CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761289Orig1s000

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:	September 28, 2022
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Michael Di, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 3
Application:	BLA 761289
Applicant:	AstraZeneca AB
Submission Date:	February 23, 2022
Product:	tremelimumab-actl
Dosage form(s):	injection
Strength and Container-Closure:	Injection: 25 mg/1.25 mL (20 mg/mL) solution in a single-dose vial Injection: 300 mg/15 mL (20 mg/mL) solution in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information and medication guide (submitted on September 28, 2022), container labels (submitted on August 16, 2022), and carton labeling (submitted on August 30, 2022) were assessed and found to be acceptable (see Appendix C) 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 and medication guide (submitted on September 28, 2022), container labels (submitted on August 16, 2022), and carton labeling (submitted on August 30, 2022) were assessed and found to be acceptable (see Appendix C) from an OBP Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information/Medication Guide (submitted on February 23, 2022 \\CDSESUB1\evsprod\bla761289\0001\m1\us\annotated-draft-label-treme-himalaya.docx)

Container Labels (submitted on February 23, 2022)

(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: Use the qualifying phrase abbreviated "Mfd by:" to indicate the applicant's name *Applicant revised as requested*

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, 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 ☐ 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

Comment/Recommendation: partial label

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: Confirm there is no text on the ferrule and cap overseal of the vials. *The Applicant confirms that there is no text on ferrule and cap and the vials comply with the United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals).*

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 there is an approximate 5mm gap on the rear of the vial after label placement. This gap extends the full length of the vial where there is sufficient remaining area uncovered for its full length of circumference to permit inspection of the contents per 21 CFR 610.60(e).*

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

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

Comment/Recommendation: Consider adding an NDC number to the vial labels *Applicant revised as requested*

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

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: Ensure that a linear barcode appears on the vial labels and indicate the location on the resubmitted mock-ups *Applicant revised as requested*

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 *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 (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

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

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

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

Package[6] Labeling Evaluation

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

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

Comment/Recommendation: Use the qualifying phrase abbreviated "Manufactured by:" to indicate the Applicant's information *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

[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.

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

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

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

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

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

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 ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, histidine, edetate disodium, and trehalose.
For example, (b) (4) (b) (4) (b) (4) In other words, the approved labeling should use the inactive ingredient established name, Trehalose (b) (4) (b) (4) See changes also for edetate disodium.

The revisions to the inactive ingredient names to appear in alphabetical order and the amounts are proposed to be recalculated as follows:

Each mL contains 20 mg of tremelimumab-xxxx, and (b) (4) edetate disodium (b) (4) (b) (4) mg), (b) (4) histidine ((b) (4) mg), L-histidine hydrochloride monohydrate ((b) (4) mg), polysorbate 80 (0.2 (b) (4) mg), (b) (4) trehalose (b) (4) 76 mg), and Water for Injection, USP.

Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the table that includes trehalose (b) (4) calculations. Ensure that all inactive ingredients with a USP monograph are provided as such.

The Applicant's proposed revisions required clarification. Add the four-letter suffix to the proper name, 'tremelimumab-actl'. *The Applicant revised as requested*

Revise [redacted] to 'edetate disodium'. *The Applicant revised as requested*

Confirm whether the amount of edetate disodium per mL [redacted] should be listed as [redacted] mg. Per your 3.2.P.1 the amount of edetate disodium [redacted] is calculated to be 0.09 [redacted] *Applicant's response: In 3.2.P.1,* [redacted] *Each mL of drug product is confirmed to contain 0.09 mg of edetate disodium.*

[redacted] Revise [redacted] to 'histidine'. *The Applicant revised as requested*
Confirm whether the amount of histidine per mL should be listed as 0.68 mg [redacted] Per your 3.2.P.1 the amount of histidine is [redacted] mg per mL. *Applicant's response:* [redacted] *Each mL is confirmed to contain 0.68 mg of histidine.*

Confirm whether the amount of L-histidine hydrochloride monohydrate per mL should be listed as 3.3 mg [redacted] Per your 3.2.P.1 the amount of L-histidine hydrochloride monohydrate is [redacted] mg per mL. *Applicant's response:* [redacted] *Each mL is confirmed to contain 3.3 mg of L-histidine hydrochloride monohydrate.*

Confirm whether the amount of polysorbate 80 per mL should be listed as 0.2 mg [redacted] Per your 3.2.P.1 the amount of polysorbate 80 is [redacted] mg per mL. *Applicant's response:* [redacted] *Each mL is confirmed to contain 0.2 mg polysorbate 80.*

Please provide the confirmed corrected names and amounts and resubmit revised 3.2.P.1 also addressing the amount of Water for Injection confirming if this should appear in the 3.2.P.1 as approximately [redacted] mM. *Applicant's response: The Water for Injection is approximately* [redacted] *M, as originally reported, and not* [redacted] *M,* [redacted]

Revise the Contents statement on the carton labeling as follows: 'One single-dose vial provides 25 mg of tremelimumab-actl in 1.25 mL (20 mg/mL). Each mL contains 20 mg of tremelimumab-actl, and edetate disodium (0.xx mg), histidine (0.xx mg), L-histidine hydrochloride monohydrate (3.x mg), polysorbate 80 (0.2x mg), trehalose (76 mg), and Water for Injection, USP.' 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: Remove [redacted] (b) (4) from the carton labeling. Our view is that 21 CFR 610.61(r) is not applicable, and thus the no statement is required for the carton labeling. *The Applicant revised as requested*

Based on CDER's current interpretation [redacted] (b) (4) and after consultation with OBP Product Quality assessors, this regulation does not apply to this product [redacted] (b) (4) (b) (4) [redacted] (b) (4) Accordingly, the phrase [redacted] (b) (4) is not required to appear on the carton labeling.

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 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

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

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A

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

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

Comment/Recommendation: We recommend adding the materials of construction for the IV bags (b) (4) *Applicant response: The Applicant proposes to remove information regarding the type of IV bags. The Applicant has conducted compatibility tests with these infusion bags and did not find any interaction with the medication. Thus, the Applicant believes the inclusion of this wording is not relevant for the prescriber. OBPL accepts removal of non-required information*

Revised the storage time for the infusion solution from '28 days' to '24 hours' refrigerated and (b) (4) to '24 hours' at room temperature per IR response dated 22Apr22. *The Applicant revised as requested*

Per OPMA, it is acceptable to revise from "the total time from (b) (4) to the start of administration should not exceed:" to "the total time from preparation to the completion of the infusion should not exceed:". *Note (b) (4) replaced with "preparation" in order to be consistent with current labeling practices. *The Applicant revised to "the total time from preparation to the start of administration should not exceed:" based on the submitted CMC Information Request Response. Acceptable per OPMA.*

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: Added the pharmacological class "cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking human IgG2 monoclonal antibody' *Applicant revised as requested*
Added the MW - please confirm approximately 149 kDa *The Applicant confirmed*
Added the dosage form *Applicant revised as requested*
Added the route of administration *Applicant revised as requested*

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles: histidine, edetate disodium, and trehalose.

For example, (b) (4) (b) (4) (b) (4) In other words, the approved labeling should use the inactive ingredient established name, Trehalose (b) (4) (b) (4) See changes also for edetate disodium.

(b) (4)

The revisions to the inactive ingredient names to appear in alphabetical order and the amounts are proposed to be recalculated per mL of solution– please confirm

Applicant's response:

Each mL contains 20 mg of tremelimumab-actl, and (b) (4) edetate disodium ((b) (4) mg), (b) (4) histidine (b) (4) mg), L-histidine hydrochloride monohydrate ((b) (4) mg), polysorbate 80 (0.2 (b) (4) mg), trehalose (76 mg), and Water for Injection, USP. The pH is approximately 5.5.

OBPL response: The Applicant's proposed revisions required clarification.

Revise (b) (4) to 'edetate disodium'. Confirm whether the amount of edetate disodium per mL (b) (4) should be listed as (b) (4) (b) (4) mg. Per your 3.2.P.1 the amount of edetate disodium (b) (4) (b) (4) is calculated to be 0.09 (b) (4) (b) (4) *Applicant revised as requested*

(b) (4)

Revise (b) (4) to 'histidine'. Confirm whether the amount of histidine per mL should be listed as 0.68 mg (b) (4) Per your 3.2.P.1 the amount of histidine is (b) (4) (b) (4) mg per mL. *Applicant revised as requested*

Confirm whether the amount of L-histidine hydrochloride monohydrate per mL should be listed as 3.3 mg (b) (4) Per your 3.2.P.1 the amount of L-histidine hydrochloride monohydrate is (b) (4) mg per mL. *Applicant's response:* (b) (4) (b) (4) *Each mL is confirmed to contain 3.3 mg of L-histidine hydrochloride monohydrate.*

Confirm whether the amount of polysorbate 80 per mL should be listed as 0.2 mg (b) (4) (b) (4) Per your 3.2.P.1 the amount of polysorbate 80 is (b) (4) mg per mL. *Applicant's response:* (b) (4) *Each mL is confirmed to contain 0.2 mg polysorbate 80.*

Provide the pH of the solution *The applicant added 'pH is approximately 5.5'*

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:	☐ Yes ☐ No ☒ N/A

xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	

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

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

Medication Guide Evaluation

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

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

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

Comment/Recommendation: added all inactive ingredients for consistency with Full PI and revised to alphabetical order *Applicant revised as requested*

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

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on September 28, 2022 \\CDSESUB1\EVSPROD\bla761289\0041\m1\us\draft-labeling-text-nonannotated-treme-himalaya.pdf)

Medication Guide (submitted on September 28, 2022 \\CDSESUB1\EVSPROD\bla761289\0041\m1\us\nonannotated-draft-medication-guide-imjudo-himalaya.pdf)

Container Labels (submitted on August 16, 2022)

(b) (4)

2 Pages of draft labeling have been withheld in full as B4 (CCI/TS) immediately following this page

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 9/28/2022 12:52:20PM
GUID: 50814c7000007a3d59329f660d8ddf02

Xu Di

Digitally signed by Xu Di
Date: 9/28/2022 01:00:33PM
GUID: 543400e20010de74ddcb797efe7f3df8

First Approval for Rare Pediatric Disease Indication/Expedited Assessment:

Recommendation: Approval

BLA 761289 Number:
Assessment Number:1
Assessment Date: September 01, 2022

Drug Name/Dosage Form	tremelimumab-actl; MEDI 1123; Imjudo™; Injection
Strength/Potency	20 mg/mL; 25 mg/vial and 300 mg/vial In vitro cell-based IL-2 reporter assay
Route of Administration	Intravenous infusion
Rx/OTC dispensed	RX
Indication	Treatment of adult patients with unresectable hepatocellular carcinoma (uHCC).
Applicant/Sponsor	AstraZeneca AB, Sweden
US agent, if applicable	AstraZeneca Pharmaceuticals LP

Product Overview:

Tremelimumab (Imjudo)) is a fully human immunoglobulin gamma-2 (IgG2) monoclonal antibody (mAb) engineered to bind to cytotoxic T lymphocyte-associated antigen-4 (CTLA-4; CD152), a cell surface receptor expressed on activated T cells. Upon T-cell activation, CTLA-4 expression is upregulated and acts to dampen immune responses, modulating and eventually switching off T-cell activation. The natural ligands for CTLA-4 are CD80 [B7.1] and CD86 [B7.2], which are present on antigen-presenting cells (APCs). Binding of CTLA-4 to CD80/CD86 functions to limit T-cell activation, primarily by competing with CD28 for access to CD80/CD86. Tremelimumab is manufactured in NS0 cells (b) (4)
Tremelimumab is supplied at a 20 mg/mL strength as a 25 mg/vial and 300 mg/vial for intravenous infusion. Tremelimumab has one N-linked glycosylation site at Asn 301 in the Fc region on each of the two heavy chains in the consensus sequence Asn-Ser-Thr (NST).

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Xu Di	OBP/Division of Biotechnology Review and Research (DBRR) III
Drug Product	Xu Di	OBP/DBRRIII
Immunogenicity	Xu Di	OBP/DBRRIII
Labeling	Vicky Borders-Hemphill	OBP Labeling
Microbiology/Facility	Maria Scott (DS)/ Virginia Carroll TL Zonglin Hu (DP) /Madushini Dharmasena TL	OPMA/DBM Branch 2
Application Team Lead	Ram Sihag	OBP/DBRRIII
Application Tertiary Reviewer	Frances Namuswe	OBP/DBRRIII

RPBM	Grafton Adams	OPRO

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Christina Leach	CDER/DROOD
Cross-disciplinary Team Lead	Jamie Brewer	CDER/OND/DO1
Medical Officer	Timil Patel	CDER/OND/OOD/DOIII
Pharmacology/Toxicology	Brian Christmas/Matthew Thompson TL	CDER/OND/OOD
Clinical Pharmacology	Yue Xiang/Hong Zhao TL	CDER/OTS/OCP/DCPI
Statistics	Jianxin Fan/Joyce Cheng TL	CDER/OTS/OB

1. Names:

a. Proprietary Name: Imjudo™
b. Trade Name: Imjudo™
c. Non-Proprietary Name/USAN: tremelimumab-actl
d. CAS Name: 745013-59-6
f. INN Name: tremelimumab-actl
g. Compendial Name: not assigned
h. OBP systematic name: MAB HUMAN (IGG2) ANTI P16410 (CTLA4_HUMAN) [MEDI1123]

Submissions Assessed:

Submission:	Date Received:	Review Completed (yes or no)
BLA 761289/001	February 23, 2022	Yes
STN BLA 761289 / 007 (response to information request #1)	May 6, 2022	Yes
BLA 761289 / 011 (response to information request #2)	May 23, 2022	Yes
BLA 761289/ 015 (response to information request #3)	June 22, 2022	Yes
BLA 761289/016 (response to information request #4)	July 6, 2022	Yes
BLA 761289/021 (response to information request #5)	July 25, 2022	Yes

BLA 761289/022 (response to information request #6)	July 29, 2022	Yes
BLA 761289/024 (response to information request #7)	August 9, 2022	Yes
BLA 761289/025 (response to information request #6 additional IR response)	August 12, 2022	Yes
BLA 761289/31 (response to information request #8)	August 22, 2022	Yes
BLA 761289/34 (response to information request #9)	August 29, 2022	Yes

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

Quality Assessment Data Sheet:

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

A. DMFs:

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Yes	Adequate information provided in the BLA.
			Yes	Adequate information provided in the BLA.
			Yes	Adequate information provided in the BLA.
			Yes	Adequate information provided in the BLA

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

IND 125409, (b) (4)

Communication/Document:	Date:
Information Request #1	April 28, 2022
Information Request #2	May 9, 2022
Information Request #3	June 14, 2022
Information Request #4	June 28, 2022
Information Request #5	July 18, 2022
Information Request #6	July 22, 2022
Information Request #7	August 2, 2022
Information Request #8	August 19, 2022
Information Request #9	August 23, 2022

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion:

AstraZeneca requested a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c) and indicated that there are no extraordinary circumstances that might significantly affect the quality of the human environment. The claim of categorical exemption is acceptable because tremelimumab is a protein product that occurs naturally and will be broken down in the environment. Therefore, tremelimumab is not expected to significantly impact the environment

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Biotechnology Products, OPQ, CDER, recommends approval of BLA 761289 for tremelimumab (Imjudo) manufactured by (b) (4) (drug substance) and (b) (4) (drug product), for AstraZeneca Pharmaceutical. The data submitted in this application are adequate to support the conclusion that the manufacture of tremelimumab 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:

    (b) (4)

    FEI: (b) (4)
  - Drug Product:

    (b) (4)

    FEI: (b) (4)

    AstraZeneca AB (Labeling, storage, and secondary packaging)
    Forskargatan-18
    151 85 Södertälje, Sweden
    FEI: 3002806411

- Fill size and dosage form:
  i). Injection: 25 mg/1.25 mL (20 mg/mL) solution in a single-dose vial.
  ii) Injection: 300 mg/15 mL (20 mg/mL) solution in a single-dose vial.

- Dating period:
  - Drug Product: 48 months at 2-8°C

- Drug Substance: A total of (b) (4) months of DS shelf life is recommended (b) (4)
- Intermediate Substance: N/A
- Stability:
  - For stability protocols: None

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

C. Benefit/Risk Considerations:

The tremelimumab manufacturing process and overall control strategy are sufficient to ensure consistent manufacture of a drug product that is safe and effective. All proposed manufacturing and testing facilities are acceptable based on their current cGMP compliance status and recent on-site inspection coverage. The approval of tremelimumab will increase treatment options for patients currently undergoing therapy for hepatocellular cancer.

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

1. PMC- 4333-4 To perform a shipping validation study under real time shipping conditions (i.e. temperature, mode of transport, shipping duration, and shipping containers and packing representative of the minimum and maximum load) using a representative commercial tremelimumab drug product lot in the final commercial container closure and packaging systems to evaluate the ability of the shipping containers to maintain the recommended temperature and to evaluate the impact of shipping from the AstraZeneca Sweden labeling and packaging site to the US Distribution Center on the physical integrity and product quality of tremelimumab drug product. The shipping validation data will be submitted in accordance with 21 CFR 601.12.

Final Report Submission: 12/31/2023

2. PMC- 4333-5 Implement (b) (4) monitoring (b) (4) (b) (4) validated by the microbial retention study.

Final Report Submission: 12/31/2023

II. Summary of Quality Assessments:

The tremelimumab product quality information supports the approval of this BLA. The tremelimumab drug substance (DS) and drug product (DP) are well characterized and free of adventitious infectious agents. The manufacturing process control parameters used in the manufacture of DS and DP were adequately validated or are supported by process characterization studies or platform knowledge/prior

experience from other monoclonal antibodies manufactured at the DS and DP manufacturing sites. The process validation results demonstrate that the proposed commercial manufacturing process can consistently produce a pure and potent product. The proposed lot release and stability specifications of DS and DP are supported by clinical and manufacturing experience. Overall, the control strategy for tremelimumab is adequate.

Two commercial DP presentations are proposed: 25 mg/vial and 300 mg/vial. A 400 mg/vial presentation was used during the clinical studies. The 25 mg/vial, 300 mg/vial and 400 mg/vial presentations were demonstrated to be comparable. The Applicant provided 48 months of real time stability data for 8 DP lots (3 lots for 25 mg/vial and 5 lots for 400 mg/vial) manufactured at commercial scale to support the proposed 48 months expiry for tremelimumab DP stored at 2 -8 °C. The proposed DP expiry is adequately supported. The Applicant provided 48- and 36- months of real time stability data for DS (b) (4) Based on the totality of the available DS and DP stability data, a total of (b) (4) months of DS shelf life will be approved (b) (4)

No significant deficiencies were identified during the review of BLA 761289 that preclude approval of this application from OPQ's perspective. The adequacy of the immunogenicity assays and a risk assessment of the immunogenicity profile of tremelimumab was performed. All the method validation results met the appropriately predefined acceptance criteria. The immunogenicity assay performance results (e.g., ADA and Nab incidences) from the clinical studies demonstrated that both ADA and Nab assays were suitable for their intended use.

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and the associated control strategies for attributes that are relevant to both Drug Substance and Drug Product. For additional information, see the primary reviews, including the Drug Substance and Drug Product Quality Review by OBP/DBRRIII (https://panorama.fda.gov/document/view?ID=62ff9b0e001c930e5affb1a39e250c21) and the Drug Substance Microbiology Review and the Drug Product Microbiology Review by OPMA (https://panorama.fda.gov/document/view?ID=62f592af00760bb299848bea55e8bc63 and https://panorama.fda.gov/document/view?ID=630f801f00039817fe650c5083b12511).

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

CQA (type)	Risk	Origin	Control Strategy	Other
Aggregates (Product related impurity)	Immunogenicity	(b) (4) on stability	(b) (4)	n/a
Fragments (product related impurity and substance)	Immunogenicity, reducing potency, safety and efficacy failure	(b) (4) on stability		n/a

Disulfide bond modifications (product related impurity)	Immunogenicity	(b) (4)	(b) (4)	n/a
Fc glycosylation (high mannose) (product related impurity)	Immunogenicity, PK	(b) (4)		n/a
Deamidation (acidic variants, light chain Asn-30) (product related impurity)	Reducing potency	(b) (4) DS and DP storage		n/a
Fc Oxidation (Met-256 and Met-432) (product related impurity)	Reducing potency	(b) (4) DS and DP storage		n/a
CDR Oxidation (Heavy chain Trp-52) (product related impurity)	Potency	(b) (4) DS and DP storage		n/a
Primary Sequence Variants	Potency, immunogenicity, PK	Cell line		n/a
Higher order structure	Potency, immunogenicity, PK	Cell line		n/a
Potency	Efficacy failure	Intrinsic to molecule, in-process and on stability		n/a
Identity	safety and efficacy failure	Intrinsic to molecule		n/a
Total protein	Inaccurate dosing	Formulation		n/a

B. Drug Substance Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

A summary of the critical quality attributes and the control strategy that is relevant specifically to the Drug Substance is shown below in Table 2.

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

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance (clarity, color)	Product stability	Formulation and storage	(b) (4)	n/a
pH	Product stability	Formulation and storage		n/a
Leachable impurities	Safety and product stability	Process-related impurities, and DS container closure system		n/a

Host Cell DNA	Immunogenicity and Safety	(b) (4)	(b) (4)	n/a
Host Cell Protein	Immunogenicity	(b) (4)		n/a
(b) (4)	Immunogenicity	(b) (4)		n/a
(b) (4)	Product stability	Formulation		n/a
(b) (4)	Product stability	formulation		n/a
Bioburden	Safety, purity, efficacy	Contamination during manufacturing process		n/a
Endotoxin	Safety and purity	Endotoxin can be introduced by raw materials and contamination during manufacturing process		n/a
Mycoplasma	Safety	Contamination during manufacturing process		n/a
Adventitious Viruses	Safety	Contamination during manufacturing process		

- Description:

  Tremelimumab drug substance is a fully human monoclonal antibody from the immunoglobulin (Ig) G2a isotype targeted against Cytotoxic T Lymphocyte-associated Antigen 4 (CTLA-4 or CD152) being developed to treat cancer. CTLA-4 is a cell surface receptor expressed on activated T cells. Tremelimumab consists of two heavy chains and two light chains covalently connected with 6 inter-chain disulfide bonds. Tremelimumab has one N-linked glycosylation site at Asn (N) 301 in the Fc region on each of the two heavy chains in the consensus sequence Asn-Ser-Thr (NST).

- Mechanism of Action (MoA):

  The MOA of tremelimumab is to block CTLA-4 from binding to B7 ligands (CD80 and CD86) on antigen-presenting cells. This blockade results in enhanced T cell mediated immune response (e.g., T cell activation, proliferation, and lymphocyte infiltration into tumors) to kill the tumor cells.

- Potency Assay:
  The potency of tremelimumab is determined using an IL-2 reporter potency assay, which is a cell-based assay using Jurkat cells expressing CTLA-4 and an IL-2-promoter driven lucifierase, and Raji cells expressing B7 ligands. The potency assay was established based on the ability of tremelimumab to block the CTLA-4-mediated inhibitory signal during T cell activation by blocking CTLA-4 from binding to B7 ligand on

the B lymphocytes. The T cell activation is correlated to activation of the IL-2 transcription factor, leading to the expression of luciferase. The generated luciferase measured by a luminometer is proportional to the T cell activity after reacting with luciferase substrate. After confirming parallelism, a constrained 4PL curve fit is performed, and the relative potency of the sample is determined by dividing the EC50 of RS by the EC50 of samples.

- Reference Materials:

(b) (4)

The qualification of reference standards is acceptable.

- Critical starting materials or intermediates:

Tremelimumab is produced in NS0 cells (b) (4) A two-tiered cell banking system comprising of the Master Cell Bank (MCB) and a Working Cell Bank (WCB), with appropriate characterization, stability testing program, and storage conditions, has been implemented to ensure consistent manufacture of the product.

- Manufacturing process summary:

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

(b) (4)

(b) (4)

From a microbiological perspective, the process is under adequate microbial control.

(b) (4)

All the process validation results for process parameters, process outputs, and additional quality attributes met the predefined acceptance criteria, which were within process characterization ranges or based on prior knowledge. All the available results from commercial scale DS lots met the acceptance criteria in terms of step yield, chromatogram profile, and product quality.

- Container closure:

(b) (4)

- Dating period and storage conditions:
A total of (b) (4) months of DS shelf life is recommende

(b) (4)

Note: The Applicant had proposed

(b) (4)

C. Drug Product Quality Summary:

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 is provided below in Table 3.

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

CQA (type)	Risk	Origin	Control Strategy	Other

Sterility	Infections in patients, product stability	Accidental during fill, container closure failure	(b) (4)	n/a
Endotoxin	Adverse reactions in patients, DP failure	Accidental throughout process		n/a
Container Closure Integrity (CCI)	Infections in patients, product stability	container closure failure		n/a
Appearance (clarity, color)	Product stability	Formulation and storage		n/a
Visible particles	Patient safety and product stability	Formulation		n/a
Osmolarity	Product stability, patient discomfort	Formulation		n/a
pH	Product stability and DP failure	Formulation		n/a
Extractable Volume	Inaccurate dosing	Filling		n/a
Sub-visible particles	Product stability	Formulation		n/a
Leachable impurities	Safety	Process-related impurities, and DP container closure system		n/a
Polysorbate 80	Product stability	Formulation		n/a

- Potency and Strength: 25 mg/vial and 300 mg/vial, protein concentration is 20 mg/mL

  The in vitro cell-based assay is used to measure the potency of tremelimumab DS and DP for release and stability testing. The potency assay is discussed above in DS section. The strength of the DP is 20 mg/mL. Tremelimumab is supplied as a 25 mg/vial and 300 mg/vial for intravenous infusion.

- Summary of Product Design:

Tremelimumab DP is a sterile, preservative-free solution intended for intravenous infusion after dilution. DP has two presentations: 25 mg/1.25 mL vial and 300 mg/15 mL vial. Each presentation contains 20 mg/mL tremelimumab in (b) (4) mM histidine/histidine-HCl monohydrate, (b) (4) mM trehalose (b) (4) mM disodium edetate (b) (4) (b) (4)% (w/v) polysorbate 80, pH 5.5.

The 25 mg/vial DP presentation is a single dose vial that contains a label claim of 25 mg of tremelimumab in a 1.25 mL volume ((b) (4) mL target fill volume (b) (4) (b) (4)). The 300 mg/vial DP presentation is a single-dose vial that contains a label claim of 300 mg of tremelimumab in a 15 mL volume ((b) (4) mL target fill volume (b) (4)).

- List of Excipients: Excipients include (b) (4) mM histidine/histidine-HCl monohydrate, (b) (4) mM trehalose (b) (4) mM disodium edetate (b) (4)% (w/v) polysorbate 80, pH 5.5.

- Reference Materials: The reference materials used for the DP are the same as the reference materials used for DS.

- Manufacturing process summary:
The manufacturing process of tremelimumab DP involves (b) (4) Bioburden and endotoxin are tested during manufacture and sterility and endotoxin are tested at DP release. Container closure integrity testing is performed during the stability program.

- Container closure:
The 25 mg/vial presentation is stored in a (b) (4) Glass vial with a grey (b) (4) elastomer (b) (4) stopper and a flip-off aluminum seal.

  The 300 mg/vial presentation is stored in a (b) (4) Glass vial with a grey (b) (4) elastomer (b) (4) stopper and a flip-off aluminum seal.

- Dating period and storage conditions: A total of 48 months at 2-8°C is given for both 25 mg/vial and 300 mg/vial presentations.

- List of co-package components, if applicable: None.

D. Biopharmaceutics Considerations: N/A
E. Novel Approaches/Precedents: No
F. Any Special Product Quality Labeling Recommendations: No

G. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
• Manufacture, testing and storage of working cell banks • Manufacture of drug substance • Release and stability testing of drug substance		(b) (4)	n/a	n/a	The PLI of the DS manufacturing site was waived based on the compliant GMP status.
Bioassay testing for release and stability of Drug Substance	AstraZeneca AB Gärtunavägen 151 85 Södertälje Sweden	FEI: 3003342394 DUNS:631892705	n/a	n/a	Approve - Based on Previous History
Master Cell Bank storage		(b) (4)	n/a	n/a	Approve - Based on Previous History
Master Cell Bank storage			n/a	n/a	Approve - Based on Previous History
Working Cell Bank storage			n/a	n/a	Approve - Based on Previous History
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug Product manufacture Release and stability testing [a]		(b) (4)	The DP manufacturing site was inspected by FDA inspectors (b) (4) and a 3-item Form FDA 483 was issued, and it is recommended that the	(b) (4)	Acceptable

			inspection be classified as VAI.	(b) (4)	
Release and stability testing [a]	(b) (4)		n/a	n/a	Approve - Based on Previous History
Release and stability testing [a]			n/a	n/a	Approve - Based on Previous History
Stability testing [b] Warehousing			n/a	n/a	Approve - Based on Previous History
Stability testing			n/a	n/a	Approve - Based on Previous History

	(b) (4)				
Release and stability testing [c]	AstraZeneca AB Gärtunavägen 151 85 Södertälje Sweden	FEI: 3003342394 DUNS: 631892705	n/a	n/a	Approve - Based on Previous History
Labeling, storage, and secondary packaging	AstraZeneca AB Forskargatan-18 151 85 Södertälje Sweden	FEI: 3002806411 DUNS:353951254	n/a	n/a	Approve - Based on Previous History

a Includes release testing (appearance, extractable volume, sterility, and endotoxin) and stability testing (appearance (visible particles), color, clarity, and sterility)
b Physicochemical testing (container closure integrity)
c Bioassay and all other testing not performed by (b) (4)
n/a not applicable

H. Facilities: OPQ recommended that the pre-license inspections (PLI) for the drug substance (DS) manufacturing site at (b) (4) (FEI: (b) (4)) be waived based on good compliance history and acceptable current GMP status.

The PLI for the drug product (DP) manufacturing facility at (b) (4) (b) (4) (FEI: (b) (4)) was conducted (b) (4) by OPMA assessors Zonglin Hu and Wayne Seifert. The inspection was system based and covered Quality, Facilities and Equipment, Production, Laboratory Control and Materials. At the conclusion of PLI, a Form 483 citation with a recommendation of VAI (Voluntary Action Indicated) was issued. Also, the GMP compliance of the facility was acceptable. The overall recommendation of OPQ for the DS and DP manufacturing facilities is acceptable.

I. Lifecycle Knowledge Management:

i. Protocols approved:

a. Drug Substance

(b) (4)

b. Drug product

8. (b) (4) Testing Protocol for 300 mg/vial presentation

c. Both Drug Substance and Drug Product

9. DS and DP annual post approval stability protocols (Tables 1and 2 for DS, Table 1for DP).
10. Comparability Protocol - New Product Introductions (this is not the new (b) (4) protocol. This is a protocol to introduce new products at DS manufacturing site (b) (4) 2.R Reginal Information)

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider:

(b) (4)

III Review documents related to this Executive Summary:

1. DS and DP product quality review memo dated August 19, 2022, by Dr. Xu Di

https://panorama.fda.gov/document/view?ID=62ff9b0e001c930e5affb1a39e250c21

2. DP microbiology review memo dated August 19, 2022, by Dr. Zonglin. Hu

https://panorama.fda.gov/document/view?ID=62f592af00760bb299848bea55e8bc63

3. Product quality microbiology/facility review memo in panorama dated August 19, 2022, by Dr. Maria Scott

https://panorama.fda.gov/document/view?ID=630f801f00039817fe650c5083b12511

4. Addendum to DS and DP product quality review memo dated August 19, 2022, by Dr. Xu Di

https://panorama.fda.gov/document/view?ID=63125f2a007c56bed9950a686b0ecc5f&activeTab=tab-document-approvals

5. Establishment inspection report for drug product by Zonglin Hu, Ph.D. and Wayne Seifert (OPQ/OPMA/DBM) will be available in CMS.

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/

RAM K SIHAG
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