

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761149Orig1s000

PRODUCT QUALITY REVIEW(S)



Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	August 14, 2020
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Sang Bong Lee, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 4
Application:	BLA 761149
Applicant:	Genentech, Inc.
Submission Date:	August 15, 2019
Product:	Enspryng (satralizumab-mwge)
Dosage form(s):	Injection
Strength and Container-Closure:	120 mg/mL in a single-dose prefilled syringe
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information, medication guide, instructions for use (submitted on August 14, 2020), and container labels and carton labeling (submitted on August 12, 2020) are acceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices (see Appendix B).

CONCLUSION

The prescribing information, medication guide, instructions for use (submitted on August 14, 2020), and container labels and carton labeling (submitted on August 12, 2020) are acceptable from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on February 19 ,2020

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Instructions for Use (submitted on August 15, 2019

<\\cdsesub1\evsprod\bla761149\0004\m1\us\ifu.docx>)

Medication Guide (submitted on June 11, 2020

<\\CDSESUB1\evsprod\bla761149\0042\m1\us\draft-med-guide-final.docx>)

Container Labels (submitted on August 15, 2019)



Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

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

Manufacturer name, address, and license number (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices (U.S license number for container bearing a partial label⁵)</i>	☐ Yes ☐ No ☒ N/A

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

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

⁵ Per 21 CFR 610.60(c) *Partial Label*. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

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

Product Strength (container label)	Acceptable
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Multiple-dose containers (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 <i>(recommended individual dose)</i>	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Medication Guide (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

No Package for container (container label)	Acceptable
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	Acceptable
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal (for vials only)	Acceptable
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☐ Yes ☐ No ☒ N/A

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

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

Applicant's response: The Sponsor confirms that there is sufficient area on the prefilled syringe to allow for visual inspection of the contents when the label is affixed to the prefilled syringe per 21 CFR 610.60(e) and ISO 11608. Photographs of the prefilled syringe with a representative label affixed are provided below. The photographs show the area of the affixed label that is void of printing to allow for visual inspection of the prefilled syringe contents.

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

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

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

Package type term (container label)	Acceptable
<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 <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Misleading statements (container label)	Acceptable
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (container label)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

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

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

Bar code label requirements (container label)	Acceptable
Regulations: 21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

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

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

Comment/Recommendation: If space permits, consider adding the net quantity (1 mL) to the container label.
Applicant's response: Due to space constraints and to avoid clutter on the container label, the Sponsor proposes to exclude the net quantity (1 mL) on the container label. The draft container label currently reads "120 mg/mL".
Acceptable

Statement of Dosage (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☐ Yes ☐ No ☒ N/A

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

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

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

Package⁶ Labeling Evaluation

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

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

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

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

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

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

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

Number of containers (package labeling)	Acceptable
Regulation: 21 CFR 610.61(f)	☒ Yes ☐ No ☐ N/A

Product Strength (package labeling)	Acceptable
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

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

Comment/Recommendation: Revise the storage information on the back panel to indicate that "After removing from the refrigerator, may be stored for up to 8 days at a temperature that does not exceed 86°F (30°C) in original carton to protect from light".
The Applicant revised as requested

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

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

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

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

Inactive ingredients (package labeling)	Acceptable
Regulations: 21 CFR 610.61, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

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

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

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

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

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

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

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

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

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

Package type term (package labeling)	Acceptable
<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> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

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

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

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

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

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

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

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

Comment/Recommendation: Add the net quantity to the ingredients list as follows:
Each syringe delivers 1 mL of solution containing 120 mg of satralizumab-mwge, L-arginine (26.1 mg), L-histidine (3.1 mg), poloxamer 188 (0.5 mg), (b) (4) (pH adjustment), and Water for Injection, USP.

The Applicant revised as requested and also acceptably revised from (b) (4) to "L-aspartic acid"

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

Comment/Recommendation: Consider revising statement of dosage from [REDACTED] (b) (4) to read "Dosage: See Prescribing Information"
 The Applicant revised as requested

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

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ 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>	☒ Yes ☐ No ☐ N/A

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

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	Acceptable
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
Regulation: 21 CFR 201.57(c)(3)(iv)] <i>Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted drug; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes); confirm product's incompatibilities, and 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>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products</i>	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	Acceptable
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ 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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Full Prescribing Information	
11 DESCRIPTION	Acceptable
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Added the clarity characteristic "clear" of the drug product
The Applicant revised as requested

