

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761121Orig1s000

PRODUCT QUALITY REVIEW(S)

Orphan Drug, Breakthrough, and Priority Review:

Recommendation: Approval

BLA Number: 761121

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Review Number: First Round

Review Date: May 24, 2019

Drug Name/Dosage Form	POLIVY (polatuzumab vedotin-xxxx ¹), for injection
Strength/Potency	140 mg/vial
Route of Administration	Infusion
Rx/OTC dispensed	Rx
Indication	(b) (4)
Applicant/Sponsor	Genentech, Inc.
Regulatory History	Granted Orphan Drug Designation on December 12, 2016. Granted Breakthrough Therapy Designation (BTD) on September 12, 2017. Rolling submission with priority review.

Product Overview

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate (ADC) that preferentially delivers an anti-mitotic agent (monomethyl auristatin E [MMAE]) to B cells, which results in anti-cancer activity against B-cell malignancies. The polatuzumab vedotin molecule consists of MMAE covalently attached to a CD79b-directed humanized IgG1 monoclonal antibody (produced in CHO cells) through the protease-cleavable linker maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (mc-vc-PAB). The polatuzumab vedotin manufacturing process was designed to deliver an average of 3.5 linked MMAE moieties per antibody molecule [drug-to-antibody ratio (DAR) = 3.5].

POLIVY (polatuzumab vedotin) is provided in single-dose (b) (4) vials as a sterile, white to grayish-white lyophilized powder with cake-like appearance and contains no preservatives. It is intended for intravenous infusion after reconstitution with sterile water for injection (SWFI) and dilution in 0.9% sodium chloride solution, 0.45% sodium chloride solution, or 5% dextrose solution. Reconstituted POLIVY contains 20 mg/mL polatuzumab vedotin in (b) (4) succinate, (b) (4) sucrose, (b) (4) polysorbate 20, pH 5.3.

Quality Review Team

Discipline	Reviewer	Branch/Division
Antibody Intermediate (AI)	Jacek Cieslak	CDER/OPQ/OBP/DBRR IV
vcMMAE Intermediate	Ben Zhang	CDER/OPQ/ONDP/DNDAP/INDBI
Drug Substance (DS)	Mate Tolnay	CDER/OPQ/OBP/DBRR IV
Drug Product (DP)		
Immunogenicity assays	Mate Tolnay and Fred Mills	
Labeling	Vicky Borders-Hemphill	CDER/OPQ/OBP
Facility	Michael Shanks	CDER/OPQ/OPF/DIA

¹ Review was completed prior to designation of the suffix.

	Zhihao Peter Qiu	
Microbiology	Diane Raccasi (AI/DS) Reyes Candau-Chacon (DP)	CDER/OPQ/OPF/DMA IV
Team Leads	LCDR Leslie A. Rivera Rosado (Product quality) Peter Qiu (Facilities) Reyes Candau-Chacon (Microbiology, AI/DS) Patricia Hughes (Microbiology, DP) Suong T Tran (Small molecule)	CDER/OPQ/OBP/DBRR IV CDER/OPQ/OPF/DIA CDER/OPQ/OPF/DMA IV CDER/OPQ/OPF/DMA IV CDER/OPQ/ONDP/DNDAPI/NDBI
Application Team Lead	LCDR Leslie Ann Rivera Rosado	CDER/OPQ/OBP/DBRR IV
Regulatory Business Project Manager	Anita Brown	CDER/OPQ/OPRO

Multidisciplinary Review Team

Discipline	Reviewer	Office / Division
RPM	Wanda Nguyen	CDER/OND/OHOP/DHP
Cross-disciplinary Team Lead	Angelo de Claro	CDER/OND/OHOP/DHP
Medical Officer	Yvette Kasamon	CDER/OND/OHOP/DHP
Pharm/Tox	Natalie Simpson Ramadevi Gudi/Christopher Sheth	CDER/OND/OHOP/DHOT
Clinical Pharmacology	Saladelain Hamed/Ruby Leong	CDER/OTS/OCP/DCPV
Statistics	Alexei Ionan/Jingjing Ye	CDER/OTS/OB/DBV

Names:

Proprietary Name: POLIVY
Non-proprietary/USAN/INN: Polatuzumab vedotin
CAS Registry Number: 1313206-42-6
Chemical Name: Immunoglobulin G1, anti-(human antigen CD79b) (human-Mus musculus monoclonal MCDS4409A heavy chain), disulfide with human-Mus musculus monoclonal MCDS4409A κ -chain, dimer, thioether with maleimidocaproyl-valinecitruilline- *p* -aminobenzyloxycarbonyl monomethylauristatin E
Company Name: DCDS4501A, DCDS4501S, RO5541077, FCU2711, GNT-038, aCD79b-vcMMAE, MCDS4409A-VC-MMAE
OBP systematic name²: CONJ: MAB HUMAN (IGG1) ANTI P40259 (CD79B_HUMAN); Mono-methyl auristatin E [DCDS4501A]

Submissions Reviewed

Submission(s) Reviewed	Document Date
STN 761121/1- BLA Original Application	11/20/2018
STN 761121/2- BLA Original Application (CMC module)	12/19/2018
STN 761121/8- Quality/ Response to Information Request	1/15/2019
STN 761121/15- Quality/ Response to Information Request	2/7/2019
STN 761121/17- Quality/ Addition of section 3.2.S.1 for the vcMMAE intermediate	2/8/2019
STN 761121/34- Quality/ Response to Information Request and Labeling	4/5/2019
STN 761121/37- Labeling/Package Insert	4/15/2019
STN 761121/39- Quality/ Response to Information Request	4/19/2019
STN 761121/41- Quality/ Response to Information Request	4/26/2019
STN 761121/42- Multiple categories/ Labeling Revisions (carton and container)	4/29/2019
STN 761121/46- Quality/ Response to Information Request	5/17/2019
STN 761121/47- Quality/ Response to Information Request	5/20/2019

² The OBP systematic name allows searching for related products in OBP's database and in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS) for safety reasons and it is different from the nonproprietary name. The tag at the end is used to separate products from different sponsors and it is generally the name used by sponsors to refer to the proposed product in their submissions.

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 ^a	Status ^b	Date Review Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	5/8/2019	
	V			2	Adequate	8/31/2017	
	III			3	N/A	N/A	
	III			3	N/A	N/A	
	V			6	N/A	N/A	The facilities reviewer looked at the DMF as part of the facilities review and any comments are noted in the facilities review memo for this BLA.

- a.** Action codes for DMF: 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").
- b.** Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application; therefore, the DMF did not need to be reviewed).

B. Other documents:

Document	Application Number	Description
IND	109409	Investigation of the use of polatuzumab vedotin for the treatment of patients with B cell malignancies. initially submitted on January 7, 2011.
IND	(b) (4)	
IND		

3. Consults: None

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761121 for POLIVY (polatuzumab vedotin) manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of POLIVY is well-controlled and leads to a product that is pure and potent. OPQ recommends that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

Manufacturing locations:

- Antibody Intermediate:
 - o [REDACTED] (b) (4)
- Drug Substance:
 - o [REDACTED] (b) (4)
- Drug Product:
 - o [REDACTED] (b) (4)

Fill size and dosage form

- 140 mg/vial, for injection

Dating period:

- Drug Product: 24 months at 2-8 °C
- Drug Substance: [REDACTED] (b) (4)
- Antibody Intermediate: [REDACTED] (b) (4)
- Stability Option:
 - o 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.
 - o For stability protocols:
 - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your antibody intermediate, drug substance, and drug product under 21 CFR 601.12.
- Exempt from lot release:
 - o Yes, POLIVY is a specified product exempted according to 21 CFR 601.2a.

C. Benefit/Risk Considerations:

The assessment of manufacturing information provided in the application and in the cross-referenced drug master file (DMF) has concluded that the methodologies and processes used for antibody intermediate, vcMMAE intermediate, drug substance, and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The antibody intermediate and drug substance manufacturing

processes are robust for removal and control of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective.

