CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761208Orig1s000

PRODUCT QUALITY REVIEW(S)

Priority Review

Recommendation: BLA Approval

BLA/NDA Number: 761208
Assessment Number: 1
Assessment Date: August 24, 2021

Drug Name/Dosage Form	tivdak (tisotumab vedotin-tftv) for injection
Strength/Potency	40 mg/vial
Route of Administration	Intravenous infusion (IV)
Rx/OTC dispensed	Rx
Indication	(b) (4)
Applicant/Sponsor	Seagen Inc.

Product Overview:

Tisotumab vedotin, also referred to as HuMax®-TF-ADC is an antibody drug conjugate (ADC) directed to tissue factor (TF), a cell surface protein expressed at elevated levels on a variety of solid tumors relative to normal tissue. The antibody, tisotumab is a human IgG1κ antibody composed of two kappa light chains and two IgG1 heavy chains expressed in Chinese hamster ovary (CHO) cell line. The small molecule drug, monomethyl auristatin E (MMAE) is a microtubule-disrupting agent attached to the antibody via a protease-cleavable linker (vc). Through the chemical conjugation between the free thiol groups on the antibody and the maleimide entity of vcMMAE, an average drug antibody ratio (DAR) of 4.0 is achieved. Tisotumab vedotin binds to TF-expressing tumor cells, which is followed by internalization of the ADC-TF complex and release of MMAE via proteolytic cleavage. MMAE disrupts the microtubule network of actively dividing cells, leading to cell cycle arrest and apoptotic cell death. In addition to direct cytotoxicity, other proposed mechanism of actions for tisotumab vedotin include killing of tumor cells by bystander cytotoxicity, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis. Tisotumab vedotin drug product (DP) is a sterile, preservative-free lyophilized powder supplied in a single-dose vial. Each DP vial contains 40.0 mg of tisotumab vedotin, (b) (4) mg of L-histidine, (b) (4) mg of L-histidine monohydrochloride, 120 mg of sucrose and 120 mg of D-mannitol. The recommended dose of tisotumab vedotin is 2 mg/kg (up to a maximum of 200 mg) given as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Product Quality (Drug Substance (DS) and DP)/Immunogenicity Assay	Arulvathani Arudchandran	OPQ/OBP/DBRRII
Product Quality (Small molecule drug)	Rohit V. Tiwari	OPQ/ONDP/DNDAPI/NDB1
Labeling	James Barlow Arulvathani Arudchandran	OPQ/OBP OPQ/OBP/DBRRII
Facility	Richard Ledwidge (DS) Maria Gutierrez-Hoffmann (DP)	OPQ/OPMA/DBMII
Microbiology	Richard Ledwidge (DS) Maria Gutierrez-Hoffmann (DP)	OPQ/OPMA/DBMII
Team Lead	Pick-Wei Lau (product quality) Candace Gomez-Broughton (facility and microbiology	OPQ/OBP/DBRRII OPQ/OPMA/DBMII

	Paresma Patel (small molecule drug)	OPQ/ONDP/DNDAPI/B1
Application Team Lead[1]	Pick-Wei Lau Patrick Lynch	OPQ/OBP/DBRRII
OBP Review Chief	Patrick Lynch	OPQ/OBP/DBRRII
RBPM	Kelly Ballard	OPQ/OPRO

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	David Nartey	DRO – Oncologic Diseases
Cross-disciplinary Team Lead	Gwynn Ison	DO1
Medical Officer	Mirat Shah	DO1
Pharmacology/Toxicology	Nikolett Biel; Tiffany Ricks	DHOT
Clinical Pharmacology	Krithika Arun Shetty; Salaheldin Hamed	OTS/OCP/DCPI OTS/OCP/DCPII
Statistics	Zhou Feng; Erik Bloomquist	OTS/OB/DBV

1. Names:
   a. Proprietary Name: Tivdak
   b. Trade Name: Tivdak
   c. Non-Proprietary Name/USAN: Tisotumab vedotin
   d. CAS Name: 1418731-10-8
   e. INN Name: Tisotumab vedotin
   f. OBP systematic name: CONJ: MAB HUMAN (IGG1) ANTI P13726 (TF_HUMAN); MONOMETHYL AURISTATIN E [HUMAXTFADC]
   g. Other names: HuMax-TF-ADC (Genmab); (b) (4)

Submissions Assessed:

Submission(s) Assessed	Document Date
BLA 761208.0001 – Original submission	February 10, 2021
BLA 761208.0003 – Stability update	March 4, 2021
BLA 761208.0013 – OBP IR response #1	April 8, 2021
BLA 761208.0016 – OBP IR response #2	April 27, 2021
BLA 761208.0023 – OBP IR response #3	May 14, 2021
BLA 761208.0027 – OBP IR response #4	May 26, 2021
BLA 761208.0032 – OPMA IR response	June 7, 2021
BLA 761208.0033 – OPMA IR response	June 10, 2021
BLA 761208.0034 – OBP IR response #5	June 14, 2021
BLA 761208.0038 – OBP IR response #6	June 25, 2021
BLA 761208.0039 – OBP IR response #7	June 28, 2021
BLA 761208.0042 – OPMA IR response	July 1, 2021
BLA 761208.0043 – OBP IR response #8	July 9, 2021
BLA 761208.0044 – OPMA IR response	July 9, 2021
BLA 761208.0046 – OPMA IR response	July 13, 2021
BLA 761208.0049 – OPMA IR response	July 22, 2021
BLA 761208.0051 – OPMA IR response	August 5, 2021
BLA 761208.0053 – OPMA IR response	August 12, 2021

[1] Dr. Pick-Wei Lau served as Application Team Lead through July 16, 2021.

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code [1]	Status[2]	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	3	N/A	N/A	Not reviewed, enough information was provided in the BLA
	III			3	N/A	N/A	
	III			3	N/A	N/A	
	II			2	Adequate	June 9, 2021	Adequate; assessed by CDER/OPQ/OND P
	V			3	N/A	N/A	Not reviewed, enough information was provided in the BLA
	V			3	N/A	N/A	
	V			3	N/A	N/A	

			(b) (4)				

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 not 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	135476	Parent IND

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion:

Seagen claimed a categorical exclusion to the environmental assessment requirements in compliance with the categorical exclusion criteria 21 CFR Part 25.31 (b), action on a BLA when the estimated concentration of the substance(s) at the point of entry into the aquatic environment will be below 1 part per billion (ppb). Seagen is not aware of any extraordinary circumstance that would require additional environmental assessment, and the analysis performed indicates that neither the amount of tisotumab vedotin nor its pharmacologically active component, MMAE, entering the environment exceeds the 1 ppb limit. Thus, no environmental assessment is required.

The claim of a categorical exclusion is accepted.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER recommends approval of STN 761208 for Tivdak manufactured by Seagen Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Tivdak 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.

The original OPQ Application Team Lead (ATL) review concluded that the OPQ recommendation was pending final assessment of a late cycle amendment pertaining to microbiology control information was completed and signed on August 10, 2021. The original ATL review memo was updated with this memo on August 13, 2021 to update the outcome of the microbiology assessment. Additional typographical corrections were made on August 24, 2021. This review reflects the final OPQ ATL review and recommendation.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance Intermediate (DSI): (b) (4)
  - SGD-1006 intermediate: (b) (4)
  - Drug Substance (DS): (b) (4)
  - Drug Product (DP): (b) (4)
- Fill size and dosage form
  40 mg/vial tisotumab vedotin as a lyophilized cake or powder in a single-dose vial for reconstitution.
- Dating period:
  - Drug Product: 36 months: 5°C
  - Drug Substance: (b) (4) months: (b) (4) °C
  - Drug Substance Intermediate: (b) (4) months: (b) (4) °C
  - Stability Option:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

- Exempt from lot release:
    - Yes: Tivdak is exempted from lot release per FR 95-29960.

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 drug substance 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 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 tisotumab drug substance intermediate (DSI) will be manufactured at (b) (4) (b) (4) the vcMMAE intermediate will be manufactured at (b) (4) (b) (4) tisotumab vedotin drug substance (DS) will be manufactured at (b) (4) (b) (4) the TIVDAK drug product (DP) at (b) (4)

Quality control testing will be performed as summarized in Summary of Quality Assessments of this document below.

In lieu of on-site pre-licensing inspections (PLI) for the DS manufacturing facility, (b) (4) and DSI manufacturing facility, (b) (4) a review of requested manufacturing site records under Section 704(a)(4) was conducted. A PLI waiver was granted for the DP manufacturing facility, (b) (4) based on its currently acceptable CGMP compliance status and recent relevant inspectional coverage. The manufacturing facility for vcMMAE (SGD-1006) intermediate, (b) (4) is found acceptable as part of quality assessment for vcMMAE intermediate. All facilities used for the manufacture and quality control testing are summarized in Sections H and I of this document.

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

The OBP product quality and immunogenicity assay, OPMA facility, microbiological DS and DP, as well as OBP labeling technical assessments are located as separate documents in Panorama.

