

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761183Orig1s000

PRODUCT QUALITY REVIEW(S)



**U.S. FOOD & DRUG
ADMINISTRATION**

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	November 16, 2022
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Deborah Schmiel, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 1
Application:	BLA 761183
Applicant:	Provention Bio, Inc.
Submission Date:	November 2, 2020
Product:	Tzield (teplizumab-mzwv)
Dosage form(s):	Injection
Strength and Container-Closure:	2 mg/2 mL (1 mg/mL) single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling submitted on November 15, 2022 were assessed and found to be acceptable (see Appendix C) from an OBP Labeling perspective.

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

n/a = not applicable for this assessment

DISCUSSION

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

CONCLUSION

The prescribing information, medication guide, container labels, and carton labeling submitted on November 15, 2022 were assessed and found to be acceptable (see Appendix C) from an OBP Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information/Medication Guide (submitted on February 17, 2022

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(b) (4)

4 Pages 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 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
Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No

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."

	☐ 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

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *Applicant's response on March 12, 2021 is acceptable.*

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 on March 12, 2021 is acceptable.*

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

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

<u>Preparation instructions (container label)</u>	<u>Acceptable</u>
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> <i>"Instructions for reconstituting the product and the resultant concentration should be included on the vial, if space permits. These instructions will inform persons responsible for preparing the product what type and volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter once reconstituted. If space permits, information on the expiration date and post-reconstitution storage should also be included."</i>	☐ Yes ☐ No ☒ N/A

<u>Package type term (container label)</u>	<u>Acceptable</u>
<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

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

<u>Prominence of required label statements (container label)</u>	<u>Acceptable</u>
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</i> <i>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

Comment/Recommendation: Ensure that a linear barcode is place on the container label and indicate the location of the linear barcode on the submitted mock-up <i>Applicant revised as requested</i>

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>	☒ Yes ☐ No ☐ N/A

<i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	
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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

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.

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

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</i> <i>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

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

Comment/Recommendation: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) 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, Dibasic Sodium Phosphate, Monobasic Sodium Phosphate, and sodium chloride.

For example, (b) (4)

(b) (4)

(b) (4)

(b) (4) (b) (4)

(b) (4)

(b) (4)

Confirm the calculated amount below.

The revisions to the inactive ingredient names to appear in alphabetical order and the amounts are proposed to be calculated as follows:

Each mL contains 1 mg of teplizumab-xxxx, dibasic sodium phosphate (0.26 mg), monobasic sodium phosphate (0.98 mg), polysorbate 80 (0.05 mg), sodium chloride (8.78 mg), and Water for Injection.

Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the table that includes (b) (4) calculations. Ensure that all inactive ingredients with a USP monograph are provided as such.

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: Remove the statement (b) (4) from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable and thus no statement is required on the labeling. <i>Applicant revised as requested</i> 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 because 1) no U.S. standard of potency has been prescribed for teplizumab products (i.e., there is no specific test method described in regulation for teplizumab products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Tzield because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase (b) (4) is not required to appear on the carton labeling.	
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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
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Bar code (package labeling)	Acceptable
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: <i>Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>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
Recommended labeling practices references: <i>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
Recommended labeling practices: <i>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

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

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

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

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

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

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

<u>Net quantity (package labeling)</u>	<u>Acceptable</u>
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>	☒ Yes ☐ No ☐ N/A

<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>	
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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

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: The proper names of biological products typically do not include a route of administration or dosage form. Therefore, the route of administration and/or dosage form should not be located inside the parentheses. Example: MYDRUG (drugimab-xxxx) injection, for subcutaneous use</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

Comment/Recommendation: Revised to the USP nomenclature for Sodium Chloride Injection *The Applicant revised as requested*

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

Comment/Recommendation: Deleted (b) (4) from this section
The Applicant revised as requested

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 or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: revise to the corrected established name for the diluent throughout all labeling for consistency *The Applicant revised as requested*
Added the statement to visually inspect parenteral products per 21 CFR 201.57(c)(3)(iv) *The Applicant revised as requested*
FDA recommends against labeling overfill (e.g., "...vial contains (b) (4) mL...". Any unused portion should be discarded. We added a discard statement appearing after the instructions to withdraw 2 mL. *The Applicant revised as requested*

Per OPMA, add room temperature storage range and revise to storage duration of 4 hours or submit supporting data for (b) (4) hours. *The Applicant revised as requested to 4 hours and inserted storage range of temperature [15°C to 30°C (59°F to 86°F)]*

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

Comment/Recommendation: Deleted (b) (4) information from this section
The Applicant revised as requested

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

Comment/Recommendation: Added the pharmacological class "a CD3-directed monoclonal antibody (humanized IgG1 kappa)". We added the IgG1 kappa subclass
Applicant revised as requested
 We deleted to mechanism of action which is found in section 12
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) 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, Dibasic Sodium Phosphate, Monobasic Sodium Phosphate, and sodium chloride. For example, (b) (4)

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

Comment/Recommendation: Add 4 letter suffix, dosage form and route of administration
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
<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: Add the 4-letter suffix to the proper name *Applicant revised as requested*
 Revised the inactive ingredient names to appear in alphabetical order and the established names for inactive to the USP/NF monographs titles *Applicant revised as requested*

MEDICATION GUIDE	
<u>MANUFACTURER INFORMATION</u>	<u>Acceptable</u>
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: Added manufacturer name and address and placeholder for US license number *Applicant revised as requested*

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on November 15, 2022

<\\CDSESUB1\EVSPROD\bla761183\0086\m1\us\agreed-upon-uspi.docx>)

Medication Guide (submitted on November 15, 2022

<\\CDSESUB1\EVSPROD\bla761183\0086\m1\us\agreed-upon-mg.docx>)

Container Labels (submitted on November 15, 2022)

(b) (4)

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



Vicky
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 11/16/2022 07:07:39AM
GUID: 50814c7000007a3d59329f660d8ddf02



Deborah
Schmiel

Digitally signed by Deborah Schmiel
Date: 11/16/2022 11:03:04AM
GUID: 525e939c0003b510f311aa53c1abf18e

First Approval for Indication
Breakthrough Review, Priority Review

Recommendation: Approval

BLA 761183
Second Round- CR Response
October 19, 2022

Drug Name/Dosage Form	Tzield (teplizumab-mzwv)/ injection
Strength/Potency	2 mg/2.0 mL (1 mg/mL concentration)
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	The delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D
Applicant/Sponsor	Provention Bio, Inc.

