CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761238Orig1s000

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:	December 14, 2022
Assessor:	Jennifer Kim, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Xiaoshi Wang, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 2
Application:	BLA 761238
Applicant:	TG Therapeutics, Inc.
Submission Date:	September 28, 2021
Product:	Briumvi (ublituximab-xiiy)
Dosage form(s):	Injection
Strength and Container-Closure:	150 mg/6 mL (25 mg/mL) in single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application to seek approval of ublituximab-xiiy for the treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling 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 and medication guide submitted on December 14, 2022, container labels, and carton labeling submitted on September 14, 2022, were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on September 28, 2022)
  \\CDSESUB1\evsprod\bla761238\0001\m1\us\ublituximab-uspi-rms-final-draft_26aug2021.docx

- Medication Guide (submitted on September 28, 2022)
  \\CDSESUB1\evsprod\bla761238\0001\m1\us\ublituximab_medguide_final_clean_26aug2021.docx

- Container Labels (submitted on September 28, 2022)

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

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

Container[4] Label Evaluation

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

Manufacturer name, address, and license number (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: The applicant written on Form FDA 356h is the licensed applicant, licensed manufacturer, or manufacturer. Revise to the appropriate qualifying phrase "Manufactured by" and revise the manufacturer address as it appears on Form FDA 356h. Relocate the US license number to appear after the manufacturer address and revise the Country-of-Origin statement to (b) (4) Manufactured by: TG Therapeutics, Inc. Morrisville, NC 27560	

[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."

U.S. License No. #### (b) (4) *The applicant revised as requested.*

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

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

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

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

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

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

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Partial label limited space considerations. See carton.	

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

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

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *The applicant confirms that there is no text on the ferrule or cap on the vial overseal.*	

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located.	

The applicant confirms that there will be sufficient area to allow for visual inspection after the label is affixed.

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

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

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

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

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

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No

	☐ N/A

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

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

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

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

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

Comment/Recommendation: Partial label limited space considerations. See carton.

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

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Partial label limited space considerations. See carton.	

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the storage information to read "Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do no freeze. Do not shake." for consistency with the prescribing information. *The applicant revised as requested.*	

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

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes

[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.

	☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation:
The applicant written on Form FDA 356h is the licensed applicant, licensed manufacturer, or manufacturer. Revise to the appropriate qualifying phrase "Manufactured by" and revise the manufacturer address as it appears on Form FDA 356h. Relocate the US license number to appear after the manufacturer address and revise the Country-of-Origin statement to (b) (4)

Manufactured by:
TG Therapeutics, Inc.
Morrisville, NC 27560
U.S. License No. ####
(b) (4)

Delete the facility information, which is not a required information for consistency with the container label and prescribing information.
The applicant revised as requested.

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

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

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

	☒ N/A

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

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

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

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the storage information to read "Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do no freeze. Do not shake." for consistency with the prescribing information. *The applicant revised as requested.*	

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

	☐ N/A

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

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

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

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the inactive ingredient list as follows: "Each vial contains 150 mg of ublituximab-xiiy in 6 mL of solution. Each mL contains 0.4 mg hydrochloric acid, 0.7 mg polysorbate 80, 9.0 mg sodium chloride, 6.4 mg sodium citrate, and Water for Injection, USP. Contains no preservative." *The applicant revised as requested.*	

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

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *In the process of revising net content statement, the applicant removed the statement* (b) (4) *from the carton labeling. Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OBP Product Quality assessors, this regulation does not apply to this product* (b) (4) *Removal of th* (b) (4) *statement is acceptable.*	

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

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

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

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A

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

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

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

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

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

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

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

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

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

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

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

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Consider revising the net quantity statement to specify the volume and package type. For example, revise "(b) (4)" to "Contains one 6 mL single-dose vial." *The applicant revised as requested.*	

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

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

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

Other (package labeling)	**Acceptable**
	☐ Yes ☐ No ☒ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Please add 4-letter suffix to the proper name throughout the labeling. *The applicant revised as requested.*	

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**

Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation:
We added "approximately" to describe the molecular weight since 147 kDa is a rounded number.
The applicant revised as requested.

