CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761262Orig1s000

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:	June 14, 2022
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Andrea George, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 1
Application:	BLA 761262 and BLA 761105.16
Applicant:	Abbvie Inc.
Submission Date:	September 16, 2021
Product:	SKYRIZI (risankizumab-rzaa)
Dosage form(s):	injection
Strength and Container-Closure:	Subcutaneous injection • Injection: 150 mg/mL in each single-dose prefilled pen. • Injection: 150 mg/mL in each single-dose prefilled syringe. • Injection: 75 mg/0.83 mL in each single-dose prefilled syringe. • Injection: 360 mg/2.4 mL in each single-dose prefilled cartridge (proposed BLA 761105.16) Intravenous infusion Injection: 600 mg/10 mL in each single-dose vial (proposed for BLA 761262)
Purpose of assessment:	The Applicant submitted a biologics license application (BLA 761262) for the intravenous induction dosing regimen for Crohn's disease and a single-dose vial presentation. The Applicant submitted an efficacy supplement (BLA 761105.16) for the subcutaneous maintenance dosing regimen for Crohn's disease administered via an On-Body Injector with a prefilled cartridge.
Recommendations:	The prescribing information/medication guide/instructions for use (submitted on May 25, 2022), container labels (submitted on January 11 and 25, 2022) and carton labeling (submitted on January 11, March 3, March 9, and March 18, 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/medication guide/instructions for use (submitted on May 25, 2022), container labels (submitted on January 11 and 25, 2022) and carton labeling (submitted on January 11, March 3, March 9, and March 18, 2022) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

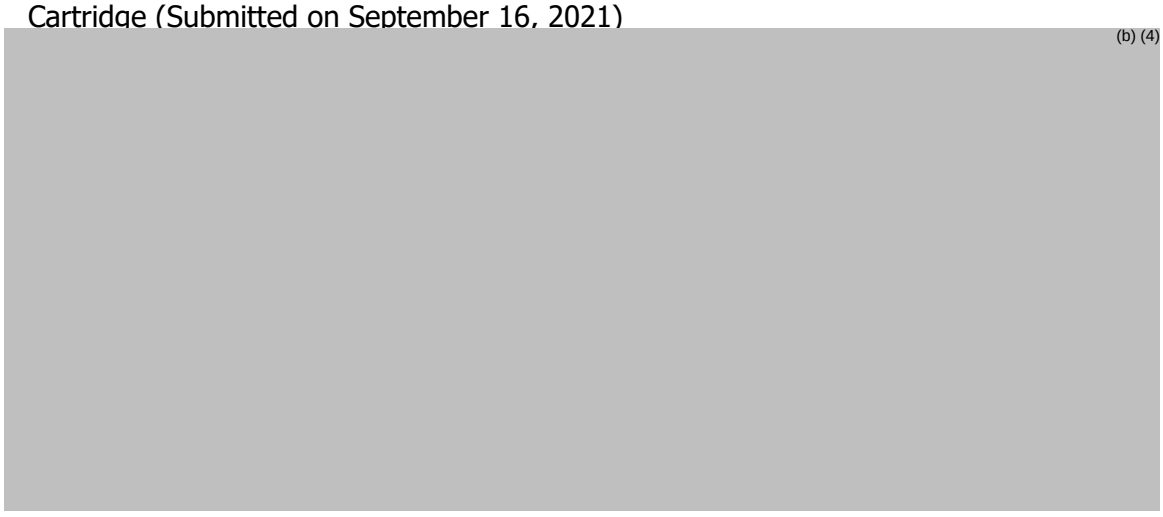
Appendix A: Proposed Labeling

Prescribing Information/Medication Guide/Instructions for Use (submitted on September 16, 2021 to BLA 761105.16 \\CDSESUB1\evsprod\bla761105\0136\m1\us\114-labeling\draft\labeling\neg-lbl-7158.pdf)

Container Labels

Cartridge (Submitted on September 16, 2021)

(b) (4)



4 Page(s) 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: For the cartridge and vial container label, revise the manufacturer's name as the name appearing on FDA form 356h as "Abbvie Inc."
The Applicant revised as requested

[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."