The polatuzumab antibody intermediate will be manufactured at (b) (4) (b) (4) the vcMMAE intermediate will be manufactured at (b) (4) (b) (4) polatuzumab vedotin drug substance (DS) will be manufactured (b) (4) (b) (4), the POLIVY drug product (DP) at (b) (4) (b) (4). Quality control testing will be performed as summarized in section E of this document. Pre-licensing inspections (PLI) were conducted at Genentech, Inc. and (b) (4) during the review cycle. The PLI for (b) (4) was waived. All facilities used for the manufacture and quality control testing were found acceptable for the proposed operations (refer to sections E and F of this document).

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in presence of polatuzumab vedotin at plasma concentrations.

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

[Draft Language]

Develop and validate an assay to evaluate the neutralizing capacity of anti-polatuzumab vedotin antibodies (ADA) detected in the patient samples. The assay should be capable of sensitively detect neutralizing ADA in the presence of polatuzumab vedotin levels that are expected to be present in serum at the time of patient sampling. The final report should include assay validation report and assay standard operating procedure.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 is a summary of product-related critical quality attributes (CQA), intrinsic to the molecule, that are relevant to the antibody intermediate (AI), drug substance (DS), and drug product (DP). The table includes the identification of the various attributes along with their risk management.

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

CQA (type)	Quality attribute	Risk ³	Origin	Control Strategy
Identity	Identity	Efficacy, Safety	Intrinsic to the Molecule	(b) (4)
Bioactivity/ Potency	Potency by Binding ⁴	Bioactivity, Efficacy, Safety	Intrinsic to the Molecule	

³ Based on Risk Ranking and Filtering assessment by the applicant and product-specific characterization and development studies.

⁴ Potency by binding is measured by separate methods for antibody intermediate (AI) and for antibody-drug conjugate (DS/DP)

CQA (type)	Quality attribute	Risk ³	Origin	Control Strategy
	Potency by Binding ³			(b) (4)
	Potency by Bioassay			
Size-related variants	HMW forms	Increased bioactivity (cytotoxicity) Potential impact to PK, Immunogenicity, and Safety.	Manufacturing process, storage	
	LMW forms (b) (4)	Potential impact on bioactivity, PK, and safety.		
Charge-Related Variants: Acidic Variants	Glycation (b) (4)	Potential impact on bioactivity	Manufacturing process. (b) (4)	
	(b) (4)		(b) (4)	
	(b) (4)	(b) (4)	(b) (4)	
	(b) (4)	No impact on binding or bioassay was observed. Potential impact to PK and safety.	(b) (4)	
Charge-Related Variants: Basic Variants	(b) (4)	Reduced bioactivity.	Manufacturing process, storage	
Oxidation-Related Variants		Reduced bioactivity. Potential impact to PK.	Manufacturing process	

CQA (type)	Quality attribute	Risk ³	Origin	Control Strategy
				(b) (4)
Glycosylation Variants	Afucosylation	Potential impact to safety (e.g., adverse events such as infusion-related reaction).	Glycosylation is an enzymatic process that occurs during the cell culture process.	(b) (4)
	High Mannose	Potential impact to PK and safety (off-target toxicity).		
Structural Variants	Free Thiol	(b) (4)	Cell culture process	(b) (4)
		Potential impact to bioactivity and PK		
	Other Cysteine forms and Trisulfides	(b) (4)		
		Potential impact on bioactivity and PK.		
Conjugation-Related Variants	Drug-to-Antibody Ratio (DAR)	(b) (4)	DS manufacturing process (conjugation)	

CQA (type)	Quality attribute	Risk ³	Origin	Control Strategy
		(b) (4)		(b) (4)
		Potential impact to PK.		
	Percent (%) Unconjugated Antibody (b) (4)	(b) (4)	DS manufacturing process (conjugation)	
		Potential impact to PK.		
	Drug Distribution	(b) (4)		
		Potential impact to PK.		
	Off-Target Conjugation	Potential impact to bioactivity (b) (4)	Off-target conjugation i.e., conjugation of vcMMAE to the polatuzumab antibody intermediate in locations other than the intended (b) (4)	
		Potential impact to PK.		
	Conjugation Site Distribution	(b) (4)	Off-target conjugation (b) (4)	

CQA (type)	Quality attribute	Risk ³	Origin	Control Strategy
		(b) (4)		
		Impact to PK and potential impact to safety.		

B. Antibody Intermediate [polatuzumab] Quality Summary

Table 2 provides a summary of the identification, risk, and lifecycle knowledge management for the antibody intermediate-specific CQAs.

Table 2: Antibody Intermediate CQA Process Risk Identification and Lifecycle Knowledge Management. (see example in Attachment 2)

CQA type	CQA	Risk	Origin	Control Strategy
Process-related impurities	Host Cell DNA	Potential impact to safety	Cell culture	(b) (4)
	Host Cell Proteins (HCP)	Potential impact to safety (e.g., possible AEs, such as anaphylactic reactions)	Cell culture	
	Leached (b) (4)	Leached (b) (4) could compete for Fc binding sites that mediate FcRn binding and may impact PK. Potential impact to PK, Immunogenicity, and safety	Purification (b) (4) (b) (4)	
	Leachables	Potential impact to safety (Immunogenicity)	Raw materials, product-contacting equipment and materials	
Microbial Control	Bioburden	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process	

CQA type	CQA	Risk	Origin	Control Strategy
	Endotoxin	Safety and Purity	Endotoxin can be introduced through raw materials and throughout the manufacturing process	(b) (4)
Adventitious Agents	General Viral Screening Assay	Safety and Purity	Raw materials, manufacturing process, facilities	
Composition and Strength	Protein Concentration	Bioactivity	Manufacturing process	
	Osmolality	Bioactivity	Formulation	
	pH	Bioactivity, stability	Formulation	
	Appearance (clarity and color)	Safety	Product, formulation	
	Polysorbate (PS) 20 Content	Safety	Formulation component	

- **Description:** Polatuzumab antibody intermediate (AI) is a humanized monoclonal antibody (mAb) of the IgG1 isotype that binds CD79b. It has a molecular weight of approximately 145 kDa.
- **Mechanism of Action (MoA):** The primary mechanism of action of polatuzumab AI is its binding to CD79b expressed on the surface of target cells.
- **Potency Assay:** "Potency by Binding," an enzyme-linked immunosorbent assay (ELISA) that measures the ability of polatuzumab AI to bind to CD79b.

- **Reference Materials:** A two-tiered reference standard (RS) system, consisting of a primary (batch 623445) and a secondary (batch 623444) RS, was established for commercial use. (b) (4)
reference standards were prepared from pooled polatuzumab AI batches 549103 and 550179. The primary RS is periodically evaluated per established stability protocols. A protocol for requalification of the primary and working reference standards and for the qualification of new reference standards are provided in the BLA. The current primary and working reference standards are suitable for their intended purposes.
- **Critical starting materials or intermediates:** Polatuzumab is produced by expression of recombinant DNA encoding the polatuzumab nucleotide sequence in a CHO (b) (4) cell line using standard cell culture techniques. (b) (4)
(b) (4)
- **Manufacturing process summary:** (b) (4)
- **Container closure:** Polatuzumab AI is stored (b) (4)
(b) (4).
- **Dating period and storage conditions:** (b) (4)

C. Drug/linker Intermediate [Maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl-monomethyl auristatin E [vcMMAE]] Quality Summary

Vedotin consists of monomethyl auristatin E (MMAE) and a protease-cleavable linker maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (mc-vc-PAB) that covalently attaches MMAE to the polatuzumab antibody. Reference is made to DMF (b) (4) for all information on the drug/linker intermediate and to the review(s) of this DMF.

Data supporting appropriate control of vcMMAE stability (hold-times), and limits on conjugatable impurities, residual solvents, and residual palladium discussed in the BLA drug substance manufacturing section were provided in the DMF and found acceptable by the ONDP assessor.