We revised the inactive ingredient list in alphabetical order.
The applicant revised as requested.

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, hydrochloric acid, polysorbate 80, sodium chloride, and sodium citrate. [redacted] (b) (4) [redacted] will need to be revised accordingly. Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the table that includes [redacted] (b) (4). Ensure that all inactive ingredients with a USP monograph are provided as such.
The applicant revised as requested.

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

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

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: The applicant written on Form FDA 356h is the licensed applicant, licensed manufacturer, or manufacturer. We revised the manufacturer information with the correct qualifying phrase and address as it appears on Form FDA 356h. *The applicant revised as requested.*	

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
Comment/Recommendation: We added the 4-letter suffix to the proper name. *The applicant revised as requested.*	

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

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised (b) (4) "sodium citrate" to ensure compliance with the Federal Food Drug, and Cosmetic Act (FD&C Act) section 502(e). We revised the inactive ingredient list in alphabetical order. *The applicant revised as requested.*	

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: The applicant written on Form FDA 356h is the licensed applicant, licensed manufacturer, or manufacturer. We revised the manufacturer information with the correct qualifying phrase and address as it appears on Form FDA 356h. *The applicant revised as requested.*	

Jennifer Kim

Digitally signed by Jennifer Kim
Date: 12/14/2022 12:55:38PM
GUID: 5e5438d2008138bdbae1db8d4abc0580

Xiaoshi Wang

Digitally signed by Xiaoshi Wang
Date: 12/14/2022 01:05:15PM
GUID: 5acb8a0d000ff95628573aa8ecd8547d

First Approval for Indication
Recommendation: BLA Approval

BLA Number: 761238
Review Number: 1
Review Date: September 6, 2022

Drug Name/Dosage Form	Briumvi (ublituximab-xiiy) injection
Strength/Potency	150 mg/6 mL
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Relapsing forms of multiple sclerosis
Applicant	TG Therapeutics, Inc.

Product Overview

Ublituximab human/mouse chimeric immunoglobulin G1 (IgG1) monoclonal antibody produced in mammalian (b) (4) cells. Ublituximab binds to CD20 on B cells and causes B cell depletion through four known functions: antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and direct cell death. The proposed indication is for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Ublituximab drug product (DP) is a sterile, essentially particle free, clear to opalescent, colorless to slightly yellow solution. Each DP vial contains 150 mg/6 mL of ublituximab at concentration of 25 mg/mL with pH of 6.5. Each mL of solution contains 25 mg ublituximab, 9.0 mg sodium chloride, 6.4 mg sodium citrate, 0.7 mg polysorbate 80, 0.4 mg hydrochloric acid and water for injection. The recommended dose for ublituximab is 150 mg for the first infusion followed 450 mg infusion two weeks later, and subsequent 450 mg infusion every 6 months.

Quality Assessment Team

Discipline	Assessor	Office/Branch/Division
Product Quality (Drug Substance (DS) and DP)/Immunogenicity Assay	Xiaoshi Wang	OPQ/OBP/DBRRII
Labeling	Jennifer Kim Xiaoshi Wang	OPQ/OBP OPQ/OBP/DBRRII
Facility	Richard Ledwidge (DS and DP)	OPQ/OPMA/DBM/BMB2
Microbiology	Reyes Candau-Chacon (DS and DP)	OPQ/OPMA/DBM/BMB2
Inspection	Madushini Dharmasena	OPQ/OPMA/DBM/BMB2
Team Lead (TL)	Yan Wang (product quality) Virginia Carroll (DS and DP microbiology and facility)	OPQ/OBP/DBRRII OPQ/OPMA/DBM/BMB2
Application Team Lead (ATL)	Yan Wang	OPQ/OBP/DBRRII
OBP Review Chief	Patrick Lynch	OPQ/OBP/DBRRII
RBPM	Melinda Bauerlien	OPQ/OPRO