Product Overview:

Teplizumab-mzwv is a humanized IgG1κ monoclonal antibody produced in CHO cells. Teplizumab is an agonist of cluster of differentiation 3 (CD3) on T lymphocytes and engages signaling through CD3ε- and NFAT-dependent signaling cascades downstream. The Fc portion of teplizumab is mutated to disallow binding of Fc receptors or complement. Teplizumab drug product is supplied as a sterile, single-dose, preservative-free solution for intravenous infusion in single-dose vials containing 2 mg/2.0 mL. Teplizumab is proposed for the delay of clinical Stage 3 type 1 diabetes in at-risk individuals.

Quality Assessment Team:

Discipline	Assessor	Branch / Division
Drug Substance/Drug Product	Deborah Schmiel	DBRR I/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facilities and Microbiology, DS	Wendy Tan	DBM/OPMA/OPQ
Microbiology Team Lead	Maxwell Van Tassell	DBM/OPMA/OPQ
Facilities Team Lead	Zhong Li	DBM/OPMA/OPQ
Application Technical Lead	Rachel Novak	DBRR I/OBP/OPQ

Multidisciplinary Assessment Team:

Discipline	Assessor	Office / Division
RPM	Supendee Dosanjh	DROCHEN/ORO/OND
Cross-disciplinary Team Lead	Michael Nguyen	DDLO/OCHEN/OND
Medical Officer	Lauren Wood-Heickman	DDLO/OCHEN/OND
Pharmacology/Toxicology	Federica Basso and Patty Brundage (TL)	
Clinical Pharmacology	Harisudhan Thanukrishnan, Jaya Vaidyanathan (TL) Elyes Dahmane, Justin Earp (TL)	DCEP/OCP/OTS DPM/OCP/OTS
Statistics	Yu (Jade) Wang, Yoonhee Kim (TL)	DBII/OB/OTS

1. Names:

- a. Proprietary Name: Tzielid
- b. Trade Name: Tzielid
- c. Non-Proprietary Name/USAN: teplizumab
- d. CAS Registry Number: 876387-05-2
- e. Common names: hOKT3γ1 (Ala-Ala), PRV-031, A78, MGA031, LY2801777
- f. INN Name: teplizumab
- g. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P07766 (CD3E_HUMAN) [PRV031]

Submissions Assessed:

Submission(s) Assessed	Document Date
761183 BLA Resubmission	2/17/2022
761183/64- IR#1 Response	6/16/2022
761183/71- IR Response (joint with OCP)	7/27/2022
761183/72- IR#2 Response	8/04/2022
761183/73- Stability Update	8/11/2022
761183/74- Impact assessment N-1 bioreactor	9/08/2022
761183/77- IR#3 Response	9/29/2022
761183/79- IR#4 Response	10/13/2022
761183- IR #5- Environmental Assessment	10/18/2022

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Date Assessment Completed	Comments

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

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

- B. Other documents:** The Complete Response Letter conveyed to the sponsor was uploaded to DARRTs on 07/02/2021. For additional information see the CMC Product Quality drug substance (DS) and drug product (DP) Reviews for the first round submission uploaded to Panorama by Deborah Schmiel and Meng Jung Chiang, respectively, on 4/16/2021. The OPQ IQA for the first round submission was uploaded to DARRTs by Jennifer Swisher on 5/14/2022.

This executive summary will only cover the CR issues that were addressed in the Complete Response. The second round CMC Product Quality review was uploaded to Panorama by Deborah Schmiel on 10/17/2022.

3. **Consults:** none

4. Environmental Assessment of Claim of Categorical Exclusion:

In accordance with 21 CFR 25.31(c), Provention Bio, Inc., claimed a categorical exclusion from the requirement described by 21 CFR 25.20 to prepare an environmental assessment.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval

The Office of Biotechnology Products, OPQ, CDER, has completed assessment of STN 761183 for Tzield manufactured by Provention Bio, Inc. The data submitted in this application are sufficient to support a conclusion that the manufacture of Tzield is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Summary of Complete Response (CR) Issues: None

C. Approval Action Letter Language:

- Manufacturing location:
 - Drug Substance: AGC Biologics, (b) (4)
 - Drug Product: (b) (4)
- Fill size and dosage form: 2 mg/2.0 mL (1 mg/mL) injection
- Dating period:
 - Drug Product: 24 months: 2-8°C
 - Drug Substance: (b) (4) months: (b) (4)
 - Not packaged
- Exempt from lot release:
 - Yes
 - Tzield is exempted from lot release per FR 95-29960.

D. Benefit/Risk Considerations:

Tzield is intended to delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D, constituting an unmet medical need for patients who are at high risk of developing T1D. This product was granted breakthrough designation and is considered medically necessary and mission critical based on "the lack of available disease-modifying therapies, significant unmet medical need, severity of T1D, and the clinical meaningfulness of a median 2-year delay of onset of T1D on a patient's quality of life outweigh the observed and potential risks of teplizumab which were self-limited and expected based on the drug's mechanism of action" (from clinical review uploaded to DARRTs on 7/2/2021).