D. Drug Substance [polatuzumab vedotin] Quality Summary

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that derive from the drug substance manufacturing process and general drug substance attributes, including process-related impurities.

Table 4: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Quality attribute	Risk	Origin	Control Strategy	
Process-Related Impurities (conjugation)	(b) (4)	Potential impact to safety	DS manufacturing process (conjugation)	(b) (4)	
	(b) (4)	Potential impact to safety	DS manufacturing process (conjugation)		
	(b) (4)	(b) (4)			
	(b) (4)	(b) (4)			

CQA (type)	Quality attribute	Risk	Origin	Control Strategy
		Potential impact to bioactivity and immunogenicity.		(b) (4)
Process-Related Impurities	Leachables	Potential impact to safety (Immunogenicity)	Raw materials, product-contacting equipment and materials	
Microbial Control	Bioburden	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process	
	Endotoxin	Safety and Purity	Endotoxin can be introduced through raw materials and throughout the manufacturing process	
Content Composition and Strength	Protein concentration	Efficacy	Manufacturing process	
	pH	Stability, Safety	Formulation	
	Excipient Content	Stability, Safety	Formulation	
	Polysorbate (PS) 20 Content	Stability, Safety	Formulation	

- Description:** Polatuzumab vedotin contains a humanized IgG1 anti-CD79b mAb (polatuzumab AI) and monomethyl auristatin E (MMAE), linked through a protease-cleavable linker, maleimidocaproyl-valine-citrulline-p- aminobenzyloxycarbonyl (mc-vc-PAB). The linker-drug is bound to the reduced interchain cysteine residues of the Ab heavy and light chains through a thioether bond between the linker maleimide and the cysteine thiol group.

- **Mechanism of Action (MoA):** Upon binding CD79b, polatuzumab vedotin is rapidly internalized and the linker is cleaved by lysosomal proteases, leading to intracellular release of MMAE. The released MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.
- **Potency Assay:** Two potency methods relevant to the MOA are included in the commercial control strategy:
 - o Potency by Binding: ELISA that measures the ability of conjugated antibody to bind to CD79b
 - o Potency by Bioassay: Cell-based bioassay that measures the ability of conjugated antibody to kill CD79b+ cells
- **Reference Materials:** A two-tiered reference standard (RS) system, consisting of a primary and a secondary RS, was established for commercial use. Batch 608784 is used as the primary RS, and Batch 608785 is used as the secondary RS. (b) (4)
(b) (4)
(b) (4) A protocol for requalification of the primary and working reference standards and for the qualification of new reference standards are provided in the BLA. The current primary and working reference standards are suitable for their intended purposes.
- **Critical starting materials or intermediates:**
 - o Antibody Intermediate: Polatuzumab AI is manufactured and stored as described above.
 - o Drug-linker Intermediate: vcMMAE is manufactured and stored as described in the DMF.
- **Manufacturing process summary:** Polatuzumab antibody intermediate is conjugated (b) (4)
(b) (4)
- **Container closure:** Polatuzumab vedotin drug substance is stored in (b) (4)
(b) (4)
- **Dating period and storage conditions:** (b) (4) months at (b) (4)

E. Drug Product [POLIVY] Quality Summary:

Table 5 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 5: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Quality Attribute	Risk	Origin	Control Strategy (b) (4)
Particles	Visible particles	Safety, immunogenicity, and stability	Manufacturing process; storage	
	Subvisible particles			

				(b) (4)
Composition, Strength	Protein content	Stability	Manufacturing process; storage	
	pH			
	Osmolality			
	Moisture			
	Reconstitution time			
Physical Characteristics	Physical state and color of lyophilized (b) (4)		Lyophilization process, product, formulation	
	Color (of the reconstituted product)	Stability	Manufacturing process; storage; contamination	
	Clarity/Opalescence (of the reconstituted product)			
Microbial Control and Sterility Assurance	Sterility	Safety, Purity, and Efficacy (degradation or modification of the product by contaminant organisms)	Bioburden may be introduced throughout the manufacturing process.	
	Endotoxin	Safety and Purity	Endotoxin can be introduced through raw materials, throughout the manufacturing process.	
	Container closure integrity	Loss of sterility during the product shelf-life	Container closure breaches during manufacturing or storage	

- **Potency and Strength:** 140 mg of polatuzumab vedotin as a lyophilized powder in a single-dose vial.
- **Summary of Product Design:** Reconstitution of the drug product with 7.2 mL of SWFI yields (b) (4) reconstituted solution containing 20 mg/mL polatuzumab vedotin.
- **List of Excipients:** (b) (4) succinate, (b) (4) sucrose, (b) (4) polysorbate 20, pH 5.3.
- **Reference Materials:** Same as polatuzumab vedotin drug substance.
- **Manufacturing process summary:** The polatuzumab vedotin drug product is manufactured as a lyophilized dosage form in a (b) (4) vial configuration designed to deliver 140 mg drug product per vial. (b) (4)

(b) (4)

- (b) (4)
- (b) (4)
- **Container closure:** (b) (4) latex-free rubber stopper. (b) (4) Seal with (b) (4) Cap.
 - **Dating period and storage conditions:** 24 months at 2 – 8°C.

F. Novel Approaches/Precedents: None

G. Any Special Product Quality Labeling Recommendations:

1. Store in a refrigerator at 2-8°C
2. Protect from light
3. Do not freeze
4. Do not shake or agitate
5. If reconstituted product is not used immediately, store refrigerated (2-8°C) for up to 48 hours or at room temperature (9-25°C) for up to 8 hours prior to dilution.
6. If diluted product is not used immediately, store the diluted POLIVY solution:

Diluent Used to Prepare Solution for Infusion	Diluted POLIVY Solution Storage Conditions
0.9% Sodium Chloride Injection, USP	Up to 24 hours at 2°C to 8°C (36°F to 46°F) or up to 4 hours at room temperature (9 to 25°C, 47 to 77°F)
0.45% Sodium Chloride	Up to 18 hours at 2°C to 8°C (36°F to 46°F) or up to 4 hours at room temperature (9 to 25°C, 47 to 77°F)
5% Dextrose Injection, USP	Up to 36 hours at 2°C to 8°C (36°F to 46°F) or up to 6 hours at room temperature (9 to 25°C, 47 to 77°F)

H. Establishment Information:

Overall Recommendation: **Approval**

Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
• Manufacture of Antibody Intermediate • In-Process Control Testing (b) (4)	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080 USA	FEI 2917293 DUNS 080129000	NAI	N/A	Approval

Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
- Quality Control (release and stability) Testing - Release of Antibody Intermediate - Storage of Antibody Intermediate - Preparation and Storage of Master Cell Bank and Working					
In-Process Control Testing (b) (4)	Genentech, Inc. 1 Antibody Way Oceanside, CA 92056 USA	FEI 3006129086 DUNS 146373191	Adequate based on history	N/A	Approval
In-Process Control Testing (b) (4)		(b) (4)	Adequate based on history	N/A	Approval
In-Process Control Testing (b) (4)			Adequate based on history	N/A	Approval
- Additional Storage Site for Part of the Master Cell Bank - Additional Storage Site for Working Cell Bank			Adequate based on history	N/A	No Further Evaluation
- Manufacture of Drug Substance - In-Process Control Testing for Drug Substance - Quality Control Testing for Drug Substance (except potency) - Stability Testing for Drug Substance (except potency), - Quality Control Testing for Drug Product (except potency, sterility, and bacterial endotoxins),			VAI	1. Testing of (b) (4) is inadequate. 2. Storage of polatuzumab vedotin drug substance is inadequate.	Approval

Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Stability Testing for Drug Product (except potency and container closure integrity testing)				(b) (4)	
- Quality Control Testing for Drug Substance and Drug Product Potency, - Stability Testing for Drug Substance and Drug Product Potency, - Stability Testing of Drug Product Container Closure Integrity, - Quality Control Testing of Identity for Finished Drug Product, - Labeling and Secondary Packaging, - Release of Finished Drug Product	(b) (4)		Adequate based on history	N/A	Approval
	(b) (4)		Adequate based on history	N/A	Approval
Release of Drug Substance			Adequate based on history	N/A	Approval

Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
	CH-4051 Basel Switzerland	DUNS 482242971			
(b) (4)			Adequate based on history. OBP and DMA/DIA/OPF concurred with an Inspection Waiver.	N/A	Approval
• Labeling and Secondary Packaging	Genentech, Inc. 4625 NW Brookwood Pkwy Hillsboro, OR 97124 USA	FEI 3007232634 DUNS 833220176	Adequate based on history	N/A	Approval
(b) (4)			Adequate based on history	N/A	Approval
(b) (4)			Adequate based on history	N/A	Approval

I. Facilities:

- **Genentech, Inc.** (FEI: 2917293) in South San Francisco, USA is responsible for the manufacture of the polatuzumab antibody intermediate. A pre-license inspection (PLI) was conducted from 03/21/2019 to 03/27/2019. No Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. Final facility recommendation is "No Action Indicated (NAI)".