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

The following post-marketing commitments (PMCs) have been discussed and agreed by the Applicant during the BLA review. These PMCs will be effective once the application is approved.

<u>OBP-1:</u>
To perform a real-time leachable study for tisotumab vedotin drug product in its commercial container closure system to detect, identify, and quantify potential organic, non-volatile, volatile, and semi-volatile species, and metals through the end of shelf life. The final study reports and risk evaluation will be submitted to the BLA.

Final report submission date: 12/2024

OBP-2:
To develop, characterize, validate, and implement functional activity assay(s) with appropriately justified acceptance criteria to control for Fc effector functions of tisotumab vedotin drug substance at release. The final study results, analytical procedures, method validation reports, and updates to the drug substance release specification will be submitted to the BLA per 21 CFR 601.12.

Final report submission date: 11/2022

OPMA-3:
Implement (b) (4) monitoring (b) (4) of tisotumab vedotin drug product and update module 3.2.P.3.4 of the BLA with (b) (4) as a Critical Process Parameter.

Final report submission date: 12/2020

OPMA-4:
Implement a validated dye ingress method for container closure integrity testing with the sensitivity to detect breaches ≤ (b) (4) µm that could allow microbial ingress.

Final report submission date: 10/2021

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 drug substance intermediate (DSI), 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 (see example in Attachment 1)

CQA (type)	Risk	Origin	Control Strategy (b) (4)	Other
Tissue Factor (TF) target binding	Efficacy	Intrinsic to the Molecule		N/A
Cytotoxicity	Efficacy and Safety	Intrinsic to the Molecule. DS manufacturing process (b) (4)		(b) (4)
Effector functions	Efficacy	Intrinsic to the Molecule. DSI and DS manufacturing process can impact effector function based on characterization studies.		(b) (4) A PMC was agreed upon to implement functional assay(s) to control for effector function on DS release.
Drug-to-antibody ratio (DAR)	Efficacy	DS manufacturing process (b) (4)		(b) (4)
Unconjugated mAb	Efficacy	DS manufacturing process (b) (4)		N/A
Identity	Efficacy and Safety	Intrinsic to the molecule		N/A
High Molecular Weight Species	PK and Safety (Immunogenicity)	Manufacturing process, storage and exposure to heat, low and high pH, oxidative and photo stresses.		(b) (4)
Low Molecular Weight Species	Efficacy	Manufacturing process, storage and exposure to heat,		(b) (4)

		photo, and low pH stresses.	(b) (4)	
Acidic charge variants	Efficacy and PK	Manufacturing Process and storage. Increase over exposure to heat, photo, oxidative and high pH stresses.		(b) (4)
Basic charge variants	Potential impact on efficacy, safety, PK	Manufacturing Process. Relatively stable (or decreasing) under stress conditions.		
(b) (4) (b) (4) impurities	Efficacy	Manufacturing Process and storage.		
(b) (4) structure	Immunogenicity, efficacy, PK	Intrinsic to the molecule. DS manufacturing process (b) (4).		N/A
Glycoform distribution	Potential impact on efficacy, safety, PK	Manufacturing Process		N/A

B. Drug Substance Intermediate [tisotumab] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy	Other
			(b) (4)	N/A
				N/A

(b) (4)	
	N/A
	N/A
	N/A
	N/A
	N/A
	N/A
	N/A
	N/A
	N/A
	N/A
	N/A

(b) (4)	
	Assessed by CDER/OPQ/OPMA
	Assessed by CDER/OPQ/OPMA
	N/A
	N/A
	N/A
	N/A

- **Description:** Tisotumab is a humanized monoclonal antibody (anti-human tissue factor), a human IgG1k derived from a Chinese hamster ovary (CHO) cell line. The theoretical molecular weight is approximately (b) (4) kDa.
- **Mechanism of Action (MoA):** The primary mechanism of action of tisotumab DSI is (b) (4)
- **Potency Assay:** (b) (4) (b) (4)
- **Reference Materials:** (b) (4) (b) (4)
- **Critical starting materials or intermediates**: Tisotumab is produced by (b) (4) (b) (4)

- **Manufacturing process summary:** Tisotumab DSI is produced at (b) (4) (b) (4)
- **Container closure:** Tisotumab DSI is stored in (b) (4) (b) (4).
- **Dating period and storage conditions:** Tisotumab is stored (b) (4) (b) (4)

C. Drug/linker Intermediate [SGD-1006 intermediate] Quality Summary

SGD-1006 intermediate 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 tisotumab 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 (b) (4) impurities, residual solvents, and residual (b) (4) discussed in the BLA drug substance manufacturing section were provided in the DMF and found acceptable by the ONDP assessor.