Based on information provided during the original submission of BLA 761183, a Complete Response (CR) Letter was issued on 7/2/2021, due to the lack of biocomparability between product used in the clinical safety studies (TN-10 study) manufactured by Eli Lilly and the to be marketed product manufactured by AGC Biologics. Specifically, the pharmacokinetics (PK) bridging study, PRV-031-004, failed between the two products. In addition, the original

submission had several product quality related issues as well as an unacceptable facility inspection at the DP manufacturing facility (b) (4)

On February 17, 2022, Provention Bio Inc. submitted a response to the CR to address the issues surrounding the biocompatibility and product quality related items. The facility issues were resolved prior to the resubmission and the facility is approved. Additional information provided in the resubmission demonstrate that the PK differences between the Lilly and AGC products still exist. The sponsor proposed to use exposure matching by increasing the dose of the AGC product to match the PK of the Lilly product based on PK simulation models (see clinical and clinical pharmacology reviews uploaded to DARRTs for more information).

While it appears that there are differences in the to be marketed product (AGC) compared to the product used in the pivotal clinical studies (Eli Lilly) that allow for a difference in PK, those differences have not been identified from a product quality perspective. Differences were noted in the analytical comparability assessment between the AGC and Eli Lilly products; however, those differences were not considered significant or would have suggested an impact on PK based on the current experience. However, the analytical comparability assessment is limited by the attributes assessed, the methods used and their capability. The risk-benefit analysis and the overall unmet medical need as communicated by the clinical teams, and the overall control strategy allows for the acceptance of the residual uncertainty. The sponsor has committed to continue to investigate what product quality differences could have contributed to the difference in PK between the AGC and Lilly products and has agreed to additional controls to ensure the product remains consistent.

From the product quality perspective, the information and data provided for the CR and additional items in the resubmission were adequately addressed and any remaining residual manufacturing issues will be addressed as post-marketing commitments (PMCs) (see list of PMCs below in Section E). For the assay development, the current assays have demonstrated suitability for their intended purpose but require optimization or a full validation exercises. The current reference standard system is one-tier and is considered suitable for testing new DS and DP lots at release and on stability; however, the sponsor is currently developing a two tier system that will be submitted to the BLA in Q3 2023. These items are considered low risk and are appropriate to resolve post-marketing given the expected benefits to patients at risk of developing T1D.

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

Several PMCs will be conveyed to the sponsor for the following items:

1. To optimize or replace the CEX charge assay.
2. To validate the HILIC HPLC assay to control glycans at release of the DS and reassess the acceptance criterion for release.
3. To validate a product-specific Host Cell Protein (HCP) assay.
4. To implement and qualify a working reference standard.
5. To continue to investigate the root cause of any product quality differences that can account for the PK differences between the AGC and Lilly products.

ATL comment: The final PMC language and proposed completion dates can be found in the approval letter for this BLA.

II. Summary of Quality Assessments:

ATL comment: This review will focus on items that were addressed as part of the Complete Response letter. There is some overlap of the previous information for ease of review. For assessment of all other DS and DP quality assessments not included here, see the OPQ IQA uploaded by Jennifer Swisher to DARRTs on 05/14/2022. For a detailed assessment of the CR issues, see the Product Quality review uploaded to Panorama by Deborah Schmiel on 10/17/2022.

A. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy (b) (4)	Other
Oxidation	Efficacy and Safety/Immunogenicity	Manufacturing process and exposure to heat stress		Additional item #4 from the CR letter was adequately addressed in the Response to CR. (b) (4)
Acidic variants (product related impurities)	Loss of potency, potential immunogenicity	Fermentation, in-process and on stability		CR issue #2 of the CR letter concerning the variability of the CEX assay has been mostly addressed and is adequate to support that the results are appropriate to control release and stability and to set shelf-life of the DS and DP. While the assay does not appear to demonstrate unacceptable variability and the root-cause of the issue from CR item #2 was identified, there is still an inherent variability within the assay. A PMC will be issued for the sponsor to continue optimization of the CEX method or to replace the method with a method with less variability.
Basic variants (product related impurities)	Potential loss of potency, immunogenicity	Fermentation, in-process and on stability		See acidic variants above.

B. Drug Substance Teplizumab Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

The following table presents CQAs derived from the drug substance manufacturing process and general drug substance attributes, as well as control strategies in place. Residual risks are addressed through PMCs.

Table 2: Drug Substance Process Risk Identification and Lifecycle Knowledge Management¹

Category	Type	Risk	Introduction	Control Strategy	Other
Glycosylation- (b) (4) (product-related impurities)	PK/Efficacy	Cell culture; affected by bioreactor conditions.	Controlled by a consistent (b) (4) does not change on stability.	(b) (4)	A PMC will be given for the sponsor to validate the HILIC HPLC assay to assess glycans.
Host Cell Proteins	Process-related impurity	Safety and Immunogenicity	Production cell line		HCP assay validation is (b) (4) (b) (4) A PMC will be given to address to validate a product-specific HCP method (Additional Comment #6 of CR letter).
Host Cell DNA	Process-related impurity	Safety and Immunogenicity	Production cell line		Adequate information was provided to support the Host Cell DNA method. (Additional Comment #6 of CR letter).
(b) (4) (Process-related impurity)	Process-related impurity	Safety and Immunogenicity	(b) (4)		(b) (4)

				(b) (4)	information was provided to support (b) (4)
(b) (4)	Process-related impurity	Safety	Cell Culture Media component		(b) (4) Adequate information was provided to support (b) (4)

○ Description

Teplizumab is a recombinant, humanized IgG1κ monoclonal antibody and consists of two heavy chains that are each composed of 449 amino acids and two light chains that are each composed of 213 amino acids. Each heavy chain contains an N-linked glycan site at asparagine 299 (Asn299). It is a humanized version of the mouse monoclonal antibody OKT3 with additional leucine to alanine mutations at positions HC 234 and 235. The Ala-Ala ("LALA") mutations reduce binding to complement and FcγR that can result in T cell activation and cytokine release syndrome. The molecular weight of (b) (4) teplizumab is (b) (4) Da.

