

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761449Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

## BLA Executive Summary

### Assessment Date: February 25, 2025

#### 1. Application/Product Information

|                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BLA number               | 761449                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Submission Type          | Original submission                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Regulatory Pathway       | Biosimilar 351(k)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Associated IND           | 129965                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Review Designation       | Standard review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Applicant                | Fresenius Kabi USA, LLC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Indication               | Rheumatoid Arthritis, Giant Cell Arteritis, Polyarticular Juvenile Idiopathic Arthritis (age ≥ 2 years), Systemic Juvenile Idiopathic Arthritis (age ≥ 2 years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Rx/OTC dispensed         | Rx                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Drug Product Name        | TYENNE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                          | tocilizumab-aazg/MSB11456                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                          | MAB HUMANIZED (IGG1) ANTI P08887 (IL6RA_HUMAN) [MSB11456]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Drug Product Description | <p>TYENNE (tocilizumab-aazg) injection is a sterile, clear, colorless to pale yellow, preservative-free solution with a pH of 6 for subcutaneous use.</p> <p>Each single-dose 0.9 mL prefilled syringe (PFS) with a needle safety device or single-dose 0.9 mL autoinjector (AI) contains 180 mg/mL tocilizumab-aazg in L-Histidine (b) (4) mg/mL, L-Arginine (b) (4) mg/mL, L-Lactic Acid (0.9 mg/mL), Polysorbate 80 (0.2 mg/mL), Sodium Chloride (0.6 mg/mL), and Water for Injection, USP.</p> <p>Hydrochloric acid and sodium hydroxide are added to adjust the pH.</p> <p>Tocilizumab-aazg is a recombinant, humanized IgG1 monoclonal antibody directed against human interleukin 6 receptors (IL-6R) and binds to the IL-6 binding site of both soluble IL-6R (sIL-6R) and membrane bound IL-6R (mIL-6R).</p> |
| Dosage Form              | Injection, solution                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

|                                  |                                                                                  |                              |                          |
|----------------------------------|----------------------------------------------------------------------------------|------------------------------|--------------------------|
| Strength                         | 162 mg/0.9 mL (180 mg/mL)                                                        |                              |                          |
| Route of Administration          | Subcutaneous (SC)                                                                |                              |                          |
| Primary Container Closure System | PFS                                                                              |                              |                          |
| Device Information               | PFS (b) (4) safety device<br>Prefilled AI                                        |                              |                          |
| Co-packaged Product Information  | Not applicable                                                                   |                              |                          |
| OPOQ Review Team                 | Discipline                                                                       | Primary                      | Secondary                |
|                                  | Product quality<br>Immunogenicity Assay<br>CAA                                   | Deepa Raghu                  | Bazarragchaa Damdinsuren |
|                                  | Microbiology                                                                     | Yuan-Chia (Charles) Kuo (DS) | Maxwell Van Tassell      |
|                                  | Facility                                                                         | Jeanne Fringer (DP)          | Zhong Li                 |
|                                  | RBPM                                                                             | Anita Brown                  |                          |
|                                  | ATL                                                                              | Bazarragchaa Damdinsuren     |                          |
| OPOQ Issued Consults             | A consult to CDRH for device components was performed under original BLA 761275. |                              |                          |

2. Recommendation and Conclusion on Approvability  
Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761449 for Tyenne manufactured by Fresenius Kabi USA, LLC. The data submitted in this application are adequate to support the conclusion that the manufacture of Tyenne is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Tyenne is highly similar to US-licensed Actemra, 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:  
[REDACTED] (b) (4)
- Drug Product:
  - [REDACTED] (b) (4)
  - Device assembly, labeling and secondary packaging: Fresenius Kabi Austria GmbH (FEI: 3003708554)  
Am Gewerbepark 6, 8402 Werndorf, Austria
  
- b. Fill size and dosage form:  
Injection, solution in single-dose PFS [REDACTED] (b) (4) safety device and in single-dose prefilled AI: 162 mg/0.9 mL
  
- c. Dating Period:
  - Drug Product:  
36 months when stored at  $5 \pm 3^{\circ}\text{C}$
  - Drug Substance:  
[REDACTED] (b) (4) months when stored at [REDACTED] (b) (4)  $^{\circ}\text{C}$
  - For packaged products: Not packaged
  - Stability Option:
    - Limited stability data
      - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
    - For stability protocols:
      - We have approved the stability protocol in your license application for the purpose of extending the expiration dating of your drug product under 21 CFR 601.12.
  
- d. Exempt from lot release:
  - Yes
  - Rationale, if exempted: Tyenne is exempted from lot release per FR 95-29960.
  