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Rania Younes/Sandra Folkendt	OND/ON/DNII
Cross-disciplinary Team Lead	Paul Lee	OND/ON/DNII
Medical Officer	Laura Baldassari and Rui Li (Safety data analysis)	OND/ON/DNII
Pharm/Tox	Barbara Wilcox/Lois Freed (TL)	OND/ON/DPTN
Clinical Pharmacology	Anantha Ram Nookala/Gopichand Gottipati (TL)	OTS/OCP/DNP
Statistics	Xiang Ling/Kun Jin (TL)	OTS/OB/DBI

1. Names:
   a. Proprietary Name: Briumvi (pending)
   b. Trade Name: Briumvi (pending)
   c. Non-Proprietary Name/USAN: Ublituximab
   d. CAS Registry Number: 1174014-05-1
   e. INN Name: Ublituximab
   f. OBP systematic name: MAB CHIMERIC (IGG1) ANTI P11836 (CD20_HUMAN) [TG1101]
   g. Other name(s): TG-1101 (company code), TGTX1101, LFB-R603, B7A (DS), PB7A (DP), PB7AA (DP), PB7AB (DP)

Submissions Assessed:

Submission(s) Assessed	Document Date (disciplines affected)
STN 761238 pre-BLA meeting	April 6, 2021
STN 761238/SN0001 (BLA submission)	September 28, 2021
STN 761238/SN0005 (Information request (IR) response)	November 22, 2021 (OPMA)
STN 761238/SN0006 (IR response)	November 24, 2021 (OPMA)
STN 761238/SN0018 (IR response)	March 1, 2022 (OBP IR-1)
STN 761238/SN0021 (IR response)	March 16, 2022 (OPMA)
STN 761238/SN0022 (IR response)	March 16, 2022 (OBP-IR2)
STN 761238/SN0023 (IR response)	March 21, 2022 (OPMA)
STN 761238/SN0026 (IR response)	April 11, 2022 (OPMA)
STN 761238/SN0027 (IR response)	April 15, 2022 (OPMA)
STN 761238/SN0031 (IR response)	May 24, 2022 (OBP-IR3)
STN 761238/SN0033 (IR response)	June 1, 2023 (OBP-IR4)
STN 761238/SN0034 (IR response)	June 6, 2022 (OPMA)
STN 761238/SN0037 (IR response)	July 8, 2021 (OBP-IR5)
STN 761238/SN0041 (IR response)	August 2/2022, 2022 (OBP-IR5)
STN 761238/SN0043 (IR response)	August 18, 2022 (OBP-IR6)
STN 761238/SN0045 (IR response)	August 22, 2021 (OBP-IR7)

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

Quality Assessment Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed	Comments
031704	V	Samsung Biologics Co., Ltd	Facilities and equipment information for Samsung Biologics, Ltd, contract manufacturing plant in Songdo, South Korea	3	Adequate	N/A	N/A
(b) (4)	II	(b) (4)		3	Adequate	N/A	N/A
	V			2	Adequate	N/A	N/A
	III			3	Adequate	N/A	N/A
	III			3	Adequate	N/A	N/A
	II			3	Adequate	N/A	N/A
	II			3	Adequate	N/A	N/A
	CBER			3	Adequate	N/A	N/A
	V			2	Adequate	N/A	N/A

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

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

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

Document	Application Number	Description
IND	(b) (4) 127265	Parent IND

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion:

