CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761034Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:

BLA: Approval

BLA 761034
Review 1

Drug Name/Dosage Form	Tecentriq (Atezolizumab) Injection for infusion
Strength	1200 mg / 20 mL
Route of Administration	Intravenous Infusion every 3 weeks
Rx/OTC Dispensed	Rx
Applicant	Genentech, Inc.
US agent, if applicable	Not Applicable

a. Names
   i. Proprietary Name: Tecentriq
   ii. Trade Name: Tecentriq
   iii. Non-Proprietary/USAN: atezolizumab
   iv. INN Name: atezolizumab
   v. Other: None
   vi. OBP systematic name: MAB HUMANIZED [redacted] (b) (4) (PD1L1_HUMAN) [MPDL3280A]

b. Pharmacologic category: Therapeutic recombinant humanized monoclonal antibody

Product Overview

Atezolizumab is a humanized monoclonal antibody based on an IgG1 framework that contains heavy chain V_HIII and light chain $V\kappa$I subgroup sequences and is produced in CHO cells. A point mutation in the amino acid sequence (N298A) results in the removal of the glycosylation site. Atezolizumab targets programmed death-ligand 1 (PD-L1) on antigen-presenting cells or tumor cells and prevents interaction with the programmed death-1 (PD-1) receptor, which is an inhibitory receptor expressed on T cells. Interference of the PD-L1/PD-1 and PD-L1/B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, and expansion. Tecentriq is presented as a sterile liquid solution for intravenous injection and it is indicated for the treatment of locally advanced or metastatic urothelial carcinoma [redacted] (b) (4) For additional information see Appendix A of the initial integrated review memo.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance (QbD)	Chikako Torigoe	Division of Biotechnology Review and Research - II
Drug Substance and Drug Product	Xianghong Jing	Division of Biotechnology Review and Research – II
Drug Substance and Drug Product TL	Joel Welch	Division of Biotechnology Review and Research – II
Microbiology Drug Substance	Maria Jose Lopez-Barragan	Division of Microbiology Assessment
Microbiology Drug Product	Natalia Pripuzova	Division of Microbiology Assessment
Facility	Wayne Seifert	Division of Inspectional Assessment
Immunogenicity	Xianghong Jing	Division of Biotechnology Review and Research - II
Regulatory Business Process Manager	Andrew Shiber	OPRO
Application Technical Lead	Joel Welch	Division of Biotechnology Review and Research – II
Microbiology Team Lead (Drug Substance)	Reyes Candau-Chacon	Division of Microbiology Assessment
Microbiology Team Lead (Drug Product)	Colleen Thomas	Division of Microbiology Assessment
Facilities Team Lead	Peter Qiu	Division of Inspectional Assessment

Cross-Discipline Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
RPM	Kim Robertson	DOP1
CDTL	Virginia Maher	DOP1
Medical Officer	Yang-Min (Max) Ning	DOP1
Clinical Pharmacology	Wentao Fu	DCPV
Statistics	Shenghui Tang	DBV
Pharm/Tox	Tiffany Ricks	DHOT

Quality Review Team – Signature Page

DISCIPLINE	REVIEWER	SIGNATURE
Drug Substance (QbD)	Chikako Torigoe	Chikako Torigoe -A Digitally signed by Chikako Torigoe -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300430897, cn=Chikako Torigoe -A Date: 2016.04.12 17:11:08 -04'00'
Drug Substance and Drug Product Immunogenicity	Xianghong Jing	Xianghong Jing -S Digitally signed by Xianghong Jing -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xianghong Jing -S, 0.9.2342.19200300.100.1.1=2000380094 Date: 2016.04.12 16:58:19 -04'00'
Drug Substance and Drug Product TL	Joel Welch	Joel T. Welch -S Digitally signed by Joel T. Welch -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joel T. Welch -S, 0.9.2342.19200300.100.1.1=2000443745 Date: 2016.04.12 20:06:22 -04'00'
Microbiology Drug Substance	Maria Jose Lopez-Barragan	Maria Jose Lopez Barragan -S (Affiliate) Digitally signed by Maria Jose Lopez Barragan -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=0012653737, cn=Maria Jose Lopez Barragan -S (Affiliate) Date: 2016.04.12 14:58:40 -04'00'
Microbiology Drug Product	Natalia Pripuzova	Natalia S. Pripuzova -S (Affiliate) Digitally signed by Natalia S. Pripuzova -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000351935, cn=Natalia S. Pripuzova -S (Affiliate) Date: 2016.04.12 14:30:38 -04'00'
Facility	Wayne Seifert	Wayne E. Seifert -S Digitally signed by Wayne E. Seifert -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001593284, cn=Wayne E. Seifert -S Date: 2016.04.13 07:54:42 -04'00'
Regulatory Business Process Manager	Andrew Shiber	Andrew Shiber -A Digitally signed by Andrew Shiber -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -A, 0.9.2342.19200300.100.1.1=0014262141 Date: 2016.04.13 08:37:26 -04'00'
Application Technical Lead	Joel Welch	Joel T. Welch -S Digitally signed by Joel T. Welch -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joel T. Welch -S, 0.9.2342.19200300.100.1.1=2000443745 Date: 2016.04.13 09:02:07 -04'00'
Microbiology Team Lead (Drug Substance)	Reyes Candau-Chacon	Maria D. Candauchacon -S Digitally signed by Maria D. Candauchacon -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000639745, cn=Maria D. Candauchacon -S Date: 2016.04.12 16:48:31 -04'00'
Microbiology Team Lead (Drug Product)	Colleen Thomas	Colleen Thomas -S Digitally signed by Colleen Thomas -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Colleen Thomas -S, 0.9.2342.19200300.100.1.1=2000334597 Date: 2016.04.12 14:52:53 -04'00'
Facilities Team Lead	Peter Qiu	Zhihao Qiu -S Digitally signed by Zhihao Qiu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu -S, 0.9.2342.19200300.100.1.1=2000438274 Date: 2016.04.13 08:42:47 -04'00'
OBP Review Chief	Juhong Liu	Juhong Liu -S Digitally signed by Juhong Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Juhong Liu -S, 0.9.2342.19200300.100.1.1=0010401517 Date: 2016.04.13 09:05:33 -04'00'