Full Prescribing Information	
15 & 16 Cytotoxic Drug	Acceptable
Regulation: 21 CFR 201.57(c)(17)(iv)	☐ Yes ☐ No ☒ N/A
Section 15: References 1. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html	
Section 16: xxxx is a cytotoxic drug. Follow applicable special handling and disposal procedures. ¹	

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

Full Prescribing Information	
MANUFACTURER INFORMATION	Acceptable
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes ☐ No ☐ 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>	☒ Yes ☐ No ☐ N/A

Medication Guide Evaluation

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

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

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

Comment/Recommendation: Revise ingredient list as follows: L-arginine, L-aspartic acid, L-histidine, poloxamer 188 and Water for Injection, USP <i>The Applicant revised as requested</i>

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

Patient Information Labeling Evaluation (N/A)

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
<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 Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Added the route of administration (see Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019))
The Applicant revised as requested

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	Acceptable
<i>Recommended labeling practices for IFU: Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). To ensure that applicable storage and handling 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>	☒ Yes ☐ No ☐ N/A

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

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	Acceptable
21 CFR 201.1, 19 CFR 134.11	☒ Yes ☐ No ☐ N/A
<i>Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). 21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information/Medication Guide/Instructions for Use (submitted on August 14, 2020)



Vicky
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 8/17/2020 01:47:04PM
GUID: 50814c7000007a3d59329f660d8ddf02



Sang Bong
Lee

Digitally signed by Sang Bong Lee
Date: 8/17/2020 03:33:11PM
GUID: 508da6d8000263e5e470ed27b1bd5a9b

Recommendation: Approval

BLA/NDA Number: **761149**

Review Number: **1**

Review Date: **7/17/2020**

Drug Name/Dosage Form	ENSPRYNG (Satralizumab-mwge) injection
Strength/Potency	120 mg/mL
Route of Administration	subcutaneous
Rx/OTC dispensed	Rx
Indication	Treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.
Applicant/Sponsor	Genentech, Inc.

Product Overview

ENSPRYNG (satralizumab-mwge) is a recombinant humanized IgG2 monoclonal antibody intended for subcutaneous administration for the treatment of NMOSD. Satralizumab-mwge targets the soluble and membrane-bound human interleukin 6 (IL-6) receptor (IL-6R) and when bound competes with IL-6 from binding to the receptor, thereby blocking downstream signaling through the IL-6R. (b) (4)

(b) (4)

Satralizumab-mwge is produced (b) (4) Chinese hamster ovary (CHO) cell line. ENSPRYNG drug product is supplied at 120mg/1.0 mL satralizumab-mwge as a sterile, single-dose, preservative free solution for subcutaneous injection in a pre-filled syringe.

Quality Review Team

Discipline	Reviewer	Branch/Division
RPBM	Kristine Leahy	OPQ/OPRO
Drug Substance	Sang Bong Lee	OPQ/OBP/DBRRIV
Drug Product	Sang Bong Lee	OPQ/OBP/DBRRIV
Immunogenicity	Sang Bong Lee	OPQ/OBP/DBRRIV
Labeling - OBP	Vicky Borders-Hemphill	OPQ/OBP
Facility	Thuy Thanh Nguyen	OPQ/OPMA/DBM1
Facility	Zhihao Peter Qiu	OPQ/OPMA/DBM
Microbiology- DS	Madushini Dharmasena	OPQ/OPMA/DBM2
Microbiology- DP	Bo Chi	OPQ/OPMA/DBM1
Team Lead - OBP	Chana Fuchs	OPQ/OBP/DBRRIV
Team Lead - Microbiology	Reyes Candau-Chacon	OPF/OPMA/DBM2
Team Lead – Facilities	Zhihao Peter Qiu	OPQ/OPMA/DBM
CDRH	Rong Guo	CDRH/OPEQ/OHTIII/DHTIIC
Team Lead – CDRH	Rumi Young	CDRH/OPEQ/OHTIII/DHTIIC
Application Team Lead	Chana Fuchs	OPQ/OBP/DBRRIV

Core Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Susan Daugherty	OND/ORO/DRON
Cross-disciplinary Team Lead	Paul Lee	OND/ON/DNII
Medical Officer	Lawrence Rodichok	OND/ ON/DNII
Non-clinical	David Hawver	OND/ON/DPTN
Clinical Pharmacology	Dawei Li	OTS/OCP/DNP
Statistics	Sharon Yan	OTS/OB/DBI

