CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761299Orig1s000

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:	February 21, 2024
Assessor:	Jennifer Kim, Labeling Assessor Office of Product Quality Assessment III
Through:	Yongmin Liu, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XIV
Application:	BLA 761299
Applicant:	Alvotech USA Inc.
Submission Date:	December 28, 2022, and August 24, 2023
Product:	Simlandi (adalimumab-ryvk)
Dosage form(s):	Injection
Strength and Container-Closure:	40 mg/0.4 mL in pre-filled syringes assembled in single-dose autoinjectors
Purpose of assessment:	The Applicant submitted a biologics license application to seek approval of Simlandi (adalimumab-ryvk) for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and plaque psoriasis as an interchangeable biosimilar to the reference product Humira (adalimumab) BLA 125057.
Recommendations:	The prescribing information, medication guide, 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

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 February 14, 2024, medication guide, instructions for use, container labels, and carton labeling submitted on February 2, 2024, and quick reference guide submitted on February 5, 2024, were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on August 24, 2023)
  \\CDSESUB1\EVSPROD\bla761299\0025\m1\us\114-labeling\114a-draft-label\1-14-1-3-package-insert-clean.pdf

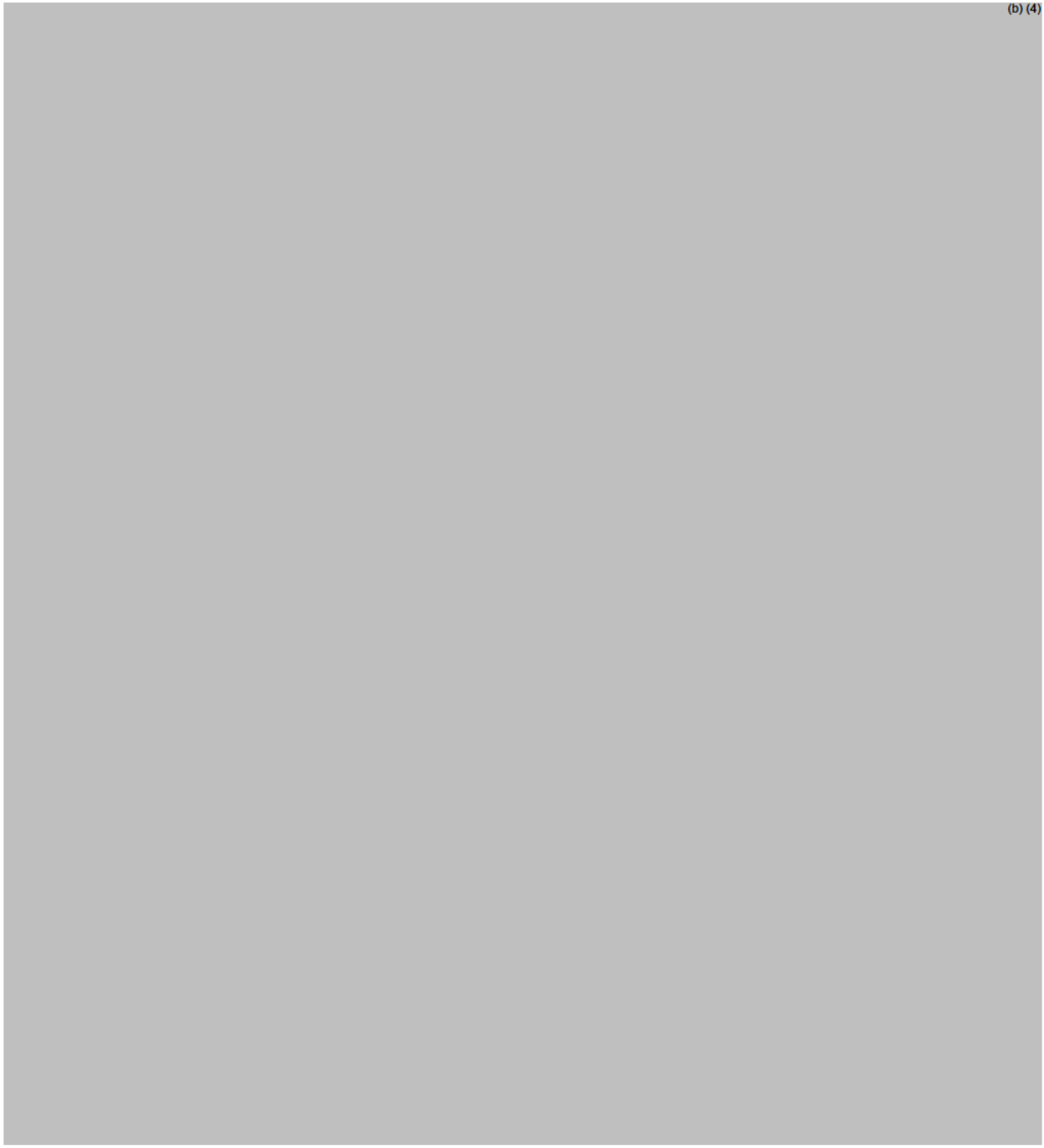
- Medication Guide (submitted on August 24, 2023)
  \\CDSESUB1\EVSPROD\bla761299\0025\m1\us\114-labeling\114a-draft-label\draft-labeling-text-med-guide-clean.pdf

- Instructions of Use (submitted on December 13, 2023)
  \\CDSESUB1\EVSPROD\bla761299\0029\m1\us\114-labeling\114c-list-drug-label\1-14-3-1-annotated-comparison-ifu.pdf

- Container Labels (submitted on November 24, 2023)

- Carton Labeling (submitted on November 24, 2023)

(b) (4)



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

Container[4] Label Evaluation

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

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.* Relocate the U.S. license number to appear with the manufacturer information to reduce confusion as follows: Manufactured By: Alvotech USA Inc. Arlington, Virginia 22209 U.S. License No. xxxx	

[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."

Marketed By: Teva Pharmaceuticals
Parsippany, NJ 07054
Product of Iceland

The applicant revised as shown below and this is acceptable from OPQA III labeling perspective:

Manufactured By: Alvotech USA Inc.
Leesburg, VA 20175
Product of Iceland
U.S. Lic. No. XXXX Iss. 1/2024
Marketed By: Teva Pharmaceuticals
Parsippany, NJ 07054

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

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, 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	☐ Yes

(Recommended individual dose)	☐ 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 would be considered a partial label. Thus, a Medication Guide statement is not required per 21 CFR 610.60(a)(7).*	

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

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 there is sufficient area to allow for visual inspection of the drug product.*

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

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

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

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *The label is small and would be considered a partial label. Thus, a package type term is not required per 21 CFR 610.60(a)(7).*	

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)	✓ Yes ☐ No ☐ N/A

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).*	
Comment/Recommendation: *The label is small and would be considered a partial label. Thus, a net quantity statement is not required per 21 CFR 610.60(a)(7).*	

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: Revise the storage information to read "Store refrigerated at 36°F to 46°F (2°C to 8°C). Protect from light. Do not freeze." *The applicant revised as requested.*	

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: *Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.*

On the blister label, relocate the U.S. license number to appear with the manufacturer information to reduce confusion. Qualifying phrases may be abbreviated to increase space as follows: "Mfd by: Alvotech USA Inc., Arlington, VA 22209 U.S. License No. xxxx, for: Teva Pharmaceuticals, Parsippany, NJ 07054".
The applicant revised as requested.

On the carton labeling, relocate the U.S. license number to appear with the manufacturer information to reduce confusion as follows:

Manufactured By:
Alvotech USA Inc.
Arlington, Virginia 22209
U.S. License No. xxxx
Product of Iceland
Marketed By:
Teva Pharmaceuticals
Parsippany, NJ 07054

The applicant revised as requested.

On February 2, 2024, the applicant submitted revised labeling with updated manufacturer address information. This is acceptable from OPQA III labeling perspective.

[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.

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
Comment/Recommendation: On the blister label, add "No preservative" statement. *The applicant revised as requested.*	

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: On the blister label, revise the storage information to read "Store refrigerated at 36°F to 46°F (2°C to 8°C). Protect from light. Do not freeze." *The applicant revised as requested.* On the carton labeling, revise the storage information to read "**Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do not freeze.** A Simlandi prefilled pen may be stored at room temperature up to a maximum of 77°F (25°C) for up to 14 days with protection from light. Use space below to record date Simlandi pen is removed from refrigerator. After removal, pen must be used within 14 days." *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: On the blister label, add route of administration statement "For Subcutaneous Use Only" to appear directly underneath the product strength. *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: On the blister label, add inactive ingredient names and its quantity. *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 adalimumab products (i.e., there is no specific test method described in regulation for adalimumab 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 Simlandi because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.*	

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

Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (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
Comment/Recommendation: See comment for manufacturer information.	

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
Comment/Recommendation: On the blister label, add the package terminology [redacted] (b) (4) "Autoinjector." *The applicant revised as requested.* On the carton labeling, revise the package type term and add the discard statement as follows: "Single-Dose Prefilled Pen. Discard unused portion." *The applicant revised as requested.*	

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
Comment/Recommendation: The back panel contains redundant information that may be deleted to reduce clutter and increase readability. We recommend deleting the following statements: [redacted] (b) (4) *The applicant revised as requested.*	

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: On the blister label, add the dosage statement "Dosage: See prescribing information." *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
Comment/Recommendation: On the blister label, add the medication guide statement ""ATTENTION: Dispense the enclosed Medication Guide to each patient". *The applicant revised as requested.*	

Other (package labeling)	**Acceptable**
	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the term [redacted] (b) (4) to read "1 Prescribing Information." and delete the statement [redacted] (b) (4) on the principal display panel. *The applicant revised as requested.*	

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: The correct terminology for the container closure system is "autoinjector". Revise (b) (4) (b) (4) to "autoinjector" throughout labeling for consistency. *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 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. *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). *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: The correct terminology for the container closure system is "autoinjector". Revise (b) (4) (b) (4) to "autoinjector" throughout labeling for consistency. *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: The correct terminology for the container closure system is "autoinjector". Revise (b) (4) (b) (4) to "autoinjector" throughout labeling for consistency. *The applicant revised as requested.* We revised the PH range based on the submission. *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

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

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

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022). *For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).*	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for IFU: Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022). *To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)*	✓ Yes ☐ No ☐ N/A

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

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022). *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

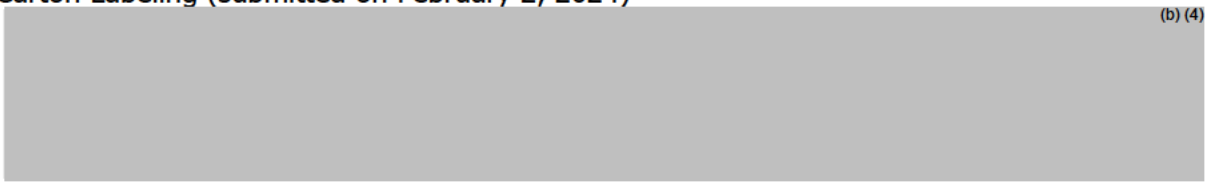
- Prescribing Information (submitted on February 14, 2024)
  \\CDSESUB1\EVSPROD\bla761299\0035\m1\us\114-labeling\114a-draft-label\1-14-1-3-package-insert-clean.pdf

- Medication Guide (submitted on February 2, 2024)
  \\CDSESUB1\EVSPROD\bla761299\0033\m1\us\114-labeling\114a-draft-label\draft-labeling-text-med-guide-clean.pdf

- Instructions for Use (submitted on February 2, 2024)
  \\CDSESUB1\EVSPROD\bla761299\0033\m1\us\114-labeling\114a-draft-label\1-14-1-3-draft-labeling-text-ifu-clean.pdf

- Container Labels (submitted on February 2, 2024)

- Carton Labeling (submitted on February 2, 2024)



3 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: 2/22/2024 08:29:26AM
GUID: 5e5438d2008138bdbae1db8d4abc0580

Yongmin Liu

Digitally signed by Yongmin Liu
Date: 2/22/2024 09:52:51AM
GUID: 5632432d003b3167c6d727f9ff58f202

BLA 761299 Resubmission OPQ Executive Summary
Assessment Date: February 2, 2024

1. Application/Product Information

BLA number	761299
Submission Type	Second Complete Response Resubmission
Regulatory Pathway	Biosimilar 351 (k)
Associated IND/BLA	IND 136459, BLA 761205
Review Designation	Standard Complete Response Resubmission (Second resubmission)
Applicant	Alvotech USA, Inc.
Indication	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: SIMLANDI
	Non-proprietary Name/Code Name: adalimumab-ryvk
	OBP Naming: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [AVT02]
Drug Product Description	The SIMLANDI (AVT02, adalimumab-ryvk) drug product (DP) is a clear, colorless, sterile, preservative-free solution for injection containing 40 mg/0.4 mL (100 mg/mL) AVT02 in a pre-filled syringe (PFS) assembled in an autoinjector (AI). SIMLANDI is an anti-tumor necrosis factor alpha (TNFα) recombinant fully human IgG1κ monoclonal antibody produced in the Chinese Hamster Ovary (CHO) (b) (4) TNFα exists in both membrane (mTNFα) and soluble (sTNFα) forms and can bind to cell surface TNF receptors p55 (TNFR1) and p75 (TNFR2) to elicit an immune response. SIMLANDI

	(AVT02, adalimumab-ryvk) is a proposed interchangeable biosimilar to US-licensed HUMIRA under BLA 761299.		
Dosage Form	Liquid		
Strength	40 mg/0.4 mL (100 mg/mL) single-dose PFS assembled in an AI		
Route of Administration	Subcutaneous injection		
Primary Container Closure System	Single use, (b) (4) glass pre-filled 1 mL syringe with a fixed needle and a rigid needle shield made from (b) (4) rubber and (b) (4) shell with a (b) (4) plunger stopper (b) (4) (b) (4) which is then assembled in an AI.		
Device Information	An AI with a subassembly unit, two housing covers and a cap remove sleeve (b) (4) (b) (4)		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Yongmin Liu	Brian Roelofs
	Drug product		
	Immunogenicity Assay		
	Facility	Richard Ledwidge	Candace Gomez-Broughton
	Microbiology	Madushini Dharmasena	
	RBPM	Nowrin Kakon	

	ATL	Brian Roelofs
OPQ Issued Consults	CDRH: ICCR 00942346 and 00942360 for AI evaluation	

Regulatory History: The original submissions for BLA 761205 proposing SIMLANDI (AVT02) as a biosimilar to US-licensed HUMIRA and BLA 761299 proposing SIMLANDI (AVT02) as an interchangeable biosimilar to US-licensed HUMIRA received complete response recommendations due to the withhold determination for the drug substance (DS) and DP manufacturing and testing facility Alvotech hf (Reykjavik, Iceland, FEI: 3013702557) after inspection. The original submissions received complete response letters (CRLs) on August 11, 2022, and December 20, 2022, respectively. A re-inspection occurred March 6 to 17, 2023 during the complete response resubmission assessment cycles for both BLA 761205 and 761299. The determination of compliance status of the facility concluded with a withhold recommendation and the initial complete response resubmissions for BLA 761205 and 761299 received CRLs on April 12, 2023, and June 28, 2023, respectively. Refer to the previous Executive Summary and Integrated Quality Assessment memoranda and addenda uploaded to Panorama on June 4, 2021, July 15, 2022, March 13, 2023, and April 11, 2023, for BLA 761205 as well as August 22, 2022, December 20, 2022, and May 26, 2023 (uploaded in DARRTS) for BLA 761299. BLA 761299 proposing SIMLANDI (AVT02) was resubmitted a second time on August 24, 2023, and a third inspection of the Alvotech hf (Reykjavik, Iceland, FEI: 3013702557) DS and DP manufacturing and testing facility was performed from January 10-19, 2024.

2. Recommendation and Conclusion on Approvability
   Recommendation: Approval

   The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761299 for SIMLANDI manufactured by Alvotech USA, Inc.. The data submitted in this application are adequate to support the conclusion that the manufacture of SIMLANDI is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that SIMLANDI is highly similar to US-licensed HUMIRA, notwithstanding minor differences in clinically inactive components. 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 and Drug Product (PFS):

Alvotech hf
Sæmundargata 15-19, Reykjavik, 101, Iceland
FEI: 3013702557

- Autoinjector (b) (4)

  FEI: (b) (4)

b. Fill size and dosage form:
SIMLANDI is supplied as a 40 mg/0.4 mL (100 mg/mL) solution in a PFS assembled in an AI.

c. Dating Period:
- Drug Product: 24 months at 2°C to 8°C. This dating period may include a single period up to 14 days at 25°C ± 2°C.
- Drug Substance: (b) (4) months at (b) (4) °C
- Intermediate Substance, if applicable: N/A
- Stability Option: N/A

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

4. Basis for Recommendation

a. Summary: Refer to the previous BLA 761205 and 761299 original and resubmission Executive Summary Memoranda and Addenda referenced above for the basis for recommendation of approval from the drug substance, drug product, immunogenicity assays, and microbiology aspects. Specifically, the original BLA 761205 IQA-CAA ATL memorandum and memorandum addendum detail the bases for the subdiscipline approval recommendations except for the facility recommendation.

This memorandum addresses the CR issue related to deficiencies identified at the previous inspections of the DS and DP manufacturing and testing facility Alvotech hf (Reykjavik, Iceland, FEI: 3013702557).

To address the deficiencies, the Applicant resubmitted BLA 761299 on August 24, 2023, and the Agency performed a third inspection of the DS and DP manufacturing and testing facility Alvotech hf (Reykjavik, Iceland, FEI: 3013702557) from January 10-19, 2024. The outcome of this inspection and the internal compliance review was an approval recommendation. Therefore, the Applicant has adequately addressed the deficiencies identified in the

previous CRL for BLA 761299. Additional microbiology information concerning the container closure integrity testing method were also submitted, assessed, and found acceptable. The OPQ recommends approval of this application.

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 adalimumab/SIMLANDI (i.e., there is no specific test method described in regulation for adalimumab/SIMLANDI that establishes an official standard of potency). We next considered whether potency is a factor for adalimumab/SIMLANDI 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 adalimumab/SIMLANDI for purposes of § 610.61(r) because lot variability is not a concern for adalimumab/SIMLANDI as adalimumab/SIMLANDI'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: Refer to the BLA 761205 Original OPQ IQA-CAA ATL Executive Summary uploaded to Panorama on June 4, 2021, and the addendum uploaded on July 15, 2022, for lifecycle considerations.

   c. Drug Product: Refer to the BLA 761205 Original OPQ IQA-CAA ATL Executive Summary uploaded to Panorama on June 4, 2021, and the addendum uploaded on July 15, 2022, for lifecycle considerations.

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

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

/s/

BRIAN A ROELOFS
02/02/2024 11:04:43 AM

MADUSHINI N DHARMASENA
02/02/2024 11:21:15 AM

BLA Executive Summary
Assessment Date: May 26, 2023

1. Application/Product Information

BLA number	761299
Submission Type	Resubmission
Regulatory Pathway	Biosimilar 351 (k)
Associated IND/BLA	IND 136459, BLA 761205
Review Designation	Standard Complete Response Resubmission
Applicant	Alvotech USA, Inc.
Indication	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: SIMLANDI
	Non-proprietary Name/Code Name: adalimumab-ryvk
	OBP Naming: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [AVT02]
Drug Product Description	The SIMLANDI (AVT02, adalimumab-ryvk) DP is a clear, colorless, sterile, preservative-free solution for injection containing 40 mg/0.4 mL (100 mg/mL) AVT02 in a pre-filled syringe (PFS) assembled in an autoinjector (AI). SIMLANDI is an anti-tumor necrosis factor alpha (TNFα) recombinant fully human IgG1κ monoclonal antibody produced in the Chinese Hamster Ovary (CHO) (b) (4) (b) (4) TNFα exists in both membrane (mTNFα) and soluble (sTNFα) forms and can bind to cell surface TNF receptors p55 (TNFR1) and p75 (TNFR2) to elicit an immune response. SIMLANDI (AVT02, adalimumab-ryvk) is a proposed biosimilar to US-licensed HUMIRA

	under BLA 761205 and proposed interchangeable under BLA 761299.		
Dosage Form	Liquid		
Strength	40 mg/0.4 mL (100 mg/mL)		
Route of Administration	Subcutaneous injection		
Primary Container Closure System	PFS assembled in an AI		
Device Information	AI		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Yongmin Liu	Brian Roelofs
	Drug product		
	Immunogenicity Assay		
	Facility	Richard Ledwidge	Candace Gomez-Broughton
	Microbiology	Madushini Dharmasena	
	RBPM	Nowrin Kakon	
	ATL	Brian Roelofs	
OPQ Issued Consults	CDRH: ICCR 00891578 and 00891581 for autoinjector evaluation		

2. Recommendation and Conclusion on Approvability
   Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of this resubmission of BLA 761299 for SIMLANDI manufactured by Alvotech USA, Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of SIMLANDI is well-controlled and will lead to a product that is pure and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Alvotech USA, Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

3. Draft Complete Response Comments and Additional Comments (if applicable):
   Following inspection of Alvotech hf, Reykjavik, Iceland (FEI: 3013702557) listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

4. Basis for Recommendation
   a. Summary: The original BLA 761299 submission received a complete response recommendation on December 20, 2022, due to the withhold determination for the DS and DP manufacturing and testing facility Alvotech hf (Reykjavik, Iceland, FEI: 3013702557) after inspection. Alvotech USA, Inc. resubmitted BLA 761299 on December 28, 2022. A re-inspection occurred March 6 to 17, 2023. The facility inspection concluded with a recommendation of withhold.
      Refer to the previous Executive Summary and Integrated Quality Assessment memorandum for BLA 761205, addendum to BLA 761205, and Executive Summary for BLA 761299 uploaded to Panorama on June 4, 2021, July 15, 2022, and August 22, 2022, respectively for previous assessments of material submitted to support this application. Additionally, refer to the Executive Summary and amendment documents uploaded to Panorama on March 13, 2023, and April 11, 2023, for the assessment of the resubmission of BLA 761205.
      The additional new information in this submission not previously submitted to BLA 761205 or 761299 for the manufacture of SIMLANDI or related to the facility inspection consisted of typographical updates, withdrawal of items intended for a future supplement, and updates to testing schedules. The information was assessed and determined to be acceptable. Refer to the OBP technical review memorandum uploaded to Panorama on May 6, 2023, for more information.

b. Subdiscipline Recommendation:

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

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

d. Potency Assessment for Labeling:
Not applicable as OPQ does not recommend approval of this application.

5. Life-Cycle Considerations
Refer to the Executive Summary and Integrated Quality Assessment for BLA 761205 uploaded to Panorama on June 4, 2021, and the addendum uploaded on July 15, 2022.

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

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

/s/

BRIAN A ROELOFS
05/26/2023 04:28:22 PM

MADUSHINI N DHARMASENA
05/26/2023 04:29:42 PM

Recommendation: Complete Response

Background: Alvotech USA, Inc. previously submitted BLA 761205 to propose AVT02 as a biosimilar to US-licensed Humira for the same indications as US-Humira and which will follow the same administration and dosing regimen as approved for US-Humira. This submission under BLA 761299 is to support an interchangeability designation for AVT02. The comparative analytical assessment of AVT02 and the manufacturing data to support the production of AVT02 were submitted and assessed under BLA 761205. Refer to the Office of Product Quality executive summary assessment memorandum and assessment memorandum addendum for BLA 761205 uploaded to Panorama June 4, 2021 and July 15, 2022 respectively for review of this information. Additional new chemistry, manufacturing, and controls data were submitted in BLA 761299 to address comments provided during the assessments of BLA 761205 and are assessed under this BLA. BLA 761205 received a complete response action letter due to deficiencies identified during the drug substance/drug product manufacturing facility inspection and a withhold determination for the facility. At the time of filing of this memorandum the identified deficiencies have not yet been resolved.

BLA Number: 761299
Review Number: 1
Review Date: August 22nd, 2022

Drug Name/Dosage Form	AVT02—adalimumab-ryvk/ Injection
Strength/Potency	40 mg/0.4 mL (100 mg/mL)
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis
Applicant/Sponsor	Alvotech USA, Inc.

Product Overview

SIMLANDI (AVT02, adalimumab-ryvk) is an anti-tumor necrosis factor alpha (TNFα) recombinant fully human IgG1κ monoclonal antibody produced in the Chinese Hamster Ovary (CHO) (b) (4) TNFα exists in both membrane (mTNFα) and soluble (sTNFα) forms and can bind to cell surface TNF receptors p55 (TNFR1) and p75 (TNFR2) to elicit an immune response. Abnormal amounts of soluble TNFα or TNFα induced signaling can be deleterious causing pathogenicity in autoimmune diseases such as rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (PJIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), and plaque psoriasis (PsO). The proposed AVT02 strength and presentation under BLA 761205 and 761299 is 40 mg/0.4 mL (100 mg/mL) in a prefilled syringe (PFS) enclosed in an autoinjector (AI). AVT02 drug product is formulated as 100 mg/mL adalimumab, (b) (4) mM sodium chloride (b) (4) mM sucrose (b) (4) and (b) (4) % (w/v) polysorbate 80 (b) (4) in water for injection. AVT02 drug substance is a clear to slightly opalescent, pale yellow liquid solution with pH (b) (4) and osmolality of (b) (4) mOsm/kg. AVT02 drug product is a clear, colorless, sterile, preservative-free solution for subcutaneous injection with pH of 5.0 - 5.6 and osmolality of (b) (4) mOsm/kg.

Quality Review Team

Discipline	Assessor	Branch/Division
Drug Substance	Samuel Mindaye/Yongmin Liu	OPQ/OBP/DBRR II
Drug Product		OPQ/OBP/DBRR II
Immunogenicity		OPQ/OBP/DBRR II
Labeling	Jennifer Kim	OPQ/OBP
Facility	Candace Gomez-Broughton	OPQ/OPMA/DBM
Microbiology Drug Substance		OPQ/OPMA/DBM
Microbiology Drug Product		OPQ/OPMA/DBM
Facility Secondary Assessor	Madushini Dharmasena	OPQ/OPMA/DBM
Microbiology Branch Chief	Candace Gomez-Broughton	OPQ/OPMA/DBM
Regulatory Business Project Manager	Teshara Bouie	OPQ/OPRO/DRBPMI/RBPMBI
Application Team Lead	Ian McWilliams/Brian Roelofs	OPQ/OBP/DBRR II
OBP Tertiary Assessor	Xianghong Jing/Patrick Lynch	OPQ/OBP/DBRR II

Multidisciplinary Review Team

Discipline	Assessor	Office/Division
RPM	Susan Rhee/Dawn Williams	ORO/DROII and ODEII/DPARP
Cross-disciplinary Team Lead	Nikolay Nikolov Snezana Trajkovic	OII/DRTM ODEII/DPARP
Signatory Authority	Nikolay Nikolov Snezana Trajkovic	OII/DRTM ODEII/DPARP
Medical Officer	Nadia Habal/Anil Rajpal Felisa Lewis Shari Targum Sandhya Apparaju/Suna Seo	OII/DRTM ODEII/DPARP ODEIII/DDDP ODEIII/DGIEP
Nonclinical	Dong Zhao	OII/DPTII
Clinical Pharmacology	Ping Ji	OCP/DCPII
Statistics	Martin Klein/Mohamed Alosh	OB/DB II

1. Names:
   a. Proprietary Name: SIMLANDI
   b. Trade Name: SIMLANDI
   c. Non-Proprietary/USAN: adalimumab-ryvk
   d. INN Name: adalimumab-ryvk
   e. Company Code: AVT02
   f. CAS Registry Number: 331731-18-1
   g. OBP systematic name: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [AVT02]

2. Pharmacologic category: Therapeutic recombinant human monoclonal antibody biosimilar.

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed
(b) (4)	III		(b) (4)	3	Adequate	N/A
	III			3	Adequate	N/A
	III			3	Adequate	N/A
	V			3	Adequate	N/A
	V			3	Adequate	N/A
	V			3	Adequate	N/A

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

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

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

Document	Application Number	Description
IND	136459	Alvotech sponsored IND under which BPD meetings were held.

3. Consults:

Discipline/Topic	Date Requested	Recommendation	Assessor
CDRH/ODE & OC	January 26, 2022	Approvable pending comments for IR	Florencia Wilson Courtney Evans (TL)

		response to be received October 2022	

4. Alvotech USA Inc. claimed a categorical exclusion from the requirement to prepare an environmental assessment for adalimumab-ryvk under 21 CFR 25.31 (a) and 21 CFR 25.31 (c). These claims are because the proposed biologic product will not increase the use of the adalimumab active moiety because the proposed biosimilar does not contain a new molecular entity and will not be administered at higher dosage levels, for longer duration or for different indications than that of the licensed reference product. Additionally, adalimumab-ryvk is considered to be a naturally occurring substance that will degrade in the environment to form carbon dioxide, water, and nitrogen. To the knowledge of Alvotech USA Inc., no extraordinary circumstances exist that would warrant the preparation of an Environmental Assessment.

   The claim of a categorical exclusion is accepted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Complete Response
The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of STN 761299 for Simlandi (adalimumab-ryvk) manufactured by Alvotech USA, Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Simlandi is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. OPQ is recommending a Complete Response letter be issued to Alvotech USA, Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

B. Summary of Complete Response Issues:

During a recent inspection of the Alvotech hf, Reykjavik, Iceland (FEI: 3013702557) manufacturing facility for this application, our field inspectors conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Additional Microbiology and Facility Inspections Comments (provided by OPMA):

1. Implement [redacted] (b) (4) the drug product.

C. Benefit/Risk Considerations:

Simlandi is a proposed interchangeable biosimilar to US-Humira. Simlandi has the same dosage form and route of administration as US-Humira. Alvotech seeks licensure for the following indications:

- Rheumatoid Arthritis (RA)
- Juvenile Idiopathic Arthritis
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Adult Crohn's Disease (CD)
- Ulcerative Colitis (UC)
- Plaque Psoriasis (PsO)

The overall control strategy includes control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The control strategy combined with in-process, release, and stability testing ensure that the drug substance and drug product manufacturing processes are well controlled and lead to a product with the expected quality attributes and free of adventitious agents. For additional details, refer to the OPQ Executive Summary memorandum and addendum uploaded to Panorama on June 4, 2021 and July 15, 2022 for BLA 761205.

The data provided under BLA 761205 support the demonstration that AVT02 is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components. For further information refer to the OPQ Executive Summary assessment memorandum and Office of Biotechnology Products (OBP) technical review uploaded to Panorama on June 4, 2021 and May 20, 2021 respectively for BLA 761205.

Analytical similarity between Simlandi and US-Humira was evaluated under BLA 761205 using a comprehensive array of analytical methods that were suitable to evaluate critical quality attributes of Simlandi and US-Humira. The numbers of lots tested and the statistical analyses were appropriate to allow for a meaningful evaluation of the results of the analytical studies.

Simlandi has the same dosage form, strength, and route of administration as US-Humira, but has a different formulation. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. The deliverable volume (mL) and fill weight data were assessed as part of manufacturing process controls. The proposed presentation of AVT02 has (b) (4) (b) (4) The strength of AVT02 prefilled syringe and autoinjector is the same as that of US-Humira (100 mg/mL).

The initial recommendation from the CDRH Office of Health Technology evaluation of the device constituents of the combination product is approvable. The final determination of additional comments or commitments is pending the review of data to be received in October, 2022.

The OBP product quality assessments including drug substance, drug product, comparative analytical assessment, and validation of immunogenicity assays, as well as the Office of Pharmaceutical Manufacturing Assessment (OPMA) drug substance and drug product microbiological assessments, are located as separate documents in Panorama.

There are no deficiencies identified in product quality, microbiology and sterility assurance, or device constituent performance information that would preclude approval. However, the final determination of compliance status of the manufacturing facilities has concluded with a withhold recommendation for the DS/DP manufacturing facility (Alvotech hf (FEI: 3013702557), Reykjavik, Iceland) AVT02 drug substance and drug product facility.

a. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Immunogenicity Assay	**-**	**Adequate**
Quality Labeling	**-**	**Ongoing**
Facilities	**-**	**Inadequate**
Microbiology	**-**	**Adequate**

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

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.

Brian Roelofs

Digitally signed by Brian Roelofs
Date: 8/22/2022 11:34:36PM
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRIAN A ROELOFS
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MADUSHINI N DHARMASENA
08/23/2022 09:25:48 AM