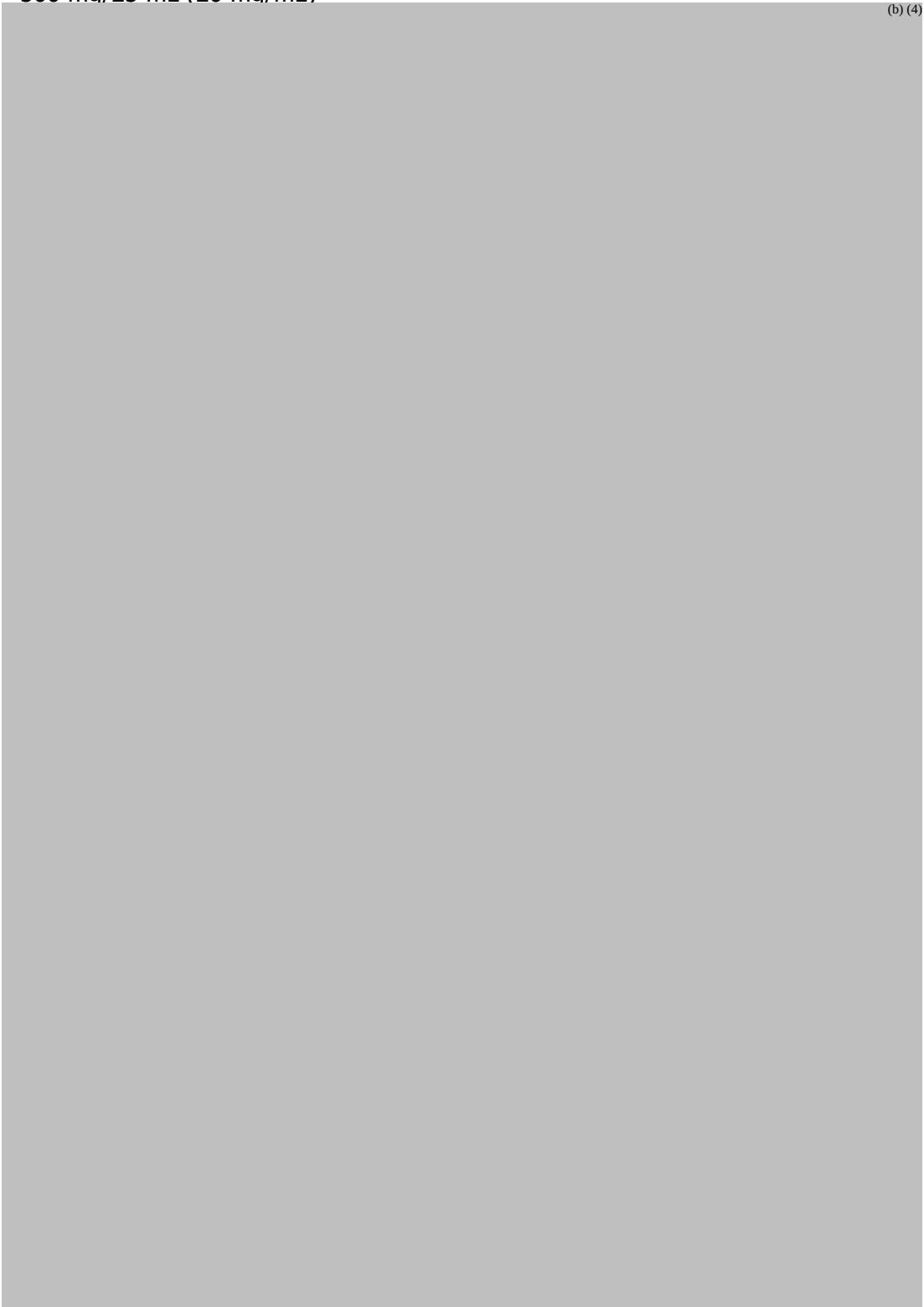


- Carton Labeling (submitted on April 30, 2019)
100 mg/5 mL (20 mg/mL)



500 mg/25 mL (20 mg/mL)

(b) (4)



Appendix B: Evaluation Tables

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

Container⁴ Label Evaluation

Proper Name (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

November 26, 2019: The applicant included the suffix, irfc, to the end of the proper name.

Manufacturer name, address, and license number (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (U.S license number for container bearing a partial label)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: needs license number

To Applicant: Please replace the placeholder XXXX with your U.S. license number.

November 15, 2019: The applicant included the license number 1752, which also appears in FDA DARRTS.

FDA Response: The applicant's revision is acceptable.

