

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761322Orig1s000

PRODUCT QUALITY REVIEW(S)



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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	August 11, 2023
Assessor:	Scott Dallas, RPh Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Milos Dokmanovic, PhD Product Quality Assessor OBP/Division of Biotechnology Review and Research 1
Application:	BLA 761322
Applicant:	Sandoz Inc.
Submission Date:	May 24, 2022
Product:	Tyruko (natalizumab-sztn)
Dosage form:	Injection
Strength and Container-Closure:	300 mg/15 mL (20 mg/mL) in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application seeking approval for a biosimilar product to the reference biologic product Tysabri® licensed under BLA 125104 for the same indications as for the reference product i.e. Multiple Sclerosis and Crohn's Disease.
Recommendations:	The prescribing information, medication guide, container label, 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 August 10, 2023, and container label, and carton labeling submitted on April 20, 2023, were assessed, and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Medication Guide (submitted on May 24, 2022)
<\\CDSESUB1\evsprod\bla761322\0001\m1\us\114-labeling\draft\labeling\pi-mg-clean.pdf>

(b) (4)

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

Comment/Recommendation:
 To applicant: Please include the dosage formulation, "injection" directly beneath the proper name, (natalizumab-xxxx). If additional space is required to include the dosage formulation, then delete the "Recommended Dosage: See prescribing information" statement.

Applicant's response: The applicant introduced the dosage formulation, injection, directly beneath the proper name, (natalizumab-xxxx).

OBPL assessment: The applicant's revision is acceptable.

April 20, 2023, submission: The applicant applied the conditionally acceptable nonproprietary name suffix "sztn" (i.e., natalizumabsztn) across all labeling.

OBPL assessment: The applicant's revision is acceptable.

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

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

	☐ No ☒ N/A

Comment/Recommendation:
 To applicant: Revise the phrase "Manufactured for:" to read "Manufactured by:". FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards".

Applicant's response: The applicant acknowledges the FDA's feedback on the correct phrasing of the "Manufactured by" statement in accordance with the 21 CFR 600.3(t) regulation.

OBPL assessment: The applicant's revision is acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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."

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

To applicant: Decrease the prominence of the "Rx Only" statement. Additionally, consider unbolding and relocating the "Rx Only" statement away from the critical information such as the upper right corner of the PDP or address this by other means.

Applicant's response: The applicant decreased the prominence of the "Rx Only" statement by unbolding the text and moving the statement to the upper right corner of the PDP.

OBPL assessment: The applicant's revision is acceptable.

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

Comment/Recommendation:

The container label is too small to include a Medication Guide statement, which is acceptable per 21 CFR 610.60(c).

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

Comment/Recommendation:

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

Comment/Recommendation:

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:

To applicant: Confirm there is no text on the ferrule and cap overseal of the vials.

Applicant's response: The applicant confirmed there is no text printed on the ferrule and cap overseal of the vials.

OBPL assessment: The applicant's response is acceptable.

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

Comment/Recommendation:

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

Applicant's response: The applicant confirmed the label does not cover the entire vial, neither in length nor in circumference. Therefore, the applicant is confident that an additional visual inspection would still be possible after attachment of the label.

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OBPL assessment: The applicant's response 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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

To applicant: Revise the phrase "One single-dose vial" to read "single-dose vial".

Applicant's Response: The applicant revised the statement as requested.

OBPL assessment: The applicant's revision is acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:
The container label is too small to include an inactive ingredient statement, which is acceptable per 21 CFR 610.60(c).

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

To applicant: Please include the dosage formulation, "injection" directly beneath the proper name, (natalizumab-xxxx).

Applicant's response: The applicant introduced the dosage formulation, injection, directly beneath the proper name, (natalizumab-xxxx).

OBPL assessment: The applicant's revision is acceptable.

April 20, 2023 submission: The applicant applied the conditionally acceptable nonproprietary name suffix "sztn" (i.e., natalizumabsztn) across all labeling.

OBPL assessment: The applicant's revision is acceptable.

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

Comment/Recommendation:

To applicant: Revise the phrase "Manufactured for:" to read "Manufactured by:". FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards".

Applicant's response: The applicant acknowledges the FDA's feedback on the correct phrasing of the "Manufactured by" statement in accordance with the 21 CFR 600.3(t) regulation.

OBPL assessment: The applicant's revision is acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation: This is a single-dose vial.

