CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761291Orig1s000

PRODUCT QUALITY REVIEW(S)

Priority Review and Breakthrough Assessment:

Recommendation: **BLA Approval**

BLA Number: 761291
Assessment Number: First Round
Assessment Date: 09/20/2022

Drug Name/Dosage Form	Tecvayli (teclistamab-cqyv)[1], injection
Strength/Potency	10 mg/mL (30 mg/ 3.0 mL) and 90 mg/mL (153 mg / 1.7 mL)
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an antiCD38 monoclonal antibody
Applicant/Sponsor	Janssen Biotech, Inc.
US agent, if applicable	N/A

Product Overview:

Teclistamab is a humanized IgG-4 bispecific antibody developed to target the CD3 receptor complex on T cells and BCMA on B cells. (b) (4) Teclistamab consists of an anti-BCMA heavy chain and light chain and an anti-CD3 heavy chain and light chain with 2 interchain disulfide bonds connecting the 2 arms.

The mechanism of action of teclistamab is through enhanced T-cell mediated cytotoxicity through recruitment of CD3-expressing T cells to the BCMA-expressing myeloma cells. With its dual binding sites, teclistamab draws CD3+ T cells in close proximity to malignant cells, resulting in T-cell activation and subsequent lysis of BCMA+ cells.

The teclistamab final drug product (DP) is a sterile solution for subcutaneous administration and it is formulated at 10 mg/mL or at 90 mg/mL teclistamab in sodium acetate (b) (4) (1.5 mg/mL), glacial acetic acid (b) (4) sucrose (b) (4) Polysorbate 20 (b) (4) and water for injection, (b) (4) Each vial contains either 30 mg (3.0 mL) or 153 mg (1.7 mL) of teclistamab. The DP is manufactured at Patheon Manufacturing Services LLC, Greensville, NC.

Teclistamab was granted orphan drug designation on 11/24/2022, breakthrough therapy designation on 5/26/2021, and priority review on 2/25/2022.

[1] Final acceptance of the proposed proprietary name and designation of the proper name for a biological product occur upon licensure of the biological product and may be subject to change prior to licensure.

Quality Assessment Team:

Discipline	Reviewer	Branch/Division
Drug Substance (DS), Drug Product (DP), and Immunogenicity assays	Andrea Franco	OPQ/OBP/DBRR IV
Inspection of DS site (704(a)4 records request review)		
Labeling	CAPT Vicky Borders-Hemphill	OPQ/OBP
DS Facilities/ Microbiology	Charles Yuan-Chia Kuo	OPQ/OPMA/DBM
DP Facilities/ Microbiology	Lindsey Brown	OPQ/OPMA/DBM
Team Leads	LCDR Leslie A. Rivera Rosado (Product quality) Zhong Li (Facilities) Maxwell Van Tassell (Microbiology)	OPQ/OBP/DBRR IV OPQ/OPMA/DBM OPQ/OPMA/DBM
OPQ RBPM	Anita Brown	OPQ/OPRO
Application Technical Lead	LCDR Leslie A. Rivera Rosado	OPQ/OBP/DBRR IV

Multidisciplinary Assessment Team:

Discipline	Reviewer	Office/Division
RPM	Felluca Denise	OND/ORO/DROOD
Cross-disciplinary Team Lead	Bindu Kanapuru	OOD/DHMII
Medical Officer	Elizabeth Hill & Andrea Baines	OOD/DHMII
Pharm/Tox	Brenda Gerkhe (TL) Michael Manning	OOD/DHOT
Clinical Pharmacology	Nan Zheng (TL) Lauren Price RPM: Bernadette Johnson-Williams	OCP/DCPI
Safety	Shan Pradhan SRPM: Stacie Woods	OOD
Pharmacometrics	Lia Man (TL) Robin Konicki	OCP/DPM
Genomics	Rosane Charlab Orbach (TL)	OCP/DTPM
Biostatistics	Qing Xu (TL) Jay Zhao	OB/DBIX
OSI	Anthony Orencia	OSI
Surveillance and Epidemiology	Neil Vora	OSE PM
	Hina Mehta (TL) Nicole Iverson	OSE/DMEPA 2
	Naomi Boston Celeste Karpow	OSE/RISK
PLT	Sharon Mills	
OPDP	Adesola Adejuwon	OPDP

1. Names:
   a. Proprietary Name: Tecvayli
   b. Trade Name: Tecvayli
   c. Non-Proprietary/USAN: Teclistamab-cqyv
   d. CAS name: 2119595-80-9

e. Common name: JNJ-64007957
f. INN Name: Teclistamab
g. OBP systematic name: BsMAB: MAB HUMANIZED (IGG4) ANTI Q02223 (TNR17_HUMAN) & ANTI P07766 (CD3E_HUMAN) [JNJ64007957]

Submissions Assessed:

Submission	Date Received	Review Completed
STN 761291/1 (Original submission)	12/28/2021	Yes
STN 761291/5 (response to OPMA IR dated 1/21/2022)	1/26/2022	Yes
STN 761291/22 (response to OPMA IR dated 4/13/2022)	4/25/2022	Yes
STN 762191/33 (response to OPMA IR dated 5/31/2022)	6/15/2022	Yes
STN 761291/35 (response to OBP IR dated 6/08/2022)	6/21/2022	Yes
STN 761291/47 (response to OBP IR dated 7/11/2022)	7/20/2022	Yes
STN 761291/49 (response to OBP IR dated 7/19/2022)	7/22/2022	Yes
STN 761291/51 (response to OPMA IR dated 7/26/2022)	8/02/2022	Yes
STN 761291/57 (response to OPMA IR dated 7/26/2022)	8/08/2022	Yes
STN 761291/78 (response to OPMA IR dated 8/31/2022; PMC language)	9/01/2022	Yes
STN 761291/81 (response to OPMA IR dated 8/31/2022)	9/08/2022	Yes

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed	Comments
(b) (4)			3	N/A		
			3	N/A		
			3	N/A		

(b) (4)	3	N/A		
	3	N/A		
	3	N/A		
	2	Adequate	06/07/2022	
	2	Adequate	10/07/2021	
	3	N/A		
	6	N/A		Sterilization validation and aseptic processing validation data was provided in the submission

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

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application; therefore, the DMF did not need to be assessed).

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

Document	Application Number	Description
IND	131272	IND application

3. Consults:

Discipline/Topic	Date Requested	Status	Recommendation	Assessor
N/A				

4. Environmental Assessment of Claim of Categorical Exclusion:

Janssen Research & Development (a division of Janssen Pharmaceutica NV), Beerse Belgium, certifies that the referenced action meets the criteria for a categorical exclusion defined in the regulations (21 CFR 25.31[c]), and that to the knowledge of Janssen R&D, no extraordinary circumstances exist. Thus, no environmental assessment needs to be performed.
Conclusion: The claim of categorical exclusion is acceptable.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761291 for Tecvayli (teclistamab-cqyv) manufactured by Janssen Biotech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Tecvayli 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:
  - Intermediate Drug Substance (b) (4)
    - Biogen, Inc.: 5000 Davis Drive, Research Triangle Park, North Carolina, USA
    - Janssen Biologics B.V. (JBV), Einsteinweg 101, 2333 CB Leiden, The Netherlands
  - Intermediate Drug Substance (b) (4)
    - Janssen Sciences Ireland UC (JSI), Barnahely, Ringaskiddy, Co. Cork Ireland.
  - Drug Substance:
    - JSI: Barnahely, Ringaskiddy, Co. Cork, Ireland
  - Drug Product:
    - Patheon Manufacturing Services LLC, Greensville, North Carolina, USA
    - Labeling and Packaging: AndersonBrecon, Inc., 4545 Assembly Drive Rockford, Illinois, USA

- Dosage form and fill size:
  - Injection: 10 mg/mL (30 mg/ 3 mL) or 90 mg/mL (153 mg/ 1.7 mL) solution in a single-use vial

- Dating period:
  - Drug Product: 12 months: 2-8 °C
  - Drug Substance: (b) (4) months: (b) (4)
  - Intermediate Substances (b) (4)
  - Stability Option:
    - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your intermediate substances, drug substance, and drug product under 21 CFR 601.12.

- Exempt from lot release:
  - Yes

- Rationale, if exempted: specified product
  Note: Tecvayli (teclistamab-cqyv), is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

The assessment of manufacturing information provided in the application concluded that the methodologies and processes used for parental antibodies intermediates, drug substance, and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective.

The teclistamab drug substance (DS) will be manufactured at JSI (FEI: 30007029098) and the Tecvayli drug product (DP) at Patheon Manufacturing Services LLC (FEI: 1018495). Pre-licensing inspections or assessments were conducted for Biogen, JBV, JSI, and Patheon and the facilities were found acceptable for the proposed operations.

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

1. Submit the final results for the low endotoxin recovery study performed to examine the effects of (b) (4) on endotoxin recovery using a known amount of standard endotoxin (CSE or RSE) (b) (4)

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA (type)	CQA	Risk (efficacy, PK/PD, immunogenicity and safety	Origin	Control Strategy
Identity	Identity	safety	Intrinsic to molecule	(b) (4)
Potency (biological activity)	BCMA binding	Efficacy	Intrinsic to molecule	
	CD3 binding (EGFR binding assay) (TR-FRET assay)	Efficacy	Intrinsic to molecule	
	T Cell Activation	Efficacy	Intrinsic to molecule	
	FcRn binding	PK	Intrinsic to molecule	
Product related variants/impurities	Charge variants (cIEF, IE-HPLC)	Although it does not have impact on efficacy, PK/PD, immunogenicity, and safety, it is classified as CQA	Bioreactor, Process Intermediate Storage, Purification, and DS/DP Storage	
	monomer (SE-HPLC and cSDS)	Efficacy	Bioreactor, Process Intermediate Storage, (b) (4) Process, Purification, DS/DP Storage	
	High molecular weight species (HMWS) (SE-HPLC)	Efficacy or immunogenicity	Bioreactor, Process Intermediate Storage, (b) (4) Process, Purification, DS/DP Storage	