Lot number or other lot identification (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	☒ Yes ☐ No ☐ 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:

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Beyond Use Date (Multiple-dose containers) (container label)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Product Strength (container label)	Acceptable
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Multiple-dose containers (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 <i>(recommended individual dose)</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Statement: "Rx only" (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and</i>	☒ Yes ☐ No

<i>Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic</i>	☐ N/A
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Comment/Recommendation:

Medication Guide (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

No Package for container (container label)	Acceptable
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

No container label (container label)	Acceptable
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Ferrule and cap overseal (for vials only)	Acceptable
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:
 To applicant: Please confirm there is no text on the ferrule and cap overseal of the vials. Refer to USP General Chapters: <7> Labeling (Ferrules and Cap Overseals).

 November 15, 2019: The applicant confirmed that there is no text on the ferrule and cap overseal of the vials.

 FDA Response: The applicant's response is acceptable.

Visual inspection	Acceptable
Regulation: 21 CFR 610.60(e)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Please confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located per 21 CFR 610.60(e).

November 15, 2019: The applicant confirmed that a sufficient area of the container is uncovered for visual inspection. The vial label has a transparent section which provides an appropriate control window in the vertical direction. For circumference, there is space both above and below the vial label.

FDA Response: The applicant's response is acceptable.

Route of administration (container label)	Acceptable
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

DMEPA recommend a change to the route of administration statement with the comment:

"Revise the statement, (b) (4)

We recommend this to minimize the risk of the product being administered without dilution."

November 15, 2019: The applicant revised the route of administration as requested.

FDA Response: The applicant's revision is acceptable.

NDC numbers (container label)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: As currently presented, the NDC number is denoted by a placeholder (0000-000-00). We request that you submit the NDC numbers for the container labels and carton labeling.

November 15, 2019: The applicant included an NDC on the container label.

FDA Response: The applicant's inclusion of the NDC is acceptable.

Preparation instructions (container label)	Acceptable
Regulation: 21 CFR 201.5(g)	☐ Yes

	☐ No ☒ N/A
<i>Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

<u>Package type term (container label)</u>	<u>Acceptable</u>
<i>Recommended labeling practices: Guidance for Industry: 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 2018) USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Combined DMEPA and OBP comment reads:

To applicant: Revise the statement, (b) (4) to minimize the risk of the entire contents of the vial being given as single dose.

November 15, 2019: The applicant revised the package type term and discard statement as requested.

FDA Response: The applicant's revisions are acceptable.

<u>Misleading statements (container label)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.6	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

<u>Prominence of required label statements (container label)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

<u>Spanish-language (Drugs) (container label)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Bar code label requirements (container label)	Acceptable
Regulations: 21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Net quantity (container label)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Statement of Dosage (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Combined DMEPA/OBP comment

To applicant: Revise the statement, (b) (4)

for labeling following the Physician Labeling Rule.

November 15, 2019: The applicant revised the dosage statement with the wording (b) (4)

FDA Response: The applicant's revision is acceptable.

Inactive ingredients (container label)	Acceptable
Regulation: 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Storage requirements (container label)	Acceptable
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: If space permits, revise the storage statement, (b) (4)

November 15, 2019: Although space on the small label is limited the applicant was able to include the storage statement as requested.

FDA Response: The applicant's revisions are acceptable.

Dispensing container (container label)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:**Package⁵ Labeling Evaluation**

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

November 26, 2019: The applicant included the suffix, irfc, to the end of the proper name.

Manufacturer name, address, and license number (package labeling)	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Consider including the phrase "Manufactured by" or "Mfg. by:" before the name sanofi-aventis U.S. LLC.

November 15, 2019: The applicant included the phrase "Manufactured by:" on the carton labeling.

FDA Response: The applicant's revision is acceptable.

Lot number or other lot identification (package labeling)	Acceptable
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Expiration date (package labeling)	Acceptable
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	☒ Yes ☐ No

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
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Comment/Recommendation:

To applicant: FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.

November 15, 2019: The applicant confirmed the expiration date is presented as YYYY-MM-DD on the carton labeling and as YYYY-MM on the vial labels.

FDA Response: The applicant's response is acceptable.

Beyond Use Date (Multiple-dose containers) (package labeling)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Preservative (package labeling)	Acceptable
Regulation: 21 CFR 610.61(e)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Number of containers (package labeling)	Acceptable
Regulation: 21 CFR 610.61(f)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Product Strength (package labeling)	Acceptable
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize</i>	☒ Yes ☐ No ☐ N/A

Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic
USP General Chapters: <7> Labeling

Comment/Recommendation:

Storage temperature/requirements (package labeling)	Acceptable
Regulation: 21 CFR 610.61(h)	☒ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Revise the storage statements, (b) (4) to "Store refrigerated at 36°F-46°F (2°C-8°C) in the carton to protect from light. Do not freeze. Do not shake."

November 15, 2019: The applicant revised the storage statement as requested.