(b) (4)
(b) (4) A request to experimentally determine the teplizumab extinction coefficient was requested in Additional Item #3 of the CR letter.
(b) (4)

○ Mechanism of action

Teplizumab binds to CD3ε and signals through the T cell receptor complex. It is thought that this signal in the absence of co-stimulatory signals or Fc receptor engagement results in weak agonistic activity. This, in turn, results in the expansion in the number and function of regulatory T cells while simultaneously reducing the function of effector CD4+ and CD8+ T cells through multiple mechanisms, ultimately resulting in diminished autoimmunity and increased beta cell survival.

○ Potency Assay

A cell-based bioassay that measures the NFAT-dependent signaling downstream of CD3ε binding by teplizumab is used to control DS and DP potency. Teplizumab is serially diluted in order to generate a standard curve and the samples are incubated with genetically engineered Jurkat T-cells expressing an NFAT response element-driven

luciferase reporter. The amount of luciferase generated is measured using a chemiluminescent substrate and the inhibition is proportional to T cell signaling. Dose-response curves are analyzed, and the potency of test articles is calculated as a percentage relative to the reference standard (RS).

○ Reference Standard(s)

(b) (4)



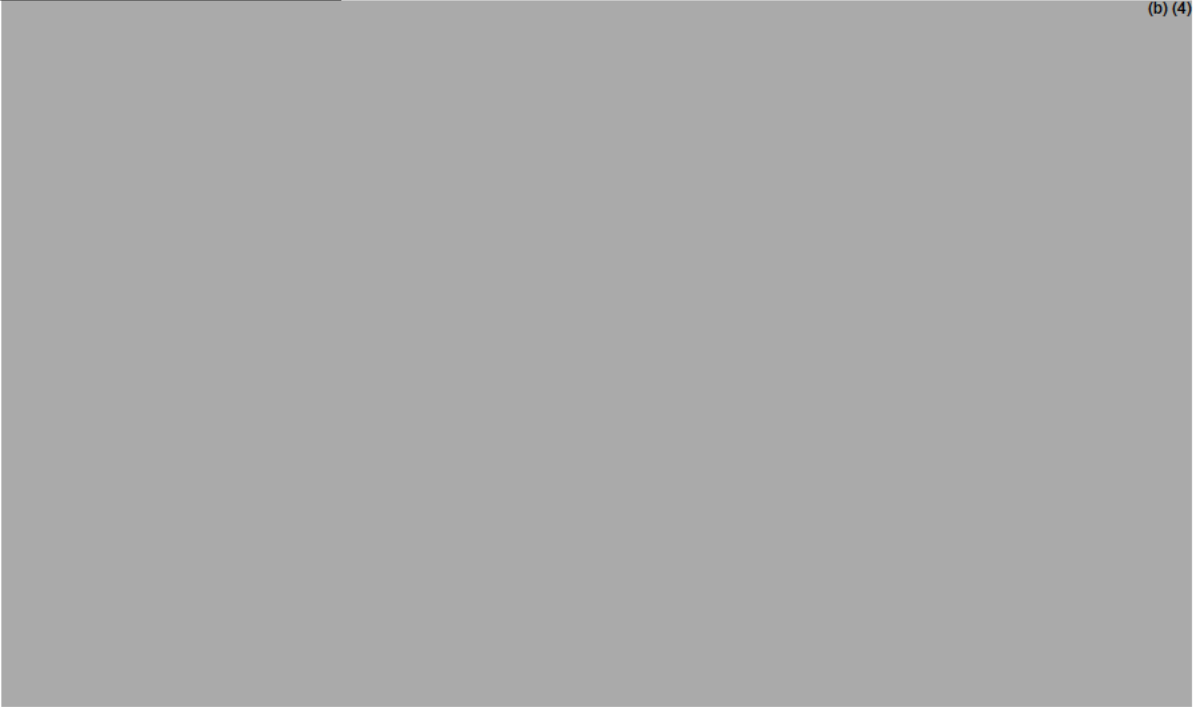
○ Critical starting materials or intermediates

(b) (4)



○ Manufacturing process summary

(b) (4)



(b) (4)

○ Container closure

The DS is stored in (b) (4). The container closure system is suitable for teplizumab, based on stability data.

○ Dating period and storage conditions

The DS will be stored at (b) (4) for (b) (4). The deficiencies with the CEX assay that hindered the ability to set shelf life from CR comment #2 have been addressed.

C. Drug Product Tzield 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

Category	Type	Risk	Introduction	Control Strategy	Other
Container closure	Process related impurities	Negative impact of leachables on product quality. Introduction of container related impurities (e.g. (b) (4))	Filling/storage	(b) (4)	Adequate data was provided in the resubmission for the leachable assessment (CR item #5)
(b) (4)	Safety and Efficacy (b) (4)		Raw material sources, manufacturing process		Method validation was provided for an in-process method (b) (4)

○ Potency and Strength

Teplizumab is supplied at 1 mg/mL in 2.0 mg/2.0 mL vials. Potency is defined as the percent activity relative to the current teplizumab RS. The potency assay is the same as described in the DS section of this memo. A CD3 binding assay is also used for DP release testing as a supplemental assay to support potency.

