CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761369Orig1s000

OTHER REVIEW(S)

ICCR FACILITIES REVIEW MEMO

Date:	December 22, 2023
To:	Kristine Leahy, Sr. Reg. Health Manager, OPRO/DRBPM1/RBPMB1 Kristine.leahy@fda.hhs.gov Office of Combination Products at combination@fda.gov **RPM:** Kristine Leahy, Senior Health Project Manager
Through:	Shruti Mistry, Assistant Director, Injection Team, OHT#3, OPEQ, CDRH
From:	Janice Ferguson, RN, Injection Team, OHT#3, OPEQ, CDRH
Applicant:	Pfizer Belgium NV Rijksweg 12 Puurs-Sint-Amands 2870 Belgium FEI#1000654629
Application # **Consult #**	BLA761369 ICC#23001105
Product Name:	Marstacimab Solution for Injection PFP 150mg/mL
Combination Product Intended Use:	**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 or B without inhibitors,**
Pre-Approval Inspection:	**YES, POST APPROVAL INSPECTION**

The Office of Gastrorenal, OBGyn, General Hospital, and Human Factors at CDRH received a consult from CDER requesting the identification of the device manufacturing sites for BLA 761369 which will require a device inspection.

PRODUCT DESCRIPTION

Information found in Seq. 0001 3.2.P.1 [Description and Composition of Drug Product (Prefilled Pen)

Marstacimab Solution for injection is provided in a Prefilled Syringe (PFS) and a Prefilled Pen (PFP) presentation. This review focuses on the PFP.

Marstacimab Solution for Injection consists of a Marstacimab PFS 150 mg/mL, assembled with pen components to form the PFP. The PFP is designed with an integral sharp's injury prevention feature, by which the needle becomes permanently shielded by the needle guard, which locks out on withdrawal from the skin, preventing access to the needle, thereby preventing needle stick injury, and allowing for safe disposal of the PFP.

Table 3.2.P.1-1. Composition of the Marstacimab 150 mg/mL Prefilled Pen

Component	Material of Construction
Power Pack Subassembly Components	
Release ring	(b) (4)
Drive spring	
150 mg/mL end click bracket	
150 mg/mL plunger rod	
Power pack housing	
Bezel	
Spring guide rod	
Front Subassembly Components	
Cap	
Needle guard	
Needle guard spring	
Outer housing	
Rigid needle shield remover	
Rigid needle shield perforated bracket	
Syringe holder	
Activation legs	
Other Components	
Syringe clip	
150 mg/mL prefilled syringe (1 mL)	See Section 3.2.P.1 Description and Composition of the Drug Product (Prefilled Syringe)

(b) (4)

[redacted]

CONSULT REQUEST DETAILS

Regarding original BLA 761369 and the Pfizer Belgium facility for DP manufacture and pen assembly, Ms. Catherine J Laufmann from the dedicated device center performed a pre-approval inspection 06/05 - 08/2023 for injector pen assembly for BLA761184 Somatrogon (mod-4023) [c-terminal peptide (ctp)-modified ICC2001105. Additionally, coverage included a For Cause inspection assignment initiated by the Center for Devices and Radiological Health (CDRH) 02/01/2019 memo regarding an anonymous informant complaint, where CDRH identified “warning letter level” Quality deficiencies of device assembly and recommended consideration of a for-cause inspection at the inspected site. The inspection was classified VAI. Based on concerns around pen assembly, a facility consult is requested for BLA 761369 as to assure a follow up inspection is not required.

REGULATORY HISTORY

The following facility was identified as being involved in the manufacturing and/or development of the Marstacimab Injection BLA761369

1. **Pfizer Manufacturing**
   Belgium NV,
   Rijksweg 12
   Puurs-Sint-Amands 2870
   Belgium
   FEI# 1000654629

Responsibility –Assembly of prefilled pen, labeling, testing and secondary packaging.
The firm is responsible for the following Quality management responsibility activities:

- 21 CFR Part 210, 211, 600-680
- 21 CFR 4.4(b)
- 21 CFR 820.20 Management responsibilities
- 21 CFR 820.30 Design Controls
- 21 CFR 820.50 Purchasing Controls
- 21 CFR 820.100 Corrective and Preventive Action

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted 6/5/2023 to 6/8/2023. The inspection covered medical device QS/Medical Device "For Cause" and was classified as VAI.

Inspection Recommendation:
(1) An inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm revealed that there was not a response by the firm to the 483 observation that was issued during the inspection in June 2023. (SEE DISCUSSION BELOW)

The firm has been inspected < 2 years ago with a VAI decision. A 483 observation was issued for CAPA activities not adequately addressed. Per the EIR the sponsor had until 12/8/2023 to respond to the 483 deficiencies and it is unclear if the sponsor has responded. Per the Combination Product Quality System Review Work Instructions, if the sponsor has adequately responded to the 483-observation deficiency, then a pre-approval inspection would not be needed. If the response does not resolve the concerns raised in the previous VAI inspection (June 2023) then a post approval inspection would be recommended. I am unable to ascertain if the firm has responded to the 483 observation.

(2) An inspection is not required because:

- The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part;

(or)

- A recent medical device inspection of the firm was acceptable.

DISCUSSION:
The Pfizer Puurs facility had a preapproval inspection conducted 6/5-8/2023 for BLA761184 Somatrogan Injection PFP (b) (4) There was a MOCK device inspection that occurred 11/19-23/2018 and an anonymous informant complainant stated "if this had been an actual FDA device inspection, an automatic import detention of the (b) (4) combination product would have been the FDA/ORA Foreign Inspection Branch recommendation. For that reason, this inspection also covered a For Cause inspection initiated by CDRH 2/1/2019 regarding that

anonymous informant complaint, where CDRH identified “warning letter level” Quality deficiencies of device assembly and recommended consideration of a for-cause inspection at the inspected site.

It was noted during the inspection that Pfizer Puurs site conducts only package shipping validation and no other design verification testing as all design verification testing is conducted by (b) (4) manufacturer. Design validation testing and handling of complaints done by Pfizer US.

This facility consult included a review of the Establishment Inspection Report (EIR) and the Issued 483 document. The following documents found in OSAR were reviewed: Attachments 4 and 6 and Exhibits: 6, 11, 20, 24-25, 29, 33, 34-48, 54, 58-59, 105 and 109. Some of the Exhibits were provided to the FDA inspector late in her inspection and were not reviewed by her during the inspection. She noted several times in her EIR report that she deferred to CDRH and that review, and assessment of the additional reports would need to be done by CDRH, however I was unable to establish if the documents provided by Pfizer Puurs had been reviewed and if so, who the reviewer was or their recommendation to the adequacy of that information.

There was one (1) 483 observation issued for:

“Corrective and preventative action activities and/or results have not been adequately addressed.”

“Specifically, during review of CAPA 6586513 initiated as a result in trends identified with injector pen devices involving blockages and underfill complaints, it was noted not all activities were adequately documented for the investigations conducted”.

The investigator had concerns about the lack of documentation of all CAPA activities, specifically lack of potential root causes (for complaints of Blocked needles, leakage, underfill of the syringe/cartridge and too much air) which were crossed out as those identified in Design and Manufacturing without any test results or rationales as to why they were considered not relevant, was not adequate to meet regulations for implementing the procedures, and documenting all activities for the CAPA. It is unclear if the sponsor has provided the CAPA activity documentation in response to the 483 observation. It is noted that the responsible individual, (b) (4) understood the above observation and promised to make corrections and respond to CDRH by 12/08/2023. I am unable to establish if a response to the 483 was provided by Pfizer Puurs.

On a high level the following items were also discussed with management by the inspector after the issuance of the 483, which were not cited but involved deficiencies in activities conducted at Pfizer Puurs and activities conducted at other Pfizer facilities related to a MOCK FDA.

(b) (4)

(b) (4)

(b) (4)

Responsibility –Manufacturer of prefilled pen components and subassemblies

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted (b) (4) The inspection covered medical device QS and was classified NAI.
The firm does not manufacture finished medical devices. It is a contract manufacturer, and it distributes finished subassembly components to drug and medical device manufacturers for further processing into finished medical devices and drug delivery systems.

(or)
An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

Inspection Recommendation:
(1) An inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm has not been performed (or) revealed major deficiencies.

(2) An inspection is not required because:

- The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part;

(or)

- A recent medical device inspection of the firm was acceptable.

Janice Ferguson, RN

Shruti Mistry

Prepared: Janice Ferguson: December 22, 2023
Reviewed: Janice Ferguson: December 22, 2023

CTS No.: ICC2301098
BLA761369

Inspectional Assignment

CDRH recommends a post approval inspection under the applicable Medical Device Regulations of Pfizer, located in Puurs-Sint-Amands, Belgium (FEI 1000654629).