FDA Response: The applicant's revision is acceptable.

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	Acceptable
Regulation: 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Multiple dose containers (recommended individual dose) (package labeling)	Acceptable
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Route of administration (package labeling)	Acceptable
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A

<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A
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Comment/Recommendation:

To applicant: Consider relocating the expression of strength on the side panels above the route of administration statement.

November 15, 2019: The applicant relocated the expression of strength on the side panels above the route of administration statement.

FDA Response: The applicant's revisions are acceptable.

Also DMEPA recommend a change to the route of administration statement with the comment: "Revise the statement, (b) (4) to "For Intravenous Infusion After Dilution." We recommend this to minimize the risk of the product being administered without dilution."

November 15, 2019: The applicant revised the route of administration statement as requested.

FDA Response: The applicant's revisions are acceptable.

Known sensitizing substances (package labeling)	Acceptable
Regulations: 21 CFR 610.61(I), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Inactive ingredients (package labeling)	Acceptable
Regulations: 21 CFR 610.61, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Please consider revising your inactive ingredient statement to read: "Each mL of solution contains 20 mg isatuximab-xxxx, histidine (1.46 mg), histidine hydrochloride monohydrate (2.22 mg), polysorbate 80 (0.2 mg), sucrose (100 mg) and water for injection." Revised the inactive ingredients to appear in alphabetical order per USP <1091> Labeling of inactive ingredients.

November 15, 2019: The applicant revised the ingredient statement as requested.

FDA Response: The applicant's revision is acceptable.

To applicant: Revise the statement of quantity per mL on the back panel of the 500 mg/25 mL carton labeling to ensure the correct quantity of isatuximab-xxxx per mL is displayed. For example, revise (b) (4) to "20 mg isatuximab-xxxx".

November 15, 2019: The applicant corrected the quantity of isatuximab on the 500 mg/25 mL carton labeling.

FDA Response: The applicant's revision is acceptable.

Source of the product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(p)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Minimum potency of product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(r)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Include the statement "No U.S. standard of potency" per 21 CFR 610.61(r).

November 15, 2019: The applicant revised the label to include the statement "No U.S. standard of potency".

FDA Response: The applicant's revision is acceptable.

Rx only (package labeling)	Acceptable
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Divided manufacturing (package labeling)	Acceptable
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes

	☐ No ☒ N/A
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Comment/Recommendation:

Distributor (package labeling)	Acceptable
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Bar code (package labeling)	Acceptable
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: <i>Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

NDC numbers (package labeling)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: As currently presented, the NDC number is denoted by a placeholder (0000-000-00). We request that you submit the NDC numbers for the container labels and carton labeling.

November 15, 2019: The applicant included an NDC on the carton labeling.

FDA Response: The applicant's inclusion of the NDC is acceptable.

Preparation instructions (package labeling)	Acceptable
Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic</i> <i>USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Package type term (package labeling)	Acceptable
<i>Recommended labeling practices: Guidance for Industry: 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 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Misleading statements (package labeling)	Acceptable
Regulation: 21 CFR 201.6	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: There are no misleading statements.

Prominence of required label statements (package labeling)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Spanish-language (Drugs) (package labeling)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No

	☒ N/A
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Comment/Recommendation:

Phenylalanine as a component of aspartame (package labeling)	Acceptable
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Sulfites; required warning statements (package labeling)	Acceptable
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Net quantity (package labeling)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Statement of Dosage (package labeling)	Acceptable
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: Revise the statement, "Dosage and Administration: (b) (4)" to "Dosage: See Prescribing Information."

November 15, 2019: The applicant revised the Dosage statement to read "Dosage and Administration: See Prescribing Information."

FDA Response: The applicant's revision is acceptable.

Dispensing container (package labeling)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Medication Guide (package labeling)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Other (package labeling)	Acceptable
	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	Acceptable

<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i>	☒ Yes ☐ No ☐ N/A
--	--

Comment/Recommendation:

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	Acceptable
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry: 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 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Dr. Lau confirmed the product strengths and overfill volumes were acceptable for this product. To Applicant: Revised to present the total strength per vial and the strength per mL (refer to USP General Chapters: <7> Labeling) November 26, 2019: The applicant agreed to present the total strength per vial and the strength per mL. FDA Response: The applicant's revisions are acceptable.

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
Regulation: 21 CFR 201.57(c)(3)(iv)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Dr. Lau confirmed the diluents, infusion bag and infusion set materials were acceptable. The applicant provided information on the pore size of the in-line filter and this information was included in the labeling.
--

Dr. Lau and the micro team confirmed the infusion solution can be stored refrigerated at 2°C to 8°C for up to 48 hours, followed by 8 hours (including the infusion time) at room temperature.