- e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable
  1. Re-evaluate the drug substance and drug product lot release and stability acceptance criteria for the degree of coloration after release data from 30

drug substance lots and corresponding drug product lots are available, and with consideration of available stability data. The final report should include the corresponding data, the analysis thereof, and any proposed changes to the drug substance and drug product release or stability specifications resulting from the assessment.

2. Re-evaluate lot release and stability acceptance criteria for the device performance attributes of the pre-filled syringe (b) (4) (PFS (b) (4)) and auto-injector device (PFS-AI) after release data from 30 PFS (b) (4) and PFS-AI lots are available, and with consideration of available stability data. The final report should include the corresponding data, the analysis thereof, and any proposed changes to the drug product release or stability specifications resulting from the assessment.

#### 4. Basis for Recommendation

- a. **Summary:** Tyenne (tocilizumab-aazg, MSB11456) is a proposed biosimilar to US-licensed Actemra (US-Actemra) that is intended to be delivered by the same routes of administration (SC) for the same indications as the US-Actemra reference product. The comparative analytical assessment (CAA) data submitted under BLA 761275 support the demonstration that Tyenne is highly similar to US-Actemra, notwithstanding minor differences in clinically inactive components and that the analytical portion of the scientific bridge to justify the use of clinical data derived from EU-approved RoActemra was established.

Tocilizumab is a recombinant, humanized IgG1 monoclonal antibody that specifically binds to the IL-6 binding site of both sIL-6R and mIL-6R and blocks the activity of IL-6. This leads to down-regulation of IL-6-driven cellular functions. The biological activity of MSB11456 is evaluated on its capability to inhibit the IL-6-induced cell proliferation in a dose-dependent manner on the DS-1 human cell line.

All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional activity. Note that the pre-license inspections manufacturing facilities were performed under the original BLA 761275.

The assessment of manufacturing information provided in this application (that is the same under the approved BLA 761275) has concluded that the methodologies and processes used for DS and DP manufacturing, release, and stability testing are sufficiently robust and controlled to ensure the consistent manufacture of a safe, pure, and potent product. The microbial control and sterility assurance strategy is sufficient to support consistent

manufacture of a sterile product and the OPMA assessors are recommending approval for this BLA from a sterility assurance and microbiology product quality perspective.

The DS manufacturing process and controls information is cross-referenced to BLA 761275. The DS is (b) (4)

The Tyenne DP-SC manufacturing includes (b) (4)

(b) (4)

(b) (4). The final DP-SC is stored at  $5 \pm 3^{\circ}\text{C}$  for long term storage.

The assessment of immunogenicity assays to detect and confirm anti-drug antibodies (ADAs) against tocilizumab in the clinical studies to support this BLA was performed under BLA 761275. The assessment concluded that the assays were adequately validated and suitable for their intended purpose. Individual assessments for each discipline are located in separate documents in Panorama.

b. Subdiscipline Recommendation:

|                      |   |                         |
|----------------------|---|-------------------------|
| Drug Substance       | - | Adequate*               |
| Drug Product         | - | Adequate with PMCs/PMRs |
| CAA                  | - | Adequate*               |
| Immunogenicity Assay | - | Adequate *              |
| Facilities           | - | Adequate                |
| Microbiology         | - | Adequate                |

\*The CMC information for these subdisciplines is provided under BLA 761275 and cross-referenced, the assessments performed for BLA 761275 are applicable to support the current BLA

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 Tyenne (i.e., there is no specific test method described in regulation for Tyenne that establishes an official standard of potency). We next considered whether potency is a factor for Tyenne 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

Tyenne for purposes of § 610.61(r) because lot variability is not a concern for Tyenne as Tyenne'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 BLA 761275

c. Drug Products (IV and SC):

i. Protocols approved for:

1. On-going stability studies (3.2.P.8.1)

2. Post-approval annual stability and commitments (3.2.P.8.2)

ii. Residual risk: No

iii. Future inspection points to consider: None

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

Appendix. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

The Comparative Analytical Assessments (CAAs) between MSB11456, U.S.-licensed Actemra (hereafter referred to as US-Actemra), and E.U.-approved RoActemra (hereafter referred to as EU-RoActemra) were performed under BLA 761275. The CAA concludes that the comparative analytical data support a demonstration that Tyenne is highly similar to US-licensed Actemra, notwithstanding minor differences in clinically inactive components.

B. Same Strength

MSB11456 under the current BLA has the same dosage forms and routes of administration as US-licensed Actemra. US-Actemra is available at these strengths: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL (all 20 mg/mL) in vials for further dilution prior to intravenous infusion, and 162 mg/0.9 mL in a prefilled syringe or prefilled autoinjector. In this BLA the Applicant is seeking approval of 180 mg/mL MSB11456 in 162 mg/0.9 mL prefilled syringe (b) (4) safety device or autoinjector. Comparative concentration (mg/mL) was assessed as part of the CAA. The extractable volume and fill weight data were also assessed in the context of manufacturing

controls. Based on the comparative concentration data and manufacturing data, the 180 mg/mL MSB11456 in 162 mg/0.9 mL prefilled syringe (b) (4) safety device or autoinjector have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as the corresponding strength of US-Actemra. Each strength of MSB11456 prefilled syringe is the same as that of US-Actemra.