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

B. Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
761034/0000	Oct 23 2015	OBP, DMA, DIA
761034/0003	Dec 11 2015	OBP, DMA
761034/0004	Dec 16 2015	DMA
761034/0007	Jan 06 2016	OBP, DMA
761034/0008	Jan 08 2016	OBP, DMA
761034/0009	Jan 19 2016	OBP, DMA
761034/0010	Jan 21 2016	DMA
761034/0011	Jan 29 2016	OBP
761034/0012	Feb 2 2016	OBP
761034/0014	Feb 17 2016	DMA
761034/0017	Feb 19 2016	OBP, DMA
761034/0020	Feb 24 2016	DMA
761034/0024	Mar 2 2016	OBP
761034/0035	Mar 18 2016	OBP
761034/0041	Mar 25 2016	OBP, DMA
761034/0049	April 11 2016	OBP, DMA

C. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	3	Adequate	N/A	N/A
	III			3	Adequate	N/A	N/A

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

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

D. Other Documents: None

3. CONSULTS: None.

Integrated Review

I. Recommendations

The Office of Pharmaceutical Quality recommends approval of BLA 761034 for Tecentriq (atezolizumab) manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Tecentriq (atezolizumab) 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.

A. Recommendation and Conclusion on Approvability

The DS and DP manufacturing process is well controlled and should consistently deliver DS and DP of desired quality.

A PMR is recommended as the the current method for detecting neutralizing anti-drug antibodies (ADA) is not tolerant to the presence of drug at the levels expected to be in some patents' serum at the time of sampling, leading to a reduced capability of detecting ADA. The development of a more sensitive and drug tolerant assay for the detection of neutralizing antibodies to atezolizumab would provide a more accurate measure and characterization of the patients' immune response to atezolizumab.

PMCs are recommended to perform additional characterization to assure (b) (4) of the MCB for atezolizumab. (b) (4)

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

Below are the draft PMC/PMRs to be proposed to the sponsor should approvability be the recommendation.

1). Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against atezolizumab in the presence of atezolizumab levels that are expected to be present in samples at the time of patient sampling.

2). Perform supplemental characterization of the MCB to provide additional assurance (b) (4) of the cell bank. This data should include evaluation of (b) (4) with respect to growth characteristics and product quality.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Management

Table 1 below is a summary of critical quality attributes and their control strategy that are relevant to both drug substance and drug product. For additional information see Appendix_A for the Drug Substance and Drug Product Quality Review: OBP Assessment,Appendix_B Drug Substance Microbiology Review: Division of Microbiology Assessment, and Appendix C Drug Product Microbiology Review: Division of Microbiology Assessment.

Table 1: Drug Substance and Drug Product CQA Identification, Risk and Lifecycle Knowledge Management

CQA	Risk	Origin	Control Strategy	Other
Potency	Efficacy	(b) (4)	(b) (4)	N/A
HMW Species	Efficacy, Pharmacokinetics, and Immunogenicity			N/A
LMW Species	Efficacy and Pharmacokinetics			N/A
(b) (4)	Efficacy, Pharmacokinetics, and Potency			Not assessed for DP release given the stability profile for DS.

			(b) (4)	
Osmolality	Safety	(b) (4)		N/A
Endotoxin	Safety			N/A

B. Drug Substance Atezolizumab Quality Summary

Table 2 below is a summary of critical quality attributes and their control strategy that are relevant to only drug substance. For additional information see Appendix_A for the Drug Substance and Drug Product Quality Review: OBP Assessment and Appendix_B Drug Substance Microbiology Review: Division of Microbiology Assessment.