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

Comment/Recommendation: Indicate where the lot number appears on the cartridge label

Applicant's response:

(b) (4)

[redacted]

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

Comment/Recommendation: Indicate where the expiration date appears on the cartridge label *Applicant's response: Figure 3 shows the location of the expiration date on the printed cartridge label. See above*

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 considerations

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. *Applicant's response: AbbVie confirms that there is no text on the ferrule and cap overseal of the vials.*

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

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located

Applicant's response: AbbVie confirms that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection of both the labeled vial and labeled cartridge. For the labeled vial, the visual area of inspection is through the clear portion of the glass vial. For the labeled cartridge, as the label is mainly transparent, the visual area of inspection is from the unobstructed area of the label and from the septum end of the cartridge barrel not covered by the label.

(b) (4)

[redacted]

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: 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: Indicate where the linear bar code appears on the container label and ensure that it is surrounded by enough white space to facilitate proper scanning
The Applicant added the barcode to the vial label but responded as follows for the cartridge label: (b) (4)

OBP Labeling's response: Requests for an exemption from the barcode appearing on the cartridge label are to be sent to the Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Silver Spring, MD 20993-0002) *The Applicant added the barcode to the cartridge label*

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

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

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

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

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

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

Comment/Recommendation: Add "No preservative" to the vial carton labeling per 21 CFR 610.61 (e). *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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: Revise the storage statement to reduce redundant language on the vial carton labeling to read as follows: **"Storage: Refrigerate at 36°F to 46° F (2°C to 8°C) in the original carton to protect from light. Do not shake. Do not freeze."** *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

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

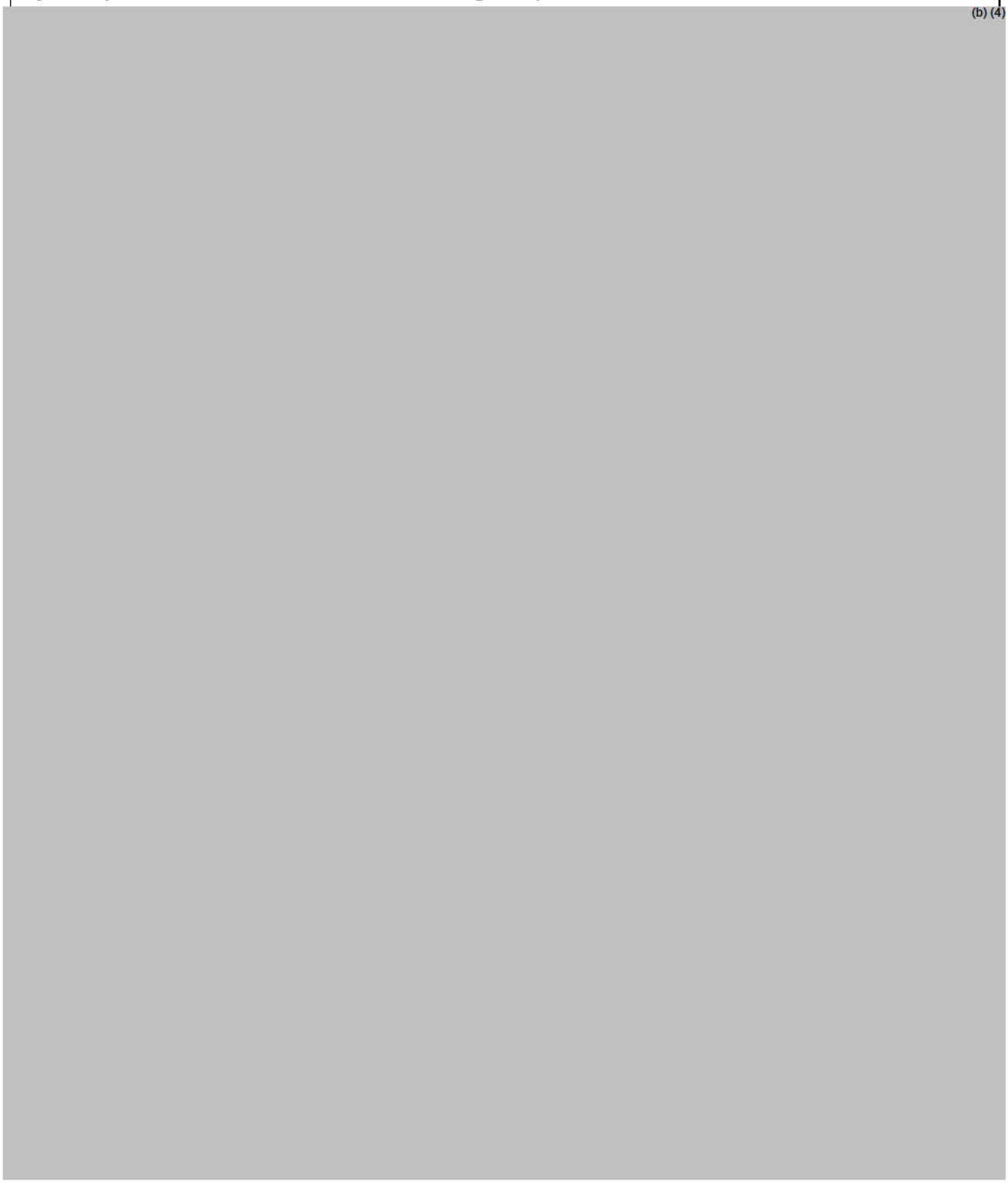
Comment/Recommendation: Revise the vial carton labeling ingredient lists as "Each mL contains 60 mg of risankizumab-rzaa and glacial acetic acid (0.054 mg), polysorbate 20 (0.2 mg), sodium acetate (b) (4) mg), trehalose ((b) (4) mg), and Water for Injection, USP.