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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.**  
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/s/  
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BAZARRAGCHAA DAMDINSUREN  
02/25/2025 05:17:32 PM

**LABELS AND LABELING ASSESSMENT**

|                                 |                                                                                                                                                                                                                                                                                               |
|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Date of Assessment:             | March 21, 2025                                                                                                                                                                                                                                                                                |
| Assessor:                       | Diana Pei, PharmD<br>Labeling Assessor<br>Office of Product Quality Assessment III (OPQA III)                                                                                                                                                                                                 |
| Through:                        | Deepa Raghu, PhD<br>Product Quality Assessor<br>OPQA III/Division of Product Quality Assessment XVI                                                                                                                                                                                           |
| Application:                    | BLA 761449                                                                                                                                                                                                                                                                                    |
| Applicant:                      | Fresenius Kabi USA, LLC                                                                                                                                                                                                                                                                       |
| Submission Date:                | July 17, 2024                                                                                                                                                                                                                                                                                 |
| Product:                        | TYENNE (tocilizumab-aazg)                                                                                                                                                                                                                                                                     |
| Dosage form(s):                 | Injection                                                                                                                                                                                                                                                                                     |
| Strength and Container-Closure: | 162 mg/0.9 mL in a single-dose prefilled syringe or single-dose prefilled autoinjector                                                                                                                                                                                                        |
| Purpose of assessment:          | The Applicant submitted a biologics license application for the approval of TYENNE (tocilizumab-aazg) for the treatment of rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis (PJIA), systemic juvenile idiopathic arthritis (SJIA), (b) (4)<br>(b) (4). |
| <b>Recommendations:</b>         | The prescribing information, medication guide, instructions for use, container labels, and carton labeling are acceptable from an OPQA III Labeling perspective.                                                                                                                              |

| <b>Materials Considered for this Label and Labeling Assessment</b> |                         |
|--------------------------------------------------------------------|-------------------------|
| <b>Materials Assessed</b>                                          | <b>Appendix Section</b> |
| 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 branded prescribing information submitted on March 6, 2025, the medication guide submitted on January 31, 2025, and the instructions for use submitted on July 17, 2024, the container labels and carton labeling submitted on February 6, 2025 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 July 17, 2024)  
<\\CDSESUB1\EVSPROD\bla761449\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-sc-and-iv.docx>
- Medication Guide (submitted on July 17, 2024)  
<\\CDSESUB1\EVSPROD\bla761449\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-sc-and-iv.docx>
- Instructions for Use (submitted on July 17, 2024)  
<\\CDSESUB1\EVSPROD\bla761449\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-pfs.docx>  
  
<\\CDSESUB1\EVSPROD\bla761449\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-ai.docx>
- Container Labels (submitted on July 17, 2024)

3 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<sup>1,2</sup> and Labeling<sup>3</sup> Standards**

**Container<sup>4</sup> Label Evaluation**

| <b>Proper Name (container label)</b>                                                                                                                                                                 | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| 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(i), 21 CFR 600.3(k) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>                                                                                 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Manufacturer name, address, and license number (container label)</b>                                      | <b>Acceptable</b>                                                                                      |
|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(i), 21 CFR 201.100(e)     | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>                       | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |
| <i>Recommended labeling practices (U.S license number for container bearing a partial label<sup>5</sup>)</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

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

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> 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.

<sup>4</sup> 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.

<sup>5</sup> 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."

Consider removing (b) (4) to create space to add in the U.S. License number. Historical practice has been to include the U.S license number with the manufacturer's information, even for container capable of only bearing a partial label.  
*The Applicant revised as recommended.*

| <b>Lot number or other lot identification (container label)</b>                                           | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| 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(i) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Expiration date (container label)</b>                                                                                                                                                                                        | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17                                                                                                                                                                                 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: USP General Chapters &lt;7&gt; Labeling, Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Beyond Use Date (Multiple-dose containers) (container label)</b>                                                                | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>Recommended labeling practices: USP General Chapters: &lt;659&gt; Packaging and Storage Requirements and &lt;7&gt; Labeling</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Product Strength (container label)</b>                                                                                                                                                                                                                                     | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)                                                                                                                                                                                                                        | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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: &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Multiple-dose containers (container label)</b>                                       | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55<br><i>(recommended individual dose)</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Statement: "Rx only" (container label)</b>                                                                                                                                                                                     | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)                                                                                                                                                                            | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (prominence of Rx Only statement)</i><br>reference: Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Medication Guide (container label)</b>          | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> 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).