CQA	Risk	Origin	Control Strategy	Other
Bioburden	Safety; product quality (b) (4)	(b) (4)	(b) (4)	N/A
Endotoxin	Safety			N/A
Host Cell Proteins	Safety and Immunogenicity			N/A
Host Cell DNA	Safety			N/A
pH	Safety and Efficacy			N/A
(b) (4)	Safety and			N/A

	Immunogenicity	(b) (4	(b) (4)
(b) (4)	Safety	(b) (4	N/A
Protein Content	Efficacy		N/A
Appearance	Safety		N/A
Identity	Safety and Efficacy	Not Applicable	N/A
(b) (4)	Safety	(b) (4	N/A
Leachables	Safety		N/A

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

1. Description

Atezolizumab is a humanized monoclonal antibody based on a human immunoglobulin G1 (IgG1) framework that contains heavy chain V_HIII and light chain V_κI subgroup sequences. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each). (b) (4)

(b) (4)

(b) (4) The drug substance is stored at (b) (4)C. For additional information see Appendixes A and B of the initial integrated review memo.

2. Mechanism of action

Atezolizumab targets programmed death-ligand 1 (PD-L1) on antigen-presenting cells or tumor cells and prevents interaction with the programmed death-1 (PD-1) receptor, which is an inhibitory receptor expressed on T cells. Atezolizumab also blocks the interaction between PD-L1 and B7.1. Interference of the PD-L1/PD-1 and PD-L1/B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming and expansion. For additional information see Appendix A of the initial integrated review memo.

3. Potency Assay

The potency assay of atezolizumab serves as a quantitative *in vitro* assay to determine the potency of both atezolizumab Drug Substance and Drug Product. The analytical procedure measures the ability of atezolizumab to block the PD-1/PD-L1 – mediated inhibition of IL-2 secretion from activated T cells. (b) (4)

(b) (4)

(b) (4) Optical density results are plotted against the atezolizumab concentrations, and a parallel line program is used to estimate the activity of the atezolizumab samples relative to the Reference Standard.For additional information see Appendix A of the initial integrated review memo.

4. Reference material(s)

A two tiered reference standard system was developed and is considered consistent with ICHQ6B recommendations. The primary reference standard is (b) (4)

The secondary Reference Standard is (b) (4) .The reference standards were rigorously characterized by both release testing and additional biochemical characterization. The reference standards are suitable for their intended uses in atezolizumab testing. For additional information see Appendix A of the initial integrated review memo.

5. Manufacturing process summary

(b) (4)

For additional information see Appendix A and Appendix B of the integrated review memo.

6. Container closure

(b) (4) The drug substance is stored at (b) (4) °C.There is minimal drug substance degradation in the CCS during the (b) (4) month dating period. For additional information see Appendix A and Appendix B of the integrated review memo.

7. Dating period and storage conditions:
The sponsor conducted real time, accelerated, and stressed stability studies to support their proposed dating period of (b) (4) months when stored at (b) (4) °C.

C. Atezolizumab Drug Product Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information on the characterization of Tecentriq see Appendix A for the Drug Substance and Drug Product Quality Technical Report: OBP Assessment and Appendix C Drug Product Microbiology Review: Division of Microbiology Assessment.

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

CQA	Risk	Origin	Control Strategy	Other
Sterility	Safety (infection) Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination could be introduced during manufacturing process or through a container closure integrity failure.	(b) (4)	N/A
Endotoxin	Safety	Contamination could be introduced throughout DP manufacturing or through a container closure integrity failure.		
Particulate Matter	Occlusion of blood vessels	Product or Process Related Impurties		N/A
Appearance	Safety	Controlled by the manufacturing process.		N/A

			(b) (4)	
Identity	Safety and Efficacy	Not Applicable		N/A

Summary of Drug Product Intended Use

a. Potency and Strength
Potency is defined as the percent activity relative to the current atezolizumab reference standard. The potency assay is the same as described in the DS section B3 of this memo. Atezolizumab is available as a 1200 mg / 20 mL strength.

b. Summary of Product Design
Tecentriq will be available as a sterile single-use vial solution for intravenous infusion.

c. Excipients
Excipients include L-histidine, glacial acetic acid, sucrose, polysorbate 20, and water for injection. The excipients used in manufacturing are acceptable because they are compendial quality standards. The excipients are safe for use since they are not of human or animal origin and therefore are of little risk for viral or TSE contamination. For additional information see Appendix A of the initial integrated review memo.

d. Reference material(s)
There is no drug product specific reference material. The primary and working reference materials are drug substance. Please see drug substance reference materials for information.

e. Manufacturing Process
The manufacturing process for drug product include the following steps: (b) (4) .