Applicant's response: Consistent with 21 CFR 201.10(d)(1), the vial carton labeling ingredient list has been revised to include the quantity of the ingredients in the single-dose vial unit. This information is considered most informative to licensed practitioners since the full contents of the vial are intended to be administered. The statement is revised as: "Each 10.0 mL vial contains 600 mg of risankizumab and glacial acetic acid (0.54 mg), polysorbate 20 (2.0 mg) sodium acetate (b) (4) mg), trehalose (b) (4) mg), and Water for Injection, USP (b) (4) "

OBP Labeling's response: Revise the vial carton labeling ingredient list to remove the trailing zeros from each mention of 10 mL. The Applicant revised as requested

Revise vial and cartridge carton labeling ingredient names to the compendial names "glacial acetic acid" and "trehalose". Ensure that qualitative and quantitative ingredient information including appearance of inactive ingredient names in alphabetical order (except water for injection) and are consistent across all labeling components.

(b) (4)



Your Description and Composition submission notes the reference standards [redacted] Confirm if your material meets the definition of the Sodium Succinate NF monograph and if so, revise accordingly.
The revisions to the inactive ingredient amounts are proposed as follows:

SKYRIZI (risankizumab-rzaa) injection 150 mg/mL prefilled syringe or prefilled pen for subcutaneous use

inactive ingredients glacial acetic acid (0.054 mg), polysorbate 20 (0.2 mg), sodium acetate (0.75 mg), trehalose (63.33 mg), and Water for Injection, USP. The pH is 5.7.

SKYRIZI (risankizumab-rzaa) injection 75 mg/0.83 mL prefilled syringe for subcutaneous use

inactive ingredients sodium succinate (0.53 mg), polysorbate 20 (0.17 mg), sorbitol (34 mg), succinic acid (0.049 mg), and Water for Injection, USP. The pH is 6.2.

SKYRIZI (risankizumab-rzaa) injection 360 mg/2.4 mL (150 mg/mL) prefilled cartridge for use with the On-Body Injector for subcutaneous use

inactive ingredients glacial acetic acid (0.13 mg), polysorbate 20 (0.48 mg), sodium acetate (1. 8 mg), trehalose (152 mg), and Water for Injection, USP. The pH is 5.7.