○ Summary of Product Design

Teplizumab is supplied as a sterile, single-dose, preservative-free solution in a type (b) (4) glass vial for intravenous infusion. Teplizumab DP (b) (4) sodium phosphate, (b) (4) sodium chloride, and 0.05 mg/mL polysorbate 80 at pH 6.1. The extractable volume is 2.0 mL.

- List of Excipients

Excipients include sodium phosphate (dibasic, (b) (4) monobasic, (b) (4)), sodium chloride, and polysorbate 80. All excipients are compendial.

- Reference material(s)

(b) (4)

- Manufacturing process summary

(b) (4)

- Container closure

The primary container closure systems for teplizumab DP consists of 2 mL type (b) (4) glass vials (b) (4) with a (b) (4) rubber stoppers (b) (4) and aluminum with (b) (4) flip-off caps (b) (4).

- Dating period and storage conditions

The DP will be stored at $5 \pm 3^{\circ}\text{C}$ for 24 months. The deficiencies with the CEX assay that hindered the ability to set shelf life from CR comment #2 have been addressed.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations: None

F. Establishment Information:

Overall Recommendation:

DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacture, storage of DS and DP, release and stability testing of DS and DP	AGC Biologics (b) (4)	(b) (4)	Approved in the previous review cycle	N/A	Approve
Residual DNA testing of DS	(b) (4)	(b) (4)	Acceptable based on previous history	N/A	Approve
Testing and Characterization of the MCB and WCB; in vitro and in vivo Viral safety testing (MCB, WCB, and EOPC).			Acceptable based on previous history	N/A	Approve
In vivo assay for viral contaminants in (b) (4) (MCB); Mycoplasma testing (MCB); Mycoplasma testing (EOPC)			Acceptable based on previous history	N/A	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacture, release and stability testing of DP, (b) (4) testing	(b) (4)	(b) (4)	Acceptable based on previous history	N/A	Approve
Particulate testing and sterility testing of DP			Acceptable based on previous history	N/A	Approve
Labeling, packaging, storage, and distribution			Acceptable based on previous history	N/A	Approve

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy was provided for the (b) (4)

A pre-license inspection was conducted at the AGC Biologics (b) (4) proposed for

Teplizumab (MGAH22) DS manufacture on [REDACTED] (b) (4) and was recommended for approval during the previous review cycle.

A. Lifecycle Knowledge Management:

a. Drug Substance:

- i. Protocols approved:
 - 1. Primary Reference Standard Requalification Protocol
 - 2. Master Cell Bank and Working Cell Bank Requalification Protocol
 - 3. Post-Approval Stability Protocol
 - 4. [REDACTED] (b) (4)
- ii. Outstanding assessment issues/residual risk: None
- iii. Future inspection points to consider: Method validation exercises and execution of methods.

b. Drug Product

- i. Protocols approved:
 - 1. Post-Approval Stability Protocol
- ii. Outstanding assessment issues/residual risk: None
- iii. Future inspection points to consider: None

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

/s/

RACHEL L NOVAK
10/19/2022 02:00:36 PM

First Approval for Indication
Breakthrough Review, Priority Review

Recommendation: Complete Response

BLA 761183
First Assessment
May 14, 2021

Drug Name/Dosage Form	Tzield (teplizumab-mzwv)/ injection
Strength/Potency	2 mg/2.0 mL (1 mg/mL concentration)
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Delay of clinical type 1 diabetes in at-risk individuals
Applicant/Sponsor	Provention Bio, Inc.

Product Overview:

Teplizumab-mzwv is a humanized IgG1κ monoclonal antibody produced in CHO cells. Teplizumab is an agonist of cluster of differentiation 3 (CD3) on T lymphocytes and engages signaling through CD3ε- and NFAT-dependent signaling cascades downstream. The Fc portion of teplizumab is mutated to disallow binding of Fc receptors or complement. Teplizumab drug product is supplied as a sterile, single-dose, preservative-free solution for intravenous infusion in single-dose vials containing 2 mg/2.0 mL. Teplizumab is proposed for the delay of clinical type 1 diabetes in at-risk individuals.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Deborah Schmiel	DBRR I/OBP/OPQ
Drug Product	Meng-Jung Chiang	DBRR I/OBP/OPQ
Immunogenicity	Meng-Jung Chiang	DBRR I/OBP/OPQ
Labeling	Koung Lee	OBP/OPQ
Facilities and Microbiology, DS	Charles Yuan-Chia Kuo	DBM/OPMA/OPQ
Facilities and Microbiology, DP	Maria Gutierrez-Hoffman	DBM/OPMA/OPQ
Microbiology Team Lead	Maxwell Van Tassell	DBM/OPMA/OPQ
Facilities Team Lead	Zhong Li	DBM/OPMA/OPQ
Application Technical Lead	Jennifer Swisher	DBRR I/OBP/OPQ
Tertiary Reviewer for OBP	Rachel Novak	DBRR I/OBP/OPQ

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Elisabeth Hanan	DROCHEN/ORO/OND
Cross-disciplinary Team Lead	Mitra Rauschecker/ Justin Penzenstadler	DDLO/OCHE/OND
Medical Officer	Lauren Wood-Heickman	DDLO/OCHE/OND
Pharmacology/Toxicology	Dan Minck and Federica Basso (TL)	
Clinical Pharmacology	Harisudhan Thanukrishnan, Manoj Khurana (TL)	DCEP/OCP/OTS

