CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761224Orig1s000

PRODUCT QUALITY REVIEW(S)

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	12/17/2021
Assessor:	Koung Lee, RPh, MSHS Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Andrea Franco, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 4
Application:	BLA 761224
Applicant:	AstraZeneca AB
Submission Date:	May 7, 2021,…12/1/2021(carton), 12/14/2021 (USPI), and 12/16/2021(containers)
Product:	TEZSPIRE (tezepelumab-ekko)
Dosage form(s):	Injection
Strength and Container-Closure:	210 mg/1.91 mL (110 mg/mL) in a single-dose vial or a single-dose prefilled syringe
Purpose of assessment:	The Applicant submitted a biologics license application for a Biologics License Application (BLA 761224) for approval to commercialize tezepelumab (solution for injection, 110 mg/mL) in the United States for the add-on maintenance treatment of patients with (b) (4) severe asthma aged 12 years and older, (b) (4)
Recommendations:	The prescribing information, container labels, and carton labeling are acceptable from an OBP labeling perspective.

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

n/a = not applicable for this assessment

DISCUSSION

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

CONCLUSION

The prescribing information (12/14/2021), container labels (12/16/2021), and carton labeling (12/1/2021) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

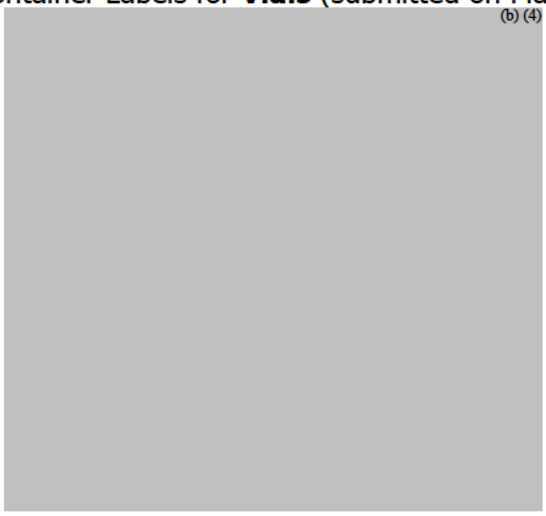
APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Patient Information (submitted on May 7, 2021)
  \\CDSESUB1\evsprod\bla761224\0001\m1\us\nonannotated-draft-label-tezepelumab-uspi.docx

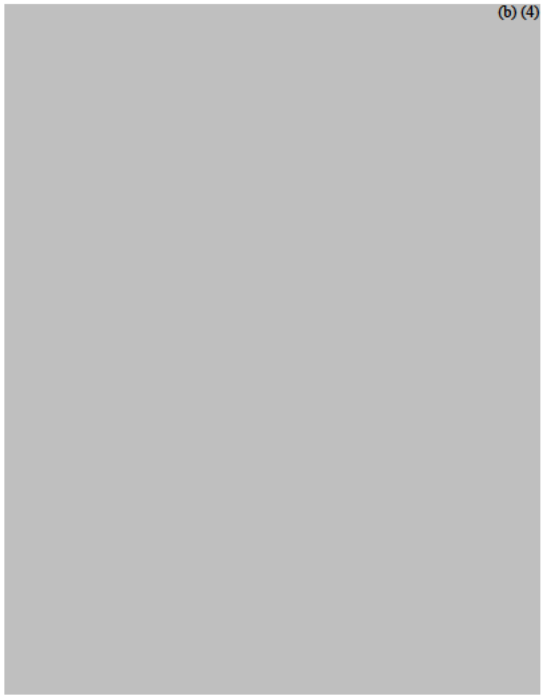
- Container Labels for **Vials** (submitted on May 7, 2021)

(b) (4)



- Container Labels for **Prefilled Syringes** (submitted on May 7, 2021)