TG Therapeutics claimed a categorical exclusion from the requirement of an Environmental Assessment in accordance with 21 CFR 25.31(b) where the substance at the point of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). TG Therapeutics calculated the total amount of ublituximab introduced into the aquatic environment as (b) (4) ppb which includes the highest amount of ublituximab that will be manufactured over the next 5 years. Based on an assessment according to 21 CFR 25.31(c), ublituximab is comprised of linked naturally occurring amino acid chains which are significantly metabolized *in-vivo* and expected to be readily and rapidly degraded in wastewater treatment systems and in the environment. Therefore, when ublituximab is exposed to the environment, it would not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Based on all above, the claim of a categorical exclusion is accepted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761238 for Briumvi (ublituximab-xiiy) manufactured by TG Therapeutics, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Briumvi (ublituximab-xiiy) is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language

- Manufacturing location:
  - Drug Substance and Drug Product:
    Samsung Biologics Co., Ltd., 300 Songo bio-daero, Yeonsu-gu Incheon, Republic of Korea (FEI: 3010479596)

- Fill size and dosage form: 150 mg/6 mL solution

- Dating period:
  - Drug Product: 24 months at 2°C to 8°C
  - Drug Substance: (b) (4) months at (b) (4) °C
  - Stability Option:
    - 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 substance and drug product under 21 CFR 601.12.

- Exempt from lot release in accordance with 21 CFR 601.2a. Ublituximab is a specified product.

C. Benefit/Risk Considerations:

Ublituximab is a recombinant IgG1 chimeric anti-CD20 monoclonal antibody that recognizes a unique epitope on the CD20 antigen that allows it to provide enhanced ADCC and retain CDC. Although a few anti-CD20 drugs are currently on the market for treatment of relapsing forms of multiple sclerosis, ublituximab provides a treatment option for patients that may have failed

other approved therapies or for patients with untreated disease that may be ineligible for other agents based on toxicity risks or comorbidities.

Review of manufacturing has identified that the methodologies used for DS and DP manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. We also recommend approval of the commercial manufacture of ublituximab DS and DP at Samsung Biologics Co., Ltd, Yeonsu-gu Incheon, Republic of Korea. The OBP (Office of Biotechnology Products) product quality and immunogenicity assay, OPMA (Office of Pharmaceutical Manufacturing Assessment) facility, microbiological DS and DP, as well as OBP labeling technical assessments are located as separate documents in Panorama.

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

The following post-marketing commitment (PMC) has been discussed and agreed by the Applicant during the BLA review.

1. To optimize the antibody-dependent cellular cytotoxicity (ADCC) Potency Assay with the goal of reducing method variability as well as implement a comprehensive and robust control strategy to control ADCC activity of ublituximab drug substance and drug product at release and stability, and to submit the proposed relevant specifications as a Prior Approval Supplement in accordance with 21 CFR 601.12 (b).

   Final Report Submission: December 2023

2. To implement and validate an analytical method to control polysorbate 80 concentration for ublituximab drug product at release and stability.

   Final Report Submission: March 2023

3. To establish a ublituximab working reference standard (WRS) and submit WRS qualification data for the first WRS as well as a WRS requalification protocol.

   Final Report Submission: January 2023

4. To develop a neutralization assay and submit a full validation report of the newly developed neutralization assay, re-analyze neutralizing antibody in patients enrolled in the pivotal clinical studies (TG1101-RMS301 and TG1101-RMS302), and evaluate the potential impact on the pharmacokinetics, pharmacodynamics, safety and efficacy of ublituximab.

   Final Report Submission: August 2024

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management for Ublituximab

Table 1: Active Pharmaceutical Ingredient CQA (critical quality attribute) Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
FcγIIIRa-158V binding (Potency)	Efficacy	Intrinsic to the molecule	(b) (4)	
ADCC activity (Potency)	Efficacy	Intrinsic to the molecule		
CDC bioassay (Potency)	Efficacy	Intrinsic to the molecule		
C1q binding (Potency)	Efficacy	Intrinsic to the molecule		
CD20 binding (Potency)	Efficacy	Intrinsic to the molecule		
ADCP	Efficacy	Intrinsic to the molecule		
Identity	Efficacy and Safety	Intrinsic to the molecule		

