CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761347Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA 761347 Resubmission OPQ Executive Summary
Assessment Date: August 16, 2024

1. Application/Product Information

BLA number	761347
Submission Type	Resubmission (original submission was withdrawn)
Regulatory Pathway	NME 351(a)
Associated IND/BLA	Clinical Development was performed under IND 140100 BLA 761034 for manufacture of atezolizumab for intravenous (IV) injection BLA 761064 for the manufacture and control of hyaluronidase (rHuPH20)
Review Designation	Standard Review
Applicant	Genentech, Inc.
Indication	The same as those for the atezolizumab IV formulation under BLA 761034: Non-small cell lung cancer, small cell lung cancer, hepatocellular carcinoma, melanoma, and alveolar soft part sarcoma.
Rx/OTC dispensed	Rx
Drug Product Name	**Proprietary Name:** TECENTRIQ HYBREZA
	Non-proprietary Name/Code Name: Atezolizumab and hyaluronidase-tqjs
	OBP Naming: Atezolizumab: MAB HUMANIZED (IGG1 N298A) ANTI Q9NZQ7 (PD1L1_HUMAN) [MPDL3280A] Hyaluronidase: RPROTFRAG P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20]
Drug Product Description	Atezolizumab SC DP is provided as a sterile, colorless-to-slightly yellow solution for subcutaneous injection with no preservatives. Each 20 mL single-dose vial contains 1875 mg/15 mL (nominal) of atezolizumab and 2000 U/mL rHuPH20. Atezolizumab SC DP is formulated with 20 mM L-

	Histidine, 240 mM Sucrose, 0.6 mg/mL Polysorbate 20, 10 mM L-Methionine, and pH-adjusted with (b) (4)% Acetic Acid to a target pH of 5.8. Atezolizumab is a humanized immunoglobulin (Ig)G1 monoclonal antibody (mAb). Atezolizumab targets PD-L1 and prevents the interaction of PD-L1 with PD-1 as well as B7.1. The interference of this interaction enhances tumor-specific T cell response and its mediated tumor cell killing. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and was engineered to eliminate Fc-effector function via a single amino acid substitution. Hyaluronidase (rHuPH20) is a glycosylated single-chain protein with 447 amino acids. rHuPH20 depolymerizes the gel-like hyaluronan (hyaluronic acid) at the site of injection resulting in a decreased resistance to fluid flow and a transient increase in permeability of the local subcutaneous tissue to support the new route of administration.		
Dosage Form	Liquid		
Strength	Each 20 mL single-dose vial contains 1875 mg/15 mL (nominal) of atezolizumab and 2000 U/mL rHuPH20.		
Route of Administration	Subcutaneous (sc)		
Primary Container Closure System	A (b) (4) glass vial with a rubber stopper crimped with an aluminum seal fitted with a plastic flip-off cap.		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance	Yongmin Liu	Brian Roelofs
	Drug product		
	Immunogenicity Assay		
	Facility	DS: Maria Scott DP: Yi Wang	Michael Shanks

	Microbiology	DS: Maria Scott DP: Yi Wang	Candace Gomez-Broughton Virginia Carroll
	RBPM	Nowrin Kakon	
	ATL	Brian Roelofs	
OPQ Issued Consults	N/A for the resubmission. ECCC and ETT were both consulted during the original submission review cycle.		

2. Recommendation and Conclusion on Approvability

Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761347 for TECENTRIQ HYBREZA manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of TECENTRIQ HYBREZA 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.

3. CMC Information for Action Letter

a. Manufacturing Location:

Drug Substance (atezolizumab SC): Roche Diagnostics GmbH, Penzberg, Germany (Roche Penzberg; FEI: 3002806560)

- **Drug Product:** Roche Diagnostics GmbH (Mannheim, Germany, FEI: 3002806559)

b. Fill size and dosage form: 20 mL single-dose vial containing 1875 mg/15 mL atezolizumab and 2000 U/mL rHuPH20

c. Dating Period:

- **Drug Product:** 24 months at 2 to 8°C
- **Atezolizumab SC Drug Substance:** (b) (4) months at (b) (4) °C

d. Exempt from lot release:

- Yes
- Rationale, if exempted: TECENTRIQ HYBREZA is exempted from lot release per FR 95-29960.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable

The following post marketing comments were proposed and accepted by the Applicant for Tecentriq Hybreza DP:

Product Quality

4637-** The (b) (4) commits to manufacture atezolizumab and hyaluronidase-tqjs using hyaluronidase manufactured at the (b) (4) by Q3 2025. To support that the (b) (4)-manufactured hyaluronidase performs the same as the (b) (4)-manufactured hyaluronidase when combined with atezolizumab in atezolizumab and hyaluronidase-tqjs, the (b) (4) will provide batch release data for one drug product batch in the 2026 annual report. This batch will be placed in the post-approval annual stability program, with stability data results reported to the Agency in subsequent annual reports.

Final Report Submission: 09/2026

Assessor comment: *At the time of filing of this memo, the PMC number was not available as the OND PMC set had not been finalized. The BLA action letter and CMC PMC Development Template will contain the final PMC number.*

4. Basis for Recommendation

a. Summary: Atezolizumab for SC administration is provided as a sterile, colorless-to-slightly yellow solution for subcutaneous injection with no preservatives. Each 20 mL single-dose vial contains 1875 mg/15 mL of atezolizumab and 2000 U/mL rHuPH20. Atezolizumab SC DP is formulated with 20 mM L-Histidine, 240 mM Sucrose, 0.6 mg/mL Polysorbate 20, 10 mM L-Methionine, and pH-adjusted with (b) (4)% Acetic Acid to a target pH of 5.8.

The atezolizumab component targets PD-L1 and prevents the interaction of PD-L1 with PD-1 as well as B7.1. The interference of this interaction enhances tumor-specific T cell response and its mediated tumor cell killing. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and was engineered to eliminate Fc-effector function via a single amino acid substitution. The hyaluronidase (rHuPH20) component is a glycosylated single-chain protein with 447 amino acids. rHuPH20 depolymerizes the gel-like hyaluronan (hyaluronic acid) at the site of injection resulting in a decreased resistance to fluid flow and a transient increase in permeability of the local subcutaneous tissue to support the new route of administration.

The assessment of manufacturing information provided in this application has concluded that the methodologies and processes used for drug substance and drug product manufacturing, release, and stability testing are sufficiently robust and

controlled to ensure the consistent manufacture of a safe, pure, and potent product. The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product and the OPMA is recommending approval for this BLA from a sterility assurance and microbial product quality perspective.
A pre-license inspection (PLI) of the DS manufacturing and testing site, Roche Diagnostics GmbH, Penzberg, Germany (Roche Penzberg; FEI: 3002806560) was conducted March 2-10, 2023, with a recommendation of approval for this site during the initial submission cycle. For the DP manufacturing site, Roche Diagnostics GmbH at Mannheim, Germany (FEI: 3002806559), the recommendation for the PLI conducted during the initial submission cycle (July 10-14, 2023) was for withhold approval, but following the reinspection conducted at the same site between March 11-20, 2024, an approval recommendation was made.
The immunogenicity assays to detect and confirm anti-drug antibodies (ADAs) and neutralizing antibodies (nAbs) against atezolizumab and hyaluronidase in the clinical studies to support this BLA were adequately validated and suitable for their intended purpose.
Individual assessments for each discipline are located in separate documents in Panorama.

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate with PMCs/PMRs**
Immunogenicity Assay	**-**	**Adequate**
Facilities	**-**	**Adequate**
Microbiology	**-**	**Adequate**

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
As an initial matter, we determined that no U.S. standard of potency has been prescribed for TECENTRIQ HYBREZA/atezolizumab and hyaluronidase-tqjs (i.e., there is no specific test method described in regulation for TECENTRIQ HYBREZA/atezolizumab and hyaluronidase-tqjs that establishes an official standard of potency). We next considered whether potency is a factor for TECENTRIQ HYBREZA/atezolizumab and hyaluronidase-tqjs within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for TECENTRIQ HYBREZA/atezolizumab and hyaluronidase-tqjs for purposes of § 610.61(r) because lot variability is not a concern for TECENTRIQ HYBREZA/atezolizumab and hyaluronidase-tqjs as TECENTRIQ HYBREZA/atezolizumab and hyaluronidase-tqjs's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:

(b) (4)