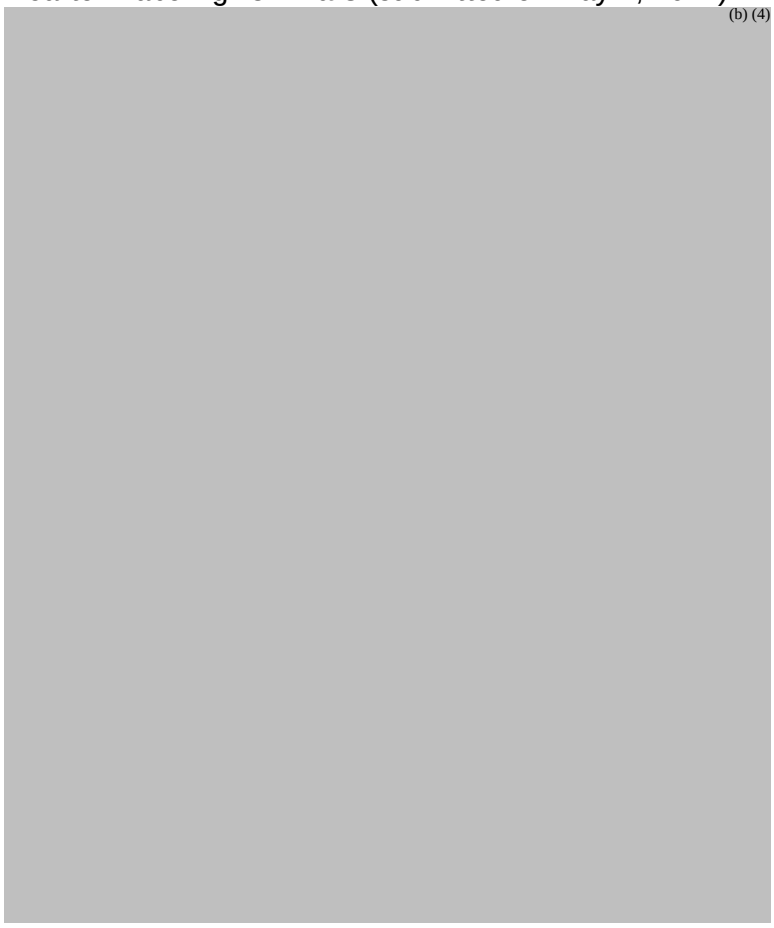
(b) (4)



(b) (4)

- Carton Labeling **for Vials** (submitted on May 7, 2021)

(b) (4)



- Carton Labeling for **Prefilled Syringe** (submitted on May 7, 2021)

(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

Comment/Recommendation:
Revise the placeholder 'Tradename' and 'tezepelumab-xxxx' to the respective conditionally approved name and suffix: 'Tezspire (tezepelumab-ekko)'. **Response:** Applicant revised as requested. Acceptable

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

[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.

Recommended labeling practices (U.S. license number for container bearing a partial label[5]) ***Partial Label has limited space to include U.S. License Number.***	☐ 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

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes

[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."

	☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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

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

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

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

Comment/Recommendation:
To applicant: Confirm there is no text on the ferrule and cap overseal of the vials.
Response: Confirmed. Acceptable

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

Comment/Recommendation:
To applicant: 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 for vials and PFS.

Response: Confirmed. Acceptable

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

Comment/Recommendation:
To applicant: If space provides, consider including the route of administration "For subcutaneous use".
Applicant added the ROA.

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

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

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

Comment/Recommendation:
To applicant: Revise to include "Single-dose vial/prefilled syringe"

Response: not enough room on the PFS label to include it. Acceptable since it is not required.

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

Prominence of required label statements (container label)	**Acceptable**

Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

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

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

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Please confirm the linear bar code will comply with 21 CFR 201.25 and 21 CFR 610.67 for the proposed prefilled syringe.

Applicant added the bar code in their 12/16/2021 response.

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

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	

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: Considered a partial label and single dose, therefore, 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

Comment/Recommendation: Considered a partial label, therefore, not required.

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

[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.

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

Comment/Recommendation: DMEPA comment

Revise the placeholder 'Tradename' and 'tezepelumab-xxxx' to the respective conditionally approved name and suffix: 'Tezspire (tezepelumab-ekko)'.

Response: Applicant revised as requested. Acceptable

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

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

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation:
To applicant: Include "To ensure consistency with the Prescribing Information, add the statement "If needed Tezspire may be stored at room temperature between 68°F to 77°F (20°C to 25°C) for maximum of 30 days. Once stored at room temperature, do not place in refrigerator. Discard after 30 days."

Date removed from refrigerator:
__/___/___.

Response: Applicant revised as requested. Acceptable

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

Comment/Recommendation:
To product quality reviewer:
Do not shake? Yes, this is accurate.
Do not Freeze? Yes, this is accurate.
Do not expose to heat? Yes, this is accurate.

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:
To product quality reviewer: Natural Rubber?
Both needle cover and vial stopper comply with USP <381> Elastomeric Closures for Injections, Physicochemical Test Procedures and USP<88> for Biological reactivity tests in vivo.

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

Comment/Recommendation:

To applicant: Revise the list of inactive ingredients to appear in alphabetical order consistent with your prescribing information and read as follows:
"Each single-dose (b)(4) vial (b)(4) delivers 1.91 mL containing 210 mg tezepelumab-xxxx, glacial acetic acid (2.8 mg), L-proline (48 mg), polysorbate 80 (0.19 mg), sodium hydroxide and water for injection, USP. The pH is 5.2.

Response: Revised. Acceptable

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

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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

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

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

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

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

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

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

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

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

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

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

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

	☒ N/A

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

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation:
To applicant: Revise the Statement of Dosage from (b) (4) (b) (4) to read "Dosage: See Prescribing Information." to be in alignment with PLR formatting.