1. Names:

- a. Proprietary Name: ENSPRYNG
- b. Trade Name: ENSPRYNG
- c. Non-Proprietary Name/USAN: satralizumab-mwge
- d. CAS Name: 1535963-91-7
- e. Common Name: RO5333787; SA237; CH5333787
- f. INN Name: satralizumab
- h. OBP systematic name: MAB HUMANIZED (IGG2) ANTI P08887 (IL6RA_HUMAN) [SA237]

Submissions Reviewed:

Submission(s) Reviewed	Document Date
0001	06/27/2019
0002	07/16/2019
0003	07/26/2019
0005 – human factors (CDRH)	8/16/2019
0008	10/02/2019
0009	10/02/2019
0012	10/22/2019
0014 - labeling	11/18/2019
0018	12/9/2019
0019 -human factors	1/21/2020
0020	2/10/2020
0021	2/12/2020
0022	2/18/2020
0023	2/18/2020
0024 - labeling	2/19/2020
0026	2/28/2020
0027	3/18/2020
0028	4/1/2020
0029	4/2/2020
0030	4/10/2020
0031	4/14/2020
0032	4/16/2020
0033	4/24/2020
0034	4/27/2020
0038	5/26/2020
0039	6/5/2020
0040	6/10/2020
0042 - labeling	6/11/2020
0043	6/23/2020

0044	7/13/2020
0046	7/14/2020
0047 - labeling	8/4/2020
0048	8/5/2020
0049 - labeling	8/6/2020

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Comments
(b) (4)	III	(b) (4)	(b) (4)	3	N/A	
	III			3	N/A	
	510K			6	adequate	(b) (4)

1. Action codes for DMF Table:

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

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

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application: NONE

3. Consults: NONE

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Product Quality (OPQ), CDER, has completed review of STN 761149 for ENSPRYNG (satralizumab-mwge) manufactured by Genentech, Inc. The office of Biotechnology products found the manufacture and control of the drug substance and drug product well controlled in a manner that will lead to a product that is pure and potent for the duration of its shelf-life. The drug substance and drug product sections of the BLA, as amended, are recommended for approval from a product quality microbiology and a sterility assurance perspective. The CDRH review finds that the device constituent parts of the combination product are approvable. In conclusion, the data submitted in this application are sufficient to support a conclusion that the manufacture of ENSPRYNG is well-controlled and will lead to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Action Letter Language:

- Manufacturing locations:
 - Drug Substance:
 - (b) (4) drug substance is manufactured at Chugai Pharma Manufacturing Co., Ltd. Kita-ku, Tokyo, Japan
 - Release and stability testing of the (b) (4) drug substance will be performed at Chugai Pharma Manufacturing Co., Ltd. Utsunomiya City, Tochigi , Japan and at Chugai Pharma Manufacturing Co., Ltd. Kita-ku, Tokyo, Japan.
 - Storage of (b) (4) drug substance will be at Chugai Pharma Manufacturing Co., Ltd. Utsunomiya City, Tochigi , Japan and at Chugai Pharma Manufacturing Co., Ltd. Kita-ku, Tokyo, Japan.
 - Drug Product:
 - The filled unassembled PFS is manufactured at Chugai Pharma Manufacturing Co., Ltd. Utsunomiya City, Tochigi, Japan
 - PFS assembly and packaging will be performed at F. Hoffmann-La Roche Ltd Kaiseraugst, Switzerland
 - Release and stability testing of the filled PFS will be at Chugai Pharma Manufacturing Co., Ltd. Utsunomiya City, Tochigi , Japan and at Chugai Pharma Manufacturing Co., Ltd. Utsunomiya City, Kita-ku, Tokyo, Japan.
 - Release testing of the assembled PFS Drug product will be performed at F. Hoffmann-La Roche Ltd Kaiseraugst, Switzerland
 - Storage of filled unassembled PFS will be at Chugai Pharma Manufacturing Co., Ltd. Utsunomiya City, Tochigi , Japan and at Hoffmann-La Roche Ltd Kaiseraugst, Switzerland.
- Fill size and dosage form
 - 120 mg/mL single-dose Pre-filled syringe, injection, for subcutaneous use.
- Dating period:
 - Drug Product: 24 months at 2°C–8°C

- Drug Substance: (b) (4) months at (b) (4) °C
- For packaged products: "Not packaged"
- Stability Option (select one below):
 - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
 - Exempt from lot release
 - Yes. ENSPRYNG is a specified product exempt from lot release in accordance with 21 CFR 601.2a.