4. Annual post-approval stability protocol

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:
   a. Real time leachable study
   b. Annual post-approval stability protocol

ii. Residual risk: See PMC documented in section 3e. The PMC was agreed to for quality data from atezolizumab SC manufactured with hyaluronidase produced at the (b) (4) . All atezolizumab SC DP manufactured to date has utilized hyaluronidase manufactured at the (b) (4) facility (referred to as (b) (4) facility by Applicant,), however both facilities are licensed to manufacture hyaluronidase that may be utilized for the production of atezolizumab SC DP under the referenced BLA 761064. The hyaluronidase from both sites has previously been shown to be comparable, so comparable manufacture of atezolizumab SC DP is expected.

iii. Future inspection points to consider: None

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRIAN A ROELOFS
08/16/2024 03:52:28 PM

VIRGINIA A CARROLL
08/16/2024 03:56:50 PM

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Product Quality Assessment III

LABELS AND LABELING ASSESSMENT

Date of Assessment:	July 24, 2024
Assessor:	Diana Pei, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Yongmin Liu, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XIV
Application:	BLA 761347-ORIG-1-RESUB-30
Applicant:	Genentech, Inc., A Member of the Roche Group
Submission Date:	November 15, 2023
Product:	Tecentriq Hybrez (atezolizumab and hyaluronidase-tqjs)
Dosage form(s):	injection
Strength and Container-Closure:	1,875 mg atezolizumab and 30,000 units hyaluronidase per 15 mL (125 mg/2,000 units per mL) in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for atezolizumab and hyaluronidase-tqjs seeking approval for the treatment of patients with (b) (4) non-small cell lung cancer, small cell lung cancer, hepatocellular carcinoma, melanoma, and alveolar soft part sarcoma.
Recommendations:	The prescribing information, medication guide, container label, and carton labeling are acceptable from an OPQA III labeling perspective.

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

n/a = not applicable for this assessment

DISCUSSION

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

CONCLUSION

The prescribing information and medication guide submitted on July 12, 2024 and container label and carton labeling submitted on November 15, 2023 were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Medication Guide (submitted on November 15, 2023) \\CDSESUB1\EVSPROD\bla761347\0030\m1\us\redlined-label-text.docx
- Container Labels (submitted on November 15, 2023)

(b) (4)

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

Container[4] Label Evaluation

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

Manufacturer name, address, and license number (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

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

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: Label is small. Required statement appears on carton labeling.

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

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

Comment/Recommendation: The product contains a container label.

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

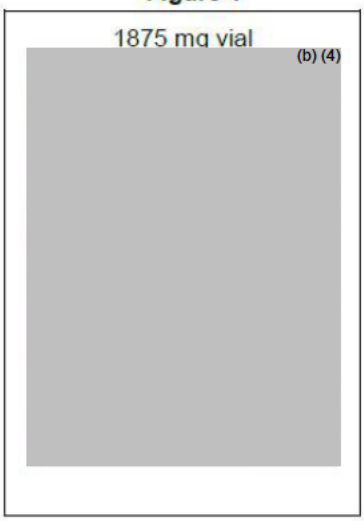
Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *Applicant's response:* *The Applicant confirms that there is no text on the ferrule and cap overseal of the vials.*

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

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located *Applicant's response:* *The label is placed around the circumference of the vial. A sufficient area of the container remains uncovered for the label's full length or circumference to permit full inspection of the vial contents.* *The viewing window between the two ends of the vial labels are:* • *Approximately 7.96 mm (0.31 in) for the 1875 mg vial*

Photo of the vial label is provided in Figure 1.

Figure 1



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

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

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	☐ Yes ☐ No ☒ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

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

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

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

Comment/Recommendation: The label does not display text in Spanish.

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

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: The label is small and could be considered a partial label. Thus, a dosage statement is not required.

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

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

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

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

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

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

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

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

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

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

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

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

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

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

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: The drug product is not made with latex (natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex).

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

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

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

Comment/Recommendation:
To Applicant: Remove the statement "No U.S. standard of potency" from the carton labeling because our view is that 21 CFR 610.61 (r) is not applicable.

Applicant's response:
The Applicant agrees to remove the statement "No U.S. standard of potency" from the carton labeling. Refer to Module 1.14.1.1 for updated draft artwork.