Response: Revised as requested. Acceptable

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

Other (package labeling)	**Acceptable**
	☐ 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*	✓ Yes ☐ No ☐ N/A

and discoloration prior to administration, whenever solution and container permit."	
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
To product quality reviewer?
Do not expose to heat? Yes, this is accurate
Do not shake? Yes, this is accurate.
Clear to opalescent, colorless to light yellow solution" Accurate? Yes

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

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: Removed (b) (4) from the text since this is information typically found in section 12 under Mechanism of Action.

Response: Revised as requested.

To product drug quality: Is MW accurate? Yes

Preservative free? Yes

Sterile? Yes

To drug product description? Accurate

Not made with natural rubber? No

Both needle cover and vial stopper comply with USP <381> Elastomeric Closures for Injections, Physicochemical Test Procedures and USP<88> for Biological reactivity tests in vivo.

To product quality description: Are the inactive ingredients quantitative amount accurate? Yes

pH accurate? Yes

Are there any pH adjusters that need to be added that were utilized? No, sodium hydroxide already included as an inactive ingredient.

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: (b) (4)	☐ Yes ☐ No ☒ N/A

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

Comment/Recommendation:
To product quality reviewer: Is this temp/storage statement supported by data? Yes

Max of 30 days at room temperature? Yes, statement is supported by thermal studies

No Natural rubber utilized? The needle cover and vial stopper comply with USP <381> and <88>

To Applicant: Relocated "with a fixed 27-gauge ½ inch needle with a needle cover" from section 11 since this information is typically found in the HOW SUPPLIED section.

Response: Applicant revised as requested.

To product quality reviewer:

Protect from light? Yes, it is accurate

Do not freeze? Yes, it is accurate

Do not shake? Yes, it is accurate

Do not expose to heat? Yes, it is accurate

To Micro reviewer: Is there any issues with micro concerning this storage and storage time frame?

36°F to 46°F (2°C to 8°C). ?

may be kept at room temperature between 68°F to 77°F (20°C to 25°C) for a maximum of 30 days?

Response from Micro reviewer: Sorry forgot to bring it up during the AT meeting just now; OPMA has no concerns with DP stored for extended periods as long as it is prior to breach of the primary container closure system, so generally no issues with PFS or with single-use vials that do not require dilution or reconstitution

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 N/A

Patient Information Labeling Evaluation

PATIENT INFORMATION LABELING	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

PATIENT INFORMATION LABELING	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for Patient Labeling: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	☐ Yes ☐ No ☒ N/A

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

PATIENT INFORMATION LABELING	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ 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

Instructions for Use Evaluation N/A

APPENDIX C. Acceptable Labels and Labeling

- Container Labels (submitted on 12/16/2021)

(b) (4)

- Carton Labeling (submitted on 12/01/2021)

(b) (4)

18 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Koung Lee

Digitally signed by Koung Lee
Date: 12/17/2021 08:13:19AM
GUID: 508da70800028c14715bf8bf6a107f74

Leslie Rivera-Rosado

Digitally signed by Leslie Rivera-Rosado
Date: 12/17/2021 08:42:14AM
GUID: 508da7420002bb7d3e8efdb59ecfa84e

Breakthrough Therapy Designation and Priority Review

Recommendation: **BLA Approval**

BLA/NDA Number: 761224
Assessment Number: First Round
Assessment Date: 11/01/2021

Drug Name/Dosage Form	Tezspire (tezepelumab-ekko), injection
Strength/Potency	110 mg/mL (210 mg)
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Tezspire is a thymic stromal lymphopoietin (TSLP) blocker, human monoclonal antibody (IgG2λ) indicated for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.
Applicant/Sponsor	AstraZeneca AB
US agent, if applicable	AstraZeneca Pharmaceuticals LP

Product Overview:

Tezepelumab is a fully human monoclonal immunoglobulin (IgG2λ) that specifically binds to human thymic stromal lymphopoietin (TSLP) and prevents its interaction with the TSLP receptor (TSLPR). TSLP, an epithelial cell-derived cytokine, occupies an upstream position in the asthma inflammatory cascade and plays a central role in the initiation and persistence of airway inflammation in asthma. Tezepelumab is indicated for the add-on maintenance treatment of patients aged 12 years and older with severe asthma.

Tezepelumab final drug product (DP) is a sterile, single-dose, preservative free, clear to opalescent and colorless to light yellow solution supplied in either a vial or an accessorized pre-filled syringe (APFS), containing 210 mg tezepelumab. The DP vial and DP APFS are intended for subcutaneous injection and contain 1.91 mL deliverable volume of 110 mg/mL tezepelumab, [redacted] (b) (4) L-proline, and [redacted] (b) (4) polysorbate 80 at pH 5.2.
The DP is manufactured at Amgen Manufacturing Limited (AML), Juncos, Puerto Rico.