To Applicant: Revised to include the verbatim statement per 21 CFR 201.57(c)(3)(iv) (Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit)

November 26, 2019: The applicant agreed to include the verbatim statement as required by the regulation.

FDA Response: The applicant's revision is acceptable.

To Applicant: Revised the names of the diluents to their official compendial names. Also, the word (b) (4) was deleted and the use of this word should be avoided with injectable products.

November 26, 2019: The applicant agreed to refer to the diluents by their official compendial names and to remove the word (b) (4) from the Section 2.5 Administration. (b) (4)

FDA Response: The applicant will be requested to revise the labeling to remove the use of the word (b) (4)

December 23, 2019: The applicant agreed with the proposed revision to delete the use of the word (b) (4)

FDA Response: The applicant's revision is acceptable.

To Applicant: Please insert the in-line filter sizes.

November 26, 2019: The applicant inserted the pore size of the filter (b) (4)

FDA Response: The applicant will be requested to revise the text to appear as: "... with a 0.22 micron in-line filter (polyethersulfone (PES), polysulfone, or nylon)."

December 23, 2019: The applicant agreed with FDA's proposed revision.

FDA Response: The applicant's revision is acceptable.

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	Acceptable
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A

<i>Recommended labeling practices references: Guidance for Industry: 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 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
--	--

Comment/Recommendation: To Applicant: Revised to include complete identifying characteristics (clarity and color) per 21 CFR 201.57(c)(4). Revised this section to display the total strength per vial and strength per mL per USP General Chapters:<7> Labeling. November 26, 2019: The applicant agreed with the proposed revisions. FDA Response: The applicant's revisions are acceptable.

Full Prescribing Information	
11 DESCRIPTION	Acceptable
Regulations: 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)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Dr. Lau confirmed the drug substance molecular weight, 148 kDa, and cell line, Chinese hamster cell. Dr. Lau confirmed the drug product is sterile, preservative-free, a clear to slightly opalescent, colorless to slightly yellow solution, essentially free of visible particles, and the qualitative and quantitative information was acceptable. Comments for the first paragraph concerning the drug substance: To Applicant: Revised to include the pharmacological / therapeutic class per 21 CFR 201.57(c)(12). To Applicant: Revised to delete information concerning the mechanism of action. The MOA should appear in section 12.1 To Applicant: Revised to include additional information concerning the composition of the drug substance. Comments for the second paragraph concerning the drug product: OBP Labeling: To Applicant: Revised to include the dosage form, that the product is sterile, and the route of administration per 21 CFR 201.57(c)(12).

OBP Labeling: To Applicant: Revised the inactive ingredients to appear in alphabetical order per USP <1091> Labeling of inactive ingredients and to consolidate the 2 separate paragraphs for the 5 mL and 25 mL vial to one paragraph.

November 26, 2019: The applicant accepted all of FDA's proposed revisions to Section 11.

FDA Response: The applicant's revisions are acceptable.

Full Prescribing Information	
15 Cytotoxic Drug reference	Acceptable
Regulation: 21 CFR 201.57(c)(17)(iv) xxxx is a cytotoxic drug. Follow applicable special handling and disposal procedures. ¹ 1.OSHA Hazardous Drugs. OSHA. [Accessed on June 9, 2017, from http://www.osha.gov/SLTC/hazardousdrugs/index.html]	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
Regulation: 21 CFR 201.57(c)(17)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Dr Lau confirmed the drug product should be protected from light, refrigerated and not shake or freeze the product. Also, the container closure system does not contain (b) (4)

To Applicant: Revised to include complete identifying characteristics per 21 CFR 201.57(c)(17).

To Applicant: Revised to help emphasis the drug product should be stored in the carton to protect the product from light.

November 26, 2019: The applicant accepted FDA's proposed revisions to Section 16.

FDA Response: The applicant's revisions are acceptable.

Full Prescribing Information	
MANUFACTURER INFORMATION	Acceptable
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes ☐ No ☐ N/A

<i>Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A
---	--

Comment/Recommendation: November 26, 2019: The applicant included the U.S. License number 1752.