Firm to be inspected:

1. **Pfizer Manufacturing**
   Belgium NV,
   Rijksweg 12
   Puurs-Sint-Amands 2870
   Belgium
   FEI# 1000654629

A limited inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the Marstacimab Injection Pre-filled Pen BLA761369.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact
Janice Ferguson, RN Nurse Consultant
Injection Team
DHT3C
OHT#3: Office of Gastrorenal, OBGyn, General Hospital and Human Factors

Secondary Contacts (if Primary is unavailable and a timely answer is required)
Shruti Mistry, Assistant Director
Injection Team
DHT3C
OHT#3: Office of Gastrorenal, OBGyn, General Hospital and Human Factors

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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/

CARLEVEVA J THOMPSON
10/04/2024 03:44:21 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	5/23/2024		
To:	Kristine Leahy, OPQ RBPM		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	OPRO/DRBPM1/RBPMB1
From	Janice Ferguson, RN, BSN OPEQ/OHT3/DHT3C		
Through (Team)	Shruti Mistry, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA761369, Marstacimab injection ICC2301021 ICCR00955072		
Recommendation	**Filing Recommendation Date: 12/4/2023** ☐ CDRH did not provide a Filing Recommendation ☑ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☑ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: Click or tap to enter a date. ☐ Device Constituent Parts of the Combination Product are Approvable. ☑ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Janice L. Ferguson -S Digitally signed by Janice L. Ferguson -S Date: 2024.05.23 09:35:07 -04'00'	Shruti N. Mistry -S	2024.05.23 10:15:59 -04'00'

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA761369
Sponsor	Pfizer, Inc
Drug/Biologic	Marstacimab injection
Indications for Use	Routine prophylaxis to prevent or reduce the frequency of bleeding episode in adults and pediatric patients 12 years of age and older with: Hemophilia A (congenital factor VIII deficiency) without factor VII inhibitors, or Hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.
Device Constituent	Pen-Injector
Related Files	NA

Review Team	
Lead Device Reviewer	*Janice Ferguson, RN, BSN*

Important Dates	
Final Lead Device Review Memo Due	6/17/2024
Interim Due Dates	**Meeting/Due Date**
Filing	12/4/2023
74-Day Letter	NA
Mid-Cycle	3/5/2024
Primary Review	7/8/2024
Internal Meeting(s)	2/6/2024-OPQ

Text in *italics* comes directly from the submission.

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☑ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	No consultants
Clinical Validation	X			
Human Factors Validation			X	
Facilities & Quality Systems	X			Post approval inspection

2.1. Comments to the Review Team

☐ CDRH does not have any further comments to convey to the review team.

☑ CDRH has the following comments to convey to the review team:

Comment #1:
See below for Post-Market Commitment comments, which is already in the submission Seq. 0001, that was discussed with CDER at a meeting on 5/15/2024 with Chana Fuchs and Jee Chung.

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☑
CDRH does not have Post-Market Commitments or Requirements	☐

Post-Market Commitment or Requirement:

In Seq. 0001 3.2.P.8.2 Pfizer has provided a Post-Approval Stability Protocol and Stability Commitment (b) (4) [redacted] Please ensure that data supporting a longer shelf-life for the PFP is reviewed by CDRH.

TABLE OF CONTENTS

3. PURPOSE/BACKGROUND

3.1. Scope

Pfizer, Inc is requesting approval of Marstacimab injection. The device constituent of the combination product is a Pen-Injector. Marstacimab injection 150 mg/mL is indicated for routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes in hemophilia A or hemophilia B. The treatment consists of one 300 mg loading dose (2 x 1 mL) followed by 150 mg once weekly administered as a subcutaneous (SC) injection. The drug/device will be primarily used at home and will be self-injected by patients 12 years and older or a caregiver. The proposed shelf-life is 24 months at 2-8° C.

Of note: Throughout the submission the sponsor refers to the device constituent as a "pen injector", however the injector manufacturer and CDRH considers this device to be an "autoinjector".

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

There is a prefilled pen presentation, so a CDRH consult will be needed for the BLA Review Cycle.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device performance Stability-device performance Essential Performance Requirements (EPR) Quality Assessment

This review will not cover the following review areas:

Compatibility of the drug product with the primary container closure Biocompatibility of the primary container closure, including needle (defer to CDER) Sterility of the primary container closure (defer to CDER) Human Factors (Defer to DMEPA)

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

None

3.2.1. Related Files

None

3.3. Indications for Use

Combination Product	Indications for Use
Marstacimab injection	Routine prophylaxis to prevent or reduce the frequency of bleeding episode in adults and pediatric patients 12 years of age and older with; hemophilia A (congenital factor VIII deficiency) without factor VII inhibitors, or hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.
Pen-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**

0001	1.14.1.2 Labeling 2.3.P Pharmaceutical Development 2.3.P.5 Control Strategy-control of DP 3.2.P.1 Description and Composition of DP 3.2.P.2 Manufacturing Process Development Product Development Design Verification Product Validation Risk Management 3.2.P.3 Manufacturers 3.2.P.3.2 Batch Formula 3.2.P.3.5 Process Validation-Manufacturing Process Process Validation-Shipping Validation Data 3.2.P.5.1 Specifications 3.2.P.5.2 Analytical Procedures-Functional Performance 3.2.P.5.3 Validation of Analytical Procedures 3.2.P.5.4 Batch Analysis 3.2.P.7 Container Closure Systems 3.2.P.8.1 Stability Summary and Conclusion 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment 3.2.P.8.3 Stability Data 3.2.R Regional Information-21 CFR 4.4(b) Description Trace Matrix for Marstacimab Prefilled Pen Human Factors Engineering Report PFP HFER Appendix 1 Human Factors Summative Biocompatibility Test report-Sensitization Biocompatibility Test Report-Irritation Biocompatibility Test Report-Cytotoxicity 5.3.5.2 B7841007 Interim 1 Sub study-Synopsis
0013	3.2.R HF Summative Testing
0018	1.11.1 Quality Information Amendment
0022	1.11.1 Quality Information Amendment Response to 13 February 2024 US Query QQR1-3 INX 100511702 INX 100361640 INX 100400334 INX 100409288 3.2.P.8.1 Stability Summary and Conclusion 3.2.P.8.3 Stability Data
0030	1.11.1 Quality Information Amendment Response to 29 March 2024 US Query QQR1 Response to 29 March 2024 US Query QQR2 3.2.P.8.1 Stability Summary and Conclusion 3.2.P.8.3 Stability Data
0033	1.14.1.1 Draft Labeling

4. DEVICE DESCRIPTION

4.1. Device Description

Marstacimab 150 mg/mL pen is a single-dose, disposable prefilled pen (PFP) for subcutaneous injection.

The drug product is contained in a 1 mL glass prefilled syringe with a 27-gauge ½ inch staked needle. The pen needle guard functions as a sharps injury prevention feature by locking the needle guard after the injection thus disabling the pen and preventing access to the needle.

The pen system is provided by (b) (4) and is designated per ISO 11608-1:2014 as D1 injector, single dose, non-replaceable container where the entire deliverable volume of the pen is to be expelled.

(b) (4)

8 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments: The instructions are concise and easy to understand. **The device has been adequately described and steps for injecting the drug product with the PFP are provided.**		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review	☑
CDRH was not consulted prior to the Filing Date; therefore, CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist			
Description	**Present**		
	Yes	**No**	**N/A**
Description of Device Constituent	X		
Device Constituent Labeling	X		
Letters of Authorization			X
Essential Performance Requirements defined by the application Sponsor	X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor	X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor	X		

Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)			X
	Reliability			X
	Biocompatibility	X		
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors			X
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation			X
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment:
Additional information was requested at midcycle and was provided

5.2. Facilities Information

Firm Name:	**Pfizer, Inc.**
Address:	Belgium NV Rijksweg 12 Puurs-Sint-Amands 2870 Belgium
FEI:	#100654629
Responsibilities:	Assembly of prefilled pen, labeling, testing and secondary packaging. The firm is responsible for the following Quality management responsibility activities: • 21 CFR Part 210, 211, 600-680 • 21 CFR 4.4(b) • 21 CFR 820.20 Management responsibilities • 21 CFR 820.30 Design Controls • 21 CFR 820.50 Purchasing Controls • 21 CFR 820.100 Corrective and Preventive Action

The Pfizer Puurs facility had a preapproval inspection conducted 6/5-8/2023 for BLA761184 Somatrogan Injection PFP (b) (4) There was a MOCK device inspection that occurred 11/19-23/2018 and an anonymous informant complainant stated "if this had been an actual FDA device inspection, an automatic import detention of the (b) (4) combination product would have been the FDA/ORA Foreign Inspection Branch recommendation. For that reason, this inspection also covered a For Cause inspection initiated by CDRH 2/1/2019 regarding that anonymous informant complaint, where CDRH identified "warning letter level" Quality deficiencies of device assembly and recommended consideration of a for-cause inspection at the inspected site.