Tezepelumab was granted a breakthrough therapy designation on 9/4/2018 and priority review on 7/7/2021.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance (DS), Drug Product (DP), and Immunogenicity assays	Andrea Franco	OPQ/OBP/DBRR IV
Labeling	CDR James Barlow	OPQ/OBP
DS Facilities/ Microbiology	Jeanne Finger	OPQ/OPMA/DBM
DP Facility/Microbiology	Wendy Tan	OPQ/OPMA/DBM
Device	Michaela Schulman	CDRH/OPEQ/OHT3/ DHT3C
Team Leads	LCDR Leslie A. Rivera Rosado (Product quality)	OPQ/OBP/DBRR IV

	Zhong Li (Facilities) Maxwell Van Tassell (Microbiology) Suzanne Hudak (Device)	OPQ/OPMA/DBM OPQ/OPMA/DBM CDRH/OPEQ/OHT3/ DHT3C
OPQ RBPM	Anita Brown and CDR Hamet Touré	OPQ/OPRO
Application Technical Lead	LCDR Leslie A. Rivera Rosado	OPQ/OBP/DBRR IV

Multidisciplinary Assessment Team:

Discipline	Reviewer	Office/Division
RPM	Linda Ebonine, Ladan Jafari (CPMS)	OND/ORO/DROII
Cross-disciplinary Team Lead	Miya Paterniti (CDTL)	OII/DPACC
Medical Officer	Jennifer Lan (MO), Miya Paterniti (CDTL)	OII/DPACC
Pharm/Tox	Anup Srivastava, Carol Galvis (TL)	OII/DPT II
Clinical Pharmacology	Jing Niu, Yunzhao Ren (TL)	OCP/DIIP
Pharmacometrics	Jingyu "Jerry" Yu (TL)	OCP/DPM
Genomics	Bart Rogers / Christian Grimstein (TL)	OCP/DTPM
Biostatistics	Susan Mayo, Yongman Kim (TL)	OB/DB III
OSI	Suyoung "Tina" Chang, Karen Bleich (TL)	OSI/DCCE/GCPAB
OSE SRPM	Cristina Attinello, Nichelle Rashid (TL)	OSE PMS
OSE/DMEPA	Lissa Owens (SE), Idalia Rychlik (TL)	OSE/DMEPA I
OSE/OPE/DEPI	Yan Li / Efe Eworuke (TL)	OSE/OPE/DEPI II
OSE/OPE/DVP	Scott Janiczak / Lisa Wolf (TL)	OSE/OPE/DVP I
OSE/OMEPRM/DRM	Donella Fitzgerald	OSE/OMEPRM/DRM
Patient Labeling	Marcia Williams (TL)	OMP/OMPI/DMPP
OPDP	Kyle Snyder	OPDP/DAPR II
DCOA	Onyeka Illoh	DCOA
OCP Office Director	Issam Zineh	OCP

1. Names:
   a. Proprietary Name/Trade Name: Tezspire
   b. Non-Proprietary/USAN/INN: Tezepelumab
   c. CAS name: 1572943-04-4
   d. Chemical name: Anti-thymic stromal lymphopoietin (TSLP) monoclonal antibody
   e. OBP systematic name: HUMAN (IGG_2) ANTI Q969D9 (TSLP_HUMAN) [MEDI9929]
   f. Other Names: AMG 157, MEDI9929

Submissions Assessed:

Submission	Date Received	Review Completed (Yes/No)
STN 761224/1 (Original BLA submission)	5/7/2021	Yes
STN 761224 /2 (Stability updates)	5/21/2021	Yes
STN 761224 /3 (response to IR #1 – OPMA)	5/21/2021	Yes
STN 761224/4 (response to IR #2 – OPMA)	6/9/2021	Yes
STN 761224/15 (response to IR #3 – OPMA and OBP)	8/23/2021	Yes
STN 761224/19 (response to IR #4 – OBP)	9/15/2021	Yes
STN 761224/22 (response to IR #5 – OPMA)	9/20/2021	Yes
STN 761224/23 (response to IR #6 – OBP)	9/27/2021	Yes
STN 761224/25 (response to IR #7 – OBP)	10/1/2021	Yes
STN 761224/26 (Response to IR #8 – CDRH and OBP)	10/7/2021	Yes
STN 761224/28 (Response to IR #9 – OBP)	10/13/2021	Yes

Quality Assessment Data Sheet:

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

A. DMFs:

DMF	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE COMPLETED
(b) (4)			3	N/A	N/A
			2	Adequate	10/12/21
			3	N/A	10/13/21
			3	N/A	N/A
			2	Adequate	10/12/21
			3	N/A	N/A

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

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

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

Document	Application Number	Description
IND	103031	Original IND submission

3. Consults:

Discipline/Topic	Date Requested	Status	Recommendation	Assessor(s)
Review of delivery device (Accessorized pre-filled syringe)	6/7/2021	Completed 10/25/2021	The device constituent of the combination product is approvable for the proposed indication. A device quality systems / facilities assessment is not required for this product because the product is not	Michaela Schulman Suzanne Hudak (TL) CAPT Alan M. Stevens (Assistant Director, DHT3C)

			an emergency (i.e., life-saving and essential[1]) treatment that are administered by non-health care professionals.	