| <b>No Package for container (container label)</b> | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.60(b)                      | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** The container is enclosed in a package.

| <b>No container label (container label)</b> | <b>Acceptable</b>                                                                                      |
|---------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.60(d)                | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** The product contains a container label.

| <b>Ferrule and cap overseal (for vials only)</b> | <b>Acceptable</b> |
|--------------------------------------------------|-------------------|
|                                                  |                   |

|                                                                                                                                         |                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |
|-----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|

**Comment/Recommendation:**

| <b>Visual inspection</b>     | <b>Acceptable</b>                                                                                      |
|------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.60(e) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> 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's response: The Applicant confirms that sufficient area of the PFS container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container. The space on the full length of the PFS (b) (4) is approximately 4 mm wide (Refer to Figure 2). The image shows the visibility of the back side of the label in the clear PFS (b) (4) transparent inspection window, but this is not the actual label that covers the whole surface of the syringe.*

**Figure 2 Visual Area of Inspection for the Prefilled Syringe**



*The Applicant confirms that sufficient area of the autoinjector container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container. The space on the autoinjector inspection window is approximately 4 mm wide (Refer to Figure 3).*

**Figure 3 Visual Area of Inspection for the Autoinjector**



| <b>Route of administration (container label)</b>                                                                                                | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)                                                                        | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>NDC numbers (container label)</b>     | <b>Acceptable</b>                                                                                      |
|------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.2, 21 CFR 207.35 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
 Add the NDC numbers or revise the XXXXX-XXX-XX to the NDC numbers or "NDC pending".  
*The Applicant added the NDC numbers.*

| <b>Preparation instructions (container label)</b>                                                                                                                           | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.5(g)                                                                                                                                                 | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |
| <i>Recommended labeling practices: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** The label is small and could be considered as a partial label. Thus, no preparation instructions is required per 21 CFR 610.60(c).

| <b>Package type term (container label)</b>                                                                                                                                                                                                                                                                                                  | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>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 &lt;659&gt; Packaging and Storage Requirements</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** The label is small and could be considered as a partial label.

| <b>No misleading statements (container label)</b> | <b>Acceptable</b> |
|---------------------------------------------------|-------------------|
|---------------------------------------------------|-------------------|

|                          |                                                                                                        |
|--------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.6 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
|--------------------------|--------------------------------------------------------------------------------------------------------|

**Comment/Recommendation:**

| <b>Prominence of required label statements (container label)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.15                                        | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Spanish-language (Drugs) (container label)</b> | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.16                         | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** The label does not display text in Spanish.

| <b>FD&amp;C Yellow No. 5 and/or FD&amp;C Yellow No. 6 (container label)</b> | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.20                                                   | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** The drug product does not contain FD&C Yellow No. 5 or 6.

| <b>Bar code label requirements (container label)</b>                                                                                                                                                                                                                                   | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.25, 21 CFR 610.67                                                                                                                                                                                                                                              | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Guidance for Industry Bar Code Label Requirements Questions and Answers (August 2011)</i><br><i>Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)</b> | <b>Acceptable</b>            |
|-------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| Regulations: 21 CFR 610.68, 21 CFR 201.26                                                                                           | <input type="checkbox"/> Yes |

|  |                                                                        |
|--|------------------------------------------------------------------------|
|  | <input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |
|--|------------------------------------------------------------------------|

**Comment/Recommendation:**

| <b>Net quantity (container label)</b>                                                                                                                                                                                                                                                                                                                                                                                                   | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.51                                                                                                                                                                                                                                                                                                                                                                                                               | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i><br><i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</i><br><i>USP General Chapters &lt;1151&gt; Pharmaceutical Dosage Forms (Excess volume in injections).</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Statement of Dosage (container label)</b>                                            | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

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

| <b>Inactive ingredients (container label)</b>                                                                                                                   | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.100, FD&C Act section 502(e)                                                                                                             | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |
| <i>Recommended labeling practices reference: USP General Chapters &lt;1091&gt; Labeling of Inactive Ingredients and USP General Chapters &lt;7&gt; Labeling</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required.

| <b>Storage requirements (container label)</b>                                                                                                                  | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>Recommended labeling practices references: USP General Chapters &lt;7&gt; Labeling, USP General Chapters &lt;659&gt; Packaging and Storage Requirements</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

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

| <b>Dispensing container (container label)</b> | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.100(b)(7)              | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**

**Package<sup>6</sup> Labeling Evaluation**

| <b>Proper name (package labeling)</b>                                                                                | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2), 21 CFR 600.3(k)                                | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Manufacturer name, address, and license number (package labeling)</b>               | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)     | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Lot number or other lot identification (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(c), 21 CFR 201.18                      | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

