CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761344Orig1s000

PRODUCT QUALITY REVIEW(S)

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	May 13, 2024
Assessor:	Jennifer Kim, Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Odile Engel, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XV
Application:	BLA 761344
Applicant:	Amgen Inc.
Submission Date:	October 12, 2023
Product:	Imdelltra (tarlatamab-dlle)
Dosage form(s):	For injection
Strength and Container-Closure:	1 mg in single-dose vial 10 mg in single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application to seek approval of tarlatamb-dlle for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.
Recommendations:	The prescribing information, medication guide, patient labeling, instructions for use, container labels, 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

The applicant initially submitted Patient Information on October 12, 2023. In an Information Request (IR) dated March 29, 2024, the agency requested the applicant to convert the Patient Information section of the proposed product labeling to a Medication Guide. In response, the applicant submitted the Medication Guide on April 9, 2024.

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 submitted on April 24, 2024, medication guide submitted on April 9, 2024, container labels submitted on April 26, 2024, and carton labeling submitted on April 24, 2024, were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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
Comment/Recommendation: *The label is small and could be considered a partial label. Thus, the qualifying phrase "Manufactured by" and the manufacturer address are not required per 21 CFR 610.60(c).*	

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

[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."

	☐ 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, 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: *The label is small and could be considered a partial label. Thus, a medication guide statement is not required.*	

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The container is enclosed in a package.*	

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. *The applicant confirms that there is no text on the vial seal (including both the plastic cap and aluminum skirt).*	

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. *The applicant confirms that sufficient area of the container remains uncovered to allow for visual inspection when the label is affixed. Visual inspection is performed from the gap between the labels. In addition, the shoulder and bottom of the vial allows for viewing as needed.* • *The circumference of the* (b) (4) *vial is* (b) (4) *The primary label length is 44.45 mm, so there is no overlap.* • *The circumference of the* (b) (4) *vial is* (b) (4) *The primary label length is 57.15 mm, so there is no overlap.*	

- *The circumference of the 10R vial is 74.77 mm to 76.03 mm. The primary label length is 57.15 mm, so there is no overlap.*

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: Revise the route of administration to read "For Intravenous Infusion after Dilution" and relocate so the route of administration appears directly underneath the product strength. IMDELLTRA (tarlatamab-xxxx) for injection xx mg/vial For Intravenous Infusion after Dilution *The applicant revised as requested.*	

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
Comment/Recommendation:	

Add the statement, "Single-Dose Vial. Discard Unused Portion" to the PDP. See 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). *The applicant revised as requested.*

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
Comment/Recommendation: *The label is small and could be considered a partial label. Thus, a net quantity is not required.*	

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, FD&C Act section 502(e)	✓ 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: *The label is small and could be considered a partial label. Thus, an inactive ingredient statement is 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
Comment/Recommendation: If space permits, revise the storage information to read "Store refrigerated at 2°C to 8°C (36°F to 46°F)." for consistency with the prescribing information.	

Due to limitation of the space, the applicant proposed to retain the existing statement in the label. This is acceptable from OPQA III labeling perspective.

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A
IV Solution Stabilizer for Imdelltra *The label is small and could be considered a partial label. The product name, manufacturer name, U.S. license number, lot number and expiration date is present on the container label.*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Add the statement, "Single-Dose Vial. Discard Unused Portion" to the PDP. See 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). *The applicant revised as requested.* DMEPA's comment: The warning statement [redacted] (b) (4) ..." may be further improved. Post-marketing reports have shown that negative statements may have the opposite of the intended meaning because the word "not" can be overlooked and misinterpreted as an affirmative action. Revise to "Use ONLY to prepare the infusion bag prior to adding reconstituted IMDELLTRA." If space allows, after the "Use ONLY..." add "DO NOT use IV Solution Stabilizer to reconstitute Imdelltra". *The applicant revised as requested.*	

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

[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.

	☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
If space permits, relocate the U.S. license number to appear with the manufacturer information and as follows:

Manufactured by: Amgen Inc.
Thousand Oaks, CA 91320-1799 U.S.A.
U.S. license No.1080

The applicant revised as requested.

Revise the country-of-origin statement to read as "Product of USA. IV Solution Stabilizer Product of Ireland"

The applicant revised as requested.