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

	☐ N/A

Comment/Recommendation: The labeling includes the statement "Contains no preservatives", which is the same statement as the reference product.

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

Comment/Recommendation: The number of containers is required if there are more than one container. In this case, the carton contains only 1 vial.

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

Comment/Recommendation:
 To applicant: Revise the product strength on the top panel to include the mg/mL strength, so the product strength appears as 300 mg/15 mL (20 mg/mL).

 Applicant's response: The applicant revised the product strength to appear as "300 mg/15 mL (20 mg/mL)".

 OBPL assessment: The applicant's revision is acceptable.

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

Comment/Recommendation:
 To applicant: Consider bolding and rephrasing the storage information to read:

Store vial refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze or shake.”

Applicant’s response: The applicant revised and bolded the storage and handling statements as requested.

OBPL assessment: The applicant’s revisions are acceptable.

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

Comment/Recommendation:

To applicant: Consider bolding and rephrasing the storage information to read:
Store vial refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze or shake.”

Applicant’s response: The applicant revised and bolded the storage and handling statements as requested.

OBPL assessment: The applicant’s revisions are acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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 applicant: Please revise the inactive ingredients "L-histidine" to read "histidine" and "L-histidine hydrochloride, monohydrate" to read "L-histidine hydrochloride monohydrate" (without the comma). The inactive ingredients should be presented with their USP/NF compendial name.

 Applicant's response: The applicant revised the inactive ingredients statement as requested.

 OBPL assessment: The applicant's revisions are acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:
 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 natalizumab products (i.e., there is no specific test method described in regulation for natalizumab 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 this product because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency

and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

Although this statement currently appears on the carton labeling of the reference product, Tysabri, this inclusion predated the Agency's renewed attention to the labeling requirement in § 610.61(r) as part of FDA's implementation of section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009. The absence of the statement for the current product should not be interpreted to mean that the Agency reached different conclusions about whether potency is a factor (within the meaning of § 610.61(r)) for the current product and its reference product.

To applicant: Remove the statement "No U.S. standard of potency" from the carton labeling. Although this statement appears on the carton labeling of the reference product, Tysabri, our current thinking is that 21 CFR 610.61(r) is not applicable, and thus no statement is required for your product's carton labeling.

Applicant's response: The applicant removed the labeling statement as requested.

OBPL assessment: The applicant's revision is acceptable.

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

Comment/Recommendation:

To applicant: Consider relocating the "Rx Only" statement to the upper right corner or to the bottom of PDP.

Applicant's response: The applicant relocated the "Rx Only" statement to the upper right corner of the PDP.

OBPL assessment: The applicant's revision is acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation: There are no misleading statements.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation: Need to revise the term "package insert" to read "prescribing information" in the "Recommended Dosage" statement. The term "prescribing information" is appropriate for labeling presented in the Physician Labeling Rule format.

To applicant: OBP and DMEPA agreed upon comment to the applicant reads: We recommend revising the statement, "Recommended Dosage: See package insert for dilution and administration directions" to "Recommended Dosage: See prescribing information."

Applicant's response: The applicant revised the statement of dosage as requested.

OBPL assessment: The applicant's revision is acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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:
The time in which the diluted solution must be administered after preparation was revised from ^{(b) (4)} to 4 hours.

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:

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:

To applicant: Include a "Protect from light" statement, because no data was submitted to support light exposure of the diluted solution for (b)(4) hours.

Applicant's Response: The applicant indicated that data were submitted in the Module 3.2.p.2.6 (eCTD 0001).

OBP's Response: Diluted solution is proposed to be stored for up to (b)(4) hours. However, Table 2, Section 3.2.P.2.6 states that diluted solution was exposed to visible light for only 4 hours during compatibility studies. Either clarify the experimental conditions of the compatibility studies and identify the specific location of the data in the BLA that support that the diluted solution does not need to be protected from light for (b)(4) hours, accept this edit that the diluted solution should be protected from light, or reduce the storage time of the diluted solution to 4 hours.

Applicant's Response: The applicant acknowledges the comment and would like to provide a clarification on the experimental conditions of the compatibility studies within the response document provided with this submission. If the explanation should not be acceptable to FDA, the applicant would prefer the third option proposed by FDA, i.e. reducing the storage time of the diluted drug product solution to 4 hours.

OBP Response: We do not find the justification acceptable. We agree with the option to remove the "protect from light" statement and require the diluted solution be administered within 4 hours of preparation.