It was noted during the inspection that Pfizer Puurs site conducts only package shipping validation and no other design verification testing as all design verification testing is conducted by (b) (4) manufacturer. Design validation testing and handling of complaints done by Pfizer US.

This facility consult included a review of the Establishment Inspection Report (EIR) and the Issued 483 document. The following documents found in OSAR were reviewed: Attachments 4 and 6 and Exhibits: 6, 11, 20, 24-25, 29, 33, 34-48, 54, 58-59, 105 and 109. Some of the Exhibits were provided to the FDA inspector late in her inspection and were not reviewed by her during the inspection. She noted several times in her EIR report that she deferred to CDRH and that review, and assessment of the additional reports would need to be done by CDRH, however I was unable to establish if the documents provided by Pfizer Puurs had been reviewed and if so, who the reviewer was or their recommendation to the adequacy of that information.

There was one (1) 483 observation issued for:

"Corrective and preventative action activities and/or results have not been adequately addressed."
"Specifically, during review of CAPA 6586513 initiated as a result in trends identified with injector pen devices involving blockages and underfill complaints, it was noted not all activities were adequately documented for the investigations conducted".

The investigator had concerns about the lack of documentation of all CAPA activities, specifically lack of potential root causes (for complaints of Blocked needles, leakage, underfill of the syringe/cartridge and too much air) which were crossed out as those identified in Design and Manufacturing without any test results or rationales as to why they were considered not relevant, was not adequate to meet regulations for implementing the procedures, and documenting all activities for the CAPA. It is unclear if the sponsor has provided the CAPA activity documentation in response to the 483 observations. It is noted that the responsible individual, (b) (4) understood the above observation and promised to make corrections and respond to CDRH by 12/08/2023. I am unable to establish if a response to the 483 was provided by Pfizer Puurs.

On a high level the following items were also discussed with management by the inspector after the issuance of the 483, which were not cited but involved deficiencies in activities conducted at Pfizer Puurs and activities conducted at other Pfizer facilities related to a MOCK FDA.

(b) (4)

Inspection Recommendation:

☑ A post-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm revealed major deficiencies.

• The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, • A recent medical device inspection of the firm revealed that there was not a response by the firm to the 483 observation that was issued during the inspection in June 2023. (SEE DISCUSSION BELOW) The firm has been inspected < 2 years ago with a VAI decision. A 483 observation was issued for CAPA activities not adequately addressed. Per the EIR the sponsor had until 12/8/2023 to respond to the 483 deficiencies and it is unclear if the sponsor has responded. Per the Combination Product Quality System Review Work Instructions, if the sponsor has adequately responded to the 483-observation deficiency, then a pre-approval inspection would not be needed. If the response does not resolve the concerns raised in the previous VAI inspection (June 2023) then a post approval inspection would be recommended. I am unable to ascertain if the firm has responded to the 483 observation.

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	Manufacturer of prefilled pen components and subassemblies

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted (b) (4) The inspection covered medical device QS and was classified NAI.
The firm does not manufacture finished medical devices. It is a contract manufacturer, and it distributes finished subassembly components to drug and medical device manufacturers for further processing into finished medical devices and drug delivery systems.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.
☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product.

Inspection Recommendation:
☐ A choose an item inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm Choose an item.

☑ An inspection is not required because:
The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

5.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☑ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☑ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☐ No ☑ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☑ No ☐ UNK

Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☑ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☑ No ☐ UNK
cGMP Risk:	
☑ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment:
The DP is indicated as a prophylactic treatment. **The combination product is low risk.**

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION

Acceptable for Filing: ☑ Yes ☐ No (Convert to a RTF Memo) ☐ N/A

Facilities Inspection Recommendation:
☐ (PAI) Pre-Approval Inspection ☑ Post-Approval Inspection ☐ Routine Surveillance
☐ No Inspection ☐ N/A

Site(s) needing inspection:
Pfizer, Inc.
Belgium NV
Rijksweg 12
Puurs-Sint-Amands
2870 Belgium

Reviewer Comments
The need for a post-approval inspection was conveyed via facilities memo to CDER on 12/21/2023 with ICC2301098.

Refuse to File Deficiencies: ☐ Yes ☑ No ☐ N/A

74-Day Letter Deficiencies: ☐ Yes ☑ No ☐ N/A

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		

Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	X		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

(b) (4)

[redacted]

Reviewer Comments:
See section 4.2 for instructions for use/steps for using the PFP

6.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Device Storage conditions and removal from refrigerator 30 min prior to dosage	X		
Warnings/Precautions	X		
Side Effects	X		
Device and site preparation	X		
Injection of drug product to include holing needle in place for 5 seconds after hearing 2nd click	X		
Confirming that drug product was given	X		
Disposal of device in sharps	X		
Patient after care	X		

Reviewer Comments:
The instructions for use are adequate.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by:
☐ Insert Consultant Name ; The full memo is located in Appendix B.
☑ The Lead Reviewer
Below is a summary of the review & recommendation:

6.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments **The labeling is adequate from a device perspective.**		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g., FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Bioequivalence Study utilized to-be-marketed device	X		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e., emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments:
Risk assessment documents requested from sponsor and were provided in Seq. 0022 (See Section 7.6 below for details)

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
*Delivery Volume	≥ 1.0 mL
*Delivery Time	(b) (4)

*Needle Extension	(b) (4)
Needle guard force Activation Force (not identified as an EPR)	
Cap Removal Force (not identified as an EPR)	
Time between clicks (Audible/visual/tactile feedback) (not identified as an EPR)	

Reviewer Comments:
Design Inputs and Output identified and are adequate.

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	**Y**
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	**Y**
IEC 60601-1-2:2014	**NA**
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	**Y**
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	**NA**
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	**Y**
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	**Y**
Applying Human Factors and Usability Engineering to Medical Devices ANSI/AAMI HE75:2009(R)2018 Human Factors Engineering-Design of Medical Devices	**Y**

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 11608-1:2014 Needle Based Injection Systems for Medical Use-Requirements and Test Methods Part-1	**Y**	
ISO 11608-5:2012 Needle Based Injection Systems for Medical Use-Automated Functions	**Y**	
ISO 23908:2011 Sharps Injury Protection-Requirements and Test Methods-Sharps Protection Features for Single-Use Hypodermic Needles, Introducers for Catheters and Needles Used for Blood Sampling	**Y**	

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A

Reviewer Comments:
Design inputs/outputs identified along with Standards utilized.
Risk assessment documents not included in the submission and were requested.**[Midcycle Deficiency #1]** the requested Risk assessment documents were provided. (see below Section 7.5/7.6) **[Midcycle Deficiency #1 RESOLVED]**

CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No

7.5. Risk Management Plan

Pfizer states that they performed a risk analysis and determined that the overall risk is acceptable and that the benefits of using the product outweigh the risks. Potential hazards, hazardous situations and related harm(s) were identified using multiple tools including:

- Hazard analysis
- Design failure mode and effects analysis (dFMEA) (from (b) (4) the pen manufacturer0
- Use failure mode and effects analysis (uFMEA) (provided in the HF testing)
- Process failure mode and effects analysis (pFMEA)

Reviewer Comments:
dFMEA and pFMEA will be requested at midcycle. **[Midcycle Deficiency #1]** The sponsor provided the requested documents. **[Midcycle Deficiency #1 RESOLVED]**

7.6. Hazard Analysis and Risk Summary Report

Information found in Seq. 0001 3.2.R [Human Factors Engineering Report Table 14 & Seq.0013 3.2.R HF Summative test protocol]
Information found in Seq. 0022 1.11.1 Quality Information Amendment

1. **Product Risk Assessment Matrix-from** (b) (4)
   A Product Risk Assessment was provided from the pen manufacturer for the single dose injector with a 1.0 mL pre-filled syringe with rigid needle shield (RNS). Table was provided that listed the following:
   a. Functional Performance-main function/component involved.
   b. Identification of Risks-potential failure modes
   c. Current controls
   d. End user assessment-harm/severity of harm
   e. Risk evaluation-probability of occurrence
   f. Risk control-additional risk control measure/design manufacturing requirement
   g. Residual Risk Evaluation-probability of occurrence/harm
   h. Risk mitigation-verification document
   i. Additional hazard generated-if applicable add new risks

2. **Design dFMEA-**
   Pfizer provided a list of components under Pfizer's design authority, their functions, potential failure modes and effects, i.e., how does the primary container interface with the final assembled device and label.
   Table provided the following:
   a. Pre-Mitigation-potential failure mode/potential causes/hazardous situation/hazardous analysis & potential harm/severity of harm/probability of harm/occurrence/ PATIENT RISK LEVEL
   b. Post-Mitigation-risk control measure/verification of implementation of risk control measures & effectiveness/probability of hazard leading to hazardous situation/occurrence of harm/patient risk level. Criteria for risk acceptability been met/is risk acceptable.