C. Benefit/Risk Considerations:

ENSPRYNG (satralizumab-mwge) prefilled syringe (PFS) is intended to deliver satralizumab subcutaneously. The proposed indicated is for the treatment of adults (b) (4) with neuromyelitis optica spectrum disorder (NMOSD). Satralizumab-mwge was granted fast track on 10/31/13, orphan drug designation on 6/30/2014, and breakthrough therapy designation on 12/18/18 under IND 118183. The proposed dosing regimen is 120 mg subcutaneous injection at weeks 0, 2, and 4, followed by a maintenance dose of 120 mg every 4 weeks. The overall control strategy for satralizumab-mwge manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, release of drug substance and drug product, and stability of these materials. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. The BLA is recommended for approval from a sterility assurance and microbiology product quality and from the pre-filled syringe device quality perspectives. The currently proposed control strategies are sufficient to ensure process consistency and that drug substance and drug product have appropriate quality and are free of adventitious agents. The technical assessments for product quality and immunogenicity assay (by OBP), microbiological drug substance and drug product, facility (by OPMA), the device components (by CDRH) and OBP labeling are located as separate documents in Panorama.

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

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

The control strategy for Satralizumab-mwge for subcutaneous administration is based on the identification of critical quality attributes (CQAs), clinical and manufacturing experience, process and product characterization and understanding, and stability data

Tables 1 and 2, below, summarize the critical quality attributes and their control strategy that are relevant specifically to the API and Drug Substance. Table 1 specifically identifies critical quality attributes intrinsic to the API.

For additional information, see the OBP quality technical assessment and the Drug Substance Microbiology technical assessment in Panorama.

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

CQA (type)	Risk	Origin	Control Strategy	Other

Target Binding (Potency)	Impact on safety and efficacy	(b) (4) storage (stability)	(b) (4)
HMWS (Product Variant)	Impact on efficacy, immunogenicity, PK, safety	Manufacturing process: (b) (4) [Redacted]	
LMWS (Product Variants)	Impact on efficacy, PK	Manufacturing process: (b) (4) [Redacted]	
Charge variants: AE-HPLC Basic region 1 and Basic region 2 (Product Variants)	Impact on efficacy, immunogenicity.	Manufacturing process: (b) (4) [Redacted] *Stability	
Charge variants: AE-HPLC Acidic region 1 and Acidic region 2 (Product Variants)	Impact on efficacy, (b) (4)	Manufacturing process: (b) (4) [Redacted] *Stability	

Asp 32 isomerization in CDR region (Product Variant)	efficacy (in CDR region)	Manufacturing process	(b) (4)
Asn 194 deamidation (Product Variant)	PK (in FcRn binding region)	(b) (4)	
(b) (4) Oxidation (in the CDR) (Product Variant)	Impact on efficacy. (in the CDR region)	(b) (4)	
(b) (4) Oxidation (Product Variant)	Impact on PK	stability/storage conditions.	
(b) (4) Oxidation (In the FcRn binding region) (Product Variant)	Impact on PK	Manufacturing process and stability	
High-mannose Glycan variants (Product Variant)	Impact on PK	(b) (4)	
Free thiols (Product Variant)	Efficacy and PK	(b) (4)	
Identity	Impact on safety and efficacy	Intrinsic to molecule.	

B. Drug Substance Satralizumab-mwge Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA	Risk	Origin	Control Strategy	Other notes
Leptospira	Safety	Raw materials or contamination (b) (4)	(b) (4)	
Bioburden (contaminant)	Safety, purity, and efficacy (degradation or modification of the product by microbial contamination)	Raw materials or contamination during manufacturing		(b) (4)
Endotoxin (contaminant)	Impact on safety and purity	Raw materials or contamination during manufacturing process		
Host Cell Proteins (Process-related impurity)	Safety, Immunogenicity	Process-related impurity from the production cell line. (b) (4)		
Host Cell DNA (Process-related impurity)	Safety			
(b) (4) (Process-related impurity)	Safety, PK, Immunogenicity			
Viruses (Contaminant)	Safety	Contamination during manufacture from raw material and personnel.		Manufacturing process is free of raw materials of animal origin, minimizing risk