Applicant's August 10, 2023, Response: The applicant accepted the revisions to remove the "protect from light" statement and to require the diluted solution be administered within 4 hours of preparation.

OBP Labeling: The applicant's revisions are acceptable.

Full Prescribing Information	
<u>3 DOSAGE FORMS AND STRENGTHS</u>	<u>Acceptable</u>
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:

Full Prescribing Information	
<u>11 DESCRIPTION</u>	<u>Acceptable</u>
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:

To applicant: The molecular weight (MW) was revised to display the glycosylated MW of 149 kDa. Please confirm that the glycosylated MW is 149 kDa.

To applicant: Revised to delete references to (b) (4)

To applicant: Please revise the inactive ingredients "L-histidine" to read "histidine" and "L-histidine hydrochloride, monohydrate" to read "L-histidine hydrochloride monohydrate". The inactive ingredients should be presented with their compendial name.

Applicant's response: The applicant accepted the revisions proposed by OBP labeling and confirmed the glycosylated MW is 149 kDa.

OBPL assessment: The applicant's responses and revisions are acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:
 To applicant: Revised to delete references to (b) (4)

 Applicant's response: The applicant deleted the references to (b) (4)

 OBPL assessment: The applicant's revisions are acceptable.

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

Comment/Recommendation:
 To applicant: Revise the phrase "Manufactured for:" to read "Manufactured by:". FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards".

Applicant's response: The applicant revised the qualifying phrase to read "Manufactured by" as requested.

OBPL assessment: The applicant's revision is acceptable.

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:

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

Comment/Recommendation: The medication is administered in a clinic, so storage and handling information is not needed.

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:
 To applicant: Please revise the inactive ingredients "L-histidine" to read "histidine" and "L-histidine hydrochloride, monohydrate" to read "L-histidine hydrochloride monohydrate". The inactive ingredients should be presented with their compendial name.

Applicant's response: The applicant revised the ingredient statement as requested.

OBPL assessment: The applicant's revisions are acceptable.

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

Comment/Recommendation:
 To applicant: Revise the phrase "Manufactured for:" to read "Manufactured by:".
 To applicant: Please include the US License number in association with the manufacturer information.

Applicant's response: The applicant revised the qualifying phrase to read "Manufactured by" and included the license number as requested.

OBPL assessment: The applicant's revisions are acceptable.

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information and Medication Guide (submitted on August 10, 2023)
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Scott
Dallas

Digitally signed by Scott Dallas
Date: 8/11/2023 02:29:57PM
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Milos
Dokmanovic

Digitally signed by Milos Dokmanovic
Date: 8/11/2023 02:34:04PM
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BLA Executive Summary

Assessment Date: June 12, 2023

1. Application/Product Information

BLA number	761322
Submission Type	Original Submission
Regulatory Pathway	351(k)
Associated IND/BLA	130966
Review Designation	Standard Review
Applicant	Sandoz, Inc.
Indication	Relapsing-remitting Multiple Sclerosis and Crohn's Disease
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name TYRUKO
	Non-proprietary Name/Code Name natalizumab-sztn
	OBP Naming Not applicable
Drug Product Description	PB006 is supplied as a 300mg/15.0mL solution formulated in 150 mM sodium chloride, 10mM L-Histidine, 0.02% polysorbate 80, at pH 5.7. PB006 is a recombinant humanized IgG4 kappa monoclonal antibody consisting of 2 heavy chains and 2 kappa light chains. PB006 targets the $\alpha 4$ subunit of leukocyte integrins $\alpha 4\beta 1$ and $\alpha 4\beta 7$.
Dosage Form	injection

Strength	300mg/15mL vial		
Route of Administration	Intravenous infusion		
Primary Container Closure System	(b) (4) glass vial with (b) (4) stopper, aluminum seal, and a flip-top cap		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Milos Dokmanovic	Riley Myers
	Drug product		
	Comparative Analytical Assessment		
	Immunogenicity Assay		
	Facility	Wendy Tan	Zhong Li
	Microbiology		Max Van Tassell
	RBPM	Anita Brown	
	ATL	Riley Myers	

2. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761322 for TYRUKO manufactured by Polpharma Biologics S.A. The data submitted in this application are adequate to support the conclusion that the manufacture of TYRUKO is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that TYRUKO is highly similar to US-licensed Tysabri, notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location

- **Drug Substance:** Polpharma Biologics S.A., (b) (4)
- **Drug Product:** (b) (4)

b. Fill size and dosage form: TYRUKO is supplied as a 300mg/15mL solution in a single dose vial

c. Dating Period

- **Drug Product:** 24 months at 5±3°C
- **Drug Substance:** (b) (4) months at (b) (4) °C
- **For packaged products:** Not packaged
- **Stability Option:**
 - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

d. Exempt from lot release

- Yes
- Rationale, if exempted: TYRUKO is exempted from lot release per FR 95-29960.