4. Environmental Assessment of Claim of Categorical Exclusion:

In Module 1 (1.12.14 Environmental Assessment – Claim for Categorical Exclusion), AstraZeneca AB/Amgen claims categorical exclusion, in accordance with 21 CFR 25.31(c), from the requirement to prepare an Environmental Assessment as tezepelumab is not expected to significantly alter the concentration of the substance, its metabolites, or degradation products in the environment. No extraordinary circumstances exist, as referenced in 21 CFR §25.21(a) or 21 CFR §25.21(b) that require submission of an Environmental Assessment.
Conclusion: The claim of categorical exclusion is acceptable.

[1] Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761224 for Tezspire (tezepelumab-ekko) manufactured by AstraZeneca AB. The data submitted in this application are adequate to support the conclusion that the manufacture of Tezspire is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance:
    - Amgen Inc. (FEI: 2026154): One Amgen Center Drive Thousand Oaks, California, 91320, United States (USA)
  - Drug Product:
    - Amgen Manufacturing Limited (FEI: 1000110364): Carr 31 KM 24.6 Juncos, Puerto Rico, 00777, United States (USA)

- Dosage form and fill size:
  - Injection: 110 mg/mL (210 mg), vials and accessorized pre-filled syringe (APFS)

- Dating period:
  - Drug Product: 36 months: 2-8 °C
  - Drug Substance: (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
  - Rationale, if exempted: specified product
    Note: Tezspire (tezepelumab-ekko) is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

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

The tezepelumab drug substance (DS) will be manufactured at Amgen Inc. (FEI: 2026154) and the Tezspire drug product (DP) at Amgen Manufacturing Limited (FEI: 1000110364). Pre-licensing inspections or assessments were conducted at Amgen, Inc. and Amgen Manufacturing Limited and the facilities were found acceptable for the proposed operations.

The Center for Devices and Radiological Health (CDRH), Office of Product Evaluation and Quality (OPEQ), Office of Health Technology 3 (OHT3), Division of Drug Delivery and General Hospital Devices, and Human Factors (DHT3C) provided an assessment of the needle safety device constituent part of the prefilled syringe product. No approvability issues were identified from a device constituent parts of the combination product. They also determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency treatment that is administered by non-health care professionals.

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

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

None.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA type	CQA	Risk	Origin	Control Strategy
Potency (biological activity)	Function of binding to TSLP and preventing binding of TSLP to its receptor	Bioactivity (efficacy)	Intrinsic to the molecule	(b) (4)
Identity	Identity (by ELISA)	Efficacy, safety, and immunogenicity	Intrinsic to the molecule	
Product-related impurities	Size-Variants: Aggregates	Potential to impact potency and to cause an immunogenic response	Cell culture, potential formation during processing and storage	
	Size-Variants: Dimer	Potential to impact potency and PK	Cell culture, potential formation during processing and storage	
	Tryptophan oxidation (CDR)	Potential to impact potency and to cause an immunogenic response	Potential formation during processing and storage	
	Fragmentation (peptide bond)	Potential impact to PK	Cell culture, potential formation during processing and storage	
Product-related variants	Charge variants	N/A	Cell culture, potential shifts in processing and storage	
	High mannose	Potential impact to PK	Cell culture	

B. Drug Substance [Tezepelumab] Quality Summary

Table 2 provides a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that derive from the drug substance manufacturing process and general drug substance attributes.

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

CQA type	CQA	Risk	Origin	Control Strategy
Process-related impurities	Host Cell DNA	N/A	Cell culture	(b) (4)
	Host Cell Proteins (HCP)	Potential to impact immunogenicity	Cell culture	
	(b) (4)	Potential to impact immunogenicity	(b) (4)	
	Extractables/Leachables	Immunogenicity, Safety	Raw materials, manufacturing process	
Adventitious Agents	Viral Safety (Adventitious viruses or mycoplasma)	Safety	Introduction from materials or environment, propagation in cell culture	
	Bioburden	Safety	Introduction from materials or environment	
	Bacterial Endotoxins	Safety	Introduction from materials or bioburden	
Composition and Strength	Protein Concentration	Potential impact to patient safety and efficacy	Formulation	
	Osmolality	Potential impact to patient safety	(b) (4) (formulation)	

CQA type	CQA	Risk	Origin	Control Strategy
	pH	Potential impact to potency	(b) (4) (formulation)	(b) (4)
	Appearance: Clarity	Reduction in clarity may indicate undesirable conditions with potential impact to safety and/or efficacy	Intrinsic to product	
	Appearance: Color	Color change may indicate tryptophan oxidation or other undesirable conditions with potential impact to safety, and/or efficacy.	Intrinsic to product	
	Visible particles	Potential impact to patient safety	Potential to be formed during processing and storage	
	Subvisible particles	Potential to impact patient safety and to cause an immunogenic response	Potential to be formed during processing and storage	
	Polysorbate 80 Content	Potential impact to safety due to potential formation or particles or other degradants if PS80 level is inadequate	(b) (4) DP formulation steps	