<sup>6</sup> 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:**

| <b>Expiration date (package labeling)</b>    | <b>Acceptable</b>                                                                                      |
|----------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(d), 21 CFR 201.17 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Beyond Use Date (Multiple-dose containers) (package labeling)</b>                                                               | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>Recommended labeling practices: USP General Chapters: &lt;659&gt; Packaging and Storage Requirements and &lt;7&gt; Labeling</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Preservative (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|----------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(e)           | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Number of containers (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(f)                   | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Product Strength (package labeling)</b>                                                                                                                                                                                          | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)                                                                                                                                                            | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)<br/>USP General Chapters: &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Storage temperature/requirements (package labeling)</b>                                                                                                     | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(h)                                                                                                                                   | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices reference: USP General Chapters: &lt;7&gt; Labeling, USP General Chapters &lt;659&gt; Packaging and Storage Requirements</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(i)                                                      | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
\*Note the carton

| <b>Multiple dose containers (recommended individual dose) (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(j)                                                     | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Route of administration (package labeling)</b>                                                                                               | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)                                                                            | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Known sensitizing substances (package labeling)</b>                                                | <b>Acceptable</b>                                           |
|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No |

|  |                                         |
|--|-----------------------------------------|
|  | <input checked="" type="checkbox"/> N/A |
|--|-----------------------------------------|

**Comment/Recommendation:** The product is not made with latex (natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex).

| <b>Inactive ingredients (package labeling)</b>                                                                                                                | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)                                                                                           | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: USP General Chapters &lt;1091&gt; Labeling of Inactive Ingredients, USP General Chapters &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Source of the product (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(p)                    | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Minimum potency of product (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(r)                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> 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 tocilizumab products (i.e., there is no specific test method described in regulation for **tocilizumab** 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 **Tyenne** 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.

The applicant did not propose to include a “No U.S. standard of potency” statement on the carton. Thus, no comment will be sent to the applicant.

| <b>Rx only (package labeling)</b>                                                                                                                                                      | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)                                                                                                                                    | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Divided manufacturing (package labeling)</b>                                                                                                                                       | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Distributor (package labeling)</b>         | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Bar code (package labeling)</b>                                                                                                                                                                                                                                                     | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.67, 21 CFR 201.25                                                                                                                                                                                                                                              | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| Recommended labeling practices references: Guidance for Industry <i>Bar Code Label Requirements Questions and Answers</i> (August 2011)<br>Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.68, 21 CFR 201.26                                                                                            | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>NDC numbers (package labeling)</b>    | <b>Acceptable</b>                                                                                      |
|------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.2, 21 CFR 207.35 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
Add the NDC numbers or revise the XXXXX-XXX-XX to the NDC numbers or "NDC pending".  
*The Applicant added the NDC numbers.*

| <b>Preparation instructions (package labeling)</b>                                                                                                                                                                                       | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)                                                                                                                                                                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i><br><i>USP General Chapters &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Package type term (package labeling)</b>                                                                                                                                                                                                                                                                                                           | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>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)</i><br><i>USP chapter &lt;659&gt; Packaging and Storage Requirements</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>No misleading statements (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.6                           | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Prominence of required label statements (package labeling)</b> | <b>Acceptable</b>                                                      |
|-------------------------------------------------------------------|------------------------------------------------------------------------|
| Regulation: 21 CFR 201.15                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No |

|  |                              |
|--|------------------------------|
|  | <input type="checkbox"/> N/A |
|--|------------------------------|

**Comment/Recommendation:**

| <b>Spanish-language (Drugs) (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.16                          | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** The label does not display text in Spanish.

| <b>FD&amp;C Yellow No. 5 and/or FD&amp;C Yellow No. 6 (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.20                                                    | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** The drug product does not contain FD&C Yellow No. 5 or 6.

| <b>Phenylalanine as a component of aspartame (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.21(c)                                        | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** The drug product does not contain phenylalanine.

| <b>Sulfites; required warning statements (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.22(b)                                    | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** The drug product does not contain sulfites.

| <b>Net quantity (package labeling)</b>                                                                                                                                                                                                                                                                                           | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.51                                                                                                                                                                                                                                                                                                        | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i><br><i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                     |  |
|-----------------------------------------------------------------------------------------------------|--|
| <i>USP General Chapters &lt;1151&gt; Pharmaceutical Dosage Forms (Excess volume in injections).</i> |  |
|-----------------------------------------------------------------------------------------------------|--|

|                                |
|--------------------------------|
| <b>Comment/Recommendation:</b> |
|--------------------------------|

| <b>Statement of Dosage (package labeling)</b>    | <b>Acceptable</b>                                                                                      |
|--------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                |
|--------------------------------|
| <b>Comment/Recommendation:</b> |
|--------------------------------|

| <b>Dispensing container (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.100(b)(7)               | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                |
|--------------------------------|
| <b>Comment/Recommendation:</b> |
|--------------------------------|

| <b>Medication Guide (package labeling)</b>         | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                |
|--------------------------------|
| <b>Comment/Recommendation:</b> |
|--------------------------------|

| <b>Other (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|---------------------------------|--------------------------------------------------------------------------------------------------------|
|                                 | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

|                                |
|--------------------------------|
| <b>Comment/Recommendation:</b> |
|--------------------------------|