Final facility recommendation: Acceptable/ Approval

- (b) (4) is responsible for the manufacture of the polatuzumab vedotin Drug Substance. A PLI was conducted from (b) (4). A five item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. Final facility recommendation is "Voluntary Action Indicated (VAI)". In the firm's written response, the firm has committed to taking appropriate corrective actions to address the deficiency and was considered adequate.

Final facility recommendation: Acceptable/ Approval

- (b) (4) is responsible for the manufacture of the polatuzumab vedotin drug product. The facility was inspected as part of a PLI for (b) (4) drug substance and drug product and was conducted by CDER/OPQ/OPF (b) (4). A three-item FDA Form 483 was issued at the end of the inspection with a recommendation of VAI and found acceptable. The PLI for polatuzumab vedotin drug product was waived based on the firm's compliance history, its current acceptable GMP status, the District file review, and the fact that the facility, (b) (4) used for the proposed Polatuzumab vedotin drug product manufacture is currently approved for the manufacture of four other FDA-approved products including two antibody drug/toxin conjugates.
Final facility recommendation: Acceptable/ Approval

J. Lifecycle Knowledge Management:

a. Antibody Intermediate:

i. Protocols approved:

Protocol	Relevant Section	Regulatory Reporting
Stability monitoring of the MCB and WCB	Section S.2.3 Control of Materials—Cell Banking System, Characterization, and Testing (Polatuzumab Antibody Intermediate)	Not reportable ^a
Preparation of future primary and secondary reference standard	Section S.5 Reference Standard	Annual Report
Stability testing of reference standard	Section S.5 Reference Standard	Not reportable ^a
Primary stability program	Section S.7.1 Stability Summary (Polatuzumab Antibody Intermediate)	Annual Report ^b
Post-approval stability program	Section S.7.2 Post-Approval Stability Protocol and Stability Commitment (Polatuzumab Antibody Intermediate)	Annual Report ^b
(b) (4) verification/ (b) (4)	Regional	Not reportable ^a

a Results are documented internally (at the applicant's site) and available during inspection.

b Updated data will be provided in the Annual Report.

In addition, the applicant commits to providing the stability results for (b) (4) Batch 3257342 at end of shelf life in the Annual Report.

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None identified.

b. Drug Substance:

i. Protocols approved:

Protocol	Relevant Section	Regulatory Reporting
Primary stability program	Section S.7.1 Stability Summary (Polatuzumab Vedotin)	Annual Report ^b
Post-approval stability program	Section S.7.2 Post-Approval Stability Protocol and Stability Commitment (Polatuzumab Vedotin)	Annual Report ^b

a Results are documented internally (at the applicant's site) and available during inspection.
b Updated data will be provided in the Annual Report.

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None identified.

c. Drug Product

i. Protocols approved:

Protocol	Relevant Section	Regulatory Reporting
Container closure leachables stability study	Section P.2 Pharmaceutical Development-Container Closure	Annual Report ^b
Preparation of future primary and secondary reference standard	Section P.6 Reference Standard	Annual Report
Stability testing of reference standard	Section P.6 Reference Standard	Not reportable ^a
Primary stability program	Section P.8.1 Stability Summary	Annual Report ^b
Post-approval stability program	Section P.8.2 Post-Approval Stability Protocol and Stability Commitment	Annual Report ^b

a Results are documented internally (at the applicant's site) and available during inspection.
b Updated data will be provided in the Annual Report.

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None identified.

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: Antibody-Drug conjugate	x		
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application		x	
16.	Comparability Protocol(s)		x	
17.	End of Phase II/Pre-BLA Agreements	x		
18.	SPOTS (special products on-line tracking system)		x	
19.	USAN assigned name	x		
20.	Other: Breakthrough Therapy Designation, Orphan Drug, Priority Review with rolling submission	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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Rivera-Rosado

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Tran

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BLA STN 761121

POLIVI (polatuzumab vedotin-xxxx¹)

Genentech, Inc.

Jacek Cieslak, Ph.D., Chemist

Mate Tolnay, Ph.D., Biologist

Leslie A. Rivera Rosado, Ph.D., Application Team Lead

Christopher Downey, Ph.D., Review Chief

Division of Biotechnology Review and Research IV

¹ Review was completed prior to designation of the suffix.

OBP CMC Review Data Sheet

1. **BLA#:** STN 761121
2. **REVIEW DATE:** May 20, 2019
3. **PRIMARY REVIEW TEAM:**

Discipline	Reviewer	Branch/Division
Antibody Intermediate (AI)	Jacek Cieslak	CDER/OPQ/OBP/DBRR IV
vcMMAE Intermediate	Ben Zhang	CDER/OPQ/ONDP/DNDAPI/NDBI
Drug Substance (DS)	Mate Tolnay	CDER/OPQ/OBP/DBRR IV
Drug Product (DP)		
Immunogenicity assays	Mate Tolnay and Frederick Mills	
Labeling	Vicky Borders-Hemphill	CDER/OPQ/OBP
Facility	Michael Shanks Zhihao Peter Qiu	CDER/OPQ/OPF/DIA
Microbiology	Diane Raccasi (AI/DS) Reyes Candau-Chacon (DP)	CDER/OPQ/OPF/DMA IV
Team Leads	LCDR Leslie A. Rivera Rosado (Product quality) Peter Qiu (Facilities) Reyes Candau-Chacon (Micro, AI/DS) Patricia Hughes (Micro, DP) Suong T Tran (Small molecule)	CDER/OPQ/OBP/DBRR IV CDER/OPQ/OPF/DIA CDER/OPQ/OPF/DMA IV CDER/OPQ/OPF/DMA IV CDER/OPQ/ONDP/DNDAPI/NDBI
Application Team Lead	LCDR Leslie Ann Rivera Rosado	CDER/OPQ/OBP/DBRR IV
Regulatory Business Project Manager	Anita Brown	CDER/OPQ/OPRO
RPM	Wanda Nguyen	CDER/OND/OHOP/DHP
Cross-disciplinary Team Lead	Angelo de Claro	CDER/OND/OHOP/DHP
Medical Officer	Yvette Kasamon	CDER/OND/OHOP/DHP
Pharm/Tox	Natalie Simpson Ramadevi Gudi/Christopher Sheth	CDER/OND/OHOP/DHOT
Clinical Pharmacology	Saladeldin Hamed/Ruby Leong	CDER/OTS/OCP/DCPV
Statistics	Alexei Ionan/Jingjing Ye	CDER/OTS/OB/DBV

4. **MAJOR GRMP DEADLINES**
 - Filing Meeting:** February 6, 2019
 - Mid-Cycle Meeting:** March 20, 2019
 - Wrap-Up Meeting:** July 10, 2019
 - Primary Review Due:** May 20, 2019
 - Secondary Review Due:** May 24, 2019
 - CDTL Memo Due:** July 22, 2019
 - PDUFA Action Date:** August 19, 2019