			(b) (4)	of new virus introduction.
Mycoplasma (Contaminant)	Safety	(b) (4)		That there are no animal derived components used in the manufacture of the product which minimizes risk of mycoplasma introduction.
Visual appearance: Color and opalescence (general)	Impact on Safety and immunogenicity	Manufacturing process and formulation		
Protein content (general)	Impact on efficacy	DS manufacture at (b) (4)		(b) (4)
pH (general)	Safety, efficacy	Manufacturing process (b) (4)		
(b) (4) (general)	Impact on efficacy through stability.	Manufacturing at the (b) (4)		
Osmolality (general)	Safety and efficacy (through stability)	Manufacturing at the (b) (4)		
(b) (4) (general)	Impact on efficacy through product stability	Manufacture at the (b) (4)		

• **Description:**

Satralizumab is a recombinant humanized IgG2 monoclonal antibody that targets the human interleukin 6 receptor (IL-6R) and thereby prevents IL-6 from binding to membrane-bound and soluble IL-6R. Satralizumab is a heterodimeric glycoprotein consisting of two 214-amino acid light chains and two 443-amino acid heavy chains. Each heavy chain contains an N-linked glycan at asparagine 295 (Asn295). The molecular mass of deglycosylated satralizumab is 143 (b) (4) Da.

The antibody was engineered (b) (4)

(b) (4) Satralizumab is produced in (b) (4) using a (b) (4) Chinese hamster ovary (CHO) cell line. (b) (4)

- **Mechanism of Action (MoA):**

Satralizumab is a humanized IgG2 monoclonal antibody (mAb) that specifically binds to soluble and membrane-bound human IL-6 receptor (hIL-6R). It is designed to achieve its pharmacological effects by blocking the binding of human interleukin-6 (hIL-6) to the hIL-6R, which in turn inhibits the downstream signal transduction pathway of hIL-6R. IL-6 is a pro-inflammatory cytokine which has been implicated in the pathogenesis of NMO and NMOSD, including in the production of pathological autoantibodies against Aquaporin-4 (AQP4) through the promotion of survival of the B cell subset which produce these antibodies.

- **Potency Assay:**

The potency of satralizumab drug substance and drug product is measured by the BaF Bioassay. This cell-based bioassay uses a hIL-6R-transfected mouse pro-B cell line (BaF/hIL6R) that depends on hIL-6 for its growth. The activity of satralizumab is measured by its ability to inhibit proliferation of the BaF cell line in the presence of hIL-6. Cellular viability is measured through Resazurin reduction reaction by optical density. The test sample dose response curves are compared against those of the reference material and an internal product control. Relative potencies are reported as U/mg for drug substance and U/mL for drug product.

- **Reference Materials:**

(b) (4)

The stability of the reference materials is monitored through a protocol. The criteria used to evaluate the stability of the RM are acceptable.

The procedures and criteria proposed in order to establish and qualify new reference materials are suitable to ensure consistency of satralizumab product quality.

- **Manufacturing process summary:**

(b) (4)



- **Container closure:**

(b) (4)



- **Dating period and storage conditions:**

Satralizumab (b) (4) drug substance stability is (b) (4) months at (b) (4) C. A stability protocol was included in the BLA to extend the drug substance shelf life.

C. Drug Product ENSPRYNG Quality Summary:

Table 4, below, provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information, see the OBP quality technical assessment and the Drug Product Microbiology technical assessment in Panorama.

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety (infection), purity, and efficacy via degradation or modification of products by microbial contamination	Manufacturing process or failure of container closure integrity	(b) (4)	

			(b) (4)
Endotoxin	Safety (pyrogenic fever, increased immunogenicity risk) and purity	Raw materials, manufacturing process or failure of container closure integrity	
Container closure integrity	Safety (maintenance of sterility during shelf life)	Storage conditions	
Osmolality	Safety	Formulation	(b) (4)
Appearance Visible Particulate Matter (product or process related impurities)	Safety and immunogenicity	DS and DP Manufacturing processes, formulation, interaction with the container closure system	
Subvisible Particulate Matter (product or process related impurities)	Safety and Immunogenicity	Manufacturing process and CCS. Could be product or foreign particles.	
Appearance: Color of solution (general)	Safety and Efficacy	Formulation, contamination or degradation	
pH (general)	Safety	Formulation	
Extractable Volume (general)	Efficacy/Dosing	DP manufacturing process	
Protein Concentration (general)	Efficacy and Safety	(b) (4)	(b) (4)
Identity (general)	Safety and Efficacy	Intrinsic to molecule	
Leachables (process-related impurities)	Safety	Manufacturing equipment and CCS	Extractables and leachable studies were conducted on the CCS and as part of an ongoing product stability study.
Poloxamer 188 (general)	Impact on product quality	(b) (4)	

- **Potency and Strength :**

ENSPRYNG is supplied as a 120 mg/mL prefilled syringe containing 1mL of satralizumab-mwge.