### Prescribing Information Evaluation

#### **PRESCRIBING INFORMATION**

| <b>Highlights of Prescribing Information</b> |                                                                                                        |
|----------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>PRODUCT TITLE</b>                         | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.57(a)(2)              | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                                                                                                                                                                                                                                                     |                                                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>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</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|

**Comment/Recommendation:**

| <b>Highlights of Prescribing Information</b>                                                             |                                                                                                        |
|----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>DOSAGE AND ADMINISTRATION</b>                                                                         | <b>Acceptable</b>                                                                                      |
| <i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Highlights of Prescribing Information</b>                                                                                                                                                                                                                                                                                                                                                            |                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>DOSAGE FORMS AND STRENGTHS</b>                                                                                                                                                                                                                                                                                                                                                                       | <b>Acceptable</b>                                                                                      |
| Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100                                                                                                                                                                                                                                                                                                                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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)<br/>USP chapter &lt;659&gt; Packaging and Storage Requirements<br/>USP General Chapters: &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Full Prescribing Information</b>                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>2 DOSAGE AND ADMINISTRATION</b>                                                                                                                                                                                                                                                                                                                                                                                                                  | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.57(c)(3)(iv)<br><i>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."</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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</i>                                                                                                                                                                                                               | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                                                                                                                                                                                                 |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components<br>Draft Guidance <i>Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry</i> (January 2023) |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|

**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).  
*Revisions sent on March 6, 2025 were all accepted.*

| <b>Full Prescribing Information</b>                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>3 DOSAGE FORMS AND STRENGTHS</b>                                                                                                                                                                                                                                                                                                                                                                                 | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.57(c)(4)                                                                                                                                                                                                                                                                                                                                                                                     | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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</i> (October 2018)<br><i>USP chapter &lt;659&gt; Packaging and Storage Requirements</i><br><i>USP General Chapters: &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Full Prescribing Information</b>                                                                                                   |                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>11 DESCRIPTION</b>                                                                                                                 | <b>Acceptable</b>                                                                                      |
| 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) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: USP General Chapters &lt;1091&gt;, USP General Chapters &lt;7&gt;</i>                   | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>Full Prescribing Information</b> |                   |
|-------------------------------------|-------------------|
| <b>15 &amp; 16 Hazardous Drug</b>   | <b>Acceptable</b> |

|                                                                                                                                                                                                                                                                                                                                                      |                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.57(c)(17)(iv)<br><br>Section 15:<br>References 1. OSHA Hazardous Drugs. OSHA.<br><a href="http://www.osha.gov/SLTC/hazardousdrugs/index.html">http://www.osha.gov/SLTC/hazardousdrugs/index.html</a><br><br>Section 16:<br>xxxx is a hazardous drug. Follow applicable special handling and disposal procedures. <sup>1</sup> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|

**Comment/Recommendation:**

| <b>Full Prescribing Information</b>                                                                                              |                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>16 HOW SUPPLIED/ STORAGE AND HANDLING</b>                                                                                     | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.57(c)(17)                                                                                                 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

Added subheadings for this section.

A "do not shake" statement was added in to remain consistent with the labeling on the carton.

*Revisions sent on March 6, 2025 were all accepted.*

| <b>Full Prescribing Information</b>                                                                                                                                                                                                                                                           |                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>MANUFACTURER INFORMATION</b>                                                                                                                                                                                                                                                               | <b>Acceptable</b>                                                                                      |
| Regulations: 21 CFR 201.100(e), 21 CFR 201.1                                                                                                                                                                                                                                                  | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

### Medication Guide Evaluation

| <b>MEDICATION GUIDE</b>                              |                                                                                                        |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b><u>TITLE (NAMES AND DOSAGE FORM)</u></b>          | <b><u>Acceptable</u></b>                                                                               |
| Regulation for Medication Guide: 21 CFR 208.20(a)(7) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>MEDICATION GUIDE</b>                              |                                                                                                        |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b><u>STORAGE AND HANDLING</u></b>                   | <b><u>Acceptable</u></b>                                                                               |
| Regulation for Medication Guide: 21 CFR 208.20(a)(2) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>MEDICATION GUIDE</b>                                                                                                                            |                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b><u>INGREDIENTS</u></b>                                                                                                                          | <b><u>Acceptable</u></b>                                                                               |
| <i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters &lt;1091&gt;)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>MEDICATION GUIDE</b>                                                                                                                                                                                                                     |                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b><u>MANUFACTURER INFORMATION</u></b>                                                                                                                                                                                                      | <b><u>Acceptable</u></b>                                                                               |
| 21 CFR 208.20(b)(8)(iii)                                                                                                                                                                                                                    | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