	Low molecular weight species (LMWS) (cSDS)	Efficacy	Bioreactor, Process Intermediate Storage, (b) (4) Process, Purification, DS/DP Storage	
Protein Structure	Higher Order Protein Structure (CD, DSC, AUC)	Efficacy	Intrinsic to the molecule	(b) (4)
	(b) (4) Oxidation (peptide mapping, MAM)	PK (impacts FcRn binding)	Bioreactor, DP Storage, light exposure	
	(b) (4) Oxidation (Peptide Mapping)	PK (impacts FcRn binding)	Bioreactor, DP Storage, light exposure	
	(b) (4) Deamidation (peptide mapping, MAM)	Efficacy	Bioreactor, Process Intermediate Storage, DS/DP Storage	
	(b) (4) Isomerization (peptide mapping, MAM)	Efficacy		
	(b) (4) Isomerization (Peptide Mapping)	Efficacy		
Carbohydrate Structure	(b) (4)	Although it does not have impact on efficacy, PK/PD, immunogenicity, and safety, it is classified as CQA	Bioreactor	
Disulfide Structure	Disulfide Structure (non-reducing cSDS and non-reducing peptide mapping)	Efficacy	(b) (4) process	
	(b) (4)	Efficacy	Bioreactor and (b) (4) process	

B. Drug Substance (teclistamab) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA (type)	CQA	Risk	Origin	Control Strategy
Process-Related Impurities	(b) (4)	Safety	Bioreactor and purification	(b) (4)
		Safety	Bioreactor and purification	
		Safety	(b) (4) column and purification	
		Efficacy	(b) (4) process and purification	
		Safety	(b) (4) process and purification	
	Microbial contamination (bioburden/sterility) (bioburden, sterility, CCIT)	Safety	MCB/WCB/ raw material, DS manufacturing process	
	Endotoxin/ pyrogen	Safety	MCB/WCB/ raw material, DS manufacturing process	
	Adventitious Virus	Safety	MCB/WCB/ raw material, DS manufacturing process	

	Mycoplasma	Safety	MCB/WCB/ raw material, DS manufacturing process	(b) (4)
	Endogenous virus (TEM)	Although it does not have impact on efficacy, PK/PD, immunogenicity, and safety, it is classified as CQA	MCB/WCB/ raw material, DS/DP process	
Composition and Strength	Excipient Concentration (acetate, sucrose, (b) (4)) (HPLC/UHPLC Excipient Assays)	Although it does not have impact on efficacy, PK/PD, immunogenicity, and safety, it is classified as CQA	Formulation, (b) (4)	
	Color of solution		Intrinsic to the molecule	
	pH	Safety	Formulation, (b) (4)	
	Protein Concentration (A280)	Efficacy	Formulation, (b) (4), DS/DP process	

- **Description:**
  Teclistamab (also referred to as JNJ-64007957) is a humanized immunoglobulin G4 (IgG4) bispecific antibody against B-cell maturation antigen (BCMA) and cluster of differentiation 3 (CD3) receptors.
  Half of teclistamab molecule is derived from the cDNA sequence of the parental antibody (b) (4) and the other half is derived from the parental antibody (b) (4) manufactured in CHO cells. (b) (4)

  Teclistamab has a molecular mass of 146.261 kD (b) (4)

- **Mechanism of Action (MoA):**
  Teclistamab binds to both BCMA on malignant B-cells and CD3 receptors on T-lymphocytes. The BCMA targeting arm engages a BCMA presenting malignant B cell followed by the engagement of an activated T cell by the CD3 binding arm, resulting in

malignant cell death due to cell lysis mediated by secreted perforin and various granzymes stored in the secretory vesicles of cytotoxic T cells.

- **Potency Assay:**

(b) (4)

- **Reference Materials:**

(b) (4)

- **Critical starting materials:**

(b) (4)

(b) (4)

- **Critical intermediates:**

(b) (4)

- **Manufacturing process summary:**

(b) (4)

- **Container closure:**

(b) (4)

- Dating period and storage conditions:
  - Drug Substance: (b) (4) months: (b) (4)
  - Intermediate Substances

(b) (4)

We recommend approval of the intermediate substances and DS stability protocols to support shelf-life extension for up to (b) (4) months.

C. Drug Product [Tecvayli] 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)	CQA	Risk	Origin	Control Strategy
Particulate Matter	Visible foreign particles (visual inspection)	Safety	DP manufacturing process, CCS, and product	(b) (4)
	Visible translucent particles (MIDI)	Safety	DP manufacturing process, CCS, product, and DP storage	
	Sub-visible particles (HIAC)	Safety, Immunogenicity	DP manufacturing process, CCS and product	
Volume in container	Extractable Volume	Efficacy	DP process (fill)	
Contamination	Microbial contamination (bioburden, sterility, CCIT)	Safety, Purity	MCB/WCB/ raw material, DS manufacturing process	
	Endotoxin/ pyrogen	Safety, Purity	MCB/WCB/ raw material,	

			manufacturing process	(b) (4)
Composition and strength	Protein Concentration (A280)	Efficacy	Formulation, (b) (4) DS/DP process	
	pH	Safety	Formulation	
	Polysorbate 20 Concentration		Formulation, DS/DP Process	
	Appearance of primary container	Although it does not have impact on efficacy, PK/PD, immunogenicity, and safety, it is classified as CQA	DP manufacturing process and raw material	