- **Description:**
  Tezepelumab is a human immunoglobulin $G_2\lambda$ monoclonal antibody directed against thymic stromal lymphopoietin (TSLP), produced in Chinese hamster ovary cells by recombinant DNA technology. Tezepelumab contains a total of 36 cysteine residues involved in both intrachain and interchain disulfide bonds. Each heavy chain contains 448 amino acids with 4 intrachain disulfides. Each light chain contains 214 amino acids with 2 intrachain disulfides. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 298. (b) (4) Alternate disulfide linkages (IgG2-A/B and IgG2-B) between the Fab and hinge regions exist. Tezepelumab has a molecular weight of approximately 147 kDa.

- **Mechanism of Action (MoA):**
  Tezepelumab binds to human TSLP with high affinity and prevents its interaction with the heterodimeric TSLP receptor. TSLP, an epithelial cell-derived cytokine, occupies an upstream position in the asthma inflammatory cascade and plays a central role in the initiation and persistence of airway inflammation in asthma.
  In asthma, both allergic and non-allergic triggers induce TSLP production. Blocking TSLP with tezepelumab reduces levels of a broad spectrum of biomarkers and cytokines associated with inflammation.

- **Potency Assay:** Receptor-ligand binding assay

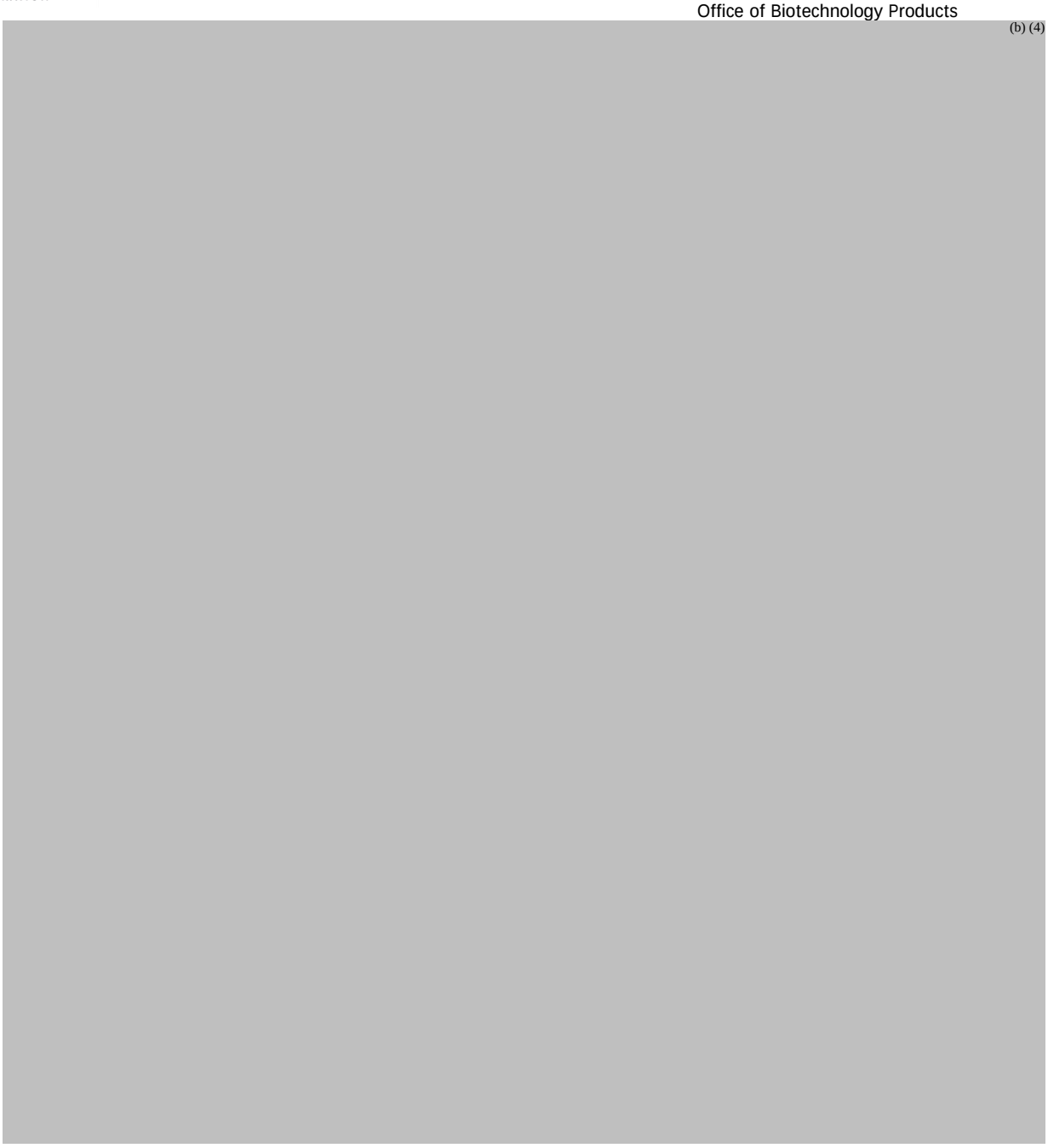
The receptor-ligand binding assay using TSLP and the TSLP receptor (TSLPR) is proposed as the potency assay for release and stability testing of tezepelumab drug substance and drug product samples. This assay is justified for this purpose since it is the most proximal measure of tezepelumab activity and directly reflects the molecular mechanism of action of tezepelumab, which is to bind TSLP and prevent it from binding to the TSLPR. Additionally, the applicant provided data demonstrating that the receptor-ligand binding assay and the cell-based reporter gene assay (both used during product development) generate statistically equivalent results.
The receptor-ligand binding assay provides a quantitative measure of the ability of tezepelumab to inhibit the binding of TSLP to TSLPR.