	Katarzyna Drozda, Christian Grimstein (TL) Elyes Dahmane, Justin Earp (TL)	DTPM/OCP/OTS DPM/OCP/OTS
Statistics	Yu (Jade) Wang, Yun Wang (TL)	DBII/OB/OTS

1. Names:

- a. Proprietary Name: Tziold
- b. Trade Name: Tziold
- c. Non-Proprietary Name/USAN: teplizumab
- d. CAS Registry Number: 876387-05-2
- e. Common names: hOKT3γ1 (Ala-Ala), PRV-031, A78, MGA031, LY2801777
- f. INN Name: teplizumab
- g. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P07766 (CD3E_HUMAN) [PRV031]

Submissions Assessed:

Submission(s) Assessed	Document Date
761183 Original BLA submission	11/2/2020
761183/9 (30-day Rolling CMC data)	12/1/2020
761183/13 (Response to IR#1)	12/18/2020
761183/14 (Response to IR#2)	12/23/2020
761183/15 (DS PPQ reports)	1/4/2021
761183/20 (Response to IR#3)	1/22/2021
761183/23 (Changes made to Module 3)	1/29/2021
761183/25 (Changes made to Module 3)	2/24/2021
761183/29 (Response to IR#4)	3/8/2021
761183/34 (Response to IR#5)	3/18/2021
761183/38 (Rolling CMC data)	3/29/2021
761183/39 (Response to IR#6)	3/31/2021
761183/40 (Response to IR#7)	3/31/2021

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)	(b) (4)	3	N/A		
	III			3	N/A		
	III			3	N/A		
	III			3	N/A		
	V	AGC Biologics	Drug substance manufacturing (b) (4)	3	N/A		
	V	(b) (4)		3	N/A		

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

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

B. Other documents: none

3. Consults: none

4. Environmental Assessment of Claim of Categorical Exclusion:

In accordance with 21 CFR 25.31(c), Provention Bio, Inc. claimed a categorical exclusion from the requirement described by 21 CFR 25.20 to prepare an environmental assessment, as this biologic product is comprised of substances that occur naturally in the environment. No extraordinary circumstances exist as described in 21 CFR 25.21 that would result in significant environmental impact from the discharge of this substance. This is acceptable.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality, CDER, has completed assessment of STN 761183 for Tzield manufactured by Provention Bio, Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Tzield is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. From a CMC standpoint, OBP is recommending a Complete Response letter be issued to Provention Bio, Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

Additionally, this application cannot be approved during this review cycle due to facility deficiencies. As of (b) (4), there is a pOAI alert for (b) (4) proposed for Teplizumab (PRV-031) DP manufacture. During an ongoing inspection of the manufacturing facility, deficiencies were conveyed to the representatives of the facility by investigators from FDA. Satisfactory resolution of the observations is required before this BLA may be approved. OPQ is recommending a withhold status, which will be communicated in the Complete Response letter to Provention to outline the deficiencies noted below.

B. Summary of Complete Response (CR) Issues:

1. Results of your ongoing real-time stability studies demonstrate unacceptable charge variation measured in teplizumab drug substance manufactured at AGC Biologics and the resulting drug product under recommended storage conditions. For instance, (b) (4)

(b) (4)

In total, these data preclude the ability to assign a shelf-life for either drug substance or drug product, not only because of the unacceptable degree of change, but also because stability behavior is not consistent between drug product lots manufactured using AGC material. This degree of change also prevents a determination as to whether there is a problem with product stability, the method, or both. Finally, the possibility that this variation arises from method variability also

introduces uncertainty into the reliability of all results generated with this method, including the analytical comparability assessment, highlighted by the difference in stability behavior between AGC lots and lots manufactured by Eli Lilly. To address these deficiencies:

- a. Provide data and information regarding the source of the variability of the teplizumab drug product and drug substance charge profile on stability as measured by the CEX-HPLC assay.
 - b. Address and remediate the source of the charge variation of teplizumab manufactured at AGC.
 - c. Address the differences in teplizumab stability behavior between clinical material manufactured at Eli Lilly and proposed commercial material manufactured at AGC Biologics.
 - d. If changes are made to the CEX-HPLC assay as a result of the investigation, provide data and information to support that these changes to the CEX-HPLC assay do not impact the data to support this application. This should include but not be limited to batch release data, stability data, in-process testing, process characterization studies, and the comparability assessment between clinical material manufactured at Eli Lilly and proposed commercial material manufactured at AGC Biologics.
2. No information was provided in Section 3.2.S.2.3 regarding your plans to monitor Master Cell Bank (MCB) and Working Cell Bank (WCB) stability. To correct this deficiency, provide cell bank requalification protocols for the MCB and WCB to include, but not be limited to, the frequency of testing, a justification for this frequency, number of vials proposed to be tested at each testing timepoint, tests proposed/ parameters to be evaluated, and appropriately justified acceptance criteria.
 3. Your protocol provided in your IR response received on March 24, 2021 (SD#39) for requalification of the primary reference standard (PRS) is deficient. The requalification protocol should ensure that the PRS remains stable over time and remains suitable for its intended purpose. In order to accomplish this, address the following in your Complete Response submission:

(b) (4)

(b) (4)

4. Insufficient information was provided regarding the levels and types of leachates in teplizumab derived from its container closure and the risk to patients from any leachates that are potentially present in the drug product during its shelf life. To address this deficiency, provide sufficient data from a leachable study to evaluate the filled drug product container closure systems when stored inverted under the recommended conditions. Perform testing at regular intervals through the end of shelf-life to include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS).

