CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761369Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: 8/26/2024

1. Application/Product Information

BLA number	761369
Submission Type	Original Submission
Regulatory Pathway	351(a)
Associated IND(s)/BLA	IND 126734
Review Designation	Standard
Applicant	Pfizer Inc.
Indication	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years of age and older with hemophilia A without factor VIII inhibitors or hemophilia B without factor IX inhibitors.
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary name: HYMPAVZI
	Established name: Marstacimab-hncq
	OBP systematic name: MAB HUMAN (IGG1) ANTI P10646 (TFPI1_HUMAN) [PF06741086]
Drug Product Description	Hympavzi is marketed in a pre-filled syringe (PFS) or pre-filled pen (PFP). Hympavzi drug product is a sterile, preservative-free solution supplied in a single-dose PFS or PFP for subcutaneous injection. Each PFS and PFP is designed to deliver a 1mL solution containing 150 mg/mL marstacimab formulated in 20mM histidine (1.12 mg/mL L-histidine and 2.67 mg/mL L-histidine monohydrochloride), 85 mg/mL sucrose, 0.05 mg/mL disodium edetate, and 0.2 mg/mL polysorbate 80, in water for injection, pH 5.8.

	Marstacimab is a human monoclonal IgG1 antibody directed against the Kunitz domain 2 (K2) of TFPI, the primary inhibitor of the extrinsic coagulation cascade. The IgG1 heavy chain has been mutated (L237A, L238A, G240A) to reduce effector functions		
Dosage Form	Injection		
Strength	150 mg/mL		
Route of Administration	subcutaneous		
Primary container closure system	pre-filled syringe (PFS) and pre-filled pen (PFP)		
Device Information	Prefilled Pen. The pen components consist of front subassembly, power pack subassembly, and syringe clip. The pen components are assembled together with the marstacimab PFS		
Co-packaged Product Information	N/A		
OPQ Review Team	Subdiscipline	Primary	Secondary
	Drug substance	Jee Chung	Chana Fuchs
	Drug product	Jee Chung	Chana Fuchs
	Immunogenicity Assay	Jee Chung	Chana Fuchs
	Facility	Liqun Zhao (DS) Wayne Siefert (DP)	Zhong Li
	Microbiology	Liqun Zhao (DS) Wayne Siefert (DP)	Maxwell Van Tassell
	OBP Labeling Reviewer	Vicky Borders-Hemphill	
	RBPM	Kristine Leahy	
	ATL	Chana Fuchs	
OPQ Issued Consults	CDRH - Janice Ferguson Strudy Mistry – TL		

2. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA STN 761369 for Hympavzi (Marstacimab-hncq) manufactured by Pfizer, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of

Hympavzi is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter
   a. Manufacturing Location:

      Drug Substance:
      - Wyeth BioPharma, Division of Wyeth Pharmaceuticals LLC, Andover, MA FEI#:1222181

      Drug Product:
      - Pfizer Manufacturing Belgium NV, Puurs-Sint-Amands, Belgium. FIE# 1000654629
        PFS and PFP Drug product manufacture, primary packaging, secondary packaging, and testing. Assembly of PFP, labeling testing secondary packaging.
      - (b) (4) Secondary packaging for PFS and AI

   b. Fill size and dosage form: 150 mg/mL single-dose prefilled syringe (PFS) and 150 mg/mL single-dose prefilled pen (PFP), injection.

   c. Dating Period:
      - Drug Product: Expiration dating period is 24 months for Hympavzi drug product PFS and PFP when stored at 2-8°C protected from light.

      - Drug Substance: Expiration dating period is (b) (4) months for Marstacimab drug substance when stored at (b) (4) °C.

      - For packaged products: Not packaged

      - Stability Option:
        Results of ongoing stability should be submitted throughout the dating period, as they become available.

        We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug product under 21 CFR 601.12

   d. Exempt from lot release:
      - Yes
      - Hympavzi is exempted from lot release per FR 95-29960 and 21 CFR 610.2(b).

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if applicable

None

4. Basis for Recommendation

a. Summary:

Marstacimab (PF-06741086) is a recombinant IgG1 lambda monoclonal antibody directed against Tissue Factor Pathway Inhibitor (TFPI), developed for treatment of hemophilia A and hemophilia B patients.