5. COMMUNICATIONS WITH APPLICANT AND OND:

Communication/Document	Date
Pre-BLA Meeting	3/27/2018
Information Request #1: DIA	1/11/2019
Information Request #2: DMA	2/1/2019
Information Request #3 – DMF correction	2/6/2019
Internal meeting: Filing	2/6/2019
Information Request #4: DMA	3/19/2019
Internal meeting: Mid-cycle	3/20/2019
Mid-cycle communication with applicant	3/25/2019
Internal meetings: Labeling	4/9/2019; 4/16/2019; 4/18/2019; 5/1/2019
Information Request #5: OBP	4/15/2019
Information Request #6: OBP/DMA	4/22/2019
Information Request #7: OBP/DMA	5/13/2019

6. SUBMISSION(S) REVIEWED:

Submission(s) Reviewed	Document Date	Review Completed (Yes/No)
STN 761121/1- BLA Original Application	11/20/2018	Yes
STN 761121/2- BLA Original Application (CMC module)	12/19/2018	Yes
STN 761121/8- Quality/ Response to Information Request	1/15/2019	Yes
STN 761121/15- Quality/ Response to Information Request	2/7/2019	Yes
STN 761121/17- Quality/ Addition of section 3.2.S.1 for the veMMAE intermediate	2/8/2019	Yes
STN 761121/34- Quality/ Response to Information Request and Labeling	4/5/2019	Yes
STN 761121/37- Labeling/Package Insert	4/15/2019	Yes
STN 761121/39- Quality/ Response to Information Request	4/19/2019	Yes
STN 761121/41- Quality/ Response to Information Request	4/26/2019	Yes
STN 761121/42- Multiple categories/ Labeling Revisions (carton and container)	4/29/2019	Yes
STN 761121/46 - Quality/ Response to Information Request	5/17/2019	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: POLIVY

Non-Proprietary/USAN/ INN: Polatuzumab vedotin

CAS name: 1313206-42-6

Common name: Immunoglobulin G1, anti-(human antigen CD79b) (human-Mus musculus monoclonal MCDS4409A heavy chain), disulfide with human-Mus musculus monoclonal MCDS4409A κ-chain, dimer, thioether with maleimidocaproyl-valinecitruilline- p - aminobenzyloxycarbonyl monomethylauristatin E

OBP systematic name²: CONJ:MAB HUMAN (IGG1) ANTI P40259 (CD79B_HUMAN); Mono-methyl auristatin E [DCDS4501A]

² The OBP systematic name allows searching for related products in OBP's database and in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS) for safety reasons and it is different from the nonproprietary name. The tag at the end is used to separate products from different sponsors and it is generally the name used by sponsors to refer to the proposed product in their submissions.

Other Names: DCDS4501A, DCDS4501S, RO5541077, FCU2711, GNT-038, aCD79b-vcMMAE, MCDS4409A-VC-MMAE

8. PHARMACOLOGICAL CATEGORY: CD79b-directed antibody–drug conjugate

9. DOSAGE FORM: For injection: 140 mg lyophilized (b) (4) in a single-dose vial.

10. STRENGTH/POTENCY:

(i) The concentration/strength of the Drug Product: 140 mg/vial; reconstituted vial contains 20 mg/mL polatuzumab vedotin

(ii) Type of potency assay (s):

o Potency by Binding: ELISA

o Potency by Bioassay: Cell-based bioassay

11. ROUTE OF ADMINISTRATION: Intravenous

12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Authorization	COMMENTS (STATUS)
(b) (4)	(b) (4)	vcMMAE intermediate	Yes	Adequate
		(b) (4)	Yes	Adequate
		(b) (4)	Yes	Not reviewed, enough information was provided in the BLA
		(b) (4)	Yes	
		(b) (4)	Yes	Adequate

13. INSPECTIONAL ACTIVITIES

Genentech, Inc. (FEI: 2917293) in South San Francisco, USA is responsible for the manufacture of the polatuzumab antibody intermediate. A pre-license inspection (PLI) was conducted from 03/21/2019 to 03/27/2019. No Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. Final facility recommendation is “No Action Indicated (NAI)”. **Final facility recommendation: Acceptable/ Approval**

(b) (4) is responsible for the manufacture of the polatuzumab vedotin Drug Substance. A PLI was conducted from (b) (4). A five item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. Final facility recommendation is “Voluntary Action Indicated (VAI)”. In the firm’s written response, the firm has committed to taking appropriate corrective actions to address the deficiency and was considered adequate. **Final facility recommendation: Acceptable/ Approval**

(b) (4) is responsible for the manufacture of the polatuzumab vedotin drug product. The facility was inspected as part of a PLI for (b) (4) drug

substance and drug product and was conducted by CDER/OPQ/OPF on (b) (4). A three-item FDA Form 483 was issued at the end of the inspection with a recommendation of VAI and found acceptable. The PLI for polatuzumab vedotin drug product was waived based on the firm's compliance history, its current acceptable GMP status, the District file review, and the fact that the facility, (b) (4) used for the proposed Polatuzumab vedotin drug product manufacture is currently approved for the manufacture of four other FDA-approved products including two antibody drug/toxin conjugates. **Final facility recommendation: Acceptable/ Approval**

14. CONSULTS REQUESTED BY OBP

None

15. QUALITY BY DESIGN ELEMENTS

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

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

- A risk-based approach was applied to evaluate the robustness of the antibody intermediate formulation, utilizing the results from a multi-parameter design of experiments (DOE) study, development studies, primary stability studies, and a risk ranking and filtering (RRF) assessment.
- The (b) (4) parameter acceptable ranges were established by RRF, limits of the control capability of the v1.0 manufacturing process, or manufacturing experience observed during clinical manufacture of the v1.0 process.
- The conjugation parameter acceptable ranges were based on RRF (including prior knowledge), control capability of the v1.0 manufacturing process, or a scale-down process parameter validation study.
- Product variants and process-related impurity CQAs are identified using an RRF tool that evaluates the impact of each product quality attribute on patient safety and product efficacy.

16. PRECEDENTS

None

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Christopher Downey, Ph.D. Review Chief Division of Biotechnology Review and Research IV (DBRR IV) Office of Biotechnology Products (OBP) Office of Pharmaceutical Quality (OPQ)	See attached
LCDR Leslie Ann Rivera Rosado Product Quality Team Leader DBRR IV, OBP, OPQ	See attached
Jacek Cieslak, Ph.D. Product Quality Reviewer DBRR IV, OBP, OPQ	See attached
Mate Tolnay, Ph.D. Product Quality Reviewer DBRR IV, OBP, OPQ	See attached

B. CC Block

Recipient	Date
Wanda Nguyen Clinical Division BLA RPM	
OBP/DBRR IV/File/BLA STN 761121	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products (OBP) recommends approval of the BLA 761121 for POLIVY (polatuzumab vedotin) manufactured by Genentech, Inc. The data submitted in this Biologics License Application support the conclusion that the manufacture of POLIVY (polatuzumab vedotin) is well controlled and leads to a product that is pure and potent. The product is free of 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 multiple production runs. It is recommended that POLIVY (polatuzumab vedotin) be approved for human use under conditions specified in the package insert.

- We recommend an expiration dating period of (b) (4) months for polatuzumab intermediate when stored at (b) (4).
- We recommend an expiration dating period of (b) (4) months for polatuzumab vedotin drug substance when stored at (b) (4).
- We recommend an expiration dating period of 24 months for polatuzumab vedotin drug product when stored at 2-8°C.
- We recommend approval of the proposed release and shelf-life test methods and specifications for polatuzumab intermediate and polatuzumab vedotin drug substance and drug product.

II. List of Deficiencies To Be Communicated

Not applicable.

III. List of Post-Marketing Commitments

PMC recommended by OBP [Draft Language]:

Develop and validate an assay to evaluate the neutralizing capacity of anti-polatuzumab vedotin antibodies (ADA) detected in the patient samples. The assay should be capable of sensitively detect neutralizing ADA in the presence of polatuzumab vedotin levels that are expected to be present in serum at the time of patient sampling. The final report should include assay validation report and assay standard operating procedure.