4. Basis for Recommendation

a. Summary:

PB006 is a proposed biosimilar to US-licensed Tysabri for the treatment of relapsing-remitting Multiple Sclerosis and Crohn's Disease. Extravasation of leukocytes into inflamed tissue is mediated by α4β1 and α4β7 interaction with vascular cell adhesion molecule 1 (VCAM-1) and mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1), respectively, which are expressed on endothelial cells. Natalizumab binds the α4 subunit, inhibiting cellular adhesion to VCAM-1 and MAdCAM-1 and subsequent transmigration, leading to reduced inflammation in the central nervous system for Multiple Sclerosis and gut mucosa for Crohn's Disease.

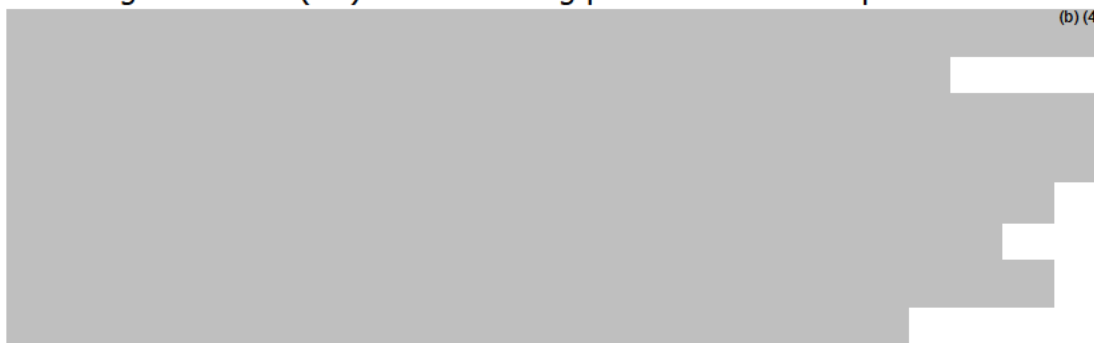
Potency of PB006 is controlled through two methods. The first is α4β1 binding by ELISA and the second is inhibition of interaction between VCAM-1 and α4β1 by ELISA. All potency results are reported as percentage relative to qualified reference material. A method was developed to evaluate inhibition of interaction between MAdCAM-1 and α4β7 by ELISA. However, the performance of both inhibition methods was comparable and given the in vivo mechanisms of action for both indications, the VCAM-1 inhibition method is sufficient for routine lot release and stability testing. Additionally, a cell-based VCAM-1 inhibition method was developed, but its performance was

comparable to the ELISA method, so it is not included in routine lot release and stability testing.

The totality of the comparative analytical evidence supports that PB006 is highly similar to US-licensed Tysabri, notwithstanding minor differences in clinically inactive components. The strength of 300 mg/15 mL PB006 in a single dose via demonstrated the same strength as that as that of US-licensed Tysabri. Refer to the Appendix for a summary of the comparative analytical assessment.

The drug substance (DS) manufacturing process consists of production at

(b) (4)



The overall PB006 control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for PB006 as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Polpharma Biologics S.A. (b) (4)

(b) (4) proposed for natalizumab-sztn DS and PB006 DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. The BLA is recommended for approval from a product quality, facility, microbiology and sterility assurance perspectives.

b. Subdiscipline Recommendation:

Drug Substance

- **Adequate**

Drug Product	-	Adequate
Comparative Analytical Assessment	-	Adequate
Immunogenicity Assay	-	Adequate
Facilities	-	Adequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
As an initial matter, we determined that no U.S. standard of potency has been prescribed for natalizumab (i.e., there is no specific test method described in regulation for natalizumab that establishes an official standard of potency). We next considered whether potency is a factor for natalizumab within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if “potency is a factor” and “no U.S. standard of potency has been prescribed.” We have determined that potency is not a factor for TYRUKO for purposes of § 610.61(r) because lot variability is not a concern for TYRUKO as TYRUKO’s manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:

1. Annual stability protocol and stability protocol for the extension of DS shelf-life
2. Stability/requalification protocol for reference materials
3. Stability/requalification protocol for Master and Working Cell Banks
4. Manufacture and qualification of new secondary reference standards
5. Concurrent (b) (4) validation protocols

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

- i. Protocols approved: Annual stability protocol and stability protocol for the extension of DP shelf-life

- ii. Residual risk: None
- iii. Future inspection points to consider: None

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

Appendix. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

To support a demonstration that PB006 is highly similar to US-licensed Tysabri and to establish the analytical component of the scientific bridge, Polpharma Biologics performed a comparative analytical assessment (CAA) using 17 lots of US-licensed Tysabri (300mg/15mL) with expiration dates ranging from November 2016 through April 2023, 38 lots of EU-approved Tysabri (300mg/15mL) with expiration dates ranging from August 2015 to August 2023, and 9 independent lots of PB006 DP with manufacture dates ranging from September 2017 to October 2020. The ages at the time of testing span the shelf-life of US-licensed Tysabri and were adequate to capture potential reference product differences over time. All PB006 lots included in the CAA and utilized in clinical studies were manufactured by the proposed commercial process. US-licensed Tysabri lots, EU-approved Tysabri lots, and PB006 lots used in the comparative clinical studies were also included in the CAA.

The CAA was comprised of an extensive comparative physicochemical and functional assessment of the quality attributes of PB006, US-licensed Tysabri, and EU-approved Tysabri and included a comparative stability study under long-term ($5\pm 3^{\circ}\text{C}$, inverted), accelerated ($25\pm 2^{\circ}\text{C}/60\pm 5\%\text{RH}$, inverted), and stress ($40\pm 2^{\circ}\text{C}/75\pm 5\%\text{RH}$, inverted) conditions through six months and a comparative assessment of their degradation profiles under several relevant forced degradation conditions including thermal stress (50°C for 28 days), oxidative stress (5% AAPH at 20°C for 48 hours), acid stress (pH 4.0 at 30°C for 21 days), photo (light) stress (526 W/m^2 UV-A light-hr + 1200 klux-hr visible light), freeze-thaw stress (5 cycles of -80°C for 22 hours followed by 20°C for 2 hours), and agitation (750 rpm at 20°C for 24 hours).

Polpharma used a risk-based approach for the statistical evaluation of the analytical results. Quality ranges for US-licensed Tysabri or EU-approved Tysabri were obtained by calculating the mean $\pm$ a standard deviation multiplier. High risk attributes, which are those directly related to the mechanism of action, utilized a standard deviation multiplier of 2.5. Moderate risk attributes, which are product variants not directly related to the mechanism of action or those attributes directly related to the mechanism of action in which orthogonal methods were included in the CAA, utilized a standard deviation multiplier of 3. Low risk attributes utilized a standard deviation multiplier of 4. Similarity and establishment of the analytical component of a scientific bridge for these high, moderate, and low risk attributes were demonstrated if $\geq 89\%$ of the PB006 lots and EU-approved Tysabri lots, respectively, were within the quality range. Quality attributes that were not amendable to statistical evaluation and/or with low criticality ranking were analyzed using side-by-side qualitative comparison.

Analytical methods used during the CAA were performed at the following testing sites:

- (b) (4)
- Polpharma Biologics AD
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

Results from method validation, qualification and verification studies were provided in the submission and adequately support the suitability of each method for its intended use during the CAA.

Polpharma is seeking licensure of 300mg/15mL PB006 single dose vial. Our assessment is that the CAA supports a demonstration that PB006 is highly similar to US-licensed Tysabri, notwithstanding minor differences in clinically inactive components, and establishment of the analytical component of the scientific bridge which justifies the relevance of data generated from studies using EU-approved Tysabri as the comparator to the assessment of biosimilarity. PB006 has the same strength, dosage form, and route of administration as US-licensed Tysabri. Polpharma used a comprehensive array of analytical methods that were suitable to evaluate the critical quality attributes of PB006, US-licensed Tysabri, and EU-approved Tysabri to support a demonstration that PB006 is highly similar to US-licensed Tysabri and to establish the analytical component of the scientific bridge. The number and type of lots tested and data analysis methods were appropriate to allow for a meaningful evaluation of the results of the CAA. While differences were observed in a limited number of attributes, these do not preclude a demonstration that PB006 is highly similar to US-licensed Tysabri.