(b) (4)

The drug product, Marstacimab injection, is provided in either a prefilled syringe or a prefilled pen (an autoinjector) containing 150 mg/mL of marstacimab for subcutaneous injection. Each prefilled syringe and prefilled pen is designed to deliver a 1mL solution containing 150 mg/mL marstacimab formulated in 20mM histidine (1.12 mg/mL L-histidine and 2.67 mg/mL L-histidine monohydrochloride), 85 mg/mL sucrose, 0.05 mg/mL disodium edetate, and 0.2 mg/mL polysorbate 80, in water for injection, pH 5.8.

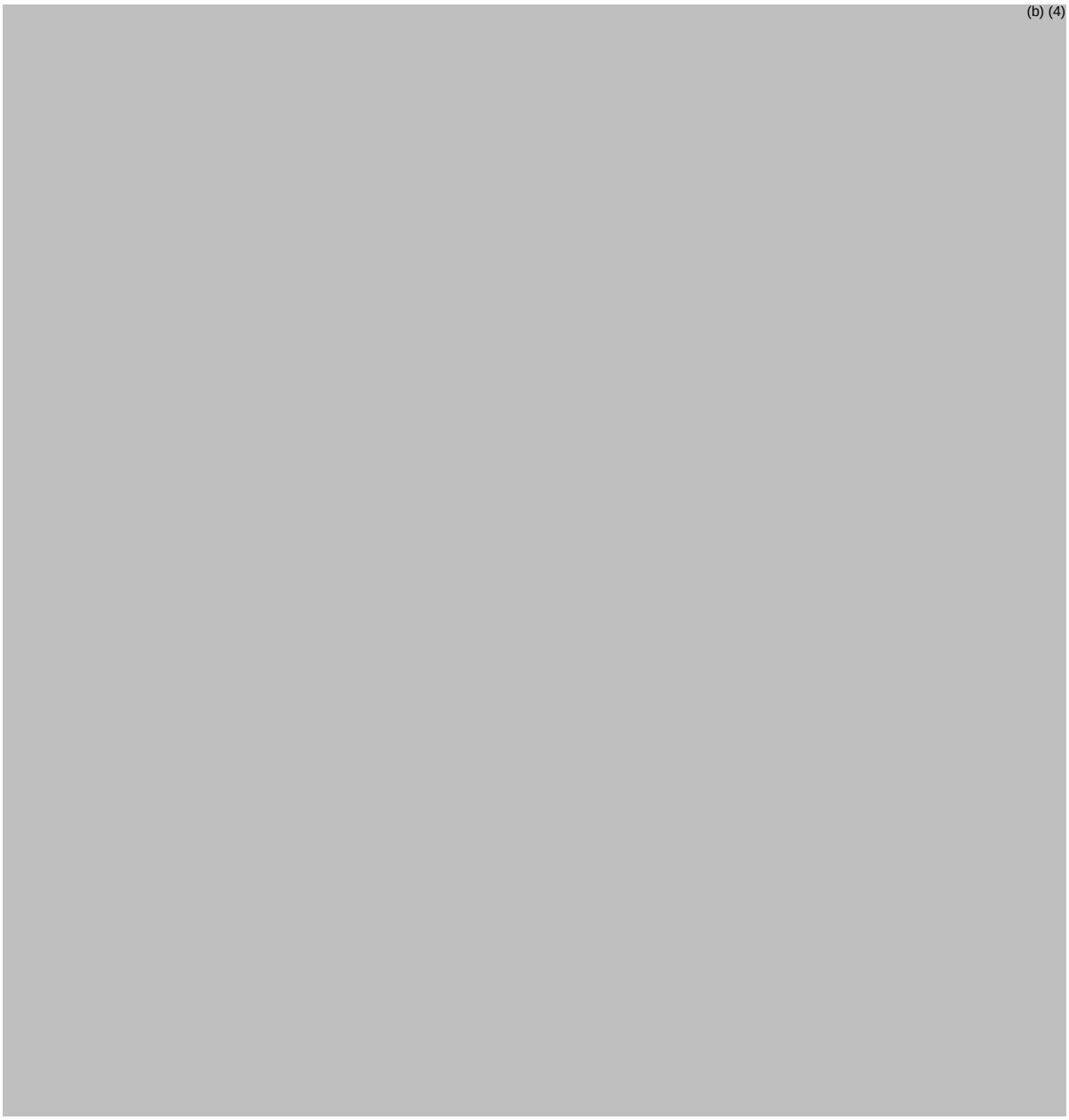
The Marstacimab mechanism of action is by binding specifically to TFPI, a multifunctional Kunitz-type serine protease inhibitor that acts at several steps of the blood coagulation cascade in the extrinsic coagulation pathway, primarily by inhibiting the initiation of coagulation, dampening procoagulant stimuli before thrombin is generated. When TFPI is present, it dampens activation of clotting through the extrinsic pathway. Marstacimab binding to TFPI prevents its inhibitory effect on the coagulation response allowing sufficient thrombin to be generated for hemostasis.