The control strategy includes in-process testing of critical and non-critical parameters and release testing of vial drug product. Critical parameters selected for routine monitoring support (b) (4), assurance of correct formulation, (b) (4), assurance of bulk DP homogeneity, and consistent and accurate fill. Process validation studies included manufacture of three consecutive commercial scale lots. Additional validation studies included:

- Validation of sterilization and aseptic manufacturing process
- Shipping qualification study
- Process simulation (media fills)

f. Container Closure System
The primary container closure system is a colorless, single use 20 mL Type 1 glass vial. It is sealed with a 20 mm (b) (4) rubber stopper, and 20 mm aluminum seal with plastic flip-off cap.

g. Expiration Date & Storage Conditions

The sponsor conducted real time, accelerated, and stressed stability studies on finished drug product, to support a dating period of 24 months when stored at 2-8°C. For further information see Appendix A of the initial integrated review memo and Appendix A of this memo.

h. List of co-packaged components N/A

D. Novel Approaches
N/A

E. Any Special Product Quality Labeling Recommendations
Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light
Do not freeze
Do not shake.

Administer immediately once prepared. If diluted TECENTRIQ infusion solution is not used immediately, it can be stored either:

- At ambient temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration for infusion.
- Under refrigeration at 2°C–8°C (36°F–46°F) for no more than 24 hours.

F. Establishment Information

G. Facilities

The subject BLA proposes manufacture of Atezolizumab Drug Substance and Drug Product at the following facilities.

DS Manufacturers for Atezolizumb

Site Name	Address	FEI #	Responsibility
(b) (4)			

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(b) (4)			
F. Hoffmann-La Roche Ltd.	Wurmisweg CH-4303 Kaiseraugst Switzerland	3003973536	Release, IPC and Stability Testing, including CCI Testing. Labeling, Secondary Packaging and Storage (Finished Goods) and Release of Finished Goods.
Genentech, Inc.	4625 NW Brookwood Pkwy Hillsboro, OR 97124 USA	3007232634	Labeling, Secondary Packaging and Storage (Finished Goods). Release of Finished Goods.

The subject BLA proposes manufacture of Atezolizumab Drug Substance and Drug Product at the following facilities.

The Atezolizumab DS manufacturing process consists of (b) (4)

The Atezolizumab DP manufacturing process consists of (b) (4) F. Hoffmann-La Roche Ltd. (FEI 3003973536) will support testing, labeling and packaging, storage and release of finished goods. Genentech, Inc. FEI 3007232634 will support labeling and packaging and release of finished goods.

For a complete summary see Appendix D: Drug Substance Facilities Review: Division of Inspectional Assessment.

H. Lifecycle Knowledge Management

a. Drug Substance

i. Protocols approved: annual stability protocol, qualification of new working reference standard, qualification of new working cell bank,

ii. Outstanding review issues/residual risk - see sections 1A and 1B of this memo for post-marketing commitments.
iii. Future inspection points to consider – Follow up on 483 citation.

b. Drug Product

i. Protocols approved: annual stability protocol, post approval lifecycle management plan,
ii. Outstanding review issues/residual risk – None
iii. Future inspection points to consider – none at this time.

Quality Assessment Summary Tables

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	x	☐	
2.	Botanical[1]	☐	x	
3.	Naturally-derived Product	☐	x	
4.	Narrow Therapeutic Index Drug	☐	x	
5.	PET Drug	☐	x	
6.	PEPFAR Drug	☐	x	
7.	Sterile Drug Product	x	☐	
8.	Transdermal[1]	☐	x	
9.	Pediatric form/dose[1]	☐	x	
10.	Locally acting drug[1]	☐	x	
11.	Lyophilized product[1]	☐	x	
12.	First generic[1]	☐	x	
13.	Solid dispersion product[1]	☐	x	
14.	Oral disintegrating tablet[1]	☐	x	

QUALITY ASSESSMENT BLA 761034 Atezolizumab

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
15.	Modified release product[1]	☐	x	
16.	Liposome product[1]	☐	x	
17.	Biosimiliar product[1]	☐	x	
18.	Combination Product _____	☐	x	
19.	Other	☐	x	

Regulatory Considerations					
20.	USAN Name Assigned		x	☐	Atezolizumab
21.	End of Phase II/Pre-NDA Agreements		☐	x	
22.	SPOTS (Special Products On-line Tracking System)		☐	x	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☐	Not available
24.	Comparability Protocol(s)[2]		x	☐	
25.	Other_____		☐	x	
Quality Considerations					
26.	Drug Substance Overage		x	☐	The vial contains a (b) (4) mL overfill to ensure a total of 20 mL extractable volume.
27.	Design Space	Formulation	☐	x	
28.		Process	x	☐	QbD element
29.		Analytical Methods	☐	x	
30.		Other	☐	☐	
31.	Real Time Release Testing (RTRT)		☐	x	
32.	Parametric Release in lieu of Sterility Testing		☐	x	
33.	Alternative Microbiological Test Methods		x	☐	Container Closure Integrity
34.	Process Analytical Technology[1]		☐	x	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	x	☐	
36.		Excipients	☐	x	
37.		Microbial	☐	☐	
38.	Unique analytical methodology[1]		☐	x	
39.	Excipients of Human or Animal Origin		☐	x	
40.	Novel Excipients		☐	x	
41.	Nanomaterials[1]		☐	x	
42.	Hold Times Exceeding 30 Days		☐	x	
43.	Genotoxic Impurities or Structural Alerts		☐	x	
44.	Continuous Manufacturing		☐	x	
45.	Other unique manufacturing process[1]		☐	x	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	x	
47.	New delivery system or dosage form[1]		☐	x	
48.	Novel BE study designs		☐	x	
49.	New product design[1]		☐	x	
50.	Other		☐	x	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