IV. Review of Common Technical Document-Quality Module 1

Environmental Assessment or Claim of Categorical Exclusion

The applicant claims a categorical exclusion from the requirement to prepare an environmental assessment in accordance with both 21 CFR 25.31(b), which applies to the small molecule linked to the biological, and 21 CFR 25.31(c). The Sponsor states that no extraordinary circumstances exist with respect to this product. There is no indication that additional environmental information is warranted. The claim of categorical exclusion is deemed acceptable.

V. Primary Container Labeling Review

Refer to review by CAPT 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

The immunogenicity screening plan is multi-tiered and overall appropriate. Adequately validated screening and confirmatory assays are used to assess the immune response in patients. Rituximab was demonstrated not to interfere with the assays. The drug tolerance of the assay, up to 20 µg/ml, is adequate. Positive samples are further characterized by determining the titer and specificity of the response. The assay used to determine specificity distinguishes the response against the antibody versus other components. There is currently no neutralizing antibody assay; this should be a PMC.

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

Polatuzumab vedotin is an antibody–drug conjugate (ADC) that contains a humanized immunoglobulin G1 (IgG1) anti-CD79b monoclonal antibody (polatuzumab antibody intermediate; MCDS4409A) and a potent antimitotic agent, monomethyl auristatin E (MMAE), linked through a protease-cleavable linker, maleimidocaproyl-valine-citrulline-paminobenzyloxycarbonyl (mc-vc-PAB). The antimitotic agent and linker are referred to as the linker-drug, vcMMAE. Polatuzumab vedotin drug product is provided in single-dose (b) (4) vials as a sterile, white to grayish-white lyophilized (b) (4) and contains no preservatives. It is intended for intravenous infusion after reconstitution with sterile water for injection (SWFI) and dilution in 0.9% sodium chloride solution, 0.45% sodium chloride solution, or 5% dextrose solution.

S. DRUG SUBSTANCE (Polatuzumab Antibody Intermediate (AI)) [reviewed by JC]

During development, three versions of the antibody intermediate (AI) manufacturing process were used: toxicology, v0.1, and v1.0. These different process versions reflect changes introduced to ensure appropriate purity and product quality, improve process stability and robustness, simplify manufacturing operations, meet facility fit requirements, and increase productivity. The applicant stated that the impacts of these process changes were assessed in phase-appropriate comparability studies that demonstrated suitability of the antibody intermediate for intended use throughout process development.

Reviewer comment:

The comparability between the AI batches manufactured from the toxicology process, process v0.1 and process v1.0 was demonstrated in the original IND submission and the IND amendments (IND 109409 submitted on 01/07/2011, [review](#) in DARRTS dated 02/02/2011). No new information was provided in the BLA regarding the comparability between toxicology process and process v0.1 and between process v0.1 and process v1.0 that was not already submitted and reviewed under IND 109409. Therefore, the comparability between product manufactured using these processes has been demonstrated.

3.2.S.1 General Information

3.2.S.1.2 Structure

MCDS4409A is a humanized monoclonal antibody based on a human immunoglobulin G1 (IgG1) framework containing heavy chain (HC) V_HIII and light chain (LC) V_LkI subgroup sequences. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two HCs (gene encodes 447 amino acid residues each) and two LCs (218 amino acid residues each). MCDS4409A is also referred to as polatuzumab antibody intermediate (AI).

The calculated molecular mass of intact antibody intermediate is 145,001 Da (peptide chains only, without HC C-terminal lysine residues and with no glycosylation). The LC and HC sequences of antibody intermediate are shown in Figure S.1.2-1 and Figure S.1.2-2, respectively (refer to [Section 3.2.S.1.2 Structure](#) in the BLA submission).

3.2.S.1.3 General Properties

Polatuzumab AI is produced using established expression techniques in Chinese hamster ovary cell culture (b) (4) as described in Section S.2.2 *Description of Manufacturing Process and Process Controls (Polatuzumab Antibody Intermediate)*. The general properties of the antibody intermediate are listed in Table S.1.3-1 below.



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Mate
Tolnay

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Jacek
Cieslak

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PRODUCT QUALITY MICROBIOLOGY ASSESSMENT AND EVALUATION

ASSESSOR: Reyes Candau-Chacon, PhD
SECONDARY ASSESSOR: Patricia Hughes, Ph.D.

BLA:	761121/0
Applicant:	Genentech, Inc.
US License Number:	1048
Submission	Original 351a BLA
Product:	polatuzumab vedotin (POLIVY)
Indication:	(b) (4)
Dosage Form:	140 mg/vial, lyophilized (b) (4) for intravenous use after reconstitution in a single-dose (b) (4) vial
Manufacturing Sites:	(b) (4)
FDA Receipt Date:	12/19/2018
Action Date:	6/19/2019

Conclusion and Approvability Recommendation

The drug product part of this BLA is recommended for approval from a sterility assurance and product quality microbiology perspective.

Product Quality Microbiology Assessment: Drug Product

Genentech has submitted this new Biologics License Application (BLA) for polatuzumab vedotin, an antibody drug conjugate (ADC) consisting on an anti-mitotic agent (monomethyl auristatin E, MMAE) linked to a CD79b-immunoglobuline G1. The ADC is targeted to B cells, and upon binding, it internalizes, the linker is cleaved by proteases, and MMAE is released, inhibiting cell division and inducing apoptosis.

The drug product (DP) is manufactured (b) (4). This application contains CMC information in an eCTD format. This assessment is limited to the manufacturing process of polatuzumab vedotin drug product section of the BLA from a sterility assurance and product quality microbiology perspective.

Drug Product Quality Microbiology Information Assessed

Sequence number	Date	Description
0002	12/19/2019	Last part of the rolling submission, including Module 3
0034	04/05/2019	Response to FDA IR sent on March 19, 2019
0041	04/26/2019	Response to FDA IR sent on April 22, 2019
0046	5/17/2019	Response to FDA IR sent on May 14, 2019
0047	5/20/2019	Response to FDA IR sent on May 20, 2019

Assessor's comment: Information (b) (4) is included in DMF

(b) (4) The DMF was assessed on 8/31/2017 and deemed adequate.

Module 1

1.14 Labeling

Section 2.4 of the label indicates that POLIVY must be reconstituted with 7.2 mL sWFI immediately before dilution in an infusion bag containing 0.9% sodium chloride, 0.45% sodium chloride, or 5% dextrose. The infusion is administered using a dedicated line with a sterile 0.2-µm filter.

If the reconstituted solution is not used immediately, it may be stored refrigerated (2°C to 8°C) for up to 36 hours, or at room temperature (9°C to 25°C) for up to 6 hours.

The solution for infusion may be stored as indicated in Table 4 from the label, duplicated below.

Diluent Used to Prepare Solution for Infusion	Solution for Infusion Storage Conditions*
0.9% Sodium Chloride	Up to 24 hours at 2°C to 8°C (36°F to 46°F) or up to 4 hours at room temperature (9 to 25°C, 47 to 77°F)
0.45% Sodium Chloride	Up to 18 hours at 2°C to 8°C (36°F to 46°F) or up to 4 hours at room temperature (9 to 25°C, 47 to 77°F)
5% Dextrose	Up to 36 hours at 2°C to 8°C (36°F to 46°F) or up to 6 hours at room temperature (9 to 25°C, 47 to 77°F)

* To ensure product stability, do not exceed specified storage durations.

Assessor's comment: Information to support the reconstitution and dilution hold times is included in section 3.2.P.2 of the BLA (Compatibility). The reconstitution and dilution times are supported by growth promotion data.

Module 3.2

P.1 Description of the Composition of the Drug Product

Polatuzumab vedotin drug product is supplied in a single-dose (b) (4) vial as a sterile lyophilized (b) (4) without preservatives to deliver 140 mg of polatuzumab vedotin. Refer to assessment of the label for reconstitution and dilution details. The final composition of the reconstituted drug product is the same as the formulated drug substance and includes 20 mg/mL polatuzumab vedotin in (b) (4) succinate, (b) (4) sucrose, (b) (4) polysorbate 20, pH 5.3.