B. Results of the Comparative Analytical Assessment

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?	Supports the Analytical Component of the Scientific Bridge?
Primary Structure	Molecular mass (intact and reduced deglycosylated mass)	Yes	Yes
	Amino acid sequence (Trypsin/Lys-C peptide digest)	Yes	Yes
	Amino acid sequence (Glu-C peptide digest)	Yes	Yes
	Amino acid sequence coverage	Yes	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?	Supports the Analytical Component of the Scientific Bridge?
Post-translational Modifications	Oxidation	Yes	Yes
	Deamidation	Yes	Yes
	Isoaspartic acid	Yes	Yes
	N-terminal variants	Yes	Yes
	C-terminal variants	Yes	Yes
	Sialylated N-glycans	Yes	Yes
	High mannose	Yes	Yes
	Galactose- α -1,3,-galactose	Yes	Yes
	Galactosylation	Yes	Yes
	Aglycosylation	Yes	Yes
	Free Thiol	Yes	Yes
	Glycation	Yes	Yes
	Site-specific glycans	Yes	Yes
Higher Order Structure	Secondary structure	Yes	Yes
	Tertiary structure	Yes	Yes
	Disulfide linkage analysis	Yes	Yes
	Fab arm exchange/half antibodies	Yes	Yes
Purity and Product-related Variants or Impurities	Charge heterogeneity	Yes	Yes
	Monomer/Dimers	Yes	Yes
	High molecular weight (HMW) species - Aggregation	Yes	Yes
	Low molecular weight (LMW) species - Fragmentation	Yes	Yes
	Hydrophobic variants	Yes	Yes
Bioactivity	Binding to α 4 β 1	Yes	Yes
	Binding to α 4 β 7	Yes	Yes
	Inhibition of interaction between VCAM-1 and α 4 β 1	Yes	Yes
	Inhibition of interaction between MAdCAM-1 and α 4 β 7	Yes	Yes
Fc-mediated Bioactivity	ADCC	Yes	Yes
	CDC	Yes	Yes
	C1q binding	Yes	Yes
	Fc γ RI binding	Yes	Yes
	Fc γ RIIa binding	Yes	Yes
	Fc γ RIIb binding	Yes	Yes
	Fc γ RIIIa binding	Yes	Yes
	Fc γ RIIIb binding	Yes	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?	Supports the Analytical Component of the Scientific Bridge?
	FcRn binding	Yes	Yes
Drug Product Attributes	Protein content	Yes	Yes
	Extractable volume	Yes	Yes
	Visible particles	Yes	Yes
	Subvisible particles	Yes	Yes

Comparative assessment of the forced degradation stability studies was performed to evaluate potential differences in the degradation profiles between PB006, US-licensed Tysabri, and EU-approved Tysabri lots under the conditions summarized above. Considering the data and justifications for the minor differences observed, the results do not preclude a demonstration that PB006 is highly similar to US-licensed Tysabri and support establishment of the analytical component of the scientific bridge.

C. Comparative Analytical Studies to Support the Use of a Non-US-Licensed Comparator Product

The comparative clinical study, PB006-03-01, supporting this application compared PB006 to EU-approved Tysabri. To support the relevance of these comparative clinical data to the assessment of biosimilarity, the applicant performed three-way pairwise analytical and PK comparisons between PB006, US-licensed Tysabri, and EU-approved Tysabri. The same analytical methods used for supporting a demonstration that PB006 is highly similar to US-licensed Tysabri were used for the pairwise analytical comparisons with EU-approved Tysabri. The minor differences observed in the analytical studies do not preclude the establishment of the analytical component of the scientific bridge. See section D below. The results support the establishment of the analytical component of the scientific bridge.

D. Assessment of Analytical Study Results

Comparative analytical assessment criteria were met for all attributes within the quality ranges with the following exceptions discussed in Table B below:

Table B: Resolution of Residual Uncertainties for Individual Critical Quality Attributes

Critical Quality Attributes with Differences	Related Critical Quality Attributes
Bioactivity	Binding to α4β7 : Six of 20 EU-approved Tysabri lots (range 91-111%) were outside the US-licensed Tysabri QR (94-106%). Only one of these EU-approved Tysabri lots was included in the comparative clinical study. Additionally, utilizing an orthogonal method (SPR), all