SKYRIZI 600 mg/10 mL (60 mg/mL) in a vial for intravenous infusion
inactive ingredients glacial acetic acid (0.54 mg), polysorbate 20 (2 mg), sodium acetate (7.5 mg), trehalose (633.3 mg), and Water for Injection, USP. The pH is X.X
Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the table that includes trehalose anhydrous and sodium acetate anhydrous calculations. Ensure that all inactive ingredients with a USP monograph are provided as such. You may submit previously approved risankizumab 150 mg/mL PFS/AI carton labeling along with the proposed PFC and vial carton labeling with revision to the inactive ingredient names using the USP/NF monograph titles while ensuring that it matches your prescribing information.
The Applicant submitted an updated Description and Composition to section 3.2.P.1 by adding a footnote to the table that includes the compendial name and amount of inactive ingredient based on USP monograph definition calculation for each presentation and revised labeling as requested. AbbVie confirms the inactive ingredient [redacted] used in the formulation for the 75 mg/0.83 mL prefilled syringe meets the definition of the Sodium Succinate NF monograph. The carton labeling for the 75 mg/0.83 mL prefilled syringe will be submitted if marketing status changes.
Delete "[redacted]..." *The Applicant revised as requested*
Add the four-letter suffix to the proper name in the ingredient list risankizumab-rzaa for the vial carton labeling *The Applicant revised as requested*

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

Comment/Recommendation: see PI

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

Comment/Recommendation: To the vial carton labeling, add "No U.S. Standard of Potency" *The Applicant revised as requested*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Comment/Recommendation: On cartridge and vial carton labeling, revise the statement of dosage to read: Dosage: See Prescribing Information. "(b) (4)" terminology is not used

for prescribing information that follows PLR format. Ensure updated and consistent language is used across all labeling components. *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: To the vial and cartridge carton labeling, add "ATTENTION: Dispense the enclosed Medication Guide to each patient" *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: Added the mg/mL expression for the single-dose vial
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	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Deleted storage information for the supplied products since this information is provided in the how supplied section of labeling
Applicant revised as requested

Revised to the compendial name for the diluent "5% Dextrose Injection" *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: Deleted the mg/mL presentation from the 0.75 mg/0.83 mL syringe since this presentation provides less than 1 mL *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)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised to the compendial name for glacial acetic acid and for trehalose. Some inactive ingredient names were revised to the compendial name per USP monograph. Submit corresponding carton labeling revisions for the 150 mg/mL prefilled syringe or prefilled pen. *Applicant revised as requested*

Added the route of administration and pH for vial *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*	☐ Yes ☐ No ☒ N/A

Section 16: 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

Comment/Recommendation: Revised to include mg/mL presentation for the vial and cartridge *The Applicant revised as requested*

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

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: Revised to the compendial name for glacial acetic acid and trehalose. *The 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

Patient Information Labeling Evaluation (N/A)

Instructions for Use Evaluation

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 Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). 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: Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). To ensure that applicable storage and handling	✓ Yes ☐ No ☐ N/A

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)	

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
Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). *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/Medication Guide/Instructions for Use (submitted on May 25, 2022 \\CDSESUB1\evsprod\BLA761105\0217\m1\us\114-labeling\draft\labeling)

Container Labels

8 Page(s) 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: 6/14/2022 07:14:14AM
GUID: 50814c7000007a3d59329f660d8ddf02

Andrea George

Digitally signed by Andrea George
Date: 6/14/2022 09:57:58AM
GUID: 59b99181005cc7b0a3e954078ede1be9

Recommendation: Approval

BLA Number: 761262
Assessment Date: February 23, 2022

Drug Name/Dosage Form	risankizumab-rzaa (Skyrizi)/injection
Strength/Potency	600 mg/vial (60 mg/mL)
Route of Administration	intravenous infusion
Rx/OTC dispensed	Rx
Indication	Induction therapy for the treatment of moderately to severely active Crohn's disease in patients aged 16 years and older
Applicant/Sponsor	AbbVie, Inc.