Assessor's comment: The description of the DP composition is adequate.

P.2 Pharmaceutical Development

This section includes the location of the information to support microbial control and sterility assurance of the DP. In addition, microbial proliferation studies in support of the label are included in this section under “compatibility”.

Assessor's comment: The reconstitution and dilution times in the original submission were not supported by growth promotion data. The applicant lowered the reconstitution and dilution times in amendment 0034 as response to an FDA information request and modified the label accordingly (the modified reconstitution and dilution times are reflected in the Table in section 1.14 of this assessment). In addition, the sponsor indicated that potential concerns of confusion by the health provider due to the multiple dilution times for the different infusion solutions is mitigated by including them in a table, however that is out of the scope of this assessment. The amendment also included a change of transportation of the diluted solution for infusion (b) (4) to 12 hours. In amendment 0041, the applicant added a statement below the table to indicate that the total storage plus transportation times of the diluted drug product should not exceed the times indicated in the table. This statement was added as a response to an FDA information request. Maximum times after reconstitution and dilution indicated in the label are supported by microbial data.

SATISFACTORY

P.2 Pharmaceutical Development

P.2.4 Container Closure System

The container closure system of the polatuzumab vedotin drug product consists of:

- (b) (4) vial (USP/Ph. Eur./JP)
- (b) (4) rubber stopper, (b) (4) (USP/Ph. Eur./JP)
- (b) (4) cap

Assessor's comment: The description is adequate. Information on leachables and extractables is deferred to OBP.

SATISFACTORY

(b) (4)

P.7 Container Closure System

The container closure is a (b) (4) latex-free (b) (4) stopper, and a (b) (4) seal with a (b) (4) cap.

Assessor's comment: The description of the container closure system is adequate.

P.8 Stability

Recommended long-term storage conditions are 2 to 8°C, protected from the light for up to 24 months

Container closure integrity of the product stored at the recommended conditions is tested annually using a validated dye-ingress method. Vials tested in the stability program passed the tested after 12 months. In addition, CCI was tested after a 50/75 temperature cycling study and resulted in no dye ingress.

SATISFACTORY

Conclusion

- I. The drug product section of the BLA, as amended, is recommended for approval from a sterility assurance and product quality microbiology perspective.
- II. Information and data in this submission not related to drug product sterility assurance and product quality microbiology perspective were not evaluated and should be reviewed by an OBP reviewer.
- III. Refer to Panorama for CGMP status of the relevant facilities.



Patricia
Hughes Troost

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Food and Drug Administration
Center for Drug Evaluation and Research
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Silver Spring, MD 20993

To: Administrative File, STN 761121
From: Diane Raccasi, Reviewer, CDER/OPQ/OPF/DMA/Branch IV
Through: Reyes Candau-Chacon, Ph.D. Quality Assessment Lead, CDER/OPQ/OPF/DMA/Branch IV
Subject: New Biologic License Application (BLA)
US License: 1048
Applicant: Genentech, Inc.
Facilities: Genentech, Inc., 1 DNA Way, South San Francisco, CA, USA (FEI 2917293)
(b) (4)
Product: Polatuzumab vedotin
Dosage: 140mg/Vial, Intravenous Use, Lyophilized (b) (4)
Indication: Treatment of adult patients with diffuse large B-cell lymphoma
Due date: May 20, 2019

Recommendation for Approvability: The drug substance part of BLA 761121 is recommended for approval from a microbial control and microbiology product quality perspective.

Review Summary

Genentech, Inc., submitted BLA 761121 to license Polatuzumab vedotin and the associated antibody intermediate, and drug substance manufacturing processes. This review contains the microbiology drug substance quality assessment of the manufacturing process of Polatuzumab vedotin bulk drug substance. All other aspects of the submission are deferred to OBP.

BLA 761121 was submitted in eCTD on December 19, 2018 in electronic format under sequence 0002.

Drug Product Quality Microbiology Information Reviewed

Description	eCTD	Date
Original BLA	0002	December 19, 2018
Information request #7	0046	May 17, 2019

Review Narrative

S DRUG SUBSTANCE ANTIBODY INTERMEDIATE

S.1 General Information

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Conclusion

- I. The Drug Substance section of this BLA, as amended, was reviewed from a microbial control and microbiology product quality perspective and it is recommended for approval.
- II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the appropriate division.
- III. A pre-license inspection of Genentech was conducted from March 25-29, 2019; a pre-license inspection of (b) (4) was conducted from (b) (4).

Appears this way on original



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Raccasi

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Reyes
Candau-Chacon

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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 REVIEW

Date of review:	June 3, 2019
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Mate Tolnay, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761121
Applicant:	Genentech, Inc
Submission Date:	December 19, 2018
Product:	Polivy (polatuzumab vedotin-piiq)
Dosage form(s):	For injection
Strength and Container-Closure:	140 mg/vial in a single-dose vial
Purpose of review:	The Applicant submitted a biologics license application for Agency review
Recommendations:	The prescribing information, container labels, and carton labeling submitted on May 28, 2019 are acceptable from an OBP labeling perspective.

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

n/a = not applicable for this review

DISCUSSION

We evaluated the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations (see Appendix B).

CONCLUSION

The prescribing information, container labels, and carton labeling submitted on May 28, 2019 were reviewed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on December 19, 2018

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Container Labels (submitted on December 19, 2018)

(b) (4)

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Appendix B: Evaluation Tables

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

Container⁴ Label Evaluation

Proper Name	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
Manufacturer name, address, and license number	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
Lot number or other lot identification	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	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</i> <i>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
Beyond Use Date (Multiple-dose containers)	Acceptable

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.

<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A
<u>Product Strength</u>	<u>Acceptable</u>
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
<u>Multiple-dose containers (recommended individual dose)</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55	☐ Yes ☐ No ☒ N/A
<u>Statement: "Rx only"</u>	<u>Acceptable</u>
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 Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A
<u>Medication Guide</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A
<u>No Package for container</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A
<u>No container label</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A
<u>Ferrule and cap overseal (for vials only)</u>	<u>Acceptable</u>
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. <i>The Applicant confirms there is no text on the ferrule and cap overseal of the vials.</i>	
<u>Visual inspection</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.60(e)	☒ Yes

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located <i>The Applicant confirms there is sufficient area of the container remains uncovered for the label's full length or circumference to permit full inspection of the vial contents.</i> (b) (4)	☐ No ☐ N/A
<u>NDC numbers</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
<u>Route of administration</u>	<u>Acceptable</u>
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
<u>Preparation instructions</u>	<u>Acceptable</u>
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: <i>see carton for instructions for reconstituting the product and the resultant concentration (XX mg/mL)</i>	
<u>Package type term</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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
<u>Misleading statements</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A
<u>Prominence of required label statements</u>	<u>Acceptable</u>

Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A
<u>Spanish-language (Drugs)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
<u>Bar code label requirements</u>	<u>Acceptable</u>
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
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
<u>Net quantity</u>	<u>Acceptable</u>
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
<u>Statement of Dosage</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise (b) (4) to read "Dosage: See Prescribing Information" <i>The Applicant revised as requested</i>	
<u>Inactive ingredients</u>	<u>Acceptable</u>

Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: see carton	
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A
Storage requirements	Acceptable
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Dispensing container	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package⁵ Label Evaluation

Proper name	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	☒ Yes ☐ No ☐ N/A
Manufacturer name, address, and license number	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
Lot number or other lot identification	Acceptable
Regulation: 21 CFR 610.61(c)	☒ Yes ☐ No ☐ N/A
Expiration date	Acceptable
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
Beyond Use Date (Multiple-dose containers)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

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.