- **Reference Materials:**
Two tezepelumab reference standards were produced. (b) (4) The primary reference standard will be used to qualify new primary and working reference standards.
A working reference standard will be qualified and implemented upon approval of the BLA to enable the two-tiered approach for commercial use. The introduction of the new working reference standard will be submitted as part of the annual report.

- **Critical starting materials or intermediates:**
(b) (4)

- **Manufacturing process summary:**
The tezepelumab drug substance manufacturing (b) (4)
(b) (4)

(b) (4)



- **Container closure:**
  The drug substance container closure system is (b) (4)

Component	Material	Supplier
[redacted]		

The CCI testing evaluated [redacted]

- **Dating period and storage conditions:** [redacted] months: [redacted] °C

C. Drug Product [Tezspire] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

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

CQA type	CQA	Risk	Origin	Control Strategy
Composition and Strength	Protein Concentration	Potential impact to patient safety and efficacy	Formulation	[redacted]
	Osmolality	Potential impact to patient safety	[redacted] (formulation)	
	pH	Potential impact to potency	[redacted] (formulation)	
	Polysorbate 80 Content	Potential impact to safety due to potential formation or particles or other degradants if PS80 level is inadequate	[redacted] DP formulation steps	
Contamination	Bioburden	Safety	Introduction from materials or environment	
	Bacterial Endotoxins	Safety	Introduction from materials or bioburden	
	Sterility	Impact to patient safety, product purity	Introduction from	

CQA type	CQA	Risk	Origin	Control Strategy
	Container closure integrity (sterility assurance)		process or breach in container integrity	(b) (4)
Particles (product or process related impurities)	Visible particles	Potential impact to patient safety	Potential to be formed during processing and storage	
	Subvisible particles	Potential to impact patient safety and to cause an immunogenic response	Potential to be formed during processing and storage	
Appearance	Clarity	Reduction in clarity may indicate undesirable conditions with potential impact to safety and/or efficacy	Intrinsic to product	
	Color	Color change may indicate tryptophan oxidation or other undesirable conditions with potential impact to safety, and/or efficacy.	Intrinsic to product	
Volume in Container	Extractable or deliverable volume	Potential impact to patient safety and efficacy	(b) (4) steps	
Process-related impurities	Extractables/Leachables	Immunogenicity, Safety	Raw materials, manufacturing process	
Functionality	Break loose force Proper device functionality	Proper device functionality	Device	

- **Potency and Strength:**
  210 mg/1.91 mL (110 mg/mL) solution in a single-dose glass vial.
  210 mg/1.91 mL (110 mg/mL) solution in a single-dose pre-filled syringe.

- **Summary of Product Design:**
  Tezepelumab drug product is supplied as a sterile, single-dose, preservative-free solution for subcutaneous (SC) injection in a vial and APFS. The APFS is a drug-device combination product that consists of a pre-filled syringe subassembly (PFS-SA), plastic plunger rod, extended finger flange and a needle guard. The needle guard is activated upon completion of injection to prevent needle sticks. The commercial APFS assembly site is Amgen Manufacturing Limited (AML), located in Juncos, Puerto Rico (USA).

  The proposed commercial presentation and formulation for the vial and APFS consists of a 1.91 mL deliverable volume of 110 mg/mL tezepelumab, (b) (4) L-proline, and (b) (4) polysorbate 80 at pH 5.2. The tezepelumab drug product is formulated with (b) (4) (b) (4) L-proline, and (b) (4) polysorbate 80, at a final pH of 5.2

(b) (4) The commercial drug product formulation description is based upon the measured excipients values.