	Color	Safety	Intrinsic to the molecule, formulation	(b) (4)
	Osmolality	Safety, stability, bioactivity	Formulation	
	Excipient Concentration (acetate, sucrose, (b) (4)) (HPLC/UHPLC Excipient Assays)	Although it does not have impact on efficacy, PK/PD, immunogenicity, and safety, it is classified as CQA	Formulation, (b) (4)	
	Turbidity	Safety	Formulation, (b) (4)	

- **Potency and Strength**:
  - 30 mg/3.0 mL (10 mg/mL) solution in a single-dose glass vial
  - 153 mg/1.7 mL (90 mg/mL) solution in a single-dose glass vial

- **Summary of Product Design:**
  - The 10 mg/mL teclistamab (JNJ-64007957) final DP is supplied as a sterile liquid in vial presentation for subcutaneous (SC) administration. Each 10 mg/mL DP vial contains 30 mg of teclistamab in a 3.0 mL nominal fill volume and an excess volume of (b) (4) mL per vial. The primary packaging consists of a (b) (4) glass vial with an elastomeric closure and an aluminum seal with a flip off cap. The DP contains no preservative and is for single use only.
  - The 90 mg/mL teclistamab final DP is supplied as a sterile liquid in vial presentation for SC administration. Each 90 mg/mL DP vial contains 153 mg of teclistamab in a 1.7 mL nominal fill volume and an excess volume of (b) (4) mL per vial. The primary packaging consists of a 2 mL (b) (4) glass vial with an elastomeric closure and an aluminum seal with a flip off cap. The DP contains no preservative and is for single use only.

- **List of Excipients:**
  Sodium acetate (b) (4) (1.5 mg/mL), glacial acetic acid (b) (4) sucrose (b) (4) Polysorbate 20 (b) (4) and water for injection, (b) (4)

- **Reference Materials**:
  Same as for teclistamab drug substance.

- **Manufacturing process summary:**
  (b) (4)

(b) (4)

- **Container closure:**
  - The container closure for the 10 mg/mL DP is a (b) (4) glass (b) (4) back vial with (b) (4) grey (b) (4) rubber stopper and (b) (4) silver aluminum seal with a royal blue flip-off cap
  - The container closure for the 90 mg/mL DP is a 2 mL (b) (4) glass (b) (4) back vial with (b) (4) grey (b) (4) rubber stopper and (b) (4) silver aluminum with orange plastic flip-off cap

- **Dating period and storage conditions:**
  The shelf life of the DP is 12 months when stored at the recommended storage condition of 5 ± 3 °C and protected from light.

  We recommend approval of the stability protocol to support DP shelf-life extension up to (b) (4) months.

D. Novel Approaches/Precedents:
To our knowledge this is the first biologic drug (BLA) to be recommended for approval which utilizes a trypsin peptide mapping multi-attribute monitoring (MAM) assay as a release and stability testing method. MAM is used to quantify the levels of (b) (4) isomerization and (b) (4) deamidation in teclistamab drug substance and 10 mg/mL and 90 mg/mL drug product.
The MAM method was reviewed by Dr. Sarah Rogstad, a mass spectrometry expert and Emerging Technologies Team member from OPQ/OTR.

E. Any Special Product Quality Labeling Recommendations:
- Single-dose vials
- Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light.
- Visually inspect Tecvayli for particles or discoloration prior to administration.

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Cell Bank Manufacturing and Cell Bank Storage	Janssen Biotech, Inc. 200 Great Valley Parkway n/a,	3001610451	No Evaluation Necessary	N/A	No Evaluation Necessary

	Malvern, PA, United States, 19355				
Drug Substance Stages (b) (4)	Biogen, Inc. 5000 Davis Drive Research Triangle Park, Durham, NC, United States, 27709	3000719749	Inspection waiver	N/A	Approve - Based on Waiver granted by OPMA/OBP
Drug Substance Stages (b) (4) (Manufacture of Parental Monoclonal Antibody (b) (4) rug Substance Stages (b) (4) (Production of Bispecific Antibody and Purification), Parental Monoclonal Antibody and Drug Substance Testing (Microbiological - Non-Sterility, Biological, Chemical/Physical); Drug Product Testing (Biological, Chemical/Physical)	Janssen Sciences Ireland UC Barnahely, Ringaskiddy, Research Triangle Park, Co. Cork, Ireland, P43 FA46	3007029098	704(a)4 Records Request	N/A	Approve - Based on 704(a)(4)
Drug Substance Stages (b) (4) (Manufacture of Parental Monoclonal Antibody (b) (4) Parental Monoclonal Antibody and Drug Substance Testing (Microbiological - Non-Sterility, Biological, Chemical/Physical);	Janssen Biologics B.V. Einsteinweg 101, Leiden, CB, the Netherlands, 2333	3002806632	Inspection waiver	N/A	Approve - Based on Waiver granted by OPMA/OBP
(b) (4) Testing (b) (4)	BioReliance Corporation 14920 Broschart Road, Rockville, MD, United States, 20850	1122041	Approve - Based on Previous History	N/A	Approve - Based on Previous History
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug Product Testing (Microbiological – Sterility, Biological, Chemical/Physical)	Janssen Biologics B.V. Einsteinweg 101, Leiden, CB, the Netherlands, 2333	3002806632	Inspection waiver	N/A	Approve - Based on Waiver granted by OPMA/OBP