Patient Information Labeling Evaluation

PATIENT INFORMATION LABELING	
<u>TITLE (NAMES AND DOSAGE FORM)</u>	<u>Acceptable</u>
<i>Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

PATIENT INFORMATION LABELING	
<u>STORAGE AND HANDLING</u>	<u>Acceptable</u>
<i>Recommended labeling practices for Patient Labeling or IFU: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

PATIENT INFORMATION LABELING	
<u>INGREDIENTS</u>	<u>Acceptable</u>
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)</i>	☒ Yes ☐ No ☐ N/A

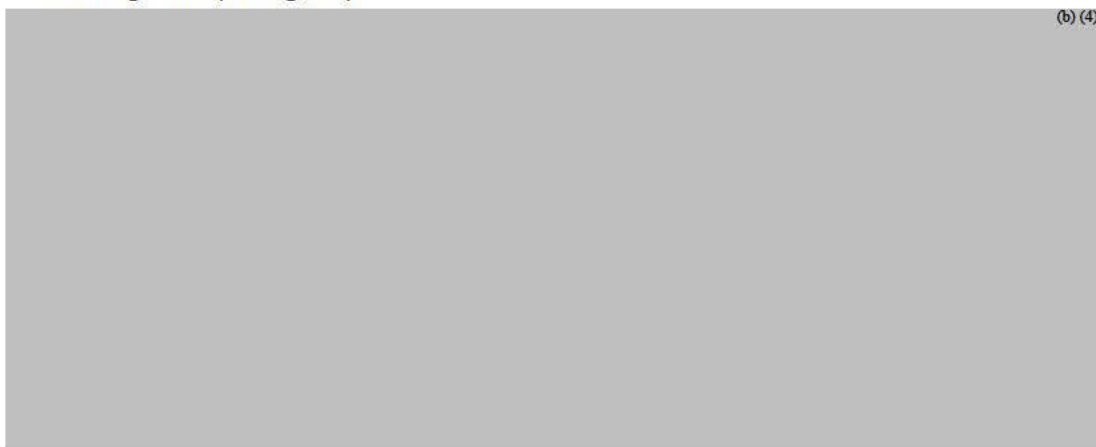
Comment/Recommendation: OBP Labeling: To Applicant: Revised the inactive ingredients to appear in alphabetical order per USP <1091> Labeling of inactive ingredients February 3, 2020: The applicant revised the order of the inactive ingredients as requested. FDA Response: The applicant's revisions are acceptable.
--

PATIENT INFORMATION LABELING	
<u>MANUFACTURER INFORMATION</u>	<u>Acceptable</u>
21 CFR 201.1, 19 CFR 134.11	☒ Yes ☐ No ☐ N/A
<i>21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

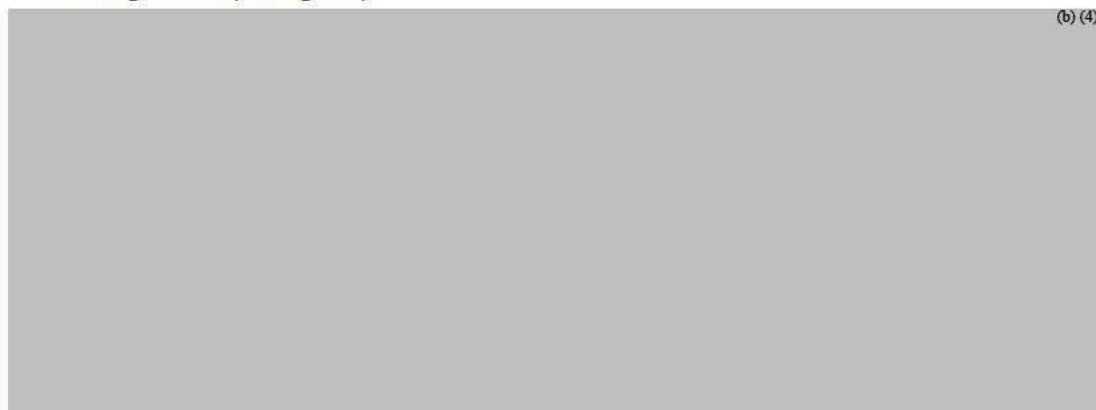
APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information – **DRAFT** (submitted on February 3, 2020)
<\\cdsesub1\evsprod\bla761113\0030\m1\us\proposedpi.docx>
- Patient Information – **DRAFT** (submitted on February 3, 2020)
<\\cdsesub1\evsprod\bla761113\0030\m1\us\proposedppi.doc>
- Container Labels (submitted on November 26, 2019)
100 mg/5 mL (20 mg/mL)



(b) (4)

500 mg/25 mL (20 mg/mL)



(b) (4)

- Carton Labeling (submitted on November 26, 2019)
100 mg/5 mL (20 mg/mL)

(b) (4)



500 mg/25 mL (20 mg/mL)

(b) (4)





Scott
Dallas

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Pick-Wei
Lau

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U.S. FOOD & DRUG
ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Center for Drug Evaluation and Research
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY ASSESSMENT & EVALUATION