Preservative	Acceptable
Regulation: 21 CFR 610.61(e)	☒ Yes ☐ No ☐ N/A
Number of containers	Acceptable
Regulation: 21 CFR 610.61(f)	☒ Yes ☐ No ☐ N/A
Product Strength	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 Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Storage temperature/requirements	Acceptable
Regulation: 21 CFR 610.61(h)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Remove the following redundant statement that appears on the side panel with the storage information: (b) (4) (b) (4) since this statement already appears on the side panel that contains the ingredient information. Revise the storage information as follows: "Store vial refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light prior to reconstitution. Reconstitute immediately before dilution. If needed after reconstitution, store unused reconstituted solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 48 hours or at room temperature (9°C to 25°C, 47°F to 77°F) up to a maximum of 8 hours prior to dilution. Discard vials of unused reconstituted solution if cumulative storage time exceeds 48 hours. Do not freeze." <i>The Applicant revised as requested</i>	
Handling: "Do Not Shake", "Do not Freeze" or equivalent	Acceptable
Regulation: 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A
Multiple dose containers (recommended individual dose)	Acceptable
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A
Route of administration	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
<u>Known sensitizing substances</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A
<u>Inactive ingredients</u>	<u>Acceptable</u>
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> <i>Comment/Recommendation:</i> Revise the inactive ingredient list to read as follows: "Each single-dose vial delivers 140 mg of polatuzumab vedotin-piiq, polysorbate-20 (8.4 mg), sodium hydroxide (3.80 mg), succinic acid (8.27 mg), sucrose (288 mg)." <i>The Applicant revised as requested</i>	☒ Yes ☐ No ☐ N/A
<u>Source of the product</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A
<u>Minimum potency of product</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.61(r)	☒ Yes ☐ No ☐ N/A
<u>Rx only</u>	<u>Acceptable</u>
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
<u>Divided manufacturing</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A
<u>Distributor</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Bar code	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
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
NDC numbers	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
Preparation instructions	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> Comment/Recommendation: Revise the preparation instructions (b) (4) to read as follows: "Reconstitute each Polivy vial with 7.2 mL of Sterile Water for Injection, USP to obtain a concentration of 20 mg/mL of polatuzumab vedotin-piiq with a pH of 5.3. Gently swirl. Do not shake." This will allow deletion of (b) (4) (b) (4) <i>The Applicant revised as requested</i>	☒ Yes ☐ No ☐ N/A
Package type term	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
Misleading statements	Acceptable
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A
Prominence of required label statements	Acceptable
Regulation: 21 CFR 201.15	☒ Yes

	☐ No ☐ N/A
<u>Spanish-language (Drugs)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
<u>Phenylalanine as a component of aspartame</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A
<u>Sulfites; required warning statements</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A
<u>Net quantity</u>	<u>Acceptable</u>
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
<u>Statement of Dosage</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2) Comment/Recommendation: Revise (b) (4) to read "Dosage: See Prescribing Information" <i>The Applicant revised as requested</i>	☒ Yes ☐ No ☐ N/A
<u>Dispensing container</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A
<u>Medication Guide</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Prescribing Information and Patient Labeling 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: Once the four-letter suffix is approved, apply the four-letter suffix to the nonproprietary name on all labels and labeling. route of administration in the product title to appear in all lower case. <i>The Applicant revised as requested</i> Revise all letters in the route of administration to appear in lower case, include the entire product title on a single line with wrapping text if needed. We revised the dosage form and route of administration in the product title to appear in all lower case. <i>The Applicant revised as requested</i>	
DOSAGE AND ADMINISTRATION	Acceptable
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i>	☐ Yes ☐ No ☒ N/A
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: "for injection" dosage forms are described as "lyophilized powders" in human drug product labeling for injectable products. The appearance of the lyophilized powder may be further described as having a cake-like appearance, which may be helpful for the health care provider when following instructions for preparation of the lyophilized powder, as in section 2 of the FPI or to provide additional information about the appearance of the powder in section 11. We revised (b) (4) to "lyophilized powder". <i>The Applicant revised as requested</i>	
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> Comment/Recommendation: We revised the diluent and intravenous solutions to USP nomenclature <i>The Applicant revised as requested</i> We deleted (b) (4) from appearing as the last bullet under "Reconstitution" subsection in section 2.4 since the instructions to withdraw the volume from the reconstituted vial occurs in the dilution subsection below. <i>The Applicant revised as requested</i> We revised the name of Table 4. (b) (4) to read "Diluted POLIVY Solution Storage Conditions" for clarity and consistency. <i>The Applicant revised as requested</i>	☒ Yes ☐ No ☐ N/A
3 DOSAGE FORMS AND STRENGTHS	Acceptable
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: We deleted (b) (4) as this is not required information for this section. <i>The Applicant revised as requested</i>	
<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> Comment/Recommendation: We revised (b) (4) to "lyophilized powder". <i>The Applicant revised as requested</i>	☒ Yes ☐ No ☐ N/A
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
Comment/Recommendation: We added the dosage form "for injection". <i>The Applicant revised as requested</i>	
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: We deleted (b) (4) since it discusses the drug substance.

The Applicant revised as requested

We revised (b) (4) to "lyophilized powder".

The Applicant revised as requested

We revised (b) (4) to "intravenous infusion" for clarity and consistency.

The Applicant revised as requested

We relocated the amounts of the inactive ingredients to appear in parenthesis after the representative inactive ingredient to differentiate the active ingredient from the inactives.

The Applicant revised as requested

We revised (b) (4) to "the final concentration is 20 mg/mL with a pH of approximately 5.3" and relocated (b) (4)

The Applicant revised as requested

16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
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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: We revised (b) (4) to "lyophilized powder".

The Applicant revised as requested

We deleted (b) (4) since this is not required information for this section.

The Applicant revised as requested

We deleted (b) (4) and added "140 mg" to appear in front of "single-dose vial".

The Applicant revised as requested

MANUFACTURER INFORMATION	Acceptable
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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



Vicky
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 6/03/2019 09:52:17AM
GUID: 50814c7000007a3d59329f660d8ddf02



Mate
Tolnay

Digitally signed by Mate Tolnay
Date: 6/03/2019 09:58:09AM
GUID: 508da6d8000263782a9fcccefaa2c6f0
Comments: Thank you.

BLA MANUFACTURING FACILITY ASSESSMENT

Application ID	BLA 761121
Drug Product Name	polatuzumab vedotin
Strengths	140 mg/vial
Dosage Form	Lyophilized (b) (4)
Administration Route	Intravenous Use
Indication	(b) (4)
Applicant Name	Genentech, Inc.
US License Number	1048
Application Type	351 (a)

I. Manufacturing Summary

Facility Assessment Recommendation: Approval

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) Genentech, Inc. (FEI 2917293), (b) (4) proposed for linker-drug intermediate, polatuzumab vedotin DS intermediate, 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.

Assessment Summary:

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
BLA-761121-ORIG-01	12/19/2018

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): N/A

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No
Choose lifecycle consideration topic(s)	



Michael
Shanks

Digitally signed by Michael Shanks

Date: 5/09/2019 02:49:05PM

GUID: 530ccee5000e6dd4f24ae71fb1d5aaa5



Zhihao Peter
Qiu

Digitally signed by Zhihao Peter Qiu

Date: 5/10/2019 08:02:23AM

GUID: 508da7480002bfb5825e149b2b4eb91d

CHAPTER I: DRUG SUBSTANCE

SGD-1006 (SG6) (or vcMMAE) DRUG SUBSTANCE INTERMEDIATE

Assessment Recommendation: Adequate

Assessment Summary: The Applicant references all CMC information on this drug-linker intermediate to DMF (b) (4). This DMF has been reviewed and found adequate to support the BLA application. BLA 761121 does not include any information on this compound.

List Submissions being assessed (*Table*):

Document(s) Assessed	Date Received
Original Submission	11/20/2018

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (*List bullet points with key information and update as needed*): N/A

Primary Drug Substance Assessor Name and Date: Ben Zhang, 03/22/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed):



Ben
Zhang

Digitally signed by Ben Zhang
Date: 5/08/2019 08:33:39AM
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Su (Suong)
Tran

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Date: 5/08/2019 10:41:08AM
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/s/

WANDA D NGUYEN
06/10/2019 11:43:11 AM