Product Overview:

Risankizumab-rzaa is a human IgG1 monoclonal antibody produced in CHO cells that targets the p19 subunit of interleukin 23 (IL-23 p19), to inhibit interaction of IL-23 with the IL-23 receptor (IL-23R). When dendritic cells and macrophages are activated, they release IL-23 and other cytokines, which stimulate production of additional cytokines from T cells. This leads to increased infiltrates of additional T cells (Th1, Th17, and Th22) in the gastrointestinal tract that clinically manifests as Crohn's disease. Elevated IL-23 has been observed in Crohn's disease patients and it is hypothesized that inhibition of IL-23R signaling through blockade of IL-23 reduces gut inflammation in these patients. Risankizumab-rzaa has been engineered with two mutations in the Fc region of the antibody to reduce Fcγ receptor and complement binding. Risankizumab-rzaa drug product is manufactured as a sterile, preservative-free, 600 mg vial. Risankizumab is proposed as a single agent for the induction phase of treatment of moderately to severely active Crohn's disease in patients aged 16 years and older.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance/Drug Product	Andrea George	DBRRI/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Microbiology and Facility	Wendy Tan	DBM/OPMA/OPQ
Microbiology Quality Assessment Lead	Maxwell Van Tassell	DBM/OPMA/OPQ
Facility Quality Assessment Lead	Zhong Li	DBM/OPMA/OPQ
Application Technical Lead	Riley Myers	DBRRI/OBP/OPQ
RBPM	Anita Brown	RBPMBI/OPRO/OPQ

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Jay Fajiculay	OND/ORO/DROII
Cross-disciplinary Team Lead	Suna Seo	OND/OII/DG
Medical Officer	Suruchi Batra	OND/OII/DG
Pharmacology/Toxicology	Dinesh Gautam	OND/OII/DPTII
Clinical Pharmacology	Cindy Pan	OTS/OCP/DIIP
Statistics	Ben Wong	OTS/OB/DBVII

1. Names

a. Proprietary Name: Skyrizi
b. Trade Name: Skyrizi
c. Non-Proprietary Name/USAN: risankizumab-rzaa
d. CAS Name: 1612838-76-2
e. Common Name: ABBV-066, BI655066
f. INN Name: risankizumab
g. OBP systematic name: MAB HUMANIZED (IGG1 L237A L238A) ANTI Q9NPF7 (IL23A_HUMAN) [BI655066]

Submissions Assessed:

Submission(s) Assessed	Document Date
STN 0001/1	September 16, 2021
STN 0002/4	October 8, 2021
STN 0004/2	October 7, 2021
STN 0005/5	October 22, 2021
STN 0007/8	December 6, 2021
STN 0014/14	December 23, 2021
STN 0018/19	January 24, 2022
STN 0023/23	February 11, 2022
STN 0024/24	February 11, 2022
STN 0025/25	February 16, 2022

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

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

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

   B. Other documents:

Document	Application Number	Description
IND	118701	Clinical study
BLA efficacy supplement	761105/S-016	Drug product for Crohn's disease maintenance therapy

3. Consults: None

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761262 for Skyrizi manufactured by AbbVie, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Skyrizi is well-controlled and leads to a product that is pure and potent. From Chemistry, Manufacture and Control (CMC) perspective, it is recommended that this product be approved for human use under conditions specified in the package insert.

C. Approval Action Letter Language:

- Manufacturing location:
    - Drug Substance: AbbVie Bioresearch Center, Inc., 100 Research Drive, Worcester, MA 01605
    - Drug Product: (b) (4) (b) (4)
- Fill size and dosage form: 600 mg single-use vial
- Dating period
    - Drug Product: 12 months: 5±3°C
    - Drug Substance (b) (4) months: ≤ (b) (4) °C
    - For packaged products: "Not packaged"
    - Stability Option
        - For stability protocols:
            - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
    - Yes
    - Rationale, if exempted: specified product in accordance with 21 CFR 601.2a
      Note: risankizumab-rzaa is exempted from lot release per FR 95-29960.