Appendix_ A:
Drug Substance and Drug Product Quality Review

1. INSPECTIONAL ACTIVITIES

A pre-licensure inspection (PLI) of the drug substance manufacturing facility at [redacted] was conducted [redacted] under FEI No. [redacted] The inspection covered the manufacturing operations for atezolizumab drug substance under BLA STN 761034. The inspection was conducted by reviewers in accordance with applicable sections of CP 7356.002M, Inspections of Licensed Therapeutic Drug Products and ICH Q7A. This inspection was limited to the drug substance manufacturing and testing of atezolizumab. This PLI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. A one-item 483 was issued; the 483 issue was related to [redacted] for the atezolizumab manufacturing process. The recommendation of the inspection is voluntary action indicated (VAI). A waiver for the inspection of the drug product facility is intended and the final waiver memo is in circulation.

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products recommends approval of BLA 761034 for Tecentriq (atezolizumab) manufactured by Roche-Genentech. The data submitted in this application are adequate to support the conclusion that the manufacture of Tecentriq (atezolizumab) 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 Office of Biotechnology Products recommends approval of the proposed lot release/stability specifications and stability protocols for atezolizumab drug substance and drug product. The Office of Biotechnology Products recommends an expiry period of [redacted] months for atezolizumab drug substance when stored at [redacted] °C and an expiry period of 24 months for atezolizumab drug product when stored at 2-8°C.

II. List Of Deficiencies To Be Communicated: None

List Of Post-Marketing Commitments/Requirement: As noted in the section describing the neutralization assay for anti-drug antibodies, poor drug tolerance is observed for the assay. A PMR is recommended. Additionally, the generation of supplemental data to aid in the assurance [redacted] of the MCB is also recommended.

III. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

A claim for a categorical exclusion is being made under 21 CFR 25.31 (c) for substances that occur naturally in the environment. This application is for marketing approval of a biologic product comprised of substances that occur naturally in the environment and approval of this action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. To the sponsor's knowledge, no extraordinary circumstances, as described in 21 CFR 25.21, exist that would result in significant impact to the environment from the discharge of this substance. This is appropriate.

V. Primary Container Labeling Review

The primary and secondary container labeling review was performed by Jibril Abdus-Samad, OBP.

VI. Review Of Common Technical Document-Quality Module 3.2

Review of Immunogenicity Assays – Module 5.3.1.4

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Drug Substance

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

The following is the provided nomenclature for atezolizumab (reproduced directly from the submission).

International Nonproprietary Name (INN):	Atezolizumab
United States Adopted Name (USAN):	Pending
British Approved Name (BAN):	Pending
Japanese Accepted Name (JAN):	Pending
World Health Organization (WHO) Reference Number:	Pending
Compendial Name:	Not applicable
Chemical Abstracts Service (CAS) Registry Number:	1380723-44-3
Chemical Name:	Immunoglobulin G1, anti-(human programmed death-1 ligand-1) (b) (4) (b) (4)
Company or Laboratory Code:	RO5541267
Other Names:	MPDL3280A Anti-PDL1 Anti-PD-L1 aPDL1 PRO#303280

3.2.S.1.2 Structure

Atezolizumab is a humanized monoclonal antibody based on an IgG1 framework that contains heavy chain V_HIII and light chain VκI subgroup sequences. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each). It has a calculated molecular mass of 144,356 Da. By design, atezolizumab incorporates an amino acid substitution (asparagine to alanine) at position 298 in the CH2 domain of each heavy chain. This substitution results in a nonglycosylated antibody that has minimal binding to Fcγ receptors and thereby prevents Fc-effector function and depletion of cells expressing programmed death-ligand 1 (PD-L1) at expected concentrations in humans.

Schematic diagrams of the sequence and structure of the antibody are presented below directly from the submission.

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3.2.S.1.3 General Properties

Atezolizumab targets programmed death-ligand 1 (PD-L1) on antigen-presenting cells or tumor cells and prevents interaction with the programmed death-1 (PD-1) receptor, which is an inhibitory receptor expressed on T cells. Atezolizumab also blocks the interaction between PD-L1 and B7.1. B7.1 is a protein found on activated B cells and monocytes that provides a costimulatory signal necessary for T cell activation and survival. Interference of the PD-L1/PD-1 and PD-L1/B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The testing and manufacture for atezolizumab is performed at the following facilities (without specific notes, all the tables and figures are reproduced directly from the submission).