- **Summary of Product Design:**

ENSPRYNG is a sterile, clear and colorless to slightly yellow solution of satralizumab-mwge for subcutaneous injection. It is presented in a prefilled 1 mL (b) (4) syringe with no preservatives. Each single-dose, 1 mL prefilled syringe contains a nominal volume of 1mL Satralizumab-mwge intended to deliver 1mL.

- **List of Excipients:**

The 120 mg/mL satralizumab drug product is formulated in 20 mmol/L L-histidine, 150 mmol/L L-Arginine, 0.5 mg/mL Poloxamer 188, at pH 6.0. L-Aspartic Acid is used to adjust pH q.s. to pH 6.0.

- **Reference Materials:**

The reference material used for testing drug product is the same one as used for drug substance. See description in the drug substance section above.

- **Manufacturing process summary:**

(b) (4)

- **Container closure:**

The primary container closure system, identified as the prefilled syringe consists of a 1 mL colorless USP/Ph. Eur./JP compliant (b) (4) syringe with a staked-in, stainless steel needle, fitted with a (b) (4) rigid needle shield and sealed with a (b) (4) plunger stopper.

The prefilled syringe is further assembled with the 510(k) cleared medical devices manufactured by (b) (4)

• **Dating period:**

The shelf life for ENSPRYNG drug product is 24 months when stored at 2-8°C.
A protocol for the extension of the drug product expiration dating was included in the BLA.

D. Biopharmaceutics Considerations: N/A

E. Novel Approaches/Precedents: None

F. Any Special Product Quality Labeling Recommendations:

Store refrigerated at 2-8°C. Protect from light. Do not freeze. Do not shake.

G. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of Drug Substance In-Process Control Testing of Drug Substance (b) (4) Quality Control Testing/Stability Testing of Drug Substance and Drug Product Release of Drug Substance; Storage of Drug Substance; Preparation and Storage of MCB/WCB	Chugai Pharma Manufacturing Co., Ltd. (CPMC) 5-1, Ukima 5-Chome, Kita-ku , Tokyo, N/A, Japan, 115-8543	3004109596	Pre-license inspection requested	VAI	Approve

(b) (4)

DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of Drug Product In-Process Control Testing of Drug Product Storage of Drug of Drug Substance and Drug Product; Storage of MCB/WCB Quality Control Testing /Stability Testing of Drug Substance and Drug Product (b) (4)	Chugai Pharma Manufacturing Co., Ltd. (CPMC) 16-3, Kiyohara Kogyodanchi , Utsunomiya City, Tochigi, Japan, 321-3231	3006942691	Pre-license inspection requested	VAI	Approve
Storage of Drug Product Assembly (including labeling, plunger rod, needle safety device, extended finger flanges assembly) Secondary Packaging; Identity Test of assembled PFS Release of Finished Product	F. Hoffmann-La Roche Ltd Wurmisweg , Kaiseraugst, N/A, Switzerland, 4303	3003973536	Approve - Based on Previous History	N/A	Approve

H. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Chugai Pharma Manufacturing Co., Ltd. (FEI 3004109596) as the drug substance manufacturing facility, Chugai Pharma Manufacturing Co., (FEI 3006942691) as drug product manufacturing facility, and F Hoffmann-La Roche Ltd (FEI 3003973536), the facility that manufactures the final assembled PFS DP.

A pre-license inspection was conducted by the CDER review team at Chugai Pharma Manufacturing Co., Ltd. (CPMC), Kita-ku, Tokyo, Japan. A 3-item 483 was presented at the end of the inspection for (a) inaccurate reflection of the process details in the BLA, inadequate control of the reference standards, and inadequate CAPAs associated with environmental monitoring. These items were adequately addressed.

A pre-license inspection was conducted by the CDER review team at Chugai Pharma Manufacturing Co., Ltd. (CPMC), Utsunomiya City, Japan. The inspection resulted in a 2-item FDA 483 for failure to establish and follow appropriate written procedure to prevent microbial contamination of drug products and for inadequately validated test methods. These items were adequately addressed.

This BLA approval is based on appropriate GMP history for the DP PFS final assembly and secondary packaging site at F. Hoffmann-La Roche Ltd, Kaiseraugst, Switzerland.

All proposed manufacturing and testing facilities are acceptable based on their current acceptable cGMP compliance status and recent relevant inspectional coverage.