D. Benefit/Risk Considerations: Crohn's disease is a chronic inflammatory disease affecting any segment of the gastrointestinal tract. Inflammation of the gastrointestinal tract inhibits the gut's normal function and leads to symptoms of fatigue, prolonged diarrhea with or without gross blood, abdominal pain, weight loss, and fever. Additionally, patients with Crohn's disease have severely impacted quality of life, and the disease can affect the patient's ability to sleep and function at work or school. Symptoms are often progressive with development of penetrating disease and stricture formation that may require hospitalization and surgery. While there are numerous treatments available for patients with moderately to severely active Crohn's disease, efficacy is limited and many of these biologic products are associated with side effects

that limit their use. These approved biologic products include infliximab, adalimumab, certolizumab, which target TNFα and are the primary treatment for most patients. Natalizumab and vedolizumab target integrins are indicated for patients who have failed or are intolerant to anti-TNFα therapy. Similar to risankizumab-rzaa, ustekinumab inhibits IL-23 signaling, but by binding a different target, IL-23p40. However, there is limited evidence that ustekinumab promotes mucosal healing whereas mucosal healing was observed in clinical subjects treated with risankizumab-rzaa. Therefore, risankizumab-rzaa may potentially address certain aspects of treatment for Crohn's disease that are currently not covered by other approved products.

The overall control strategy for risankizumab-rzaa manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, process monitoring tests, release, and stability testing ensures process consistency, and drug substance (DS), and drug product (DP) that have appropriate quality and are free of adventitious agents.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable: None

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy	Other
IL-23 binding (potency)	Potency	Intrinsic to the molecule. Potency can be impacted by aggregation, fragmentation, (b) (4)	(b) (4)	(b) (4)
Identity	Safety and Efficacy	Intrinsic to the molecule.		
High molecular weight species (HMWS)	Potency and immunogenicity	Manufacturing process and exposure to light stress. The level of HMW is at about (b) (4) % and does increase over shelf-life.		
Low molecular weight species (LMWS)	Potency	Manufacturing process (cell culture process).		

		The level of LMWS is around (b) (4)% and does not increase over shelf-life.	(b) (4)
(b) (4) oxidation in CDR	Potency	Exposure to light and chemical stress. The level of (b) (4) oxidation is (b) (4)% for both sites, as determined by LC-MS peptide mapping.	
(b) (4) oxidation in FcRn binding site	Pharmacokinetics	Exposure to light stress. The level of (b) (4) oxidation is (b) (4)% for all sites, as determined by LC-MS peptide mapping.	
(b) (4) deamidation in the CDR and FcRn binding regions	Potency and Pharmacokinetics	Manufacturing process (pH stress).	
Appearance of Solution (visible particulates, color and clarity)	Safety and Efficacy	Formulation, contamination or degradation	
Protein Content	Efficacy	Manufacturing process	
pH	Safety and Efficacy	Formulation process	
Osmolality	Safety and Efficacy	Formulation	
(b) (4)	Safety	Formulation	

B. Drug Substance [risankizumab-rzaa] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management. (see example in Attachment 2)

CQA (type)	Risk	Origin	Control Strategy	Other

Residual HCP	Immunogenicity	Production cell line HCP levels in DS are consistent at <(b) (4) U/mg (or <(b) (4) ng/mg).	(b) (4)	
Residual DNA	Safety	Production cell line		Sufficient process development and process performance validation data were provided to demonstrate adequate clearance to support the removal of residual DNA testing from lot release.
Residual (b) (4) (Process-related impurity)	Safety and Immunogenicity	Process related impurity leached from (b) (4) (b) (4)		
Residual (b) (4) (Process-related impurity)	Safety	Expansion and Production bioreactor		
Cell Culture Derived Impurities (b) (4)	Safety	Process related impurities		
Viruses (Contaminant)	Safety	Contamination during manufacture, most likely during cell culture operations.		
Mycoplasma (Contaminant)	Safety	Mycoplasma would most likely be introduced during cell culture operations.		
Endotoxin	Safety and Purity	Raw materials contamination during manufacturing		