3. **Process FMEA**
   Process pFMEA identified, evaluate and control risks associated with the process(es) used to manufacture Marstacimab PFP. Hazard Analysis list for the PFP and the risk of patient harm which can result from the identified failure modes.

4. **A UFMEA was provided as part of the Human Factors testing.**
   Critical Tasks, potential use error/harm and implemented risk control measures were identified.

Reviewer Comments :
Appropriate risks/hazards were identified in the documents provided in the submission and in the information requests. Risk occurrence and mitigation was included. Design, user, and process FMEAs were provided.
A UFMEA was provided in the Human Factors Engineering Report.
The hazard assessment is acceptable.

7.7. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Additional information will be requested regarding Risk Analysis. **[Midcycle Deficiency #1]** The sponsor has provided a Risk assessment from the pen manufacturer, an dFMEA and a pFMEA which evaluates the process for the final assembly, labeling and packaging of the pen. User FMEA was included in the Human Factors evaluation. **[Midcycle Deficiency #1 RESOLVED]**		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: **2/13/2024**	**Date/Sequence Received:** **2/27/2024**
Information Request #1 Question #1	In 3.2.P.2.4 you state that a risk analysis was performed using multiple tools including hazard analysis, design failure mode and effects analysis (dFMEA), use failure mode and effects analysis (uFMEA) and process failure mode and effects analysis (pFMEA). However, your dFMEA and your pFMEA could not be located for review. This information is required to assess the overall risk of the subject Prefilled Pen (PFP). Please provide the dFMEA and the pFMEA documents for review.	
Sponsor Response	The documentation is attached as requested. Three documents are included which encompass the design and process FMEA activities: • INX100511702 is [redacted (b) (4)] Product Risk Assessment Matrix (PRAM), which evaluates the PFP risks from the perspective of the design and manufacturing process of the PFP components. [redacted (b) (4)] is the platform name for the PFP enclosing the PFS, and [redacted (b) (4)] internal project name for the marstacimab PFP. • INX100361640 is Pfizer's dFMEA, which evaluates the primary container (prefilled syringe) interfaces to the final assembled PFP and label. • INX100400334 is Pfizer's pFMEA, which evaluates the process for final assembly, labeling and packaging of the PFP.	
Reviewer Comments	The sponsor provided the requested risk assessment document. Risks appropriate for this device type were identified and documented. **The response is acceptable.**	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

8. DESIGN VERIFICATION REVIEW

8.1. Performance/Engineering Verification

8.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Delivered Volume	≥ 1mL	Y	Y	Y	Y
Delivery Time	(b) (4)	Y	Y	Y	Y
Needle Extension		Y	Y	Y	Y
Cap Removal Torque (not identified as EPR)		Y	Y	Y	Y
Needle Guard Force-Activation force (not identified as EPR)		Y	Y	Y	Y
Time between clicks (not identified as EPR)		Y	Y	Y	Y
Needle Guard Override Deflection (not identified as EPR)		Y	Y	N	Y

Reviewer Comment:
The sponsor has only provided stability testing for 2 lots of PFP, in addition, the accelerated data at 6 months does not meet acceptance criteria.
[Midcycle Deficiency # 2] The proposed shelf-life for the PFP is 24 months. The sponsor has provided stability testing for 2 lots of the subject PFP under real time conditions for 36/12 months respectively. The accelerated aged testing did not meet the acceptance criteria for delivery time and delivery volume. **[Midcycle Deficiency #2 NOT RESOLVED]** A request for the additional stability data will be requested. **[IR #2 Q#1]** The sponsor has provided updated stability data for the subject PFP. Real time data for all EPRs was provided for 2 lots of PFP for 36m/24m respectively. **These data met were within the specifications to demonstrate the 24-month proposed shelf-life. [IR#2 Q#1 RESOLVED]**

8.1.2. Verification of Design Inputs Evaluation

Design Input	Design Output	Verification Method	Results/Deviations	Adequately Verified (Y/N)	Validated through Clinical, Human Factors or Other	Adequately Validated (Y/N)
Delivery Volume	≥ 1mL	Per ISO 11608-1:2014	≥ 1 mL	Y	HF & lot release	Y
Delivery Time	(b) (4)	Per ISO 11608-1:2014	5.9 seconds-8.4 seconds	Y	HF & lot release	Y
Needle Extension		Per ISO 11608-1:2014	LTL-5.4-5.6mm UTL-6.3-6.5 mm	Y	HF & Lot release, Batch testing	Y
Cap Removal Torque (not identified as EPR)		Per ISO 11608-1:2014	0.1 N*m-0.3 N*m	Y	HF & Batch analysis	Y
Needle Guard Force-Activation force (not identified as EPR)		Per ISO 11608-1:2014	9.2N-10.3 N	Y	HF& Batch Analysis	Y
Time between clicks (not identified as EPR)		Per ISO 11608-1:2014	4.0 seconds-7.9 seconds	Y	HF & Batch Analysis	Y
Needle Guard Override Deflection (not identified as EPR)		Per ISO 11608-1:2014	2.6mm-2.8 mm at 81N of force	Y	Batch Analysis	Y

Reviewer Comment
The device verification testing was done per ISO 11608-1:214 in all conditions for PFP categorized as D1.
The testing is acceptable.

PREFILLED PEN VERIFICATION TESTING

Information found in Seq. 0001 3.2.P.2 [Product Development PFP Feedback Features]

(b) (4)

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Reviewer Comment:
Homogeneity Testing was done on one lot of samples after labeling and packaging. Performance testing was conducted during lot run over multiple shifts. The test results compared devices from different timepoints in the run with historic test results from previous testing. Historic estimate of variability in calculations to establish upper and lower control limit acceptance criteria was used. The results demonstrated that samples taken from any timepoint could be representative of the entire lot. **Note: Device inspector commented during the site inspection done June 2023 that sampling of the device was only done at the end of the run only and not at different timepoints (beginning, middle, end of the run) during production. Device non-conformities could be observed if performance testing was done throughout the lot run.**

PERFORMANCE TESTING PER ISO 11608-1 & ISO 11608-5

Information found in Seq. 0001 3.2.P.2.4 [Design Verification (Prefilled Pen)]

Table 3.2.P.2.4-2. ISO 11608-1 Dose Accuracy Results for the Marstacimab 150 mg/mL Prefilled Pen

Requirement Description	Test Condition Requirement	Acceptance Criteria	Results
The pen shall be designed so that the labeled volume can be accurately delivered at the stated test condition requirement.	Cool atmosphere testing: preconditioning for at least 4 hours at 5±3 °C	Appearance: Any marking essential for the safe use of the pen shall remain visible, easily legible, and indelible. No cracks or compromised assembly bonds, joints, and alignments that might impact safe function. Attribute test Dose Accuracy: ≥1.0 mL Variable test (b) (4)	Appearance: Pass Dose Accuracy: Pass LTL = 1.0 mL (Sample size = 60)
	Standard atmosphere testing: preconditioning for at least 4 hours at 23±5 °C/50±25% RH		Appearance: Pass Dose Accuracy: Pass LTL = 1.0 mL (Sample size = 60)
	Warm atmosphere testing: preconditioning for at least 4 hours at 40±2 °C/50±10% RH		Appearance: Pass Dose Accuracy: Pass LTL = 1.0 mL (Sample size = 60)
The pen shall be subjected to the test condition requirement and then accurately deliver the labeled volume at 23±5 °C/50±25% RH.	Free-fall testing: drop from a height of 1000 mm (3 orientations)	Appearance: Any marking essential for the safe use of the pen shall remain visible, easily legible, and indelible. No cracks or compromised assembly bonds, joints, and alignments that might impact safe function. Attribute test Container Appearance: The container is not completely fractured or has lost its contents in such a way that it is obvious to the user. Attribute test Dose Accuracy: ≥1.0 mL Variable test (b) (4)	Appearance: Pass Container Appearance: Pass Dose Accuracy: Pass LTL = 1.0 mL (Sample size = 30 in total [10 per orientation])