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

1. [REDACTED] (b) (4) – concurrent validation
2. [REDACTED] (b) (4) – concurrent validation
3. [REDACTED] (b) (4)
4. [REDACTED] (b) (4)
5. [REDACTED] (b) (4)
6. Cell bank stability Monitoring
7. [REDACTED] (b) (4)
8. Container closure leachables stability study – continuation of protocol
9. Primary stability program – continuation of stability under protocol of stability lots in the BLA
10. DS post-approval stability program – up to [REDACTED] (b) (4)

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:

1. Container closure leachables stability study – continuation of current protocol
2. Qualification protocol for preparation of future primary and secondary reference material
3. Stability testing of reference standard
4. Primary stability program – continuation of stability under protocol of the stability lots in the BLA
5. DP Post-approval stability program – up to 36 months at 5°C (and 6 months at 25°C).

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	x		
2.	Naturally Derived Product		x	
3.	Botanical		x	
4.	Human Cell Substrate/source material		x	
5.	Non-Human Primate Cell Substrate/Source Material		x	
6.	Non-Primate Mammalian Cell Substrate/source material	x		
7.	Non-Mammalian Cell Substrate/Source Material		x	
8.	Transgenic Animal source		x	
9.	Transgenic Plant source		x	
10.	New Molecular Entity	x		
11.	PEPFAR drug		x	
12.	PET drug		x	
13.	Sterile Drug Product	x		
14.	Other: [fill in information]			
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]		x	
16.	Comparability Protocol(s)		x	
17.	End of Phase II/Pre-NDA Agreements		x	
18.	SPOTS (special products on-line tracking system)		x	
19.	USAN assigned name	x		
20.	Other [fill in]			
Quality Considerations				
21.	Drug Substance Overage		x	
22.	Design Space	Formulation		x
23.		Process		x
24.		Analytical Methods		x
25.		Other		x
26.	Other QbD Elements	x		
27.	Real Time release testing (RTRT)		x	
28.	Parametric release in lieu of Sterility testing		x	
29.	Alternative Microbiological test methods		x	
30.	Process Analytical Technology in Commercial Production		x	
31.	Non-compendial analytical procedures	Drug Product	x	
32.		Excipients		x
33.		Drug Substance	x	
34.		Human or Animal Origin		x
35.	Excipients	Novel		x
36.	Nanomaterials		x	
37.	Genotoxic Impurities or Structural Alerts		x	
38.	Continuous Manufacturing		x	
39.	Use of Models for Release		x	
40.	Other {fill-in}			



Chana
Fuchs

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Zihao Peter
Qiu

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Date: 8/13/2020 06:43:53AM
GUID: 508da7480002bfb5825e149b2b4eb91d

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 7/14/2020
To: Administrative File, **STN 761149/0**
From: Bo Chi, Ph.D., CDER/OPQ/OPMA/DBM/Branch I
Endorsement: Reyes Candau-Chacon, Ph.D., Quality Assessment Lead,
CDER/OPQ/OPMA/DBM/Branch II
Subject: Addendum to review memo for New Biologic License Application (BLA)
STN761149 dated May 14, 2020
Applicant: Genentech, Inc.
US License: **1048**
Facility: Chugai Pharma Manufacturing Co., Ltd. (CPMC), Utsunomiya, Tochigi, Japan
FEI: 3006942691
Product: Enspryng® (Satralizumab-mwge)
Dosage: Prefilled syringe, 120 mg/mL, subcutaneous injection
Indication: Adults [REDACTED] (b) (4) for the treatment of
Neuromyelitis Optica Spectrum Disorders (NMOSD)
PDUFA date: August 15, 2020

Recommendation: The drug product part of this BLA, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective.

Review Summary

Data from shipping validation OQ studies are reviewed herein. The relevant amendments reviewed are provided in the table below:

Sequence number	Date	Description
0038	5/26/2020	Response to IR
0043	6/23/2020	Response to IR
0044	1/13/2020	Response to IR

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Satisfactory

Conclusion

- I. The drug product section of the BLA, as amended, is recommended for approval from a sterility assurance and product quality microbiology perspective.
- II. Information and data in this submission not related to drug product sterility assurance and product quality microbiology were not evaluated and should be reviewed by an OBP reviewer.
- III. See Panorama for GMP status of the relevant facilities.