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P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

Atezolizumab drug product is presented in vials as a sterile, single-use, colorless to slightly yellow solution for intravenous (IV) infusion and does not contain preservatives. Each 20 mL vial contains 1200 mg of atezolizumab, a nominal fill volume of 20 mL, at a target pH of 5.8. The manufacturing fill parameters were selected to deliver the net quantity declared on the label. This is ensured by a minimum fill volume of (b) (4) mL.

The drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% (w/v) polysorbate 20, pH 5.8 (refer to Table P.1-1 below). The container closure system consists of a Ph. Eur./USP/JP Type I glass vial with a rubber stopper and crimped with an aluminum seal fitted with a plastic flip-off cap (Details in Section P.7 Container Closure System).

The DP liquid concentrate is administered to patients by intravenous (IV) infusion after dilution in isotonic sodium chloride solution. For IV dosing, 20 mL of atezolizumab liquid concentrate is withdrawn from the vial and diluted in a 250 mL polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing sterile, nonpyrogenic 0.9% aqueous sodium chloride solution.

Table P.1-1 Composition of Drug Product

Ingredient	Nominal Amount per Vial	Target Concentration	Function	Standard Specifications
Atezolizumab	1200 mg	60 mg/mL	Active ingredient	Section S.4.1 *Specification*
L-Histidine	62.0 mg	20 mM	(b) (4)	USP/Ph. Eur./JP
Glacial Acetic Acid	16.5 mg[a]	(b) (4)		USP/Ph. Eur./JP
Sucrose	821.6 mg	120 mM		NF/Ph. Eur./JP
Polysorbate 20	8.0 mg	0.04% (w/v)		NF/Ph. Eur./JPE
Water for Injection	QS to 20.0 mL	NA		USP/Ph. Eur./JP
(b) (4)				

Abbreviations: JPE = Japanese Pharmaceutical Excipients; NA = not applicable; NF = National Formulary; QS = quantity sufficient.

(b) (4)

Reviewer comments: *The (b) (4) ml overfill volume complies with USP<1151> requirement for the total 20mL labeled size. Compatibility study with one batch of diluted atezolizumab DP in the PVC infusion bag supports the conclusion of no quality impact on the physicochemical attributes of the product in the diluted solutions under the recommended storage condition, 2-8 ℃ for 24 hours.*

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

Atezolizumab is the active ingredient in the drug product. The concentration and composition of formulated atezolizumab occur at the drug substance, and no further compounding or dilution is performed during drug product manufacturing.

3.2.P.2.1.2 Excipients

The formulation excipients are L-histidine, glacial acetic acid, sucrose, and polysorbate 20. (b) (4) atezolizumab is formulated with the excipients at pH 5.8. These excipients are commonly used in formulating protein pharmaceuticals, and the sponsor conducted formulation development studies to show the compatibility with atezolizumab (in Section P.2.2).

3.2.P.2.1.2.1 Histidine Acetate (L-Histidine and Glacial Acetic Acid), (b) (4)

Histidine acetate functions (b) (4) .

3.2.P.2.1.2.2 Sucrose

Sucrose functions (b) (4)

3.2.P.2.1.2.3 Polysorbate 20

Polysorbate 20 functions (b) (4)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

The objective of the atezolizumab drug product formulation development was to develop a formulation that is stable and robust for manufacturing, storage, transportation, and administration of atezolizumab by IV infusion injection.

Two single-use formulations were used during development and are designated as F01and F03.

F01 formulation: Designated for toxicology studies and early Phase I and Phase II clinical trials; It contains (b) (4) mg/mL atezolizumab formulated at pH (b) (4) with (b) (4) mM histidine acetate, (b) (4) mM sucrose, and (b) (4) mg/mL (b) (4) % w/v) polysorbate 20.

F03 formulation: Commercial formulation and used for Phase I, Phase II, and Phase III clinical trials; It contains 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, and 0.4 mg/mL (0.04% w/v) polysorbate 20 at pH 5.8, and was developed to deliver a nominal amount (net quantity) of 1200 mg of atezolizumab per vial.

3.2.P.2.2.1.1 Formulation Development Studies

Formulation F03 was selected as the Drug Product formulation (F03) for Phase III clinical trials and commercial use, as a result of formulation development studies. This F03 formulation was shown to maintain the stability of Drug Product when stored, shipped, and handled as recommended.

The drug substance is filled directly into 20 mL Type I glass vials to produce the final drug product. The assays used for the formulation development studies include: SE-HPLC, ICIEF, Color, appearance, and clarity, UV spec scan, pH, and turbidity measurement.

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Appendix_ B:
Drug Substance Microbiology Quality Review

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

DRUG SUBSTANCE MICROBIOLOGY QUALITY REVIEW

Date: 4/10/2016

To: Administrative File, STN 761034/0

From: Maria Jose Lopez Barragan, PhD., Reviewer, CDER/OPQ/OPF/DMA/BIV

Through: Reyes Candau-Chacon, PhD., Acting Quality Assessment Lead, CDER/OPQ/OPF/DMA/BIV

Subject: New Biologic License Application (BLA): Priority review

US License: 1048

Applicant: Genentech, Inc.