Drug Product Manufacturing and Primary Packaging; Drug Product Testing (Chemical/Physical, Microbiological – Sterility, Microbiological - Non-Sterility)	Patheon Manufacturing Services LLC 5900 Martin Luther King Jr. Hwy, Greenville, NC, United States, 27834	1018495	Inspection waiver	N/A	Approve - Based on Waiver granted by OPMA/OBP
Drug Product Testing (Chemical/Physical)	Cilag AG Hochstrasse 201, Schaffhausen, Switzerland, 8200	3002806695	No evaluation necessary	N/A	No evaluation necessary
Drug Product Secondary Packaging	AndersonBrecon, Inc. 4545 Assembly Drive, Rockford, IL, United States, 61109	1421377	No evaluation necessary	N/A	No evaluation necessary

G. Facilities:

Janssen Sciences Ireland UC (JSI) (FEI 3007029098)
JSI is responsible for the manufacture of JNJ-64007957 (teclistamab) DS (b) (4) located in JSI, Co. Cork, Ireland. JSI operates as a multi-product cGMP facility which used to manufacture biological products including commercially licensed US product in the proposed manufacturing areas. The facility was most recently inspected by CDER/OPQ on 4/26-30/2021 in support of BLA (b) (4) and classified as VAI. Due to lack of comprehensive inspectional coverage (b) (4) the Agency used its authority under Section 704(a)(4) to request records from the proposed manufacturing facility JSI in lieu of performing an on-site pre-license inspection (PLI) for BLA 761291/0. The request followed the procedures described in the FDA Staff Manual Guide SMG 9004.1, Policy and Procedures for Requesting Records in Advance of or In Lieu of a Drug Inspection (Effective Date: August 25, 2017).
On March 1, 2022, the Agency requested pre-inspection audit documents in support of the manufacture of the teclistamab DS at JSI. On March 17, and April 13 of 2022, JSI submitted the requested documents in support of BLA 761291/0. The document review is captured in CMS WA 442073.
The proposed drug substance manufacturing facility is found to be acceptable to support the approval of BLA 761291/0.

Please refer to Section F for information regarding other manufacturing and testing facilities.

H. Lifecycle Knowledge Management:

a. Drug Substance and Drug Product:

i. Protocols approved:

- Stability Programs for Master Cell Bank and Working Cell Banks
- Requalification and Stability Monitoring of Primary and Working Reference Materials
- Future Primary and Working Reference Materials Preparation and Qualification

(b) (4)

- Drug Substance Stability Protocol and protocol for shelf-life extension
- Drug Product Stability Protocol and protocol for shelf-life extension
- Comparability Protocol for New Product Introduction at JSI
- Comparability Protocol for New Product Introduction at JBV
- Comparability Protocol for New Product Introduction at Patheon

ii. Outstanding assessment issues/residual risk: None identified

iii. Future inspection points to consider: None identified

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/s/

LESLIE A RIVERA ROSADO
09/20/2022 03:55:14 PM

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	August 29, 2022
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Andrea Franco, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 4
Application:	BLA 761291
Applicant:	Janssen Biotech, Inc.
Submission Date:	December 28, 2021
Product:	Tecvayli (teclistamab-cqyv)
Dosage form(s):	injection
Strength and Container-Closure:	30 mg/3 mL (10 mg/mL) in a single-dose vial 153 mg/1.7 mL (90 mg/mL) in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information and medication guide (submitted on August 26, 2022), container labels (submitted on July 22, 2022), and carton labeling (submitted on August 5, 2022) were assessed and found to be acceptable (see Appendix C) 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

n/a = not applicable for this assessment

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 prescribing information and medication guide (submitted on August 26, 2022), container labels (submitted on July 22, 2022), and carton labeling (submitted on August 5, 2022) were assessed and found to be acceptable (see Appendix C) from an OBP Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information/Medication Guide (submitted on December 28, 2021 \\CDSESUB1\evsprod\bla761291\0001\m1\us\annotated-draft-labeling-text.doc)

Container Labels (submitted on December 28, 2021)

(b) (4)

1 Page of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] 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
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

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
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	☐ Yes ☐ No ☒ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Add the required manufacturer's name to the 153 mg/1.7 mL vial label and if space permits add the US license number
The applicant added the manufacturer's name as requested

[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.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

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

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
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	✓ Yes ☐ No ☐ N/A

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

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
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*	✓ Yes ☐ No ☐ N/A

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

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Add the required Rx only statement to the 153 mg/1.7 mL vial label *The Applicant did not add the Rx Only statement citing partial label*

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

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

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

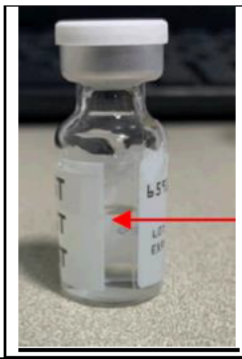
Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *Applicant's response: A batch number is printed on the aluminum ferrule. There is no text on the cap overseal*
OBPL response: Acceptable since no cautionary statement is needed and other statements or features including, but not limited to, identifying numbers or letters, such as code numbers, lot numbers, company names, logos, or product names, etc., may appear on the side (skirt)

surface of the ferrule on vials containing injectable products, but not on the top (circle) surface of the ferrule or cap overseal.