Date: 12 February 2020
To: Administrative File, BLA 761113/0
From: Scott Nichols, Ph.D., Reviewer
OPQ/OPF/DMA/BIV
Through: Patricia Hughes, Ph.D., Branch Chief
OPQ/OPF/DMA/BIV
Subject: New 351(a) Biologics License Application (BLA)
US License Number: 1752
Applicant: Sanofi-Aventis US, LLC
Manufacturing Site: Sanofi Chimie, 9 quai de Jules Guesde, BP 35, Virty-sur-Seine cedex,
France 94403
(FEI: 3002808000)
Product: Sarclisa® (isatuximab, SAR650984)
Dosage: 100 mg/5 mL (20 mg/mL) solution for intravenous infusion
Indication: (b) (4)

Action Date: 30 April 2020

CONCLUSION AND APPROVABILITY RECOMMENDATION: The drug substance portion of BLA 761113/0, as amended, is recommended for approval from a microbial control and a microbiological product quality perspective. Please refer to the assessment memo from Dr. Virginia Carroll for an assessment of sterility assurance and microbiological product quality for the drug product (DP) portions of the BLA.

PRODUCT QUALITY MICROBIOLOGY ASSESSMENT: DRUG SUBSTANCE

DRUG SUBSTANCE QUALITY MICROBIOLOGY INFORMATION REVIEWED

Sequence number	Date	Description
0001	12 April 2019	Original Biologics License Application
0014	15 October 2019	Response to FDA Information Request dated 30 September 2019

0026	16 January 2020	Response to FDA Information Request dated 8 January 2020
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Reviewer Comment:

Module 3 was submitted to the eCTD prior to the FDA stamp date: 30 April 2019.

ASSESSMENT NARRATIVE

(b) (4)

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Scott
Nichols

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Patricia
Hughes Troost

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Date: 2/13/2020 03:35:23PM
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BLA 761113

Sarclisa (Isatuximab)

Chih-Jung (CJ) Hsu, Ph.D., Quality Reviewer for Drug Substance and Immunogenicity Assay
Pick-Wei Lau, Ph.D., Quality Reviewer for Drug Product and Analytical Methods
Yan Wang, Ph.D., Team Lead

Division of Biotechnology Review & Research II (DBRRII)
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

1. BLA#: STN 761113
2. Review Date: 01/24/2020
3. Primary Review Team:
 - a. **Medical Officer:** Bindu Kanapuru and Nicole Gormley (Cross-Disciplinary Team Lead)
 - b. **Pharm/Tox:** Shwu-Luan Lee
 - c. **Product Quality Team:**
 OPQ/OBP: Chih-Jung Hsu (DS and Immunogenicity Assay), Pick-Wei Lau (DP and Analytical Methods) and Yan Wang (Team Lead)
 OPQ/OPMA:
 Microbiology: Scott Nichols (DS), Virginia Carroll (DP) and Jessica Hankins (Quality Assessment Lead)
 Facility: Thuy Thanh Nguyen and Peter Zhihao Qiu (Quality Assessment Lead)
 OPQ/OBP labeling: Scott Dallas
 OPQ RBPM: Marquita Burnett and Anh-Thy Ly
 - d. **Clinical Pharmacology:** Amal Ayyoub
 - e. **Statistics:** Laura Fernandes
 - f. **RPM:** Saumya Nathan and Kimberly Scott
4. Major GRMP Deadlines:
 - a. OND Filing Meeting: 06/19/2019
 - b. OND Mid-cycle internal meeting: 09/26/2019
 - c. OND Late-cycle internal meeting: 12/16/2019
 - d. Primary review due: 01/24/2020
 - e. Secondary review due: 01/31/2020
 - f. PDUFA action date: 04/30/2020

5. Communications with Sponsor and OND:

Communication/Document:	Date	Submission	Review Status
Rolling Submission	04/12/2019	STN 761113/SN0001	Complete
Original Submission	04/30/2019	STN 761113/SN0002	Complete
Filing review memo	06/21/2019		Complete
Information Request #1	11/27/2019	STN 761113/SN0019	Complete
Information Request #2	12/09/2019	STN 761113/SN0020	Complete
Information Request #3	12/23/2019	STN 761113/SN0023	Complete
Information Request #4	01/02/2020	STN 761113/SN0024	Complete
Information Request #5	01/17/2020	STN 761113/SN0027	Complete
Information Request #6	01/17/2020	STN 761113/SN0028	Complete
Information Request #7	01/22/2020	STN 761113/SN0029	Complete

6. Drug Product Name/Code/Type:
 - a. Proprietary Name: Sarclisa
 - b. Trade Name: SARCLISA®
 - c. Non-Proprietary Name/USAN: Isatuximab
 - d. CAS Registry Number: 1461640-62-9

- e. Common Name: Immunoglobulin G1, anti – (human CD38 antigen) (human-Mus musculus monoclonal hu38SB19 heavy chain), disulfide with human-Mus musculus monoclonal hu38SB19 light chain, dimer
- f. INN Name: Isatuximab
- g. OBP systematic name: MAB CHIMERIC (IGG1) ANTI P28907 (CD38_HUMAN) [SAR650984]
- h. Other name (s): hu38SB19 and SAR650984 (company code)