The potency assay used for drug substance and drug product release and stability testing is an in vitro colorimetric assay that measures the ability of marstacimab to bind to TFPI and inhibit complex formation with Factor Xa (FXa). Potency is defined as the percent activity relative to an in-house reference standard using an in vitro colorimetric assay that measures the ability of marstacimab to bind to TFPI and inhibit

complex formation with Factor Xa (FXa). Free FXa is detected using a chromogenic substrate, Spectrozyme FXa, measured at 405 nm.

The same two-tier reference standard program consisting of a primary (PRM) and working (WRM) reference materials is in use for testing of the drug substance and drug product. (b) (4) The current PRM will be used to qualify future working reference materials, and the WRM will be used to for routine release and stability testing. Protocols for requalification/stability of the PRM and WRM were provided in the BLA. The WRM stability will also be monitored by trending the results from routine testing. A protocol for qualification of a new WRM was also included in the BLA.

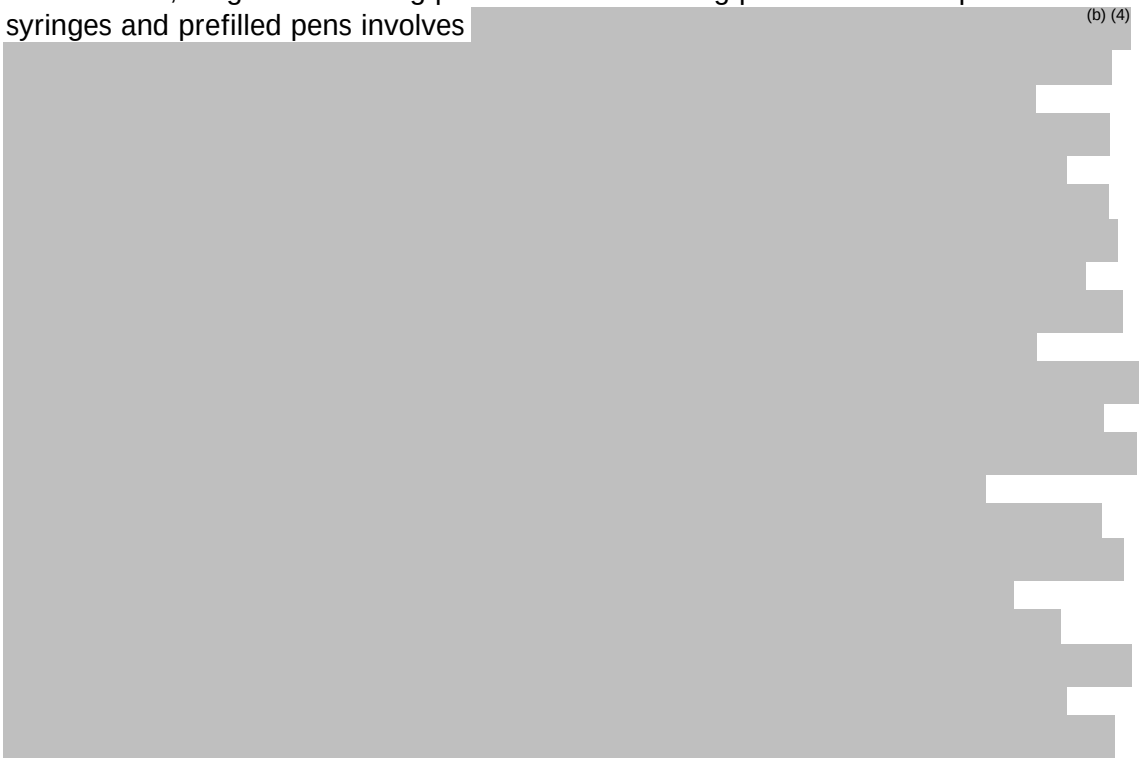
(b) (4)



(b) (4)

The Hympavzi drug product is manufactured at Pfizer Manufacturing Belgium NV, Puurs-Sint-Amands, Belgium. The drug product manufacturing process for both prefilled syringes and prefilled pens involves

(b) (4)



(b) (4)

Labeled and packaged drug product is tested for identity per 21 CFR 610.14
The overall marstacimab 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 marstacimab 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 assessment of manufacturing information provided in this application has concluded that the methodologies and processes used for the drug substance and drug product manufacturing, release, and stability testing are sufficiently robust and controlled to ensure the consistent manufacture of a safe, pure, and potent product.