Information request:

1. Update Section 3.2.P.3.3 with information on DP shipping, including the shipping route and temperature, shipper information (including active or passive shippers), and if temperature is continuously monitored during routine shipments.
2. You had proposed in amendment dated 6/23/2020 (sequence 43) to remove the (b) (4) shipper from the BLA and had removed most of the information on the (b) (4) from P.3.5. However, it appears that (b) (4) was inadvertently left in P.3.5. Remove (b) (4) from Section 3.2.P.3.5.



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Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 5/14/2020
To: Administrative File, STN 761149/0
From: Bo Chi, Ph.D., CDER/OPQ/OPMA/DBM/Branch I
Endorsement: Reyes Candau-Chacon, Ph.D., Quality Assessment Lead, CDER/OPQ/OPMA/DBM/Branch II
Subject: New Biologic License Application (BLA)
Applicant: Genentech, Inc.
US License: 1048
Facility: Chugai Pharma Manufacturing Co., Ltd. (CPMC), Utsunomiya, Tochigi, Japan
 FEI: 3006942691
Product: Enspryng[®] (Satralizumab-mwge)
Dosage: Prefilled syringe, 120 mg/mL, subcutaneous injection
Indication: Adults [redacted] (b) (4) for the treatment of Neuromyelitis Optica Spectrum Disorders (NMOSD)
PDUFA date: August 15, 2020

Recommendation: The drug product part of this BLA, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective. Data from shipping validation OQ studies will be reviewed in an addendum memo.

Review Summary

Genentech has submitted this new Biologics License Application (BLA) for satralizumab, a recombinant humanized monoclonal antibody for the treatment of adult [redacted] (b) (4) [redacted] with neuromyelitis and neuromyelitis spectrum disorder. The drug substance (DS) is manufactured at Chugai Pharma Manufacturing Co., Ltd. (CPMC), Tokyo, Japan. The drug product (DP) is manufactured at Chugai Pharma Manufacturing Co., Ltd. (CPMC), Utsunomiya, Tochigi, Japan. This application contains CMC information in an eCTD format.

This review contains an assessment of the satralizumab drug product section of the BLA from a sterility assurance and product quality microbiology perspective. The amendments reviewed are provided in the table below:

Sequence number	Date	Description
0001	6/27/2019	Original BLA submission
0008	10/2/2019	Response to IR
0009	10/2/2019	Response to IR
0014	11/18/2019	Response to IR
0023	2/18/2020	Response to IR

0026	2/28/2020	Response to IR
0027	3/18/2020	Response to IR
0028	4/1/2020	Response to IR
0029	4/2/2020	Response to IR
0030	4/10/2020	Response to IR
0034	4/27/2020	Response to IR

(b) (4)



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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, **STN 761149/0**
From: Madushini Dharmasena, Ph.D., DMA Branch IV
Through: Reyes Candau-Chacon, Ph.D., Quality Assessment Lead, DMA Branch IV
Subject: New BLA for the treatment of in adults (b) (4) with Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorders (NMOSD).
US License: 1048
Applicant: Genentech, Inc.
Product: Enspryng (satralizumab)
Dosage: 120mg/1mL Prefilled syringe for Subcutaneous Injection
Facilities: Chugai Pharma Manufacturing Co., Ltd. (CPMC), 5-1, Ukima 5-Chome, Kita-ku Tokyo, Japan (FEI: 3004109596)
Receipt Date: 08/15/2019
Action Date: 03/12/2020

Recommendation for Approvability: The Drug Substance (DS) portion of STN 761149/0 was reviewed from a product quality microbiology perspective and is recommended for approval.

Review Summary

Genentech, Inc. submitted a new Biologics License Application (BLA) for Enspryng (satralizumab) at dose of 120mg in 1mL prefilled syringe for subcutaneous injection. Satralizumab is a humanized engineered IgG2 monoclonal antibody that targets the human interleukin 6 receptor (IL-6R) and thereby prevents IL-6 from binding to membrane-bound and soluble IL-6R. Satralizumab is a heterodimeric glycoprotein consisting of two 214-amino acid light chains and two 443-amino acid heavy chains. Satralizumab is produced in (b) (4) using (b) (4) Chinese hamster ovary (CHO) cell line.

DS Quality Microbiology Information Reviewed

Sequence number	Date	Description
eCTD 0001	06/26/2019	Original BLA
0003	07/26/2019	Response to information request sent on 07/17/2019

0020	02/10/2020	Response to information request sent on 01/22/2020
0022	02/18/2020	Response to information request sent on 02/03/2020
0023	02/18/2020	Response to information request sent on 02/12/2020

(b) (4)

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Madushini
Dharmasena

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Reyes
Candau-Chacon

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