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

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

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

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

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

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

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

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

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

Comment/Recommendation: The label does not display text in Spanish.

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

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

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

Comment/Recommendation: The drug product does not contain phenylalanine.

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

Comment/Recommendation: The drug product does not contain sulfites.

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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

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

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

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

Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

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

Recommended labeling practices references: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: To Applicant: Provide the clarity of the solution.

Applicant has updated and added the clarity of the solution.

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Revise to "human recombinant" after hyaluronidase. The official name from USP Dictionary of USAN and the display name in FDA GSRS is hyaluronidase (human recombinant).

The applicant has revised as requested.

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

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

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Medication Guide Evaluation

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

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

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

Comment/Recommendation: To Applicant: Revise the active ingredient to "atezolizumab and hyaluronidase-tqjs".

The applicant has revised as requested.

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

APPENDIX C. Acceptable Labels and Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

- Prescribing Information and Medication Guide (submitted on July 12, 2024)
  \\CDSESUB1\EVSPROD\bla761347\0044\m1\us\draft-labeling-text.docx
- Container Label (submitted on November 15, 2023)
  \\CDSESUB1\EVSPROD\bla761347\0030\m1\us\11001668.pdf

(b) (4)

- Carton Labeling (submitted on November 15, 2023)

Diana Pei

Digitally signed by Diana Pei
Date: 7/31/2024 11:29:42AM
GUID: 6352da2c009ad0777a2c3b47ec094b9a

Yongmin Liu

Digitally signed by Yongmin Liu
Date: 7/31/2024 03:59:45PM
GUID: 5632432d003b3167c6d727f9ff58f202

BLA Executive Summary Addendum
Assessment Date: September 3, 2023

Addendum: This addendum has been prepared following the determination of compliance status for the drug product manufacturing facility for STN 761347. The final determination of compliance status of the manufacturing facilities has concluded with a withhold approval recommendation for the drug product manufacturing facility (Roche GmbH (FEI: 3002806559), Mannheim, Germany). For all other assessment information, including the review of drug substance and drug product manufacturing processes, immunogenicity assays and microbiology, refer to the OPQ IQA executive summary memorandum uploaded to DARRTS on July 21, 2023.

(b) (4)

1. Application/Product Information

BLA number	761347
Submission Type	Original Submission
Regulatory Pathway	NME 351(a)
Associated IND/BLA	Clinical Development was performed under IND 140100 BLA 761034 for manufacture of atezolizumab for intravenous (IV) injection BLA 761064 for the manufacture and control of hyaluronidase (rHuPH20).
Review Designation	Standard Review
Applicant	Genentech, Inc.
Indication	The same as those for the atezolizumab intravenous (IV) formulation under BLA 761034:

	Non-small cell lung cancer, small cell lung cancer, hepatocellular carcinoma, melanoma, and alveolar soft part sarcoma.
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: TECENTRIQ HYBREZA
	Non-proprietary Name/Code Name: Atezolizumab and hyaluronidase-tqjs
	OBP Naming Atezolizumab: MAB HUMANIZED (IGG1 N298A) ANTI Q9NZQ7 (PD1L1_HUMAN) [MPDL3280A] Hyaluronidase: RPROTFRAG P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20]
Drug Product Description	Tecentriq Hybreza (Atezolizumab for subcutaneous (SC) administration) DP is provided as a sterile, colorless-to-slightly yellow solution for subcutaneous injection with no preservatives. Each 20 mL single-dose vial contains 1875 mg/15 mL (nominal) of atezolizumab and 2000 U/mL rHuPH20. Atezolizumab SC DP is formulated with 20 mM L-Histidine, 240 mM Sucrose, 0.6 mg/mL Polysorbate 20, 10 mM L-Methionine, and pH-adjusted with (b) (4)% Acetic Acid to a target pH of 5.8. Atezolizumab is a humanized immunoglobulin (Ig)G1 monoclonal antibody (mAb). Atezolizumab targets PD-L1 and prevents the interaction of PD-L1 with PD-1 as well as B7.1. The interference of this interaction enhances tumor-specific T cell response and its mediated tumor cell killing. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and was engineered to eliminate Fc-effector function via a single amino acid substitution. rHuPH20 is a glycosylated single-chain protein with 447 amino acids. rHuPH20 depolymerizes the gel-like hyaluronan (hyaluronic acid) at the site of injection resulting in a decreased resistance to fluid flow and a transient increase in permeability of the local