Facility CR Comment:

5. During an ongoing inspection of the (b) (4) manufacturing facility, deficiencies were conveyed to the representatives of the facility by investigators from FDA. Satisfactory resolution of the observations is required before this BLA may be approved.

C. Summary of Non-CR Issues (provided by OBP and OPMA):

1. Determine the extinction coefficient for teplizumab experimentally in order to ensure that the concentration of teplizumab is determined correctly in release and stability testing.
2. In your submission received on March 29, 2021 (SD#38), you provided data to demonstrate that oxidation of (b) (4) affects teplizumab potency (Section 3.2.S.7.1, Table 19 and Figure 12). Because limited data were available to demonstrate that the gene reporter assay has adequate and consistent sensitivity to oxidation of (b) (4) in the complementarity determining region of teplizumab, an analytical method should be developed for release and stability testing of teplizumab drug substance and drug product that can accurately assess and (b) (4) with adequate acceptance criteria for these purposes. Provide the final method validation report, analyses, and justification to support the proposed acceptance criteria.
3. Perform and provide results of potency by CD3 binding assay using stressed teplizumab samples to demonstrate the stability-indicating capability of the assay.
4. Product-specific validation data were missing from the validation reports of multiple methods to control process-related impurities in the teplizumab drug substance manufacturing process. For methods to quantify host-cell protein, host-cell DNA, (b) (4) and (b) (4) perform product-specific validation to demonstrate acceptable accuracy, repeatability, intermediate precision, specificity, quantitation limit, linearity, and range of each method for its intended purpose. Provide the corresponding validation reports, data, and analyses.

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(b) (4)

D. Benefit/Risk Considerations:

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

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy	Other
Oxidation	Efficacy and Safety/Immunogenicity	Manufacturing process and exposure to heat stress	(b) (4)	Additional item #2 for the CR letter to add method for (b) (4)
High molecular weight species/aggregates (product related impurities)	Safety/Immunogenicity, Efficacy, and potentially PK	Manufacturing process and exposure to heat stress. Minimal change is expected during		n/a

		storage through expiry.	(b) (4)	
Fragments (product related impurities)	Immunogenicity, reduced activity (b) (4) DP failure	Manufacturing process and exposure to heat and potentially extreme light stress. Minimal change is expected during storage through expiry.		n/a
Acidic variants (product related impurities)	Loss of potency, potential immunogenicity	Fermentation, in-process and on stability		CEX-HPLC data demonstrates unacceptable variability; CR issue #1
Basic variants (product related impurities)	Potential loss of potency, immunogenicity	Fermentation, in-process and on stability		CEX-HPLC data demonstrates unacceptable variability; CR issue #1
Potency	Efficacy	Intrinsic to the molecule. Impacted by oxidation, fragmentation, and aggregation. Minimal change is expected during storage through expiry.		Fc is mutated to prevent antibody effector functions through FcR or complement binding
Identity	Safety and Efficacy	Intrinsic to the molecule		n/a

B. Drug Substance Teplizumab Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

The following table presents CQAs derived from the drug substance manufacturing process and general drug substance attributes, as well as control strategies in place. Residual risks are addressed through Complete Response comments as well as Additional Comments to be communicated in the Complete Response Letter (refer to Sections I.B and I.C of this review, above).

Table 2: Drug Substance Process Risk Identification and Lifecycle Knowledge Management¹

Category	Type	Risk	Introduction	Control Strategy	Other
Host Cell Proteins	Process-related impurity	Safety and Immunogenicity	Production cell line	(b) (4)	HCP assay validation is (b) (4) Additional item #4 addresses product-specific validation of this method.
Host Cell DNA	Process-related impurity	Safety and Immunogenicity	Production cell line		HCD assay validation is (b) (4) Additional item #4 addresses further product-specific validation of this method.
(b) (4) (Process-related impurity)	Process-related impurity	Safety and Immunogenicity	Leaching from (b) (4)		(b) (4) assay validation is (b) (4)

¹ Control strategies for standard CQAs for which there are no unexpected risks are as follows: (b) (4)

(b) (4)

				(b) (4)	(b) (4)
Leachables	Process-related impurity	Safety	Process-contact surfaces		Additional item #4 addresses further product-specific validation of this method.
Viruses	Contaminant	Safety	Contamination during manufacture, most likely during cell culture operations		Complete Response item #4 for DP leachable study; this study would be expected to identify/capture any leachables from DS and DP processes.
					n/a

- **Description**

Teplizumab is a recombinant, humanized IgG1κ monoclonal antibody and consists of two heavy chains that are each composed of 449 amino acids and two light chains that are each composed of 213 amino acids. Each heavy chain contains an N-linked glycan site at asparagine 299 (Asn299). It is a humanized version of the mouse monoclonal antibody OKT3 with additional leucine to alanine mutations at positions HC 234 and 235. The Ala-Ala ("LALA") mutations reduce binding to complement and FcγR that can result in T cell activation and cytokine release syndrome. The molecular weight of deglycosylated teplizumab is 145,098 Da.

(b) (4)

A request to experimentally determine the teplizumab extinction coefficient is found in Additional Item #1, above, which will be incorporated into the CR letter.

- **Mechanism of action**

Teplizumab binds to CD3ε and signals through the T cell receptor complex. It is thought that this signal in the absence of co-stimulatory signals or Fc receptor engagement results in weak agonistic activity. This, in turn, results in the expansion in the number and function of regulatory T cells while simultaneously reducing the function of effector

CD4+ and CD8+ T cells through multiple mechanisms, ultimately resulting in diminished autoimmunity and increased beta cell survival.