Facilities: (b) (4)
FEI: (b) (4) (Drug Substance Manufacturer)

Product: Atezolizumab (Tecentriq®)

Dosage: 1200 mg/20 mL (60 mg/mL) liquid solution in single-use vials for intravenous injection

Indication: Treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4)

PDUFA date: 9/12/2016 (Target date: 5/18/2016)

Recommendation for approvability: The drug substance part of BLA 761034 is recommended for approval from a microbial control and microbiology product quality perspective.

Summary

Genentech, Inc. has submitted BLA 761034 to obtain approval of atezolizumab. Atezolizumab is a humanized recombinant monoclonal IgG1 antibody for treatment of locally advanced or metastatic urothelial carcinoma (mUC) (b) (4)

BLA 761034 was submitted in eCTD format as a rolling BLA. The original application was submitted on 10/23/2015 and contained all components related to manufacturing and non-clinical data in Modules 2, 3 and 4, as well as a majority of Module 1. The remainder of Module 1 and Clinical Module 5 were submitted on 1/12/2016.

This review contains the assessment of atezolizumab bulk drug substance from a microbiological quality perspective.

Drug Substance Quality Microbiology Information Reviewed

Description	eCTD Sequence	Date
Original BLA	0000	10/23//2015
Amendment	0007	1/5/2016
Amendment (revised from 0007)	0009	1/19/2016
Amendment	0010	1/21/2016
Amendment	0012	2/2/2016
Amendment	0020	2/24/2016

3.2.S DRUG SUBSTANCE

S.1 General Information

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids), and is produced in Chinese hamster ovary (CHO) cells. Atezolizumab reactivates the antitumor immune response by targeting human PD-L1 and inhibiting its interaction with its receptors PD-1 and B7.1.

The description is satisfactory

S.2 Manufacture

S.2.1 Manufacture(s)

The following facilities are involved in the manufacture, release testing, and stability testing of atezolizumab drug substance:

Site	Responsibilities
(b) (4)	• Drug substance manufacture • DS in-process and release testing [B] • DS release and storage
	• DS and DP in-process and release testing [E] • DS and DP stability testing
	• DS in-process testing
	• DS in-process testing
	• DS in-process testing
	• DP manufacturing • DS release testing • DP in-process and release testing • DS and DP stability testing
	• DS in-process testing

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SIGNATURE PAGE

Maria Jose Lopez Barragan, PhD.
Primary Reviewer

Reyes Candau-Chacon, PhD.
Acting Quality Assessment Lead

Appendix_ C:
Drug Product Microbiology Quality Review

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Natalia Pripuzova, Ph.D.
QUALITY ASSESMENT LEAD: Colleen Thomas, Ph.D.

Date:	08 April, 2015
BLA:	761034
Applicant:	Genentech, Inc.
US License Number:	1048
Submission Reviewed:	Original BLA (Breakthrough Therapy Designation)
Product:	Tecentriq (atezolizumab)
Indication:	Locally advanced or metastatic Urothelial Carcinoma
Dosage Form:	1200 mg/20mL (60 mg/mL), liquid single-use vial for intravenous infusion.
Manufacturing Sites:	(b) (4) (FEI: (b) (4)
FDA Receipt Date:	23 October 2015
Action Date:	18 May 2016

Approvability Recommendation: The Drug Product section of the BLA was reviewed from product quality microbiology prospective. The BLA as amended is recommended for approval.

Summary: BLA761034 was submitted in electronic format on 23-October-2015 to license atezolizumab for treatment of patients with metastatic urothelial carcinoma. Atezolizumab is designated as breakthrough therapy. Atezolizumab is a humanized monoclonal antibody (based on human immunoglobulin G1 framework), non-glycosylated. Atezolizumab inhibits ligation of programmed death-ligand 1 (PD-L1) to programmed death-1 (PD-1) and B7.1, thereby inhibiting

attenuation of T-cell activation; inhibition of PD-L1 ligation to PD-1 and B7.1, restores T-cell anti-tumor function. The single-use DP is sterile, preservative-free colorless to slightly yellow solution for intravenous (IV) infusion containing 60 mg/mL atezolizumab and is presented in vials. It is administered intravenously by infusion after dilution with isotonic saline, in a clinical setting. The drug substance (DS) is manufactured and quality control (QC) tested at the (b) (4) . The DP is manufactured and QC tested at the (b) (4) .

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	23 October 2015	Original BLA
0007	05 January 2016	Response to IR
0014	17 February 2016	Response to IR
0043	31 March 2016	Response to IR

Reviewer's comment: An additional IR was sent on 7 April 2016. The request asked the sponsor to update section 3.2.P.3.3 to include identification of the fill line. The response was not received prior to the primary review due date, but the reviewer will confirm that the BLA file was updated as requested.

Drug Product Review

Module 3.2

P.1 Description and Composition of the Drug Product

Atezolizumab DP is presented in vials as a sterile, single-use, colorless to slightly yellow solution for intravenous (IV) infusion and does not contain preservatives. Each 20 mL vial contains 1200 mg of atezolizumab, a nominal fill volume of 20 mL, at a target pH of 5.8. The composition of DP is presented in Table P.1-1, copied below from the submission.