Requirement Description	Test Condition Requirement	Acceptance Criteria	Results
The pen shall be subjected to the test condition requirement and then accurately deliver the labeled volume at 23±5 °C/50±25% RH.	Dry heat preconditioning – acceptable high storage temperature testing: preconditioning for at least 96 hours at 30±2 °C/75±5% RH	Appearance: Any marking essential for the safe use of the pen shall remain visible, easily legible, and indelible. No cracks or compromised assembly bonds, joints, and alignments that might impact safe function. Attribute test Dose Accuracy: ≥1.0 mL Variable test (b) (4)	Appearance: Pass Dose Accuracy: Pass LTL = 1.0 mL (Sample size = 60)
	Cold storage preconditioning – acceptable low storage temperature testing: preconditioning for at least 96 hours at 5±3 °C		Appearance: Pass Dose Accuracy: Pass LTL = 1.0 mL (Sample size = 60)
The pen shall be subjected to the test condition requirement and then accurately deliver the labeled volume at 23±5 °C/50±25% RH.	Vibration testing preconditioning	Appearance: Any marking essential for the safe use of the pen shall remain visible, easily legible, and indelible. No cracks or compromised assembly bonds, joints, and alignments that might impact safe function. Attribute test Container Appearance: The container is not completely fractured or has lost its contents in such a way that it is obvious to the user. Attribute test Dose Accuracy: ≥1.0 mL Variable test (b) (4)	Appearance: Pass Container Appearance: Pass Dose Accuracy: Pass LTL = 1.0 mL (Sample size = 20)

Test conditions and acceptance criteria for Appearance, Container Appearance and Dose Accuracy were assigned as stated in ISO 11608-1:2014.
RH = relative humidity; LTL = lower tolerance limit

Table 3.2.P.2.4-3. Functional Testing Performed on the Marstacimab 150 mg/mL Prefilled Pen

Attribute	Test Condition Requirement	Acceptance Criteria	Results
Cap Removal The rotation torque when twisting off the cap including the rigid needle shield.	Cool atmosphere testing: preconditioning for at least 4 hours at 5±3 °C	Appearance: Any marking essential for the safe use of the pen shall remain visible, easily legible, and indelible. No cracks or compromised assembly bonds, joints, and alignments that might impact safe function. Attribute test Container Appearance (free-fall and vibration testing only): The container is not completely fractured or has lost its contents in such a way that it is obvious to the user. Attribute test Cap Removal Torque: (b) (4) N•m Variable test (b) (4)	Appearance: Pass Cap Removal Torque: Pass UTL = 0.3 N•m (Sample size = 60)
	Standard atmosphere testing: preconditioning for at least 4 hours at 23±5 °C/50±25% RH		Appearance: Pass Cap Removal Torque: Pass UTL = 0.2 N•m (Sample size = 60)
	Warm atmosphere testing: preconditioning for at least 4 hours at 40±2 °C/50±10% RH		Appearance: Pass Cap Removal Torque: Pass UTL = 0.1 N•m (Sample size = 60)
	Free-fall testing: drop from a height of 1000 mm (3 orientations)		Appearance: Pass Container Appearance: Pass Cap Removal Torque: Pass UTL = 0.2 N•m (Sample size = 30 in total [10 per orientation])
	Dry heat preconditioning – acceptable high storage temperature testing: preconditioning for at least 96 hours at 30±2 °C/75±5% RH		Appearance: Pass Cap Removal Torque: Pass UTL = 0.2 N•m (Sample size = 60)
	Cold storage preconditioning – acceptable low storage temperature testing: preconditioning for at least 96 hours at 5±3 °C		Appearance: Pass Cap Removal Torque: Pass UTL = 0.2 N•m (Sample size = 60)
	Vibration testing preconditioning		Appearance: Pass Container Appearance: Pass Cap Removal Torque: Pass UTL = 0.2 N•m (Sample size = 20)

Attribute	Test Condition Requirement	Acceptance Criteria	Results
Needle Guard Force (Activation Force) The force required to fully depress the needle guard.	Cool atmosphere testing: preconditioning for at least 4 hours at 5±3 °C	Appearance: Any marking essential for the safe use of the pen shall remain visible, easily legible, and indelible. No cracks or compromised assembly bonds, joints, and alignments that might impact safe function. Attribute test Container Appearance (free-fall and vibration testing only): The container is not completely fractured or has lost its contents in such a way that it is obvious to the user. Attribute test Needle Guard Force: (b) (4) N Variable test (b) (4)	Appearance: Pass Needle Guard Force: Pass UTL = 10.1 N (Sample size = 60)
	Standard atmosphere testing: preconditioning for at least 4 hours at 23±5 °C/50±25% RH		Appearance: Pass Needle Guard Force: Pass UTL = 9.5 N (Sample size = 60)
	Warm atmosphere testing: preconditioning for at least 4 hours at 40±2 °C/50±10% RH		Appearance: Pass Needle Guard Force: Pass UTL = 9.2 N (Sample size = 60)
	Free-fall testing: drop from a height of 1000 mm (3 orientations)		Appearance: Pass Container Appearance: Pass Needle Guard Force: Pass UTL = 10.3 N (Sample size = 30 in total [10 per orientation])
	Dry heat preconditioning – acceptable high storage temperature testing: preconditioning for at least 96 hours at 30±2 °C/75±5% RH		Appearance: Pass Needle Guard Force: Pass UTL = 9.8 N (Sample size = 60)
	Cold storage preconditioning – acceptable low storage temperature testing: preconditioning for at least 96 hours at 5±3 °C		Appearance: Pass Needle Guard Force: Pass UTL = 9.5 N (Sample size = 60)
	Vibration testing preconditioning		Appearance: Pass Container Appearance: Pass Needle Guard Force: Pass UTL = 9.6 N (Sample size = 20)

Attribute	Test Condition Requirement	Acceptance Criteria	Results
Needle Extension The distance between the bearing face of the fully depressed needle guard and the needle tip.	Cool atmosphere testing: preconditioning for at least 4 hours at 5±3 °C	Appearance: Any marking essential for the safe use of the pen shall remain visible, easily legible, and indelible. No cracks or compromised assembly bonds, joints, and alignments that might impact safe function. Attribute test Container Appearance (free-fall and vibration testing only): The container is not completely fractured or has lost its contents in such a way that it is obvious to the user. Attribute test Needle Extension: (b) (4) mm Variable test (b) (4)	Appearance: Pass Needle Extension: Pass LTL = 5.6 mm, UTL = 6.4 mm (Sample size = 60)
	Standard atmosphere testing: preconditioning for at least 4 hours at 23±5 °C/50±25% RH		Appearance: Pass Needle Extension: Pass LTL = 5.6 mm, UTL = 6.3 mm (Sample size = 60)
	Warm atmosphere testing: preconditioning for at least 4 hours at 40±2 °C/50±10% RH		Appearance: Pass Needle Extension: Pass LTL = 5.6 mm, UTL = 6.3 mm (Sample size = 60)
	Free-fall testing: drop from a height of 1000 mm (3 orientations)		Appearance: Pass Container Appearance: Pass Needle Extension: Pass LTL = 5.4 mm, UTL = 6.5 mm (Sample size = 30 in total [10 per orientation])
	Dry heat preconditioning – acceptable high storage temperature testing: preconditioning for at least 96 hours at 30±2 °C/75±5% RH		Appearance: Pass Needle Extension: Pass LTL = 5.5 mm, UTL = 6.4 mm (Sample size = 60)
	Cold storage preconditioning – acceptable low storage temperature testing: preconditioning for at least 96 hours at 5±3 °C		Appearance: Pass Needle Extension: Pass LTL = 5.4 mm, UTL = 6.4 mm (Sample size = 60)
	Vibration testing preconditioning		Appearance: Pass Container Appearance: Pass Needle Extension: Pass LTL = 5.4 mm, UTL = 6.4 mm (Sample size = 20)

Attribute	Test Condition Requirement	Acceptance Criteria	Results
Time Between Clicks The time duration from the first click to the second click.	Cool atmosphere testing: preconditioning for at least 4 hours at 5±3 °C	Appearance: Any marking essential for the safe use of the pen shall remain visible, easily legible, and indelible. No cracks or compromised assembly bonds, joints, and alignments that might impact safe function. Attribute test Container Appearance (free-fall and vibration testing only): The container is not completely fractured or has lost its contents in such a way that it is obvious to the user. Attribute test Time Between Clicks: (b) (4) s Variable test (b) (4)	Appearance: Pass Time Between Clicks: Pass UTL = 7.9 s (Sample size = 60)
	Standard atmosphere testing: preconditioning for at least 4 hours at 23±5 °C/50±25% RH		Appearance: Pass Time Between Clicks: Pass UTL = 5.5 s (Sample size = 60)
	Warm atmosphere testing: preconditioning for at least 4 hours at 40±2 °C/50±10% RH		Appearance: Pass Time Between Clicks: Pass UTL = 4.0 s (Sample size = 60)
	Free-fall testing: drop from a height of 1000 mm (3 orientations)		Appearance: Pass Container Appearance: Pass Time Between Clicks: Pass UTL = 6.1 s (Sample size = 30 in total [10 per orientation])
	Dry heat preconditioning – acceptable high storage temperature testing: preconditioning for at least 96 hours at 30±2 °C/75±5% RH		Appearance: Pass Time Between Clicks: Pass UTL = 5.4 s (Sample size = 60)
	Cold storage preconditioning – acceptable low storage temperature testing: preconditioning for at least 96 hours at 5±3 °C		Appearance: Pass Time Between Clicks: Pass UTL = 6.2 s (Sample size = 60)
	Vibration testing preconditioning		Appearance: Pass Container Appearance: Pass Time Between Clicks: Pass UTL = 5.7 s (Sample size = 20)