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

Comment/Recommendation: 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
Applicant's response: On the 2R Vial (shown below), there is a 4.27 mm wide clear window that allows for visual inspection of the contents when the label is affixed to the vial. On the 6R Vial (shown below), there is a 4.11 mm wide clear window that allows for visual inspection of the contents when the label is affixed to the vial.



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
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

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

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
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	☐ Yes ☐ No ☒ N/A

Package type term (container label)	**Acceptable**
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*	✓ Yes ☐ No ☐ N/A

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

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

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

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

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No

	☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *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*	✓ Yes ☐ No ☐ N/A

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

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
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 *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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

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

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

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

Package[6] 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
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

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
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

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

Expiration date (package labeling)	Acceptable
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

[6] 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.

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

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

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

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
Recommended labeling practices 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*	✓ Yes ☐ No ☐ N/A

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

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

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

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
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

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

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

Comment/Recommendation: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients), the established names and amounts for inactive ingredients in your product have been revised according to the USP/NF monographs title and per the monograph definition. Revise the ingredient information to the compendial names and definitions. Inactive ingredient amounts were calculated per the USP monograph

definition for sodium acetate. [redacted]

Resubmit an updated Description and Composition to section 3.2.P.1 [redacted] Ensure that all inactive ingredients with a USP monograph are provided as such.

Each 3 mL single-dose vial contains 30 mg of teclistamab-xxxx, [redacted] glacial acetic acid (0.72 mg), polysorbate 20 (1.2 mg), sodium acetate (2.7mg), sucrose (240 mg), and Water for Injection, USP.

Each 1.7 mL single-dose vial contains 153 mg of teclistamab-xxxx, [redacted] glacial acetic acid (0.41 mg), polysorbate 20 (0.68 mg), sodium acetate [redacted] sucrose (140 mg), and Water for Injection, USP.

Applicant response: The Applicant agrees to update the inactive ingredient name [redacted] to the compendial name 'sodium acetate'. [redacted]

Additionally, the Applicant agrees to update the inactive ingredient name [redacted] o the compendial name 'edetate disodium'. [redacted] *These established names and the amounts are aligned with the revised draft USPI submitted to the Agency for review on August 1, 2022 (Seq No. 0050), for which updated 3.2.P.1 Description and Composition of the Drug Product sections were provided.*
The Applicant revised as requested

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

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

Comment/Recommendation: Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OBP Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for teclistamab products (i.e., there is no specific test method described in regulation for teclistamab products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Tecvayli because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling. 21 CFR 610.61(r) is not applicable and thus no statement is required on the labeling.[7]

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
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	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

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

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *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)*	✓ Yes ☐ No ☐ N/A

[7] Weiner J. Memorandum. Applicability of 21 CFR 610.61(r). BLA 761291. Silver Spring (MD): FDA, CDER, ORP (US); 2022 August 15.

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

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

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
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 *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

Package type term (package labeling)	**Acceptable**
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*	✓ Yes ☐ No ☐ N/A

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

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

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

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

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

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

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
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 *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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

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

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
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	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

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
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling	✓ Yes ☐ No ☐ N/A

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* *USP General Chapters: <7> Labeling*	

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Add the clarity of the solutions (e.g., clear)
The applicant added 'clear to slightly opalescent'

Consider indicating that the storage condition is for product drawn up in the syringe(s) *The applicant revised as requested*

Consider removing [redacted] (b) (4) Relocate the equilibration information to a separate bullet since this information applies to both the refrigerated vial and the syringe *The applicant revised as requested*

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
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) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the clarity of the solutions (e.g., clear) *The applicant added 'clear to slightly opalescent'*

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
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised to read as the pharmacological class instead of as the mechanism of action ("bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager antibody") *The applicant revised as requested*
Add the clarity of the solution (e.g. clear) *The applicant added 'clear to slightly opalescent'*
To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients), the established names and amounts for inactive ingredients in your product have been revised according to the USP/NF monographs title and per the monograph definition. Inactive ingredient amounts were calculated per the USP monograph definition for sodium acetate. [redacted] (b) (4) Confirm these recalculations.
Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the table [redacted] (b) (4) Ensure that all inactive ingredients with a USP monograph are provided as such.

Applicant's response: The USP monograph titled "Sodium Acetate" covers various forms of sodium acetate [redacted] (b) (4) *Similarly, EDTA monograph is titled "Edetate Disodium"* [redacted] (b) (4) *Thus, the naming of* [redacted] (b) (4)
inactive ingredient was revised to edetate disodium [redacted] (b) (4)
[redacted]
o Table 1 in 32P1 Description and Composition of the Drug Product, Liquid in Vial, 30 mg/vial (10 mg/mL) and Table 1 in 32P1 Description and Composition of the Drug Product, Teclistamab Liquid in Vial, 153 mg/vial (90 mg/mL).