High Molecular Weight (HMW) species/Aggregates (Product related impurity)	Pharmacokinetics (PK), and Safety (Immunogenicity)	Manufacturing process, storage and exposure to high pH, heat and light	(b) (4)
LMW species/Fragments (Product related impurity)	Efficacy	Manufacturing process, and exposure to high pH, heat and light	
Heavy chain (b) (4)	PK	Manufacturing process and exposure to oxidation reagent stress and photo stress Minimal change is expected on stability due to high temperature and pH stress Significant increased under photo stress	
(b) (4)	PK	Bioreactor conditions Minimal change is expected on stability	
Glycosylation	Efficacy and Safety	Introduced during manufacturing process	
Charge variant profile (Acidic variants)	Efficacy, PK/ Pharmacodynamics (PD)	Manufacturing process and exposure to high pH, heat and light	
Charge variant profile (Basic variants)	Efficacy, PK/PD	Manufacturing process and exposure to low pH, and high pH	

B. Drug Substance (Ublituximab) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
(b) (4) Concentration	Efficacy (Product oxidation) and Stability	Formulation component	(b) (4)	N/A
Quantity	Efficacy	Manufacturing process		N/A
pH (General)	Efficacy and Stability	Formulation components and stability		N/A
Osmolality (General)	Stability	Composition of the DS		N/A
Appearance (Includes degree of opalescence and color of solution) (General)	Stability	Formulation components and stability		N/A
Host Cell DNA (Process related impurity)	Safety	Production cell line, bioreactor and harvest, cell viability and % viable cell density		N/A
Host Cell Protein (Process related impurity)	Immunogenicity	Production cell line, bioreactor and harvest cell viability and % viable cell density		N/A
(b) (4) (Process related impurity)	Safety	Purification through the (b) (4)		N/A
Adventitious viruses, endogenous virus (Process related impurity)	Safety	Cell banks, raw materials		(b) (4)
Mycoplasma (Process related impurity)	Safety	Cell banks, raw materials		
Endotoxin (contaminant)	Safety and Purity	Raw materials and manufacturing process		N/A

Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials and manufacturing process	(b) (4)	N/A
Leachables (Process-related impurity)	Safety and Stability	From manufacturing contact material and the DS container closure system (CCS)		Risk for leachables from CCS is low (b) (4)
Culture medium additives (b) (4)	Safety	Preculture medium, or production bioreactor medium		Levels are below toxicological concern based on the risk assessment

- Description:
Ublituximab is a recombinant IgG1 chimeric monoclonal antibody which binds to CD20. Ublituximab is produced from (b) (4) Ublituximab is composed of two identical immunoglobulin kappa light chains (LCs) and two identical immunoglobulin gamma heavy chains (HCs). The predominant N-termini species for both the HC and the LC are modified to pyroglutamate and the predominant C-termini of the HCs include C-terminal lysine truncations. Ublituximab contains 32 cysteines leading to 16 disulfide bonds and two glycosylation sites located on Asparagine N298 of HCs. The non-glycosylated ublituximab has an overall molecular weight of approximately 144,184.8 Da.

- Mechanism of Action (MoA):
Ublituximab targets the cluster of differentiation CD20 antigen expressed on the surface of pre-B and mature B lymphocytes. Upon binding to CD20, ublituximab mediates B-cell lysis through engagement of immune effector cells by directly activating intracellular death signaling pathways (direct cell death), and/or activation of the complement cascade. The immune effector cell mechanisms include ADCC and ADCP.

- Potency Assays:
  - A SPR binding assay is used to determine the relative binding activity of the ublituximab to FcγIIIRa-158V. Specifically, FcγRIIIa 158V receptor is immobilized on the chip surface using covalent amine coupling chemistry. The binding is measured in response units. The kinetics of the binding reaction is determined by measuring changes in SPR due to the increase in mass in the close proximity to the biosensor chip surface. The equilibrium dissociation constants (KD) and the relative affinities of each sample relative to the RS are determined. The binding signals are exported into PLA software to determine the relative binding response. Results are reported as % potency relative to RS for FcγRIIIa 158V receptor.