7. Pharmacological Category: Therapeutic monoclonal antibody to the human CD38 antigen

8. Dosage Form: Solution in (b) (4) glass vial

9. Strength/Potency:

(i): The concentration/strength of the Drug Product: 100 mg/5 mL and 500 mg/25 mL

(ii): Type of potency assay(s):

- Cell-based complement dependent cytotoxicity (CDC) bioassay
- Cell-based antibody dependent cell mediated cytotoxicity (ADCC) bioassay
- CD38 binding assay

10. Route of Administration: Intravenous infusion

11. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Yes	No review was required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review was required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review was required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review was required as all the relevant information related to compatibility with the product was in the BLA

12. Inspectional Activities:

The pre-license inspection of the drug substance manufacturing site at Sanofi Chimie (Vitry-sur-Seine, France 9440) (FEI: 3002808000) was conducted on June 24 – 28 and July 1 – 2, 2019 by Pick-Wei Lau and Yan Wang from OPQ/OBP, and Scott Nichols from OPQ/OPMA. The inspection covered the manufacturing of drug substance. The inspection was system based and covered Quality, Production, Laboratory Control, Materials, and Facilities and Equipment Systems. A two-item FDA Form 483 was issued to the firm.

- Observation 1: (b) (4)
- Observation 2: (b) (4)

It was recommended that the inspection be classified as voluntary action indicated.

The pre-license inspection of the drug product manufacturing site, Sanofi-Aventis Deutschland GmbH at Frankfurt, Germany (FEI: 3003195501) was waived based on that the same facility has been inspected by ORA in May 2019. The inspection was classified VAI. There were no concerns related to manufacture of sterile product (b) (4) at the facility. In addition, the pre-license inspection (b) (4) was completed (b) (4) and no Form 483 was issued and recommended approval.

13. Consults Requested by OBP: None

14. Quality by Design Elements:

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

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

15. Precedents: None

16. Administrative:

Signature Block

Name and Title	Signature and Date
Chih-Jung Hsu, Ph.D. Primary reviewer, DBRRII/OBP/OPQ/CDER	See electronic signature and date
Pick-Wei Lau, Ph.D. Primary reviewer, DBRRII/OBP/OPQ/CDER	See electronic signature and date
Yan Wang, Ph.D. Team Leader, DBRRII/OBP/OPQ/CDER	See electronic signature and date

Summary of Quality Assessments

1. Primary Reviewer Summary Recommendation:

The data submitted in this Biologics License Application support the conclusion that the manufacture of Sarclisa (isatuximab) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. It is recommended that Sarclisa (isatuximab) be approved for human use under conditions specified in the package insert.

2. List of Deficiencies to be Communicated: None

3. List of Post-Marketing Commitments/Requirements:

To complete a real-time leachables study using the final container closure system with isatuximab drug product for each presentation to identify any potential leachables in final isatuximab drug product at initial, 6, 12, 24 and 36 months under storage condition between 2°C - 8°C.

Final Report Submission:

09/2021

CMC protocols approved within the BLA761113 for isatuximab

CTD section	Protocol	Brief summary	Reporting Category
3.2.S.2.3	Preparation of a new WCB	(b) (4)	The full-scale qualification data confirming the suitability of the new WCB for use in routine manufacturing will be submitted in the Annual Report .
3.2.S.2.5	Concurrence validation protocol (b) (4)		Results will be reported in Annual Report following study completion
3.2.S.2.5	Concurrence validation protocol (b) (4)		Results will be reported in Annual Report following study completion
3.2.S.2.5	Concurrence validation protocol (b) (4)		Results will be reported in Annual Report following study completion
3.2.S.2.5	Concurrence validation protocol (b) (4)		Results will be reported in Annual Report following study completion
3.2.S.7.2	Annual stability protocol for DS (b) (4)		Stability updates will be provided annually as part of the Annual Report
3.2.P.8.2	Annual stability protocol for DP	At 5 °C ± 3 °C at least one bath per year for each strength at initial, 1, 3, 6, 9, 12, 18, 24 and 36 months, according to the tests and AC listed in 3.2.P.8.3 Stability Data and 3.2.P.5.1 Specification, respectively	Stability updates will be provided annually as part of the Annual Report

4. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

Sanofi US Services Inc claims categorical exclusion from the requirements of environmental assessment (BLA section 1.12.14) based on 21 CFR §25.15(d) under the provisions of 21 CFR 25.31(c), 21 CFR 25.34(b). Thus, no environmental assessment needs to be performed. Categorical Exclusion is appropriate for this product and should be granted.