D. Drug Substance [tisotumab vedotin] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA (type) (b) (4)	Risk	Origin	Control Strategy (b) (4)	Other
(Process-related impurities)	Safety			Assessed by CDER/OPQ/ONDP

(b) (4) (Process-related impurities)	Safety	(b) (4)	
(b) (4) (Process-related impurities)	Safety		
(b) (4) (Process-related impurities)	Safety		
(b) (4) (Process-related impurities)	Safety		
Leachables	Safety, Purity		N/A
Endotoxin (contaminant)	Safety, Purity		Assessed by CDER/OPQ/OPMA
Bioburden	Safety, Purity, and Immunogenicity		
Appearance	Stability		N/A
Protein concentration	Efficacy		N/A
pH	Efficacy and Stability		N/A
Osmolality	Stability		N/A

- **Description:** Tisotumab vedotin is an antibody-drug conjugate (ADC) composed of tisotumab DSI 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 (b) (4) interchain cysteine residues of the

antibody heavy and light chains through a thioether bond between the linker maleimide and the cysteine thiol group.

- **Mechanism of Action (MoA):** The primary MoA is the cytotoxicity upon binding of the ADC to tissue factor-expressing tumor cells, followed by internalization of tisotumab vedotin and subsequent release of MMAE via proteolytic cleavage of the valine-citrulline linker. Intracellular MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptosis of the cells. The ADC can also induce antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) activities as part of its MoA.
- **Potency Assay:** The following potency methods relevant to the MoA are included in the commercial control strategy:
  (1) Antigen binding by ELISA measures the ability of tisotumab vedotin DS to bind to target tissue factor. Activity is reported as relative to reference material.
  (2) Cell-based cytotoxicity bioassay measures the ability of tisotumab vedotin DS to kill A431 cells expressing TF (tissue factor). Activity is reported as relative to reference material.
  (3) A Post-Marketing Commitment was made by the Applicant to implement functional activity assay(s) to control for Fc effector functions of tisotumab vedotin DS at release.
- **Reference Materials:** (b) (4) (b) (4)
- **Critical starting materials or intermediates:**
  - Antibody Intermediate: Tisotumab DSI is manufactured and stored as described above.
  - Drug-linker Intermediate: vcMMAE is manufactured and stored as described in the DMF.
- **Manufacturing process summary:** Tisotumab vedotin DS manufacturing process is (b) (4)
- **Container closure:** Tisotumab vedotin DS is stored (b) (4) (b) (4)
- **Dating period and storage conditions:** (b) (4) months at (b) (4) °C

E. Drug Product [TIVDAK] Quality Summary:

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced during the DP manufacturing process	(b) (4)	Assessed by CDER/OPQ/OPMA team
Endotoxin (contaminant)	Safety, Purity, and Immunogenicity	Raw materials, contamination may be introduced during the DP manufacturing process		Assessed by CDER/OPQ/OPMA Team. Endotoxin may originate from reconstitution liquid (SWFI) and diluent. Overall endotoxin safety to be ensured through labeling (administration procedures).
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS		PMC to complete a real time leachables study using the final CCS for DP through the shelf-life
Quantity	Efficacy	Manufacturing process		N/A
After reconstitution				
pH (General)	Efficacy and Stability	Formulation components and Manufacturing process	(b) (4)	N/A
Osmolality (General)	Stability	Composition of the DP		N/A
Appearance (General)	Stability	Formulation components and stability		N/A
Subvisible particles (General)	Safety and Immunogenicity	Manufacturing process and CCS, subvisible particles could be product or foreign particles		N/A
Lyophillized				
Appearance (General)	Stability	Manufacturing process	(b) (4)	N/A
Reconstitution time	Stability	Manufacturing process and stability		N/A
Residual moisture	Stability	Manufacturing process and stability		N/A

- **Potency and Strength:** 40 mg of tisotumab vedotin as a lyophilized cake or powder in a single-dose vial for reconstitution.
- **Summary of Product Design:** Reconstitution of the DP with 4.0 mL of sterile water for injection (SWFI) results in 10 mg/mL tisotumab vedotin.
- **List of Excipients:** Each mL of reconstituted DP contains the following excipients:
  - D-mannitol (30 mg)
  - L-histidine (2.11 mg)
  - L-histidine monohydrochloride (3.44 mg)
  - Sucrose (30 mg)
- **Reference Materials:** Same as tisotumab vedotin DS.
- **Manufacturing process summary:** The tisotumab vedotin DP is manufactured on the (b) (4)
- **Container closure:** Tisotumab vedotin DP is packaged (b) (4) (b) (4)
- **Dating period and storage conditions:** 36 months at 5°C