- Potency Assay

A cell-based bioassay that measures the NFAT-dependent signaling downstream of CD3ε binding by teplizumab is used to control DS and DP potency. Teplizumab is serially diluted in order to generate a standard curve and the samples are incubated with genetically engineered Jurkat T-cells expressing an NFAT response element-driven luciferase reporter. The amount of luciferase generated is measured using a chemiluminescent substrate and the inhibition is proportional to T cell signaling. Dose-response curves are analyzed, and the potency of test articles is calculated as a percentage relative to the reference standard (RS).

- Reference Standard(s)

(b) (4)

- Critical starting materials or intermediates

(b) (4)

- Manufacturing process summary

(b) (4)



(b) (4)

- Container closure
The DS is stored in (b) (4)
(b) (4) The container closure system is suitable for
teplizumab, based on stability data.
- Dating period and storage conditions
Data precluded setting an expiry for DS due to unacceptable charge variation under
real-time storage conditions at (b) (4) Inconsistent fluctuations in
charge variation were also noted at (b) (4)
(b) (4) and under all conditions in the DP stability
program as well (see DP section below and CR item #1 under Section I.B.)

C. Drug Product Tzield 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

Category	Type	Risk	Introduction	Control Strategy	Other
Sterility	Contaminant	Safety, Purity, and Efficacy	Manufacturing process, failure of the container closure integrity	(b) (4)	Applicant committed to implementing (b) (4)
Endotoxin	Contaminant	Safety, Purity	Raw materials, manufacturing process		n/a

Appearance (color and turbidity of solution)	General	Safety and efficacy (product stability)	Formulation, contamination, or degradation	(b) (4)	n/a
Osmolarity	General	Product stability, patient discomfort	Formulation		n/a
pH	General	Product stability, DP failure	Formulation		n/a
Particulate matter	Product or process-related impurities	Immunogenicity, patient safety	Stability, manufacturing process, container closure system		n/a
Dose Uniformity	General	Inaccurate dosing	In-process		n/a
Container closure	Sterility assurance	Safety (sterility assurance)	Breach during manufacture or storage		CR item #4 requests leachable data
Extractable volume	General	Inaccurate dosing	Manufacturing process		n/a
(b) (4)	Safety and Efficacy (b) (4)		Raw material sources, manufacturing process		(b) (4) Additional Item #8

○ Potency and Strength

Teplizumab is supplied at 1 mg/mL in 2.0 mg/2.0 mL vials. Potency is defined as the percent activity relative to the current teplizumab RS. The potency assay is the same as described in the DS section above. A CD3 binding assay is also used for DP release testing as a supplemental assay to support potency. However, its validation did not cover the stability-indicating nature of the assay, as only unstressed samples were used. Additional validation is requested in Additional Item #3, above.

○ Summary of Product Design

Teplizumab is supplied as a sterile, single-dose, preservative-free solution in a type (b) (4) glass vial for intravenous infusion. Teplizumab DP (b) (4) sodium phosphate, (b) (4) sodium chloride, and 0.05 mg/mL polysorbate 80 at pH 6.1. The extractable volume is 2.0 mL.

○ List of Excipients

Excipients include sodium phosphate (dibasic, (b) (4) monobasic, (b) (4)), sodium chloride, and polysorbate 80. All excipients are compendial per USP.

- Reference material(s)

(b) (4)

- Manufacturing process summary

(b) (4)

- Container closure

The primary container closure systems for teplizumab DP consists of 2 mL type (b) (4) glass vials (b) (4) with a (b) (4) rubber stoppers (b) (4) and aluminum with (b) (4) flip-off caps (b) (4).

- Dating period and storage conditions

Data precluded setting an expiry for DP due to unacceptable charge variation under real-time conditions ($5 \pm 3^{\circ}\text{C}$ upright and inverted). Inconsistent fluctuations in charge variation were also observed in DP stored at $25 \pm 2^{\circ}\text{C}/60\% \text{ RH}$ upright, $40^{\circ}\text{C}/75\% \text{ RH}$ inverted, and under all conditions in DS stability program as well (see DS section above and CR item #1 under Section I.B.).

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations: Labeling review was not completed given that the BLA will receive a Complete Response letter.

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacture, storage of DS and DP, release and stability testing of DS and DP	AGC Biologics (b) (4)	(b) (4)	Pre-license inspection requested	WITHHOLD	Approve
(b) (4) testing of DS	(b) (4)		Acceptable based on previous history	N/A	Approve
Testing and Characterization of the MCB and WCB; in vitro and in vivo Viral safety testing (MCB, WCB, and EOPC).			Acceptable based on previous history	N/A	Approve
In vivo assay for viral contaminants in (b) (4)			Acceptable based on previous history	N/A	Approve
Mycoplasma testing (MCB); Mycoplasma testing (EOPC)					
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacture, release and stability testing of DP, (b) (4) testing	(b) (4)		Acceptable based on previous history	N/A	Withhold based on pOAI alert
Particulate testing and sterility testing of DP			Acceptable based on previous history	N/A	Approve
Labeling, packaging, storage, and distribution			Acceptable based on previous history	N/A	Approve

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for the AGC Biologics (FEI (b) (4)), proposed for Teplizumab (MGAH22) DS manufacture.

As of (b) (4), there is a (b) (4) alert for (b) (4) proposed for Teplizumab (MGAH22) DP manufacture. During an ongoing inspection of the manufacturing facility, deficiencies were conveyed to the representatives of the facility by investigators from FDA. Satisfactory resolution of the observations is required before this BLA may be approved.

H. Lifecycle Knowledge Management: Not Applicable

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/

JENNIFER F SWISHER
05/14/2021 03:59:28 PM

JENNIFER F SWISHER on behalf of RACHEL L NOVAK
05/14/2021 04:00:55 PM