Attribute	Test Condition Requirement	Acceptance Criteria	Results
Delivery Time The time duration for the device to deliver the full contents of the syringe.	Cool atmosphere testing: preconditioning for at least 4 hours at 5±3 °C	Appearance: Any marking essential for the safe use of the pen shall remain visible, easily legible, and indelible. No cracks or compromised assembly bonds, joints, and alignments that might impact safe function. Attribute test Container Appearance (free-fall and vibration testing only): The container is not completely fractured or has lost its contents in such a way that it is obvious to the user. Attribute test Delivery Time: (b) (4) s Variable test (b) (4)	Appearance: Pass Delivery Time: Pass UTL = 8.4 s (Sample size = 60)
	Standard atmosphere testing: preconditioning for at least 4 hours at 23±5 °C/50±25% RH		Appearance: Pass Delivery Time: Pass UTL = 5.9 s (Sample size = 60)
	Warm atmosphere testing: preconditioning for at least 4 hours at 40±2 °C/50±10% RH		Appearance: Pass Delivery Time: Pass UTL = 4.3 s (Sample size = 60)
	Free-fall testing: drop from a height of 1000 mm (3 orientations)		Appearance: Pass Container Appearance: Pass Delivery Time: Pass UTL = 6.5 s (Sample size = 30 in total [10 per orientation])
	Dry heat preconditioning – acceptable high storage temperature testing: preconditioning for at least 96 hours at 30±2 °C/75±5% RH		Appearance: Pass Delivery Time: Pass UTL = 5.7 s (Sample size = 60)
	Cold storage preconditioning – acceptable low storage temperature testing: preconditioning for at least 96 hours at 5±3 °C		Appearance: Pass Delivery Time: Pass UTL = 6.6 s (Sample size = 60)
	Vibration testing preconditioning		Appearance: Pass Container Appearance: Pass Delivery Time: Pass UTL = 6.0 s (Sample size = 20)

Attribute	Test Condition Requirement	Acceptance Criteria	Results
Needle Guard Override – Deflection The needle guard deflection when at least 80 N load is applied to the locked-out needle guard.	Cool atmosphere testing: preconditioning for at least 4 hours at 5±3 °C	Appearance: Any marking essential for the safe use of the pen shall remain visible, easily legible, and indelible. No cracks or compromised assembly bonds, joints, and alignments that might impact safe function. Attribute test Container Appearance (free-fall and vibration testing only): The container is not completely fractured or has lost its contents in such a way that it is obvious to the user. Attribute test Needle Guard Override – Deflection: Needle guard displacement distance at [redacted] (b) (4) mm Variable test [redacted] (b) (4)	Appearance: Pass Needle Guard Override – Deflection: Pass UTL = 2.7 mm (Sample size = 60)
	Standard atmosphere testing: preconditioning for at least 4 hours at 23±5 °C/50±25% RH		Appearance: Pass Needle Guard Override – Deflection: Pass UTL = 2.8 mm (Sample size = 60)
	Warm atmosphere testing: preconditioning for at least 4 hours at 40±2 °C/50±10% RH		Appearance: Pass Needle Guard Override – Deflection: Pass UTL = 2.9 mm (Sample size = 60)
	Free-fall testing: drop from a height of 1000 mm (3 orientations)		Appearance: Pass Container Appearance: Pass Needle Guard Override – Deflection: Pass UTL = 2.7 mm (Sample size = 30 in total [10 per orientation])
	Dry heat preconditioning – acceptable high storage temperature testing: preconditioning for at least 96 hours at 30±2 °C/75±5% RH		Appearance: Pass Needle Guard Override – Deflection: Pass UTL = 2.6 mm (Sample size = 60)
	Cold storage preconditioning – acceptable low storage temperature testing: preconditioning for at least 96 hours at 5±3 °C		Appearance: Pass Needle Guard Override – Deflection: Pass UTL = 2.7 mm (Sample size = 60)
	Vibration testing preconditioning		Appearance: Pass Container Appearance: Pass Needle Guard Override – Deflection: Pass UTL = 2.8 mm (Sample size = 20)

Attribute	Test Condition Requirement	Acceptance Criteria	Results
	The pen shall not perform any part of its disabled functionality during free-fall testing. The drop should not disable needle guard lockout. Free-fall testing of disabled pen: Free-fall testing: drop from a height of 1000 mm (3 orientations)	Needle Guard Override – Deflection: Needle guard displacement distance at [redacted] (b) (4) mm Variable test [redacted] (b) (4)	Needle Guard Override – Deflection: Pass UTL = 2.8 mm (Sample size = 60 in total [20 per orientation])

Test conditions and acceptance criteria for Appearance and Container Appearance were assigned as stated in ISO 11608-1:2014.
RH = relative humidity; UTL = upper tolerance limit

PREFILLED PEN PERFORMANCE TESTING AFTER SHIPPING

Information found in Seq. 0001 3.2.P.3.5 [Process Validation and/or Evaluation Shipping Data]

Table 3.2.P.3.5-4. Marstacimab 150 mg/mL Prefilled Pen Transportation Study Test Results

Test Description	Acceptance Criteria	Sample Size per Group	Control Group	Transportation Study Test Group	Pass/Fail
Appearance	Prefilled pen assembly is complete, and the cosmetic appearance is acceptable. The label is clearly printed, attached correctly and is not peeling.	460	Meets test	Meets test	Pass
Cap Removal Torque	Each sampled pen: (b) (4) N•m	119	Max: 0.2	Max: 0.2	Pass
Needle Guard Force (Activation Force)	Each sampled pen: (b) (4) N		Max: 10.7	Max: 10.5	Pass
Needle Extension	Each sampled pen: (b) (4) mm		Min: 5.3 Max: 5.7	Min: 5.2 Max: 6.2	Pass
Time Between Clicks	Each sampled pen: (b) (4)		Max: 7.2	Max: 8.5	Pass
Delivery Time	Each sampled pen:		Max: 7.6	Max: 8.1	Pass
Delivered Volume	Each sampled pen:		Min: 1.0	Min: 1.0	Pass
Needle Guard Locks Out After Activation	Meets test		Meets test	Meets test	Pass
Container Closure Integrity	Pass	60	Meets test	Meets test	Pass

Prefilled pen lot: GA6703
N = Newtons; N•m = Newton meters; s = seconds

PREFILLED PEN PERFORMANCE -STABILITY

Information found in Seq. 0030 3.2.P.8.3

Table 3.2.P.8.3-2. Stability Data for Marstacimab 150 mg/mL Prefilled Pen Lot EC3195 Stored at 5±3 °C

Time (Months)	Appearance	Cap Removal Torque	Needle Guard Force (Activation Force)	Needle Extension		Time Between Clicks	Delivery Time	Delivered Volume
Acceptance Criteria[a]	Pen assembly is complete, and the cosmetic appearance is acceptable. The label is clearly printed, attached correctly and is not peeling. No visible degradation is apparent compared to a reference sample.	(b) (4) Report maximum result	Report maximum result	Report minimum and maximum results		Report maximum result	Report maximum result	≥1.0 mL Report minimum result
0[b]	Meets test	0.2	11.1	5.3	6.2	6.9	7.3	1.0
1	Meets test	0.2	9.7	5.3	6.1	6.7	7.1	1.0
3	Meets test	0.1	9.7	5.5	6.1	7.3	7.7	1.0
6	Meets test	0.2	11.3	5.2	5.8	6.7	6.9	1.0
9	Meets test	0.2	9.6	5.3	5.8	6.9	7.3	1.0
12	Meets test	0.2	9.7	5.6	6.0	8.7	9.2	1.0
18	Meets test	0.2	9.9	5.5	5.9	8.0	8.3	1.0
24	Meets test	0.2	10.2	5.5	5.9	8.8	8.7	1.0
30	Meets test	0.2	10.0	5.5	6.0	8.6	8.6	1.0
36	Meets test	0.2	10.0	5.5	6.0	11.0	10.6	1.0

a. The information provided represents the specification and test method strategy used at the time of testing.
b. Initial data (t0) are from release testing.
N = Newtons; N•m = Newton meters; s = seconds