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	EU-approved Tysabri lots were within the US-licensed Tysabri QR. Therefore, the observed differences in $\alpha 4\beta 7$ binding do not preclude the establishment of the analytical component of the scientific bridge.
Post-translational Modifications	Free Thiol: All nine PB006 lots (range: 0.30-0.37 molSH/molAb) were outside the US-licensed Tysabri QR (0.07-0.21 molSH/molAb) and the EU-approved Tysabri QR (0.04-0.20 molSH/molAb). Higher concentrations of free thiol could lead to disulfide bond mispairing and molecule instability. However, no thioether bonds or incorrectly bound disulfide bonds were detected in PB006 by LC-ESI-MS, and data from all other methods that resolve higher order structure (e.g., FRIT, CD, Fluorescence spectroscopy, Fab arm exchange kinetics by FRET, reduced and non-reduced CE-SDS) support that PB006 is similar to US-licensed Tysabri in higher order structure. Finally, forced degradation studies and stability data also support that PB006 is similar to US-licensed Tysabri in degradation pathways and rates. Therefore, the observed differences in free thiol do not preclude a demonstration that PB006 is highly similar to US-licensed Tysabri and establishment of the analytical component of the scientific bridge. Deamidation: Two PB006 lots (range: 2.0-2.1% and 1.2-1.3%, respectively) were above the results for US-licensed Tysabri for HC N55 and HC N364 (range: <0.5-1.8% and <0.5-1.2%, respectively). HC N55 is in the CDR and deamidation of this residue could potentially impact product potency. However, data from all bioactivity assays support that these lots with up to 0.3% difference in deamidation do not have any difference in potency. HC N364 is not in the CDR and a 0.1% difference in deamidation would not be expected to impact product safety and PK. Therefore, the observed differences in deamidation of HC N55 and HC N364 do not preclude a demonstration that PB006 is highly similar to US-licensed Tysabri. Oxidation: The following PB006 and EU-approved Tysabri lots were above the results for US-licensed Tysabri for the following residues: HC Met255: all nine PB006 lots (range: 7.0-9.7%; US-licensed Tysabri range: 1.7-4.6%); HC W420/M431: seven PB006 lots (range: 0.9-2.0%; US-licensed Tysabri range: 0.5-1.0%) and three of 27 EU-approved Tysabri lots (range: $\leq 1.4\%$, US-licensed Tysabri range: 0.5-1.0%); HC M110/W113: four of 27 EU-approved Tysabri lots (range: $\leq 1.1\%$, US-licensed Tysabri range: $\leq 0.8\%$); LC M33/W35: eight of 27 EU-approved Tysabri lots (range: $\leq 0.8\%$, US-licensed Tysabri range: $\leq 0.5\%$);

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	HC M81: 10 of 27 EU-approved Tysabri lots (range: $\leq 1.2\%$, US-licensed Tysabri range: $\leq 0.9\%$); and HC M361: four of 27 EU-approved Tysabri lots (range: $\leq 2.0\%$, US-licensed Tysabri range: $\leq 1.5\%$). All residues other than HC M110/W113 and LC M33/W35 are not in the CDR and forced degradation studies support that up to 16% oxidation of these residues do not impact product bioactivity. Fc effector function is not a natalizumab mechanism of action, and published literature supports that up to 50% oxidation in HC Met 255 does not impact FcRn binding. As a result, these minor differences would not be expected to impact PK. Finally, although HC M110/W113 and LC M33 are in the CDR and oxidization of these residues could potentially impact binding, data from bioactivity assays support that there is no difference in potency despite a 0.3% difference in oxidation at these residues. Therefore, the observed differences in oxidation do not preclude a demonstration that PB006 is highly similar to US-licensed Tysabri and establishment of the analytical component of the scientific bridge. N-terminal signal peptide: The signal peptide was not detected in any PB006 lot. US-licensed Tysabri lots contained 3.1-5.7% signal peptide and EU-approved Tysabri lots contained 2.4-7.4% signal peptide; the QR approach was not utilized for this variant. Public literature (Kotia R.B. and Raghani R.R. <i>Analyt Biochem</i> 2010) and product characterization data support that the signal peptide does not impact product bioactivity. Therefore, the observed differences in the signal peptide do not preclude a demonstration that PB006 is highly similar to US-licensed Tysabri and establishment of the analytical component of the scientific bridge. C-terminal leucine amidation: Five PB006 lots (range: 0.6-0.8%) for C-terminal Leucine amidation ($\leq$LOQ [0.5%]) were above the results for US-licensed Tysabri (range: "not detected"). Five PB006 lots (range: 0.6-0.8%) were also above the results for EU-approved Tysabri (range: "not detected"). Public literature (Tsubaki M. et. al. <i>Inter J Bio Marcom</i> 2013 and Shah B. <i>J Pharma Sci</i> 2022) and product characterization data support that the C-terminal Leucine amidation does not impact product bioactivity. Therefore, the observed differences in C-terminal Leucine amidation do not preclude a demonstration that PB006 is highly similar to US-licensed Tysabri and establishment of the analytical component of the scientific bridge.
Glycosylation	Galactosylation: Eight PB006 lots (range: 44.23-47.11%) were outside the US-licensed Tysabri QR (20.5-43.1%). Increased galactosylation may increase C1q binding and CDC activity. However, this is not a natalizumab mechanism of action. Therefore, the observed differences in galactosylation do not preclude a demonstration that