Table P.1-1 Composition of Drug Product

Ingredient	Nominal Amount per Vial	Target Concentration	Function	Standard Specifications
Atezolizumab	1200 mg	60 mg/mL	Active ingredient	Section S.4.1 *Specification*
L-Histidine	62.0 mg	20 mM	(b) (4)	USP/Ph. Eur./JP
Glacial Acetic Acid	16.5 mg[a]	(b) (4)		USP/Ph. Eur./JP
Sucrose	821.6 mg	120 mM		NF/Ph. Eur./JP
Polysorbate 20	8.0 mg	0.04% (w/v)		NF/Ph. Eur./JPE
Water for Injection	QS to 20.0 mL	NA		USP/Ph. Eur./JP
(b) (4)				

Abbreviations: JPE = Japanese Pharmaceutical Excipients; NA = not applicable; NF = National Formulary; QS = quantity sufficient.

(b) (4)

Reviewer's comment: *This information is provided in this review memo for reference.*

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container Closure Integrity

The DP is filled in 20 mL Type I glass vials sealed with 20 mm rubber stoppers and crimped with 20 mm aluminum seals fitted with plastic flip-off caps. To ensure the integrity of the container closure system throughout the lifecycle of the product container closure integrity testing (CCIT) has is conducted during the following stages using the following methods:

- Initial development of the product packaging system through performance validation of the capping and crimping process (*Section 3.2.P.3.5*)
- CCIT during routine production using the high-voltage leak detection (HVLD) machine or helium leak method
- Stability assessments using the helium leak method, both annually and at the end of shelf life (*Section 3.2.P.8, Stability*).

CCIT using the helium leak method is performed on a sample set of vials from each validation batch and an annual stability batch.

Reviewer's comment: *The helium leak method and its validation are described and reviewed under Section* ***P.8.3.1****, Stability Data. Container Closure Integrity Testing: Analytical Procedure and Validation. The capping and crimping process parameters were validated using the three process validation batches in large scale manufacturing and described in* ***Section 3.2.P.3.5****, Process Validation and Evaluation. Vial integrity testing was performed on three product validation batches using either a high-voltage leak detection (HVLD) machine* (b) (4) *) or the helium leak method* (b) (4) *The CCIT method with high-voltage leak detection (HVLD) machine is validated and described in* ***Section 3.2.P.3.5.***

SATISFACTORY

P.2.6 Compatibility

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Appendix_ D:
Facility Review

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 03/17/2016
To: Administrative File, STN 761034/0
From: Wayne Seifert, Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Steven Fong, Ph.D., Microbiologist, CDER/OPQ/OPF/DIA
Subject: New Biologic License Application (BLA)
US License: 761034
Applicant: Genentech, Inc.
Mfg Facility: Drug Substance: (b) (4). (FEI (b) (4))
Drug Product: (b) (4) (FEI (b) (4))
Product: Tecentriq (Atezolizumab)
Dosage: Liquid Single-Use, 1200 mg/20mL (60 mg/mL), Intravenous Infusion
Indication: Metastatic Urothelial Carcinoma (mUC)
Due Date: 04/23/2016

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

SUMMARY

The subject BLA proposes manufacture of Tecentriq (Atezolizumab) DS at (b) (4) (FEI: (b) (4)), and Atezolizumab DP at (b) (4) (FEI (b) (4)). Both sites are multi-product, contract manufacturing facilities. The final dosage form consists of a single use vial containing 60 mg/mL Atezolizumab API.

Atezolizumab is a humanized antibody based on human immunoglobulin G1 (IgG1) that contains heavy chain V_HIII and light chain V_KI subgroup sequences. The recombinant antibody is produced in Chinese Hamster Ovary (CHO) cells and consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each).

The Atezolizumab DS manufacturing process consists of (b) (4)

(b) (4)

.

The facilities performing manufacturing, testing, and packaging of Atezolizumab DS and DP, and the descriptions of the facilities used for DS and DP manufacture, were reviewed and found to be adequate.

An information requests submitted 12/30/2015 is presented at the end of the Review. A response to this IR, SDN 8 was provided on 01/18/2016.

ASSESSMENT

3.2.S.2. DRUG SUBSTANCE FACILITIES

The proposed Atezolizumab DS Manufacturer, Preparation, Testing and Storage Facilities are provided in Table 1.

TABLE 1: DS Manufacturers for Atezolizumb

Site Name	Address	FEI #	Responsibility
(b) (4)			

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CONCLUSION

Adequate descriptions were provided for the DS and DP facilities proposed for Atezolizumab manufacture. The subject BLA is recommended for approval from a facilities assessment perspective.

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Wayne Seifert
Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1

_____

Steven E. Fong, M.S., Ph.D.
Microbiologist
OPF Division of Inspectional Assessment
Branch 1