  - A cell-based assay is used to determine the CDC bioactivity on target cells expression the CD20 antigen. Specifically, CD20 expressing human mantle cell lymphoma Jeko-1 cells are seeded and incubated in plates. Then diluted

ublituximab samples, RS and rabbit serum as the source of complement are added to the well for additional incubation. The CDC mediated cell lysis is measured by adding Cell Titer-Glo™ reagent. At the end of the assay the plates are read using a SpectraMax M5 plate reader. SoftMax Pro is used to analyze the data with weighted nonlinear regression using a 4-parameter logistic fit. The resulting data is evaluated using the Softmax Pro software for potency against the RS. Results are reported as % potency relative to the RS.

- An ELISA based C1q binding assay is used to determine the relative binding activity of the ublituximab to the C1q antigen. Specifically, ublituximab samples and RS are first coated on ELISA plates, horse radish peroxidase (HRP) conjugated human C1q is then incubated with samples on the plate. The bound HRP, in the presence of tetramethylbenzidine (TMB) substrate, generates a colorimetric signal. The resulting data is evaluated using the SoftMax Pro software for potency against the RS. C1q binding activity results are reported as percentage potency relative to the RS.

- A cell-based assay is used to determine the relative binding activity of the ublituximab to the CD20 antigen. Specifically, CD20 expressing Jeko-1 target cells are seeded onto MSD plates. Ublituximab samples and RS are incubated and allowed to bind to Jeko-1 cells. Then anti- human Fc detection antibody conjugated with streptavidin-SULFOTAG™ is used to emit electrochemiluminescence signal. Plates are read immediately on a MSD Reader using Workbench 4.0. The resulting data is evaluated using the PLA software. Binding activity results are reported as percentage potency relative to the RS.

- Reference Materials:

(b) (4)

- Critical Starting Materials or Intermediates:

(b) (4)

(b) (4)

- Manufacturing Process Summary:

(b) (4)

- Container Closure System:

(b) (4)

- Dating Period and Storage Conditions:
  The dating period for the formulated DS is (b) (4) months when stored at (b) (4)

C. Drug Product (Ublituximab) Quality Summary:

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

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

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process or failure of container closure integrity	(b) (4)	N/A
Endotoxin (contaminant)	Safety (pyrogenic fever), Purity, and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing process or failure of container closure integrity		N/A
Container closure integrity (sterility assurance)	Safety (failure in closure integrity may lead to contamination and loss of sterility or evaporation/leakage impacting concentration or content)	Container closure breaches during manufacture or storage		N/A
Quantity	Efficacy	Manufacturing process		N/A
Appearance (Degree of opalescence, color, visible particles) (Product and process related impurities)	Safety, Immunogenicity and stability	Manufacturing material, formulation components, stability and CCS		N/A
Particulate matter for subvisible particles (Product or process related impurities)	Safety and Immunogenicity	Manufacturing process and CCS; subvisible particles could be product or foreign particles		N/A
Polysorbate 80 Concentration	Efficacy (Product oxidation) and Stability	Formulation component		N/A
pH (General)	Efficacy and Stability	Formulation components and stability		N/A

Extractable volume (General)	Efficacy/Dosing	Fill process	(b) (4)	N/A
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS		The DP shelf-life will be granted to 24 months at 2-8°C, and can be extended to 36 months

- Potency and Strength:
  Ublituximab is supplied as 25 mg/mL solution in one strength (i.e., 150 mg/6 mL). Potency is defined as the percent activity relative to the current ublituximab primary reference standard. The potency assays include CDC bioassay and FcγIIIRa-158V binding assay which are the same as described in the DS section of this memo.