OBPL response: We acknowledge your response to the revisions of the inactive ingredient names and amounts. Our intent is to ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) **by using established names for drugs** (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, *"Sodium Acetate" and "Edetate Disodium"* We agree that the Sodium Acetate USP/NF monograph [redacted] per the monograph DEFINITION. The approved labeling should use the inactive ingredient established name (monograph title), 'Sodium Acetate', [redacted] Your updated Description and Composition submitted to section 3.2.P.1 will then include a footnote [redacted] We agree that the Edetate Disodium USP/NF monograph [redacted] per the monograph DEFINITION. The approved labeling should use the inactive ingredient established name (monograph title), 'Edetate Disodium', [redacted] Your updated Description and Composition submitted to section 3.2.P.1 will then include a footnote [redacted] *The Applicant revised as requested*

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the clarity of the solution (e.g. clear) *The applicant added 'clear to slightly opalescent'* Added the mg/mL presentation of strength *The applicant revised as requested*

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

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
STORAGE AND HANDLING	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☐ Yes ☐ No ☒ N/A

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to the compendial name for 'sodium acetate' and 'edetate disodium' per the USP monograph. *The Applicant revised as requested*

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the US license number *The Applicant revised as requested*

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on August 26, 2022
\\CDSESUB1\EVSPROD\bla761291\0077\m1\us\draft-labeling-text-uspi.pdf)

Medication Guide (submitted on August 26, 2022
\\CDSESUB1\EVSPROD\bla761291\0077\m1\us\draft-med-guide-clean.doc)

Container Labels (submitted on July 22, 2022)

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Vicky Borders-Hemphill

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Andrea Franco

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Date: 8/29/2022 12:11:14PM
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BLA STN 761291

Tecvayli (teclistamab-cqyv)

Janssen Biotech, Inc.

This BLA participated in Project Orbis

Andrea Franco, Ph.D., Staff Fellow
Leslie A. Rivera Rosado, Ph.D., Team Lead

Office of Biotechnology Product
Division of Biotechnology Review and Research IV

OBP CMC Review Data Sheet

1. **BLA#:** BLA761291

2. **REVIEW DATE: 5/9/2022; revised 7/25/2022**

3. **PRIMARY PRODUCT QUALITY REVIEW TEAM:**

Discipline	Reviewer	Branch/Division
Drug Substance (DS), Drug Product (DP), and Immunogenicity assays	Andrea Franco	OPQ/OBP/DBRR IV
Inspection of DS site		OPQ/OBP/DBRR IV
Labeling	CAPT Vicky Borders-Hemphill	OPQ/OBP
DS Facilities/ Microbiology	Charles Yuan-Chia Kuo	OPQ/OPMA/DBM
DP Facilities/ Microbiology	Lindsey Brown	OPQ/OPMA/DBM
Team Leads	LCDR Leslie A. Rivera Rosado (Product quality) Zhong Li (Facilities) Maxwell Van Tassell (Microbiology)	OPQ/OBP/DBRR IV OPQ/OPMA/DBM OPQ/OPMA/DBM
OPQ RBPM	Anita Brown	OPQ/OPRO
Application Technical Lead	LCDR Leslie A. Rivera Rosado	OPQ/OBP/DBRR IV

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Felluca Denise	OND/ORO/DROOD
Cross-disciplinary Team Lead	Bindu Kanapuru	OOD/DHMII
Medical Officer	Bindu Kanapuru (CDTL) Elizabeth Hill & Andrea Baines	OOD/DHMII
Pharm/Tox	Brenda Gerkhe (TL) Michael Manning	OOD/DHOT
Clinical Pharmacology	Nan Zheng (TL) Lauren Price	OCP/DCPI
Pharmacometrics	Lia Man (TL) Robin Konicki	OCP/DPM
Genomics	Rosane Charlab Orbach	OCP/DTPM
Biostatistics	Qing Xu (TL) Jay Zhao	OB/DBIX
OSI	Anthony Orencia	OSI
OSE PM	Neil Vora	OSE PM
OSE/DMEPA	Nicole Iverson/Hina Mehta TL	OSE/DMEPA
Safety:	Shan Pradhan, Stacie Woods	
PLT	Sharon Mills	
OSE/DRISK	Naomi Boston Celeste Karpow	OSE/RISK
OPDP	Adesola Adejuwon	OPDP

4. MAJOR GRMP DEADLINES

Filing Meeting: 2/18/2022
Mid-Cycle Meeting: 3/28/2022
Day 74: 3/12/2022
Primary Review Due: 6/5/2022
Late cycle Meeting: 6/26/2022
Wrap-Up Meeting: 7/7/2022
CDTL Memo Due: 7/15/2022
PDUFA Action Date: On 7/12/2022 the goal date was extended from 8/28/2022 to 11/28/2022

5. COMMUNICATIONS WITH SPONSOR AND OND:

Communication/Document	Date
CMC Pre-BLA Meeting	Meeting comments were sent on 5/21/2021 Meeting was canceled by Janssen on 5/25/2021
Filing meeting with OND	2/15/2022
Orientation meeting with Janssen	2/4/2022
Information request #1 (OPMA)	1/21/2022
Midcycle meeting with OND	3/16/2022 and 4/12/2022
Midcycle meeting with Janssen	4/28/2022
Labeling meeting with OND	5/16/2022
Information request #2 (OPMA)	4/19/2022
Information request #3 (OPMA)	6/2/2022
Information request #4(OBP)	6/10/2022
Late cycle meeting with OND	6/28/2022
Information request #5 (OBP)	7/13/2022
Late cycle meeting with Janssen	7/19/2022
Information request #6 (OBP)	7/19/2022
Labeling meeting with OND	7/25/2022

6. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
STN 761291/1	12/28/2021	Yes
STN 761291 /5 (response to IR #1 - OPMA)	1/26/2022	Yes
STN 761291/22 (response to IR #2 - OPMA)	4/25/2022	Yes
STN 762191/33 (response to IR #3 – OPMA)	6/15/2022	Yes
STN 761291/35 (response to IR #4 – OBP)	6/21/2022	Yes
STN 761291/47 (response to IR #5 – OBP)	7/20/2022	Yes
STN 761291/49 (response to IR #6 – OBP)	7/22/2022	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

a. Proprietary Name: Tecvayli
b. Trade Name: Tecvayli
c. Non-Proprietary/USAN: Teclistamab-cqyv
d. CAS name: 2119595-80-9
e. Common name: JNJ-64007957
f. INN Name: Teclistamab
g. Compendial Name: N/A
h. OBP systematic name: BsMAB: MAB HUMANIZED (IGG4) ANTI Q02223 (TNR17_HUMAN) & ANTI P07766 (CD3E_HUMAN) [JNJ64007957]
i. Other Names: None

8. PHARMACOLOGICAL CATEGORY: Anti-neoplastic

9. DOSAGE FORM: Injection

10. STRENGTH/POTENCY:

(i) The concentration/strength of the Drug Product: 10 mg/mL (30 mg/ 3.0 mL) and 90 mg/mL (153 mg / 1.7 mL)
(ii) Type of potency assay (s): NFAT reporter gene assay.

11. ROUTE OF ADMINISTRATION: Subcutaneous injection

12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
			Yes	No review required as all the relevant information related to

(b) (4)		compatibility with the product was in the BLA.
	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.

13. INSPECTIONAL ACTIVITIES

Teclistamab drug substance (DS) is manufactured at Biogen, Inc. (FEI# 3000719749) (b) (4) Janssen Biologics B.V. (FEI# 3002806632) (b) (4) and at Janssen Sciences Ireland UC (JSI) (FEI# 30007029098) (b) (4) . The drug product (DP) is manufactured at Patheon Manufacturing Services (FEI# 1018495).

The pre-license inspection for Biogen Inc., Janssen Biologics B.V., and Patheon Manufacturing Services were waved based on their inspection history. A record review in lieu of an on-site inspection was performed for JSI by Dr. Andrea Franco, Dr. Charles Yuan-Chia Kuo, and Dr. Zhong Li. The requested documents were reviewed and found adequate.
Final facilities recommendation: Approval based on prior inspection history and 704(a) records review.

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

Risk assessments to identify critical quality attributes of teclistamab and to identify process parameters for assessment in process characterization studies were performed according to methods described in the submission and review of Module 3.

16. PRECEDENTS

This is the first BLA which utilizes a trypsin peptide mapping multi-attribute monitoring (MAM) assay as a release and stability testing method. MAM is used to quantify the levels of (b) (4) isomerization and (b) (4) deamidation in teclistamab drug substance (DS) and 10 mg/mL and 90 mg/mL drug product (DP).

The MAM method was reviewed by Dr. Sarah Rogstad, a mass spectrometry expert and Emerging Technologies Team member from OPQ/OTR.

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
LCDR Leslie Ann Rivera Rosado, Ph.D.	

Product Quality Team Leader DBRR IV, OBP, OPQ	See attached
Andrea Franco, Ph.D. Product Quality Reviewer DBRR IV, OBP, OPQ	See attached

B. CC Block

Recipient	Date
Denise Felluca Clinical Division BLA RPM	
OBP/DBRR IV File/BLA STN 761291	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products recommends approval of BLA 761291 for Tecvayli (teclistamab-cqyv) manufactured by Janssen Biotech, Inc. from a product quality perspective based on the review of the information and data provided in the application.

II. List Of Deficiencies To Be Communicated

Not applicable.

III. List Of Post-Marketing Commitments/Requirement

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

In Module 1 (1.12.14 Environmental Assessment – Claim for Categorical Exclusion), Janssen claims categorical exclusion, in accordance with 21 CFR 25.31(c), from the requirement to prepare an Environmental Assessment as Janssen Research & Development (a division of Janssen Pharmaceutica NV), Beerse Belgium, certifies that the referenced action meets the criteria for a categorical exclusion defined in the regulations (21 CFR 25.31[c]), and that to the knowledge of Janssen R&D, no extraordinary circumstances exist. Thus, no environmental assessment needs to be performed.

***Assessor's Comment**: The claim of categorical exclusion is acceptable.*

V. Primary Container Labeling Review

Refer to review by Vicky Borders-Hemphill.

VI. Review Of Common Technical Document-Quality Module 3.2

This document.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

This document.

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Sarah Rogstad

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Leslie Rivera-Rosado

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