### Instructions for Use Evaluation

| <b>INSTRUCTIONS FOR USE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>TITLE (NAMES AND DOSAGE FORM)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>Acceptable</b>                                                                                      |
| <i>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: &lt;1&gt; Injections, Nomenclature and Definitions, Nomenclature form).</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>INSTRUCTIONS FOR USE</b>                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>STORAGE AND HANDLING</b>                                                                                                                                                                                                                                                                                                                                                                                                           | <b>Acceptable</b>                                                                                      |
| <i>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)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
*After discussion with OTBB, it was determined that the "Do not shake" statement will be added first to the reference product and then to BLA 761275 and BLA 761449.*

| <b>INSTRUCTIONS FOR USE</b>                                                                                                                        |                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>INGREDIENTS</b>                                                                                                                                 | <b>Acceptable</b>                                                                                      |
| <i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters &lt;1091&gt;)</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b>INSTRUCTIONS FOR USE</b>                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>MANUFACTURER INFORMATION</b>                                                                                                                                                                                                                                                                                                                                                                 | <b>Acceptable</b>                                                                                      |
| 21 CFR 201.1, 19 CFR 134.11                                                                                                                                                                                                                                                                                                                                                                     | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

**APPENDIX C. Acceptable Labels and Labeling**

*To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.*

- Prescribing Information (submitted on March 6, 2025)  
<\\CDSESUB1\EVSPROD\bla761449\0014\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-sc.docx>
- Medication Guide (submitted on January 31, 2025)  
<\\CDSESUB1\EVSPROD\bla761449\0014\m1\us\114-labeling\114a-draft-label\annotated-draft-labeling-text-medication-guide-sc.docx>
- Instructions for Use (submitted on July 17, 2024)  
<\\CDSESUB1\EVSPROD\bla761449\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-pfs.docx>
- Container Labels (submitted on February 6, 2025)

(b) (4)

- Carton Labeling (submitted on February 6, 2025)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page



Diana  
Pei

Digitally signed by Diana Pei

Date: 3/21/2025 11:14:15AM

GUID: 6352da2c009ad0777a2c3b47ec094b9a



Deepa  
Raghu

Digitally signed by Deepa Raghu

Date: 3/21/2025 11:22:29AM

GUID: 629f525a0001e48074940814811016a6

**BLA STN 761449**

**Tyenne [toripalimab-aazg]**

**Manufacturer: Fresenius Kabi USA, LLC**

Deepa Raghu, Ph.D., Primary Assessor  
Bazarragchaa Damdinsuren, M.D., Ph.D., Application Technical Lead

Division of Product Quality Assessment XVI  
Office of Product Quality Assessment III (OPQA III)  
Office of Pharmaceutical Quality (OPQ)  
Center for Drug Evaluation and Research (CDER)

## OPQA III CMC Assessment Data Sheet

1. BLA#: 761449

2. Assessment Date: February 16, 2024

3. Primary Assessment Team:

Product Quality Team:

OPQ/OPQAIII: Deepa Raghu, Bazarragchaa Damdinsuren (ATL)

OPQ/OPMA: Yuan-chia Charles Kuo (DS), Jeanne Fringer (DP), Maxwell Van Tassell (Microbiology TL), Zhong Li (Facility TL)

OPQ/OPRO: Anita Brown (RBPM)

Clinical: Thomas Herndon, Raquel Tapia (TL)

Pharmacology/Toxicology: Eleni Salicru

Clinical Pharmacology: Soo Hyeon Shin, Ping Ji (TL)

OND RPM: Chau Nguyen

4. Major GRMP Deadlines:

a. Submission received: 7/17/2024

b. Filing Meeting: 9/13/2024

c. BsUFA date: 7/17/2025

5. Drug Product Name/Code/Type:

a. Proprietary/Trade Name: TYENNE

b. Non-Proprietary Name/USAN: tocilizumab-aazg/tocilizumab

c. CAS Name: 375823-41-9

d. Common Name: MSB11456

e. INN Name: tocilizumab

f. OPQAIII systematic name: MAB HUMANIZED (IGG1) ANTI P08887 (IL6RA\_HUMAN)  
[MSB11456]

6. Pharmacological Category: MSB11456 is a proposed biosimilar to US-licensed Actemra (humanized monoclonal IgG1 antibody) that binds to interleukin 6 receptor (IL-6R)

7. Dosage Form: Injection, solution in single-dose prefilled syringe (b) (4)  
safety device and single-dose prefilled autoinjector

8. Strength/Potency:

(i): The concentration/strength of the Drug Product: 162 mg/0.9 mL (180 mg/mL)

(ii): Type of potency assay(s): Inhibition of IL-6-induced cell proliferation

9. Route of Administration: Subcutaneous injection

10. Inspectional Activities: The inspectional activities for manufacturing facilities are completed under BLA 761275 which are applicable to this BLA.