Table 3.2.P.8.3-3. Stability Data for Marstacimab 150 mg/mL Prefilled Pen Lot FR0508 Stored at 5±3 °C

Time (Months)	Appearance	Cap Removal Torque	Needle Guard Force (Activation Force)	Needle Extension		Time Between Clicks	Delivery Time	Delivered Volume
Acceptance Criteria[a]	Pen assembly is complete, and the cosmetic appearance is acceptable. The label is clearly printed, attached correctly and is not peeling. No visible degradation is apparent compared to a reference sample.	[redacted] (b) (4)						≥1.0 mL
		Report maximum result	Report maximum result	Report minimum and maximum results		Report maximum result	Report maximum result	Report minimum result
0[b]	Meets test	0.2	10.7	5.3	6.0	6.2	6.6	1.0
3	Meets test	0.2	10.1	5.3	5.9	5.9	6.2	1.0
6	Meets test	0.2	10.3	5.4	5.9	6.2	6.8	1.0
12	Meets test	0.1	10.2	5.3	6.0	7.2	7.3	1.0
24	Meets test	0.2	10.2	5.2	5.8	9.8	9.3	1.0

a. The information provided represents the specification and test method strategy used at the time of testing.
b. Initial data (t0) are from release testing.
N = Newtons; N•m = Newton meters; s = seconds

Post approval Commercial Stability

Table 3.2.P.8.2-1. Post-Approval Commercial Stability Protocol for Marstacimab Prefilled Pen Stored at 5±3 °C

Attribute	Test Intervals
Appearance	0, Annually, PFS Exp
Needle Extension	
Delivery Time	
Delivered Volume	

PFS = prefilled syringe
PFS Exp = pen testing performed at end of shelf life of the prefilled syringe, which is determined by the date of manufacture of the prefilled syringe.

Reviewer Comment:
The sponsor has not provided testing for 3 lots of the subject PFP that meet the acceptance criteria to the proposed shelf-life (b) (4). 2 device lots were provided (b) (4) under accelerated aged conditions , and they did not meet the acceptance criteria. Of note: there is not clear guidance on the number of lots that sponsors are required to provide in a marketing application. [**Midcycle Deficiency #2]** The sponsor has clarified that they are proposing a 24-month shelf-life. Performance testing on 2 lots of PFP was provided. The devices were real time aged to 36/12 month respectively, and the test results met their acceptance criteria with no-out of specifications noted. The sponsor will need to provide testing on the 2 stability lots to demonstrate the proposed shelf-life of 24 months **[Midcycle Deficiency #2 NOT RESOLVED**] Data for the lot FR0508 at 24 months will be requested. **[IR#2Q#1**] The sponsor provided data for 2 lots of PFP (Lot EC3195 & FR0508) to 24 months under real time conditions, with a sample size of 60 for each time point. All results met their acceptance criteria with no-out of specification results. **[IR#2 Q#1 RESOLVED]**
The sponsor provided a post approval protocol for the Prefilled Syringe (PFS) for extending the shelf-life (b) (4). However, there was no post approval process for extending the shelf-life beyond 24 months for the PFP. CDER included a deficiency to have the sponsor explain the process for shelf-life extension of the PFP potentially to (b) (4) (the same as the PFS) **[IR #2 Q #2]** The sponsor response is that the PFP expiration dating is based on the PFS expiration date and that they overall function of the pen components is (b) (4) (long-term storage) and that no additional testing would be needed. This strategy was discussed with CDRH management and deemed unacceptable. An extension of the PFP shelf-life would need testing of the EPRs for the pen to be submitted and reviewed. This will be discussed with CDER and will be conveyed to the sponsor via this memo. However, for the purpose of this review the sponsor has provided stability testing for 2 lots of the PFP at the recommended storage temperature of 5±3°C for the proposed 24-month shelf life. In Seq. 0001 3.2.P.8.2 The sponsor proposes to place a minimum of 1 lot of PFP in a commercial stability program on long-term storage each year. Testing will be performed annually from the date of manufacture of the pen until the end of shelf-life of the PFS which is determined by the date of manufacture of the PFS. The EPRs to be tested were identified acceptable. This was discussed with CDER on 5/15/2024. **[IR#2 Q#2 RESOLVED]**

BIOCOMPATIBILITY TESTING

Information found in Seq. 0001 in 3/2/P.2.4 [Prefilled Pen Biocompatibility Evaluation Table 3.2.P.2.4-6] &3.2.R Regional Information [Biocompatibility Test Reports]

Contact Classification: Surface contacting- intact skin.
Contact Duration: Prolonged exposure (> 24 hours to 30 days)

Test Article:
1mL Drug Delivery Device Components (cap, rigid needle shield-perforated bracket, needle guard, outer housing, bezel)

Endpoints Evaluated:

Table 3.2.P.2.4-6. Marstacimab 150 mg/mL Prefilled Pen Components Biocompatibility Test Results

Test	Test System	Acceptance Criteria	Result
Cytotoxicity	Cytotoxicity- MEM Elution Test Name: Fibroblast cell Organism: Mouse Cell Line: (b) (4) (b) (4) Source: (b) (4) (b) (4)	(b) (4)	Pass Cells treated with the test article extract exhibited a response of grade 0 (no reactivity) at 24 and 48 hours.
Irritation	Intracutaneous (Intradermal) Reactivity Test Species: Rabbit Strain: New Zealand White Source: (b) (4) (b) (4) Number Used: 3 Initial Weight: 2.9 – 3.4 kg Age: Adult Sex: Female Identification: Ear tags and cage cards		Pass Saline extract: The overall mean score for the test article was 0.0. The overall mean score for the control was 0.0. The difference between the overall mean scores was 0.0. The differences between average test scores and average control scores were not greater than 1.0 at all observation periods. Cottonseed oil extract: The overall mean score for the test article was 1.0. The overall mean score for the control was 1.0. The difference between the overall mean scores was 0.0. The differences between average test scores and average control scores were not greater than 1.0 at all observation periods. All positive control animals used in the historical positive control study exhibited a strong irritation response to the positive control and the difference between the positive control average score and the control average was greater than 1.0. In addition, the differences between the positive control and control average scores were greater than 1.0 at all observation periods.

Test	Test System	Result
Sensitization	Maximization Test for Delayed-Type Hypersensitivity Species: Guinea Pig Strain: Hartley, Albino Source: (b) (4) (b) (4) Number Used: 34 Sex: Male Age: Young adult Initial Weight: Saline Group: 334 to 391 g Cottonseed Oil Group: 344 to 422 g Identification: Unique identification and cage card	Pass No sensitization reactions or patterns in animals exposed to test article extracted either in saline or cottonseed oil. The test animals did not receive scores higher than those of the negative control animals. All positive control animals used in the historical positive control study exhibited a strong sensitization response to the challenge dose compared to that of the control animals.

Reviewer Comment:
The appropriate Biocompatibility endpoints were tested for this type and duration of patient contact. **The testing results were acceptable.**

8.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A

Reviewer Comments

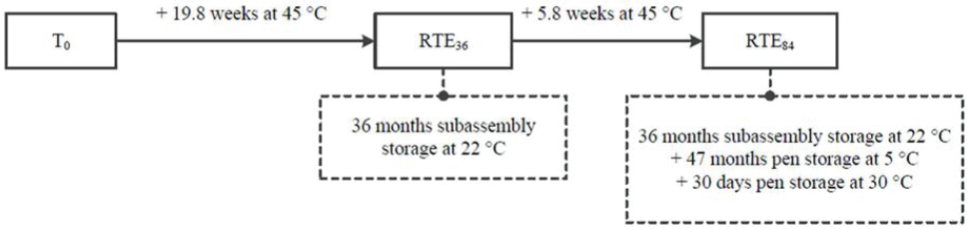
The sponsor has provided performance testing on the PFP for all EPRs and attributes with batch testing, verification testing, pen manufacturer verification testing, ship testing. This testing is acceptable. Stability data is requested due to the accelerated aged data not meeting the EPR specification as well as only 2 lots of PFP data included in the submission. [**Midcycle Deficiency #2]** The sponsor clarified the proposed shelf-life is 24 months not (b) (4) which was indicated in the submission, however only data for one lot of the PFP was provided to the proposed shelf-life. **[Midcycle Deficiency #2 NOT RESOLVED]** Requested clarification of the timeline for when the 2nd lot of PFP data would be available. **[IR#2Q#1]** The sponsor provided the data for 2 lots of PFP for all EPRs under long-term storage conditions to (b) (4) 24 months respectively. Sample size of 60 devices per timeline all met the acceptance criteria for EPR specifications. **[IR#2Q#1 RESOLVED]**

CDER had wanted clarification of the sponsor post market commitment to extend the shelf-life beyond the proposed 24-month timeline. **[IR#2Q#2]** The sponsor stated that the PFP expiration data would be based on the PFS expiration and that the pen components themselves have a (b) (4) shelf-life. However, expiration dating should be based on acceptable testing of the final finished device not on component expiration, as performance of the syringe within the Pen itself could be affect the performance of the finished device. This was discussed with CDRH management, Shruti Mistry AD and Porsche Bennett, TL. To extend the shelf-life beyond the proposed 24-month performance testing of the EPRs will need to be submitted. **Of note:** the sponsor did provide a post approval stability protocol and proposes to place a minimum of 1 lot of PFP in a commercial stability program on long-term storage each year. Testing will be performed annually from the date of manufacture of the pen until the end of shelf-life of the PFS which is determined by the date of manufacture of the PFS. The EPRs to be tested were identified acceptable. This was discussed with CDER on 5/15/2024 meeting. **[IR#2Q#2 RESOLVED] Of note:** for the purpose of this memo, the sponsor has provided adequate stability testing to claim a 24-month shelf-life.

CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No

	Date Sent: 2/13/2024	**Date/Sequence Received:** 2/27/2024
Information Request #1 Question #2	We acknowledge that you have provided some device functionality testing for the subject Prefilled Pen (PFP) in Seq. 0001 of the submission. However, you have not provided adequate testing to demonstrate that the subject device will function as intended to the end of its proposed shelf life of (b) (4) months. FDA has observed the following: a. In 3.2.P.8.3 you provided stability testing (accelerated aged) for two (2) devices lots, EC3195 and FR0508 to support your (b) (4) month shelf life. However, the testing did not meet the acceptance criteria at 3 and 6 months for time between clicks, delivery time, and the deliverable volume/dose accuracy for the 2 lots you presented. b. Only two (2) PFP lots were tested to the end of the proposed shelf-life. We generally recommend providing 3 GMP lots of the drug/device product to be tested to account for lot-to-lot variability. Please provide summary data and test reports for a total of 3 PFP lots for stability testing (either real time or accelerated aged testing). This testing should include cap removal torque, needle guard force (activation force), needle extension, time between clicks, delivery time and delivery volume that meet the acceptance criteria to demonstrate that the subject PFP can meet its performance specifications to the end of your proposed shelf life of (b) (4) months.	

	Include the number of samples tested at each timepoint. Your sample size should be based on your risk assessment and should provide an adequate level of statistical assurance of 95% confidence with 95% reliability that your device will perform as intended to the end of its proposed shelf-life. This is important since device failure could lead to adverse events such as under or missed doses or accidental needle stick injury.
Sponsor Response	A shelf life for the PFP of (b) (4) months represents a target for development as stated in the Quality Target Product Profile (QTPP) in Section 3.2.P.2 Pharmaceutical Development - Introduction (Prefilled Pen). Based on evidence provided in the submission, a shelf life claim of 24 months at the recommended temperature of 2-8 °C and for a single period up to 7 days at a maximum of 30 °C, but not exceeding the original expiration date, is being sought at this time. This is determined from the date of manufacture of the marstacimab prefilled syringe (PFS). As presented in the submission, 2 PFP lots (EC3195 and FR0508) are currently enrolled in stability studies since there is no clear guidance requiring the submission of data for 3 lots. Updated stability data are provided for each of these lots, see Section 3.2.P.8.1 Stability Summary and Conclusion (Prefilled Pen), Section 3.2.P.8.3 Stability Data-Long Term Stability Data (Prefilled Pen), Section 3.2.P.8.3 Stability Data-Time Out of Refrigeration Stability Data (Prefilled Pen), and Section 3.2.P.8.3 Stability Data-Thermal Cycling Stability Data (Prefilled Pen). A third lot is planned for addition to the stability program, and data will be submitted in Annual Report updates. Results up to 36 months are presented for lot EC3195, and up to 12 months for lot FR0508. The data show there are no notable changes to any of the functional performance attributes, so, continue to support storage at the recommended storage conditions to 24 months. If requested, additional stability data for lot FR0508 will be included during the ongoing assessment to further support the shelf life of 24 months. A test sample size of 60 PFP per time point for ongoing long term and accelerated studies is selected based on binomial principles. This provides 95% confidence that the true lot failure rate is no more than 5% (95% probability content) for each time point. It is recognized that the PFP failed to meet the acceptance criteria for Time Between Clicks, Delivery Time and Delivered Volume on accelerated aging studies at 3 or 6 months, but this is accounted for in the shelf-life claim as storage of no longer than 7 days is permitted at a maximum of 30 °C. As noted in Section 3.2.P.8.1 Stability Summary and Conclusion (Prefilled Pen), these results are attributed to changes in syringeability forces and stalling of the plunger rod before reaching the end of travel for the PFS due to storage at accelerated conditions. The conditions under which these performance attributes failed are beyond those proposed for the PFP in the user setting. To support changes in the PFS being the root cause of these results, a report with design verification results for accelerated aging of commercially representative PFP is provided (INX100409288 (b) (4) Design Verification (DV) Report - Accelerated Aging for (b) (4) 1mL (A-000064-TR-S008)). As part of design verification activities to evaluate functional performance of the pen over the shelf life, the stability of the subassemblies (power pack subassembly and front subassembly) and the syringe clip was evaluated by aging these for up to 25.6 weeks using an accelerated temperature of 45 °C. The Real Time Equivalent (RTE) storage times were calculated using the Arrhenius equation (in line with guidance from ASTM F1980-21),

	which considers the activation energies of the materials used. 25.6 weeks at 45 °C represents storage of subassemblies for 36 months (19.8 weeks) followed by storage as an assembled PFP for a further 48 months (5.8 weeks). At each time point, the test samples were assembled with the prefilled syringe prior to being tested. Testing is illustrated in Figure 1. **Figure 1. Accelerated Aging Stability of Marstacimab Prefilled Pen Subassemblies and Syringe Clip**  The accelerated aging report presents information related to sample numbers, the relevant statistical assurances that the PFP will function as intended to the end of the proposed shelf life, and each of the functional performance tests [cap removal torque, needle guard force (activation force), needle extension, time between clicks ('audible clicks'), delivery time ('injection time') and delivered volume ('dose accuracy')]. The results are presented from page 15 of the report. (b) (4) as referred to in the report, is the platform name for the PFP enclosing the PFS, and (b) (4) name for the marstacimab PFP.
Reviewer Comments	The sponsor will be asked to provide timeline for when real time stability testing will be available for lot FR0508 to 24-month.
Response Adequate:	☐ **Yes** ☑ **No, See IR #2 Q#1 Sent on 3/29/2024**

Follow-On Deficiency	**Date Sent: 3/29/2024**	**Date/Sequence Received: 4/12/2024**
Information Request #2 Question #1	In your response to Question #2 of the information request dated 2/27/2024 you state that a 24-month shelf life is being sought for the Prefilled Pen (PFP) at this time and you provided real time stability data for lot EC3195 at 5±3°C up to 36 month and up to 12 months for lot FR0508. In addition, you state that "additional stability data for lot FR0508 will be included during the ongoing assessment to further support the shelf life of 24 months". In Seq. 0022 Table 3.2.P.8.3-1 the PFP manufacture date is listed as NOV-2021. Therefore, provide the timeline for the 24-month functional testing assessment for lot FR0508 and indicate when that data would be available for review.	
Sponsor Response	Updated stability data up to 24 months are provided for PFP lot FR0508. The data show there are no notable changes to any of the functional performance attributes, so continue to support storage at the recommended storage conditions to 24 months. The following sections have been updated: ☐ Section 3.2.P.8.1 Stability Summary and Conclusion (Prefilled Pen) ☐ Section 3.2.P.8.3 Stability Data-Long Term Stability Data (Prefilled Pen)	
Reviewer Comments	The sponsor has provided stability testing of all EPRs for 2 lots of PFP devices to (b) (4) 24 month respectively. Sample size of 60 per time point. Summary results provided and all test results met their acceptance criteria to support the proposed 24month shelf-life. **This response is acceptable.**	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

	Date Sent: 3/29/2024	Date/Sequence Received: 4/12/2024
Information Request #2 Question #2	The initial requested shelf life for the marstacimab 150 mg/mL prefilled Syringe (PFS) is 24 months at 5±3 °C (section 3.2.P.8.1.1). A post approval stability protocol for the PFS drug product was provided (b) (4) In section 3.2.P.8.1 you state that the overall shelf life for the PFP is based on the marstacimab prefilled syringe shelf life, while the response to Question #2 of the information request dated 2/27/2024 discusses a 24-month shelf life sought for the PFP but does not address the fact that the extension of the PFS expiration dating is stated as also relevant to the PFP. No additional stability-extending protocols were included in section 3.2.P.8.2 