- **List of Excipients:** (b) (4) L-proline, and polysorbate 80
- **Reference Materials:** Same as tezepelumab drug substance.
- **Manufacturing process summary:**
The tezepelumab drug product manufacturing process consists of (b) (4) (b) (4) The commercial drug product manufacturing site is Amgen Manufacturing Limited (AML), located in Juncos, Puerto Rico (USA).
(b) (4) Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at release. Container closure integrity testing using a validated method is included in the stability program.
- **Container closure:**
  - **Vial:** 5 cc (b) (4) glass with 13 mm (b) (4) elastomeric stopper and an aluminum seal with flip-off dust cover
  - **APFS:** 2.25 mL (b) (4) glass syringe with a staked needle (27 G x ½ in.) covered with an elastomeric needle shield and a (b) (4) plunger stopper (b) (4) (b) (4) A plastic plunger rod is attached to the prefilled syringe. Syringe subassembly is inserted into an automatic needle guard with extended finger flange.
- **Dating period and storage conditions:** 36 months at 2 – 8 °C

D. Novel Approaches/Precedents: None identified.

E. Any Special Product Quality Labeling Recommendations:

- Each vial and pre-filled syringe contain a single dose
- Protect from light until time of use
- Store refrigerated between 2°C to 8°C. If necessary, the product may be kept at room temperature (20°C to 25°C) for a maximum of 30 days. Do not put back in the refrigerator once the product has reached room temperature. After removal from the refrigerator, the product must be used within 30 days or discarded.
- Visually inspect for particles or discoloration prior to administration.

F. Establishment Information:

Overall Recommendation: **Approve**			
DRUG SUBSTANCE			
Facility name and address	**FEI**	**Responsibilities and profile code(s)**	**Status**
Amgen Inc. (Amgen Thousand Oaks or ATO) One Amgen Center Drive, Thousand Oaks, California, United States (USA), 91320	2026154	Drug substance manufacture; drug substance (b) (4) lot release, and stability testing; (b) (4) bulk testing: bioburden; working cell bank production; master cell bank and working cell bank storage; drug product (in vial and APFS) lot release and stability testing. CBI	**Approve** - Based on 704(a)(4)
(b) (4)			**Approve** - Based on Previous History
Amgen Inc. (Louisville Distribution Center - referred to as LDC) 12000 Plantside Drive, Louisville, Kentucky, USA, 40299	3003750095	Master cell bank and working cell bank storage; drug product (in vial and APFS) distribution NEC	No Evaluation Necessary
(b) (4)			**Approve** - Based on Previous History
DRUG PRODUCT			
Amgen Manufacturing Limited (AML) Carr 31 KM 24.6, Juncos, Puerto Rico, USA, 00777	1000110364	Drug substance (b) (4) lot release, and stability testing; drug product manufacture (in vial), labeling and packaging; drug product (in APFS) manufacture, primary packaging and labeling; drug product (in vial and APFS) (b) (4) lot release, and stability testing; APFS assembly and testing; APFS secondary packaging; distribution. Performs BET and Sterility, CCIT – SVS FACTS 2019 AC. Current BPDR opened 2021. Last inspection in 2020 covered CBI. 2019 inspection covered BLA (b) (4)	**Approve** - Based on Inspection

G. Facilities:

Amgen Inc. (ATO)
In lieu of an on-site pre-approval inspection for the tezepelumab drug substance (DS) manufacturing facility, ATO (FEI 2026154), a review of requested manufacturing site records under Section 704(a)(4) was conducted and found satisfactory. On July 9, 2021, the Agency requested pre-inspection audit documents in support of the manufacture of the tezepelumab DS at ATO (FEI 2026154). On July 26, 2021, ATO submitted the requested documents (refer to FDA Form 4003 attachment) in support of BLA 761224.

Manufacture of tezepelumab DS takes place in (b) (4) a multiproduct facility that manufactures clinical and commercial products. Tezepelumab (b) (4) occurs in rooms (b) (4) Other products manufactured in the same areas are (b) (4) (b) (4) The proposed drug substance manufacturing facility is found to be acceptable to support the approval of BLA 761224, tezepelumab. (b) (4)

Amgen Manufacturing Limited (AML)
An on-site inspection of the Tezspire drug product manufacturing facility at AML was conducted on August 30, 2021 to September 08, 2021 as requested by CDER-DBM. A 4-Item FDA Form 483 was issued for (b) (4) The Investigator's initial recommendation was "Withhold". AML provided responses to the 483 Observations via email on September 20, 2021. The responses were reviewed and deemed satisfactory. The review memo is included in (b) (4)

H. Lifecycle Knowledge Management:

a. Drug Substance and Drug Product

i. Protocols approved:
- Qualification of new working cell banks
- (b) (4)
- (b) (4)
- Qualification of future reference standards
- Post-approval stability protocols for DS and DP

ii. Outstanding assessment issues/residual risk: None identified

iii. Future inspection points to consider: None identified

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/

LESLIE A RIVERA ROSADO
11/10/2021 02:21:04 PM