11. Consults Requested by OPQAIII: No consult at this time. The prior assessments of device components of AI and PFS by CDRH under BLA 761275 are applicable to this BLA.

12. Quality by Design Elements: None

13. Precedents: None

14. Administrative:

| Name and Title                                                     | Signature and Date |
|--------------------------------------------------------------------|--------------------|
| Bazarragcha Damdinsuren, M.D., Ph.D.<br>Application Technical Lead | See attached       |
| Deepa Raghu, Ph.D., Primary assessor                               | See attached       |

## Primary Assessor Summary Recommendation:

The Office of Product Quality Assessment III (OPQA III) recommends approval of the BLA 761449 for Tyenne (tocilizumab-aazg, MSB11456) manufactured by Fresenius Kabi USA, LLC. The data submitted in this BLA, specifically Module 3 DP-SC sections, is identical to the information assessed in BLA 761275 (approved on 3/5/2024) for the manufacture of Tyenne (tocilizumab-aazg) for SC administration with cross-reference to Modules 3, 4 and 5 of BLA 761275.

**Assessor's comments:** *The applicant has submitted this original BLA on 7/17/2024 for Tyenne SC presentations cross-referencing to modules 3,4 and 5 of BLA 761275 (see cover letter and section 1.4.4 in SDN:1)* (b) (4)

*(refer to the BLA 761275).*

*The original BLA submission did not contain CMC information (i.e., Module 3) for the Tyenne SC presentations linked to the specific indications with SC administration, and hence we communicated the following IR comments to the applicant on 12/20/2024:*

1. On September 13, 2024, you amended BLA 761449 to request review the BLA for subcutaneous (SC) use only. (b) (4)  
(b) (4)  
(b) (4). Therefore, submit CMC information for MSB11456 (tocilizumab-aazg) for SC administration to BLA 761449 (i.e., Module 3 Drug Product sections for Prefilled Syringe (b) (4) safety device (162 mg/0.9 mL) and Autoinjector (162 mg/0.9 mL)), which is intended to be licensed under this BLA. Additionally, provide a statement confirming that no previously unapproved changes to the content are introduced for the CMC information for SC presentations in BLA 761449 with this transfer. If there are previously unapproved changes included in BLA 761449 the transfer, identify the unapproved changes, and provide supporting information for the proposed changes, as applicable.
2. Update the cross-reference to previously submitted information document submitted in section 1.4.4 to include the specific sections in BLA 761275 (e.g., 3.2.S Drug Substance) that are needed to support manufacturing and controls of the MSB11456 (tocilizumab-aazg) drug product for SC administration.
3. We remind you that the following post-marketing commitments (PMCs) included in the Approval letter for BLA 761275 (issued on March 5, 2024) will also apply to BLA 761449. Confirm that you agree to the following PMCs to this BLA per the timetable you submitted to BLA 761275 on February 7, 2024. [See 1.11.1, SDN:11 for details of the PMCs.]

*In response to the IR (submitted on 1/13/2025), the applicant has submitted and included the CMC information of MSB11456 DP SC formulation into Module 3 of this BLA. I have verified that all the information provided in this BLA is the same as the contents of the original BLA 761275. The applicant further states that there are unapproved changes to the content introduced for the CMC information for SC presentations in BLA 761449. These were previously submitted under BLA 761275 (3 supplements - SN:0080, SN:0085, SN:0090, which are currently approved) and are applicable to BLA 761449 for SC products. The applicant has confirmed that no other previously unapproved changes to the content are introduced for the CMC information for SC presentations in BLA 761449. Finally, the applicant agreed that the PMCs included in the approval letter for BLA 761275 will also apply to BLA 761449 (see 1.11.1, SDN:12 for details).*



Deepa  
Raghu

Digitally signed by Deepa Raghu

Date: 2/16/2025 03:10:24PM

GUID: 629f525a0001e48074940814811016a6



Bazarragchaa  
Damdinsuren

Digitally signed by Bazarragchaa Damdinsuren

Date: 2/16/2025 03:12:11PM

GUID: 50afa2ce0005f62310093b8bdc00b898