	subcutaneous tissue to support the new route of administration.		
Dosage Form	Liquid. Atezolizumab SC drug substance (DS) is a clear and colorless solution.		
Strength	Each 20 mL single-dose vial contains 1875 mg/15 mL (nominal) of atezolizumab and 2000 U/mL rHuPH20.		
Route of Administration	Subcutaneous (sc)		
Primary Container Closure System	A (b) (4) glass vial with a rubber stopper crimped with an aluminum seal fitted with a plastic flip-off cap.		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance (DS)	Yongmin Liu	Brian Roelofs
	Drug product (DP)	Yongmin Liu	Brian Roelofs
	Immunogenicity Assay	Yongmin Liu	Brian Roelofs
	Facility	DS: Maria Scott DP: Yi (Eva) Wang	Michael Shanks
	Microbiology	DS: Maria Scott DP: Yi (Eva) Wang	Virginia Carroll
	RBPM	Nowrin Kakon	
	ATL	Brian Roelofs	
OPQ Issued Consults	Emerging Technology Team (ETT): Consult was issued for assessment by the ETT concerning the use of Raman spectroscopy-based ID method for finished ID		

	testing. The ETT determined that the method is suitable for the intended purpose. (b) (4)

2. Recommendation and Conclusion on Approvability
   Recommendation: Complete Response

   The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761347 for TECENTRIQ HYBREZA manufactured by Genentech, Inc.. The data submitted in this application are not sufficient to support a conclusion that the manufacture of TECENTRIQ HYBREZA is well-controlled and will lead to a product that is pure and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Genentech, Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

3. Draft Complete Response Comments and Additional Comments (if applicable):

   Facility Inspections
   During a recent inspection of the Roche Diagnostics GmbH (FEI: 3002806559) manufacturing facility for this BLA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this BLA may be approved.

4. Basis for Recommendation
   a. Summary: Tecentriq Hybreza (Atezolizumab for subcutaneous (SC) administration with hyaluronidase (rHuPH20)) DP is provided as a sterile, colorless-to-slightly yellow solution for subcutaneous injection with no preservatives. Atezolizumab is a humanized immunoglobulin (Ig)G1 monoclonal antibody (mAb) that targets PD-L1 and prevents the interaction of PD-L1 with PD-1 as well as B7.1. The interference of this interaction enhances tumor-specific T cell response and its mediated tumor cell killing. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells

and was engineered to eliminate Fc-effector function via a single amino acid substitution. rHuPH20 is a glycosylated single-chain protein with 447 amino acids that depolymerizes the gel-like hyaluronan (hyaluronic acid) at the site of injection resulting in a decreased resistance to fluid flow and a transient increase in permeability of the local subcutaneous tissue to support the new SC route of administration.

Assessments of product quality from the Office of Biotechnology Products (OBP) and the microbiological safety from the Office of Pharmaceutical Manufacturing Assessment (OPMA) concluded with recommendations of approval. The DS manufacturing and testing site, Roche Diagnostics GmbH, Penzberg, Germany (Roche Penzberg; FEI: 3002806560) pre-license inspection (PLI) concluded with an approval recommendation.

The outcome of the determination of compliance status of the Roche Diagnostics GmbH (Mannheim, Germany, FEI: 3002806559) facility following PLI is for a withhold of this facility. Therefore, satisfactory resolution of the deficiencies is required before this BLA may be approved.

The immunogenicity assays to detect and confirm anti-drug antibodies (ADAs) against atezolizumab and rHuPH20 in the clinical studies to support this BLA were adequately validated and suitable for their intended purpose.

Individual assessments for each discipline are located in separate documents in Panorama.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assay	-	Adequate
Facilities	-	Inadequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable however a complete response is recommended for the application due to facilities deficiencies.

d. Potency Assessment for Labeling:

Not applicable as OPQ does not recommend approval of this application.

5. Life-Cycle Considerations

Not applicable as OPQ does not recommend approval of this application.

a. Established Conditions based on ICH Q12 principles: No

Comments: (b) (4) .

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRIAN A ROELOFS
09/03/2023 01:05:50 PM