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: 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
Comment/Recommendation: Relocate "Do not freeze" statement to appear with the storage information as follows: Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze. ATTENTION: Dispense the enclosed Medication Guide to each patient. *The applicant revised as requested.*	

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
Comment/Recommendation: Revise the route of administration to read "For Intravenous Infusion after Dilution". *The applicant revised as requested.* We recommend including a statement on the principal display panel to indicate that the product must be reconstituted and further diluted prior to administration. For example, "Must be reconstituted with sterile water for injection and further diluted." *The applicant revised as requested.*	

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, FD&C Act section 502(e)	✓ 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: Revise the content statement to read "Each vial of IMDELLTRA contains 1 mg of tarlatamab-xxxx, and also contains glutamic acid (0.72 mg), polysorbate 80 (0.04 mg), sucrose (37.1 mg), and sodium hydroxide as needed for adjustment to pH 4.2. After reconstitution with 1.3 mL of Sterile Water for Injection, the resulting concentration is 0.9 mg/mL." *The applicant revised as requested.* Revise the content statement to read "Each vial of IMDELLTRA contains 10 mg of tarlatamab-xxxx, and also contains glutamic acid (3.7 mg), polysorbate 80 (0.2 mg), sucrose (194.4 mg), and sodium hydroxide as needed for adjustment to pH 4.2. After reconstitution with 4.4 mL of Sterile Water for Injection, the resulting concentration is 2.4 mg/mL." *The applicant revised as requested.*	

Add the inactive ingredient information of the IV Solution Stabilizer included in the carton as follows: "Each vial of IV Solution Stabilizer contains (b) (4) citric acid monohydrate (36.75 mg), lysine hydrochloride (1598.8 mg), polysorbate 80 (7 mg), sodium hydroxide to adjust pH to 7.0, and water for injection. *The applicant revised as requested.*

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: *Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OPQA III Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for tarlatamab products (i.e., there is no specific test method described in regulation for tarlatamab 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 [trade name/this product] 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.* Remove the statement "No U.S. standard of potency" from the carton labeling because our view is that 21 CFR 610.61® is not applicable. *The applicant revised as requested.*	

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) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☐ 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

No 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
Comment/Recommendation: Relocate "Do not freeze" statement to appear with the storage information as follows: Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze. ATTENTION: Dispense the enclosed Medication Guide to each patient. *The applicant revised as requested.*	

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
Comment/Recommendation: We added additional information that further dilution is required. *The applicant revised as requested.*	

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 *Draft Guidance Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry* (January 2023)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised to the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit." per 21 CFR 201.57(c)(3)(iv). *This comment was not communicated to the applicant by the decision of the review team. The statement "Inspect parenteral drug products for particulate matter and discoloration prior to administration. Inspect that the solution is clear to opalescent, colorless to slightly yellow. Do not use if the solution is cloudy or has particulates." is included instead.* We added a statement that the reconstituted solution should be used within 4 hours of reconstitution. *The applicant revised as requested.* We revised to the typical room temperature range for consistency with other product labeling. *The applicant revised as requested.*	

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: We added additional information that further dilution is required. *The applicant revised as requested.* We added a description of identifying characteristics of the dosage forms. *The applicant revised as requested.*	

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), FD&C Act Section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) we revised the inactive ingredient by using established names for drugs (i.e., drug products and ingredients). The established name is the USP/NF monographs title, "glutamic acid". *The applicant revised as requested.* We revised the inactive ingredient list to appear in alphabetical order. *The applicant 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
Comment/Recommendation: We revised language for clarity.	

The applicant revised as requested. We revised to the typical room temperature range for consistency with other product labeling. *The applicant revised as requested.*

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
Comment/Recommendation: We added U.S. license number to the manufacturer information. *The applicant revised as requested.*	

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

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

Patient Information Labeling Evaluation: NA

Instructions for Use Evaluation: NA

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.

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Jennifer Kim

Digitally signed by Jennifer Kim
Date: 5/13/2024 09:01:11AM
GUID: 5e5438d2008138bdbae1db8d4abc0580

Odile Engel

Digitally signed by Odile Engel
Date: 5/13/2024 09:44:15AM
GUID: 59c00e8700e3b574f8dfa86aa5b675a4