Bioburden	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials and manufacturing process	(b) (4)

- Description: Risankizumab-rzaa is a humanized monoclonal immunoglobulin G1 (IgG1 isotype) consisting of two identical heavy chains (HC) and two identical light chains (LC) covalently linked through inter- and intra-chain disulfide bonds. Each HC and LC are composed of 449 and 214 amino acids, respectively. Each HC contains a leucine to alanine substitution at amino acid residues 237 and 238 within the Fc domain to minimize the potential for effector function and deletion of lysine at the C terminus to reduce potential for charge heterogeneity. A single N-linked glycosylation site is in the CH2 domain of each HC at asparagine residue 297.

  The extinction coefficient was calculated and confirmed experimentally to be 1.52 mL x mg^{-1} x cm^{-1} at 280 nm.

- Mechanism of Action (MoA): Risankizumab-rzaa selectively binds to IL-23 p19 and inhibits binding of IL-23 to its receptor. This in turn, inhibits IL-23 inflammatory responses that contribute to the pathogenesis of Crohn's disease. The generation and characterization of risankizumab-rzaa was undertaken to include selectivity for the p19 over the p40 subunit, to overcome the high-affinity binding between IL-23 to IL-23R and favorable biophysical properties.

- Potency Assay: Biological activity of risankizumab-rzaa is evaluated using a human embryonic kidney cell line (HEK293) that constitutively expresses the human IL-23R complex (IL-23R and IL-12Rβ1 subunits) and STAT3. The Reporter Gene Assay (RGA) bioassay is a luciferase reporter-gene assay which measures the activation of the human IL-23R/STATB pathway. Upon IL-23 binding to the IL-23R, STAT3 is phosphorylated and activates transcription of the STAT3 responsive reporter construct firefly luciferase. The luciferase activity is then quantified. In the presence of risankizumab, IL-23 cannot bind the IL-23R, leading to the inhibition of luciferase activity. To measure risankizumab potency, HEK293 cells are co-incubated with increasing amounts of risankizumab-rzaa and a 4-parameter (4-PL) unconstrained logistic analysis is used to calculate the dose response curve. Potency is reported as a percentage relative to the reference standard.

- Reference Materials: The two-tiered reference material system consists of a primary reference standard (PRS) and a working reference standard (WRS). (b) (4)

  he procedures and criteria used

to qualify future PRSs and to qualify and re-qualify new WRSs are acceptable to ensure minimal drift in potency over time.

- Critical starting materials or intermediates: The production cell line for risankizumab was derived from CHO (b) (4)
(b) (4)

- Manufacturing process summary: The risankizumab-rzaa CMC2 (b) (4) mg/mL (b) (4) DS is manufactured at AbbVie Bioresearch Center Inc., Worcester, MA, using a (b) (4)
(b) (4)

- Container closure: Risankizumab-rzaa CMC2 (b) (4) mg/mL (b) (4) DS is (b) (4)
(b) (4)

- Dating period and storage conditions: The dating period for CMC2 (b) (4) mg/mL (b) (4) DS is (b) (4) months when stored at ≤(b) (4) °C.

C. Drug Product [risankizumab-rzaa] Quality Summary:

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

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

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety (Infection), Purity and Efficacy (degradation or modification of products by contaminating microorganisms)	Contamination may be introduced throughout the manufacturing process	(b) (4)	
Endotoxin (contaminant)	Safety, purity, and immunogenicity	Raw materials; contamination may be introduced throughout the DP manufacturing process		Provides over a (b) (4) fold safety factor.
Container closure integrity	Safety	Container closure breaches during storage. May be impacted by storage conditions.		
Extractable volume DP	Accurate dosing	(b) (4)		
Leachables (process-related impurities)	Safety	Manufacturing equipment and CCS		

			(b) (4)
Subvisible Particulate Matter (Product or Process Related Impurities)	Safety and Immunogenicity	Manufacturing process and CCS.	
Visible Particles	Safety and Immunogenicity	Through the DP manufacturing process via extended hold times and contact with materials (filters, bioprocessing bags, etc.).	