5. Primary Container Labeling Review:

The carton and container labels are reviewed by OBP. The OBP carton and container labeling review will be uploaded as a separate file in Panorama.

6. Review of Common Technical Document- Quality Module 3.2 and module 2.3, Quality Overall Summary. The review of Module 2.3 and 3.2 are included in this review.

7. Review of Immunogenicity Assays- Module 5.3.1.4

Isatuximab immunogenicity was evaluated from six clinical studies using a validated anti-drug antibody (ADA) assay and neutralization antibody (NAb) assay. ADA confirmed positive samples from EFC14335 pivotal study were further examined for neutralizing activity via NAb assay.

A three-tiered approach (screening, confirmatory and titer) was developed for ADA PandA assay. The detection of ADA is established via the binding of immobilized ADA to soluble ruthenium-labeled isatuximab. The assay sensitivity was validated in the range of (b) (4) ng/mL. The drug tolerance level was validated at (b) (4) µg/mL of isatuximab to detect (b) (4) ng/mL ADA positive control. These validation parameters are adequate to assess ADA level

in the C trough concentration range of (b) (4) µg/mL of isatuximab. The sponsor reported that ADA positive is (b) (4)% from all six clinical studies and no confirmed positive results were found in the pivotal study. With respect to NAb assay, a non cell-based competitive ligand binding (CLB) assay was established via immunopurification and electrochemiluminescence immunoassay (ECLIA). The assay sensitivity was validated at (b) (4) ng/mL, and drug tolerance level was validated at (b) (4) µg/mL of isatuximab. Additional data support that the Nab assay can detect (b) (4) ng/mL NAb positive control when (b) (4) µg/mL isatuximab presents. Overall, both Panda and CLB assays are validated to assess the immunogenicity posed by isatuximab IV administration. Based on the clinical data, the immunogenicity risk is low for using isatuximab.

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Lau

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Chih-Jung (CJ)
Hsu

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Yan
Wang
(OPQ/OBP)

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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

Primary Reviewer: Virginia Carroll, PhD
Secondary Reviewer: Jessica Hankins, PhD
Branch Chief: Patricia Hughes, PhD

BLA: 761113/0
Applicant: Sanofi Aventis US LLC
US License Number: 1752
Submission Reviewed: 351(a) BLA
Product: SARCLISA (isatuximab)
Indication: Multiple myeloma (Orphan Designation)
Dosage Form: Concentrate for solution for injection, intravenous infusion, 20 mg/mL (500 mg/25 mL and 100 mg/5 mL single-use vials)
Manufacturing Sites (DP): Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany (FEI 3003195501)
FDA Receipt Date: 4/30/2019
Action Date: 2/28/2020

Conclusion and Approvability Recommendation

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

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0001	4/12/2019	Module 3 Pre-submission of BLA
0004	5/24/2019	Response to IR
0005	6/7/2019	Response to IR
0014	10/15/2019	Response to IR
0021	12/18/2019	Response to IR
0022	12/20/2019	Response to IR

A letter of authorization was provided upon request (sequence 0005) for the following drug master file (DMF):

DMF #	DMF Holder	Referenced Information	Site	DMF Review
(b) (4)				

Module 1.14

Labeling

2.1 Dosage and Administration

Isatuximab is administered at 10 mg/kg body weight as an intravenous infusion (IV) in combination with pomalidomide and dexamethasone. The doses are administered weekly for the first cycle and every two weeks afterward.

2.4 Preparation for Administration

Based on patient weight, the appropriate volume of isatuximab concentrate should be withdrawn and diluted in an infusion bag with 250 mL of 0.9% sodium chloride or 5% dextrose.

2.5 Administration

The prepared infusion solution should be used within 48 hours when stored at 2-8°C, followed by 8 hours (including infusion time) at room temperature. The maximum rate for the first infusion is 150 mL/hour but may be increased to 200 mL/hour for subsequent infusions.

Reviewer's Comment: The microbial challenge studies to support the post-dilution storage conditions of drug product are provided in section 3.2.P.2.6.

Module 3.2

P.1 Description and Composition of the Drug Product

Isatuximab is available as a sterile 20 mg/mL concentrate for solution for infusion in two single-use vial presentations: 500 mg/25 mL and 100 mg/5 mL. The two vial sizes are 30 mL and 6 mL. The composition of the drug product solution includes (b) (4) mM histidine, (b) (4) % (w/v) sucrose and (b) (4) % polysorbate 80, pH 6.0. Overfill volumes are (b) (4) mL ((b) (4) g) and (b) (4) mL ((b) (4) g) for the 500 mg and 100 mg presentations, respectively.

P.2 Pharmaceutical Development

(b) (4)

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Virginia
Carroll

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Patricia
Hughes Troost

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