BLA Executive Summary
Assessment Date: 4/29/2024

1. Application/Product Information

BLA number	761344
Submission Type	Original Submission (Orphan Drug Designation, Breakthrough Therapy Designation, Real-Time Oncology Review, Project Orbis)
Regulatory Pathway	NME 351(a)
Associated IND/BLA	IND 134859
Review Designation	Priority Review
Applicant	Amgen Inc.
Indication	Extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy (This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).)
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: IMDELLTRA
	Non-proprietary Name/Code Name: tarlatamab-dlle
	OBP Naming: FUS: MABFRAG HUMAN (IGG1 SCFC); MABFRAG HUMAN (SCFV) ANTI Q9NYJ7 (DLL3_HUMAN); MABFRAG HUMAN (SCFV) ANTI P07766 (CD3E_HUMAN) [AMG757]
Drug Product Description	IMDELLTRA (tarlatamab-dlle) for injection is a sterile, preservative-free, white to slightly yellow, lyophilized

	powder supplied in 1 mg or 10 mg strength in a single-dose vial for reconstitution and further dilution. Each 1 mg vial contains tarlatamab-dlle (1 mg), glutamic acid (0.72 mg), polysorbate 80 (0.04 mg), sucrose (37.1 mg), and sodium hydroxide to adjust pH to 4.2. After reconstitution with 1.3 mL of Sterile Water for Injection the resulting concentration is 0.9 mg/mL IMDELLTRA. The amount of reconstituted IMDELLTRA to add to the IV bag is 1.1 mL. Each 10 mg vial contains tarlatamab-dlle (10 mg), glutamic acid (3.7 mg), polysorbate 80 (0.2 mg), sucrose (194.4 mg), and sodium hydroxide to adjust pH to 4.2. After reconstitution with 4.4 mL of Sterile Water for Injection the resulting concentration is 2.4 mg/mL IMDELLTRA. The amount of reconstituted IMDELLTRA to add to the IV bag is 4.2 mL. Tarlatamab-dlle is a bispecific T cell engager (BiTE) that consists of two single-chain variable fragment (scFv) binding domains, one specific for delta-like ligand 3 (DLL3) and the other specific for the T-cell co-receptor CD3, fused to a single chain fragment crystallizable half-life extension (scFc HLE) moiety. Tarlatamab-dlle is aglycosylated by engineering and is produced using recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. The fusion protein has 982 amino acids, with a molecular weight of approximately 105 kDa.
Dosage Form	Lyophilized powder for injection
Strength	• 1 mg of lyophilized powder in a single-dose vial for reconstitution and further dilution • 10 mg of lyophilized powder in a single-dose vial for reconstitution and further dilution
Route of Administration	Intravenous (IV) Infusion

Primary Container Closure System	[redacted] (for 1 mg strength) or [redacted] (for 10 mg strength) Type [redacted] clear colorless glass vial, closed with an elastomeric stopper with [redacted] film laminated on product contact surface and an aluminum seal flip-off cap.		
Device Information	Not applicable		
Co-packaged Product Information	For each package containing one single-dose vial of 1 mg or 10 mg IMDELLTRA, two vials of 7 mL IV Solution Stabilizer (IVSS) are co-packaged. IVSS is used to coat the IV bag prior to addition of reconstituted IMDELLTRA to prevent adsorption of IMDELLTRA to IV bags and IV tubing. It is not used to reconstitute IMDELLTRA. IVSS is supplied as a sterile, preservative-free, colorless to slightly yellow, clear solution. Each vial of IVSS contains citric acid monohydrate (36.75 mg), lysine hydrochloride (1598.8 mg), polysorbate 80 (7 mg), sodium hydroxide to adjust pH to 7.0, and water for injection. The primary container closure system is the same as IMDELLTRA drug product, except that the vial size is [redacted]		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Davinna Ligons	Nailing Zhang
	Drug product	Odile Engel	Nailing Zhang
	Immunogenicity Assay	Yanyan Cao	Ian McWilliams
	Facility	Michael Shanks	Virginia Carroll
	Microbiology	Maria (Reyes) Candau-Chacon	Virginia Carroll
	RBPM	Shazma Aftab	N/A
	ATL	Nailing Zhang	

	Review Chief	Maria-Teresa Gutierrez-Lugo
OPQ Issued Consults	None	

2. Recommendation and Conclusion on Approvability

Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761344 for IMDELLTRA (tarlatamab-dlle) manufactured by Amgen Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of IMDELLTRA (tarlatamab-dlle) 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:** (b) (4) [redacted]
- **Drug Product:**
  - Manufacturing: Amgen Inc. (Referred to as Amgen Thousand Oaks or ATO), Thousand Oaks, California 91320, USA (FEI: 2026154)
  - Labeling and secondary packaging: Amgen Manufacturing Ltd (Referred to as AML), Juncos, Puerto Rico 00777, USA (FEI: 1000110364)
- **IV Solution Stabilizer (IVSS):**
  - Manufacturing: Amgen Technology (Ireland) Unlimited Company (Referred to as ADL), Dun Laoghaire, Dublin A96 F2A8, Ireland (FEI: 3002808497)
  - Labeling and secondary packaging (same as IMDELLTRA drug product): Amgen Manufacturing Ltd (Referred to as AML), Juncos, Puerto Rico 00777, USA (FEI: 1000110364)

b. Fill size and dosage form:

- 1 mg of lyophilized powder in a single-dose vial
- 10 mg of lyophilized powder in a single-dose vial

c. Dating Period:
   - Drug Substance: (b) (4) months at (b) (4) °C
   - For packaged products:
     - Drug Product: 30 months at 2°C - 8°C, protected from light
     - IV Solution Stabilizer (IVSS) (b) (4) months at (b) (4) °C, (b) (4)
   - Stability Option:
     - For stability protocols:
       - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your (b) (4) drug product under 21 CFR 601.12.

d. Exempt from lot release:
   - Yes
   - IMDELLTRA 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

   One OPMA PMC (to be submitted by 01/31/2026) is listed below:

   - To develop a Monocyte Activation Test (MAT) for reliable endotoxin detection of the IVSS. The method feasibility study results will be submitted to the Agency by January 2025. If the method feasibility study is successful, method validation with three batches of IVSS product will be submitted by January 2026. If the MAT method proves infeasible, Amgen commits to develop an alternative endotoxin detection method which is not subject to low endotoxin recovery for the IVSS and to provide a timeline for those studies.

4. Basis for Recommendation
   a. Summary:
   IMDELLTRA (tarlatamab-dlle) is a bispecific T cell engager (BiTE) that binds to DLL3 expressed on the surface of tumor cells and CD3 expressed on the surface of T-cells, leading to T-cell activation, release of inflammatory cytokines, and lysis of DLL3-expressing cells. It is indicated for treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy. Potency of IMDELLTRA (tarlatamab-dlle) is controlled using a T cell-dependent cellular

cytotoxicity (TDCC) assay, in which HuT-78 effector T cells expressing CD3 and SHP-77-Luc cells expressing DLL3 are co-incubated in the presence of various concentrations of IMDELLTRA (tarlatamab-dlle). The cytotoxic effect is determined by IMDELLTRA (tarlatamab-dlle) concentration-dependent decrease in luminescence. Potency results are reported as percentage relative to a qualified reference material.

The manufacture of drug substance uses (b) (4)

The drug product manufacturing process (b) (4)

No approvability issues were identified from a sterility assurance or microbiology product quality perspective. All facilities used for the manufacture and quality control testing were found acceptable for the proposed operations. Pre-licensing inspections (PLI) for the drug substance manufacturing facility at (b) (4) and the IV Solution Stabilizer (IVSS) manufacturing facility at ADL were waived based on inspection history. An on-site PLI for the DP manufacturing facility at ATO was conducted 1/29/2024 – 2/6/2024 and a 5-item Form FDA 483 was issued to the firm at the end of the inspection. The responses to 483 items were reviewed and found satisfactory.

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in presence of IMDELLTRA at concentrations presented in patient samples. The cell-based neutralizing antibody (NAb) assay is fit-for-purpose only when NAb levels are high; when NAb levels are low, the assay has drug tolerance issues and results are uninterpretable. However, after discussion with the clinical pharmacology review team, it was determined that development of a new NAb assay is not necessary, because in the pivotal study 20200491 ADA rates are low and have low titer. The need for future NAb assay development will be assessed when additional clinical data become available.

The overall IMDELLTRA (tarlatamab-dlle) control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance, the drug product, and the IV Solution Stabilizer (IVSS). The manufacturing processes and overall control strategies for IMDELLTRA (tarlatamab-dlle) are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The BLA is recommended for approval from the product quality, facility, microbiology and sterility assurance perspectives.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
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 IMDELLTRA (i.e., there is no specific test method described in regulation for IMDELLTRA that establishes an official standard of potency). We next considered whether potency is a factor for IMDELLTRA 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 IMDELLTRA for purposes of § 610.61(r) because lot

variability is not a concern for IMDELLTRA as IMDELLTRA'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)

      ii. Residual risk: None

      iii. Future inspection points to consider: None

   c. Drug Product:
      i. Protocols approved:
         - Stability protocols for drug product shelf-life extension
         - Post-approval stability protocols for drug product
         - Post-approval stability protocol for IV Solution Stabilizer (IVSS)

      ii. Residual risk: None

      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/

NAILING ZHANG
04/29/2024 02:37:18 PM

MARIA T GUTIERREZ LUGO
04/29/2024 02:41:07 PM