F. Novel Approaches/Precedents:

Use of authority under Section 704(a)(4) to request records from the (b) (4) manufacturing facilities in lieu of performing on-site pre-license inspections of the DSI (b) (4) (b) (4) and DS (b) (4) manufacturing facilities. Refer also to the FDA Staff Manual Guide SMG 9004.1, *Policy and Procedures for Requesting Records in Advance of or in Lieu of a Drug Inspection.*

Rationale:

Sec. 704 (a)(4) (FDASIA Sec. 706) Records Request for (b) (4) and (b) (4) were initiated due to satisfactory inspectional history of the two facilities and travel restrictions during COVID19 pandemic.

G. Any Special Product Quality Labeling Recommendations:

- Store vials refrigerated at 2°C to 8°C in the original carton
- Do not freeze
- Do not shake
- Reconstituted solution:
  - Reconstituted with Sterile Water for Injection (SWFI).
  - Do not expose to direct sunlight.

- Should be clear to slightly opalescent, colorless to brownish-yellow and free of visible particles.
- May be stored for up to 24 hours in refrigeration at 2°C to 8°C or at room temperature ((b) (4) to 25°C) up to a maximum of 8 hours prior to dilution.

- Dilution in infusion bag:
  - Diluted with 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, or Lactated Ringer's Injection USP. Diluted solution may be stored for up to 18 hours, 24 hours, and 12 hours for each respective diluent at 2°C to 8°C.
  - Do not expose to direct sunlight.
  - Mix diluted solution by gentle inversion.
  - Should be clear to slightly opalescent, colorless to brownish-yellow and free of visible particles.

H. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE INTERMEDIATE (tisotumab antibody intermediate)					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
• Manufacturing, release testing, and stability testing • MCB and WCB manufacture and storage	(b) (4)		Pending document review	Pending	Approve
Master cell bank and working cell bank storage			No Evaluation Necessary	N/A	Approve
(b) (4)			Facility was found compliant based on profile code	N/A	Approve
DRUG SUBSTANCE INTERMEDIATE (vcMMAE intermediate)					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacturing, release testing, and stability testing	(b) (4)		Facility was found compliant based on profile code	N/A	Approve
Storage of stability samples			No Evaluation Necessary	N/A	Approve
Release testing (b) (4)			Facility was found compliant based on profile code	N/A	Approve
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation

Manufacturing, release testing, and stability testing	(b) (4)		Pending document review	Pending	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
• Manufacture of drug product • Release testing (sterility, endotoxin, subvisible particles only) • Stability testing (subvisible particles, container closure integrity only)	(b) (4)		Waived	N/A	Approve
• Release testing except for sterility, endotoxin, subvisible particles • Stability testing except for subvisible particles, container closure integrity			Pending document review	Pending	Approve
Secondary packaging and labeling			Facility was found compliant based on file review	N/A	Approve

I. Facilities:

(b) (4)

(b) (4)

J. Lifecycle Knowledge Management:

i. Protocols approved:

(b) (4)

(b) (4)

ii. Outstanding assessment issues/residual risk:

Four PMCs are recommended (listed in Section D above) to address the residual risks that pertain to (1) potential leachables from the commercial container closure system for tisotumab vedotin DP, (2) control strategy for Fc effector functions for tisotumab vedotin DS, (3) (b) (4) monitoring (b) (4) (b) (4) of tisotumab vedotin DP, and (4) validation of the dye ingress method for container closure integrity testing.

iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
Product Type					
1.	Recombinant Product		x		
2.	Naturally Derived Product			x	
3.	Botanical			x	
4.	Human Cell Substrate/source material			x	
5.	Non-Human Primate Cell Substrate/Source Material			x	
6.	Non-Primate Mammalian Cell Substrate/source material		x		
7.	Non-Mammalian Cell Substrate/Source Material			x	
8.	Transgenic Animal source			x	
9.	Transgenic Plant source			x	
10.	New Molecular Entity		x		
11.	PEPFAR drug			x	
12.	PET drug			x	
13.	Sterile Drug Product		x		
14.	Other: 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, Priority Review, Accelerated Approval		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

Patrick Lynch

Digitally signed by Patrick Lynch
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/s/

KELLY R BALLARD
08/24/2021 04:30:37 PM

PATRICK J LYNCH
08/24/2021 04:34:31 PM