The assays used for immunogenicity assessment in the clinical studies to support this BLA were found to be adequately validated and suitable for their intended purpose.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assay		Adequate
Facilities	-	Adequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):
A categorical exclusion is claimed by Applicant from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c) and is deemed acceptable.

d. Potency Assessment for Labeling:
Potency is not a factor.
As an initial matter, we determined that no U.S. standard of potency has been prescribed for Marstacimab-hncq (i.e., there is no specific test method described in regulation for Marstacimab-hncq that establishes an official standard of potency). We next considered whether potency is a factor for Marstacimab-hncq 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 Hympavzi for purposes of § 610.61(r) because lot variability is not a concern for Hympavzi as R Hympavzi’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:

- MCB and WCB stability protocol
- Qualification of New Working Cell Bank
- Concurrent validation protocol to establish the maximum number [redacted] (b) (4) at commercial scale
- Concurrent validation protocol to establish the maximum number [redacted] (b) (4) at commercial scale
- Primary and working reference standard stability protocols
- Qualification of new Working Reference Standard
- Drug Substance annual stability protocol
- [redacted] (b) (4) filtration
- [redacted] (b) (4) filtration
- Comparability Protocol for Introduction of New Products at [redacted] (b) (4)
- Comparability Protocols for two Alternative DS Containers

ii. Residual risk: None.

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:

- Drug product annual stability protocols for PFS and PFP
- Drug product stability protocol for extension of shelf life of the PFS and PFP.
- Comparability Protocol for Introduction of an additional assembly and labelling Line for Prefilled Pen at Pfizer Puurs in Belgium

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.

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/

CHANA FUCHS
09/26/2024 12:33:57 AM

LABELS AND LABELING ASSESSMENT

Date of Assessment:	September 18, 2024
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Jee Chung Reviewer, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XVI
Application:	BLA 761369
Applicant:	Pfizer, Inc.
Submission Date:	October 11, 2023
Product:	Hympavzi (marstacimab-hncq)
Dosage form(s):	injection
Strength and Container-Closure:	150 mg/mL in single-dose prefilled syringe or single-dose prefilled pen
Purpose of assessment:	The Applicant submitted a biologics license application Agency assessment
Recommendations:	The Prescribing Information and Patient Information (submitted on September 13, 2024), Instructions for Use (submitted on August 30, 2024), and container labels and carton labeling (submitted on July 3, 2024) were assessed and found to be acceptable from an OPQA III 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 Patient Information (submitted on September 13, 2024), Instructions for Use (submitted on August 30, 2024), and container labels and carton labeling (submitted on July 3, 2024) were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

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

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

Container[4] Label Evaluation

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

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

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

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	☐ Yes ☐ No ☒ N/A

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

Comment/Recommendation:
(b) (4)

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

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

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	☐ Yes ☐ No ☒ N/A

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

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

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

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

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

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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, FD&C Act section 502(e)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

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

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

Package[6] Labeling Evaluation

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

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

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

[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.

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

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

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

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: Revised the room temperature storage for readability to read as follows: "If needed, the syringe may be stored one-time at room temperature (up to 86ºF (30ºC) in the original carton to protect from light for up to 7 days. Once stored at room temperature, do not return to the refrigerator and discard after 7 days."
The Applicant revised similarly as requested

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

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

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

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

Comment/Recommendation: Revise the statement "Not made with natural rubber latex" to read as follows in bold print on the principal display panel: "Caution: The Rigid Needle Shield Contains Natural Rubber Latex Which May Cause Allergic Reactions." since the rigid needle shield contains dry natural rubber according to the DMF (b) (4) The term "natural rubber" includes natural rubber latex, dry natural rubber, and synthetic latex or synthetic rubber that contains natural rubber in its formulation.