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	PB006 is highly similar to US-licensed Tysabri and establishment of the analytical component of the scientific bridge. Sialylation: Five PB006 lots (range: 0.42-0.79%) were outside the US-licensed Tysabri QR (0.8-5.8%). While sialylation has a low potential to impact Fc effector functions, it has the potential to impact other antibody functional domains and could result in differences in bioactivity related to the Fab arm functionality. In addition, sialylated glycan levels may increase serum half-life. However, data from bioactivity assays supports that these minor differences do not impact PB006 and FcRn binding. Therefore, the observed differences in sialylation do not preclude a demonstration that PB006 is highly similar to US-licensed Tysabri and establishment of the analytical component of the scientific bridge.
Product-related variants	Charge heterogeneity: Three PB006 lots (range: 10-10.6%) were outside the US-licensed Tysabri QR (11.1-21.6%) for basic variants and four PB006 lots (range: 10-11.6%) were outside the EU-approved Tysabri QR (11.7-19.6%). As a result, two PB006 lots (range: 76.3-76.5%) were outside the US-licensed Tysabri QR (62.9-76.2%) for the main variant and three PB006 lots (range: 75.7-76.5%) were outside the EU-approved Tysabri QR (65.7-75.5%). Product characterization data support that these differences are likely due to the observed differences in N-terminal signal peptide between PB006 and US-licensed Tysabri, and that they do not impact product potency. Therefore, the observed differences in charge heterogeneity do not preclude a demonstration that PB006 is highly similar to US-licensed Tysabri and establishment of the analytical component of the scientific bridge. Hydrophobic variants: All nine PB006 lots (range: 6.5-8.5%) were outside the US-licensed Tysabri QR (0-1.7%) and the EU-approved Tysabri QR (0-1.9%). Product characterization data support that these differences are due the observed differences in C-terminal leucine amidation between PB006 and US-licensed Tysabri, which do not impact product bioactivity. Therefore, the observed differences in hydrophobic variants do not preclude a demonstration that PB006 is highly similar to US-licensed Tysabri and establishment of the analytical component of the scientific bridge.
Protein concentration	Three PB006 lots (range: 21.2-22.0 mg/mL) were outside the US-licensed Tysabri QR (18.4-21.0 mg/mL) and the EU-approved Tysabri QR (18-21.1 mg/mL). These three lots were manufactured early in development, prior to thorough process characterization. The setpoint for the control strategy was adjusted prior to Process Performance Qualification and all subsequent lots are within the US-licensed Tysabri QR. Therefore, the observed differences in protein concentration do not preclude a demonstration that PB006 is highly similar to US-licensed Tysabri and establishment of the analytical component of the

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	scientific bridge. It also does not preclude the conclusion that PB006 has the same strength as US-licensed Tysabri.

E. Same Strength

PB006 has the same dosage form and route of administration as US-licensed Tysabri. Polpharma is seeking licensure of 300mg/15mL single dose vial. US-licensed Tysabri is available at this strength and in this presentation. Comparative protein concentration (mg/mL) assessed as part of the comparative analytical assessment, and deliverable volume and fill weight data assessed as part of manufacturing process controls were used to inform the assessment of whether the strength of PB006 is the same as that of US-licensed Tysabri. Based on the comparative analytical assessment and manufacturing data, the 300mg/15mL PB006 single dose vial has the same total content of drug substance in units of mass in a container and the same concentration of drug substance in unit of mass per unit volume as that of US-licensed Tysabri.

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