- Summary of Product Design:
  Ublituximab is supplied as a sterile, single-dose, preservative-free solution for intravenously infusion in one strength. Each vial of 150 mg/6 mL strength is filled with a fill volume from (b) (4) mL.

- List of Excipients:
  Each mL of solution contains 25 mg ublituximab, 9.0 mg sodium chloride, 6.4 mg sodium citrate, 0.7 mg polysorbate 80, 0.4 mg hydrochloric acid and water for injection. The pH is 6.5.

- Reference Materials:
  The same reference standards are used for formulated DS and DP.

- Manufacturing Process Summary:
  (b) (4)

(b) (4)

- Container Closure System:
  The primary CCS for ublituximab DP consists of a (b) (4) colorless (b) (4) vial closed with a (b) (4) rubber stopper. The stopper contains a (b) (4) on the product contact surface. The flip-off seal contains high quality aluminum and plastic materials.

- Dating Period and Storage Conditions:
  The dating period for the 150 mg/6 mL strength DP is 24 months when stored at 2°C to 8°C.

- List of Co-Package Components (if applicable): None

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Store in a refrigerator at 2°C to 8°C in the original carton
- Protect from light
- Do not freeze
- Do not shake

F. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
MCB/WCB Manufacturer and Storage	(b) (4)		No evaluation necessary	N/A	No evaluation necessary
DS Manufacturer	Samsung Biologics Co., Ltd. 300 Songo bio-daero, Yeonsu-gu, Incheon, Republic of Korea.	3010479596	Facility was found compliant based on file review	N/A	Approve based on waiver granted by OPMA/OBP
Cell Bank Storage and Testing	(b) (4)		No evaluation necessary	N/A	No evaluation necessary

WCB Manufacturer and Storage	(b) (4)	(b) (4)	No evaluation necessary	N/A	No evaluation necessary
(b) (4) Testing and Cell Bank Testing			Approve based on History	N/A	Approve based on History
Potency Testing for Release and Stability			Approve based on History	N/A	Approve
DS Lot Disposition	TG Therapeutics 3020 Carrington Mill Blvd Suite 475, Morrisville, NC, USA, 27560.	3016405037	No evaluation necessary	N/A	No evaluation
DRUG PRODUCT					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP Manufacturer	Samsung Biologics Co., Ltd. 300 Songo bio-daero, Yeonsu-gu, Incheon, Republic of Korea.	3010479596	PLI required	(b) (4)	Approve based on Inspection

Potency Testing for Release and Stability	(b) (4)	(b) (4)	Approve based on History	N/A	Approve based on History
Packaging and Labeling	Packaging Coordinators, LLC 3001 Red Lion Rd, Philadelphia, PA, USA, 19114.	1000522077	Approve based on History	N/A	Approve based on History
DP Storage	(b) (4)	(b) (4)	No evaluation necessary	N/A	No evaluation necessary
Identity Testing			Approve based on History	N/A	Approve based on History
DP Lot Disposition	TG Therapeutics 3020 Carrington Mill Blvd Suite 475, Morrisville, NC, USA, 27560.	3016405037	No evaluation necessary	N/A	No evaluation necessary

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Samsung Biologics Co., Ltd. (FEI 3010479596), proposed for ublituximab DS and DP manufacture. The pre-license inspection (PLI) of the DS facility was waived based on previous inspectional history of the manufacturing suite. A PLI of the DP facility was conducted on (b) (4). A three item 483 was issued to the firm on (b) (4). The final outcome of the inspection was voluntary action indicated (VAI). All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

(b) (4)

(b) (4)

[redacted]

ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.P.8.2	Annual stability protocol for DP with shelf-life extension	At least one lot per year if manufactured will be placed on stability at 2-8°C (initial, 3, 6, 9, 12, 18, 24 and 36 months)	Results will be reported in Annual Report.

ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None

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

/s/

YAN WANG
09/06/2022 07:07:45 PM