Applicant's response: (b) (4)

Product Quality assessor determined that (b) (4) is free of latex as stated in the response. The statement "Not made with natural rubber latex" will be retained.

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

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: 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 marstacimab products (i.e., there is no specific test method described in regulation for marstacimab 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 Hympavzi 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.

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☐ Yes ☐ No ☒ N/A

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

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

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

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

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

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

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

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

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

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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

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

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv) *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components Draft Guidance *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry* (January 2023)	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices references: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Deleted (b) (4) as this is not required information for 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), FD&C Act Section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised to the pharmacological class from (b) (4) r" to read as "…is a tissue factor pathway inhibitor (TFPI)-antagonist…" *The Applicant revised as requested*

Revised from "…has a molecular mass of approximately (b) (4) kDa." to "approximately 146 kDa" (b) (4). *The Applicant accepted the proposed revision*

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

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

Comment/Recommendation: Deletion of the table is recommended to reduce redundancy. The strength presentation was relocated to the first paragraph and the NDC numbers were relocated to the respective paragraph below. *The Applicant accepted the proposed revision*

Deleted "Each prefilled syringe [pen] contains 1 mL solution for injection." since this is included in section 11 (Description). *The Applicant accepted the proposed revision*

Addition of "needle guard" terminology is recommended for clarity of pen feature. Applicant's response: *Applicant proposes to add "needle guard" terminology in the text under the subheading as shown because inclusion of Needle Guard in the subheading is inconsistent with the terminology (subheading) of the PFS (the nomenclature does not include presence of the rigid needle shield which is the syringe equivalent component) and is also inconsistent with other marketed PFPs which do not distinguish the presence of not of a needle guard in the dosage form itself or in the description, includin* (b) (4) *which has similar pen design*. OPQA III labeling has no objection to the applicant's proposal.

Revised the room temperature storage for readability to read as follows: "If needed, TRADENAME may be stored one time at room temperature [up to 86ºF (30ºC)] in its original carton to protect from light for up to 7 days. Once stored at room temperature, do not return to the refrigerator and discard after 7 days." *The Applicant accepted the proposed revision.*

Revised to provide that the rigid needle shield contains natural rubber latex according to the DMF (b) (4) *Applicant's response:* (b) (4) *Thus, Pfizer proposes to keep the original submitted content.*

Product Quality assessor determined that (b) (4) is free of latex as stated in the response. The statement "Not made with natural rubber latex" will be retained.

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Patient Information Labeling Evaluation

PATIENT INFORMATION LABELING	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

PATIENT INFORMATION LABELING	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for Patient Labeling: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised the room temperature storage for readability. Applicant's response: *Applicant proposes to revise* (b) (4) *to "at" here and in all instances describing the storage conditions in the PI, PPI and IFUs.* OPQA III labeling has no objection to the applicant's proposal

PATIENT INFORMATION LABELING	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

PATIENT INFORMATION LABELING	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ 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

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022*). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).*	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for IFU: Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022*). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised the room temperature storage for readability in the syringe and pen IFUs. Applicant's response: *Applicant proposes to revise* (b) (4) *to "at" here and in all instances describing the storage conditions in the PI, PPI and IFUs.* OPQA III labeling has no objection to the applicant's proposal

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

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022*).* *21 CFR 610.61 (add the US license number for consistency with the carton labeling),* *21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)*	✓ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

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

Prescribing Information (submitted on September 13, 2024 \\CDSESUB1\EVSPROD\bla761369\0054\m1\us\lab-1556-0-4-pkg-insert-clean.pdf)

Instructions for Use (submitted on August 30, 2024 \\CDSESUB1\EVSPROD\bla761369\0053\m1\us\lab-1577-0-2-pkg-insert-clean.pdf and \\CDSESUB1\EVSPROD\bla761369\0053\m1\us\lab-1576-0-2-pkg-insert-clean.pdf)

Patient Information (submitted on September 13, 2024 \\CDSESUB1\EVSPROD\bla761369\0054\m1\us\lab-1575-0-4-pkg-insert-clean.pdf)

3 Page(s) 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: 9/18/2024 08:43:10AM
GUID: 50814c7000007a3d59329f660d8ddf02

Jee Chung

Digitally signed by Jee Chung
Date: 9/18/2024 09:35:52AM
GUID: 508da6da000265c6b990d788ce889c0b