- Potency and Strength: Risankizumab-rzaa is supplied at 600 mg/10 mL in a single-use vial. Potency is defined as the percent activity relative to the current reference standard. The potency assay is the same as described for the DS.

- Summary of Product Design: Risankizumab-rzaa 600 mg vial is presented as a sterile, preservative-free, non-pyrogenic liquid formulation in glass vial for intravenous injection at a concentration of 60 mg/mL. The extractable volume is 10 mL.

- List of Excipients: (b) (4) mM sodium acetate (b) (4) 0.9 mM acetic acid, (b) (4) mM trehalose (b) (4), and 0.2 g/L polysorbate 20 (PS20) at pH (b) (4)

- Reference Materials: The same reference material is used for DS and DP.

- Manufacturing process summary: Risankizumab-rzaa 60 mg/mL DP is manufactured at (b) (4) The DP manufacturing process consists of (b) (4) (b) (4)

(b) (4)

- Container closure: The primary container closure system for (b) (4) (b) (4) glass vial that is sealed with a grey 20 mm (b) (4) rubber stopper and aluminum flip cap with a (b) (4). Appropriate compatibility studies were performed for the container closure system.

  The secondary container closure system consists of a box, which is sufficient for protection from light.

- Dating period and storage conditions: The dating period for risankizumab-rzaa 60 mg/mL DP is 12 months when stored at 5±3°C.

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

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations: None

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Cell Bank Manufacturing and Storage	(b) (4)		No Evaluation Necessary	N/A	NEC
DS Manufacture, release and stability testing except bioassay, cell bank manufacturing and storage	AbbVie Bioresearch Center Inc.	3003684386	Inspection history	N/A	Approved based on 704(a)(4)

DS release and stability testing, all tests except bioburden, BET, and HCP, cell bank storage	AbbVie Biotechnology Ltd	300462772	Inspection history	N/A	Approved based on profile
DS release and stability testing for bioassay	(b) (4)		Inspection history	NA	Approved based on ORA District file review
Unprocessed bulk harvest testing			Inspection history	N/A	Approved based on Profile
Unprocessed bulk harvest testing			Inspection history	N/A	Approved based on Profile
DS storage			No evaluation necessary	N/A	NEC
DS storage and storage of the bulk vial			No evaluation necessary	N/A	NEC
Storage of DP stability samples			No evaluation necessary	N/A	NEC
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Release and stability testing of bulk vial, tryptic peptide mapping, CEX-UV, UP-SEC, CGE-NR, RGA bioassay, PS20	AbbVie Biotechnology Ltd	300462772	Inspection history	N/A	Approved based on profile
Packaging, Labeling and storage of the DP	AbbVie Inc	3009751352	Inspection history	N/A	Approved based on profile
Release and stability testing of the bulk vial all tests except sterility, storage of the bulk vial stability samples	(b) (4)		Inspection history	N/A	Approved based on ORA District file review
Manufacturing, in-process testing, release testing for BET, sterility and storage of the bulk vial			Inspection history	N/A	Approved based on PLI waiver granted by OPMA/OBP
Release and sterility testing of the bulk vial			Inspection history	N/A	Approved based on profile
DS release and stability testing of the bulk vial			Inspection history	N/A	Approved based on ORA District file review
Packaging, labeling and storage of the DP	AbbVie SrL	3002806277	Inspection history	N/A	Approved based on profile

G. Facilities: Please refer to Table F for information.

H. Lifecycle Knowledge Management:

a. Drug Substance:
    i. Protocols approved:
        1. Annual stability protocol
        2. Qualification protocols for future primary and working reference standards
        3. Re-qualification protocols for primary and working reference standards
        4. Qualification protocol for new working cell bank
    ii. Outstanding assessment issues/residual risk: None
    iii. Future inspection points to consider: None

b. Drug Product
    i. Protocols approved: Annual stability protocol
    ii. Outstanding assessment issues/residual risk: None
    iii. Future inspection points to consider: None

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/

RILEY C MYERS
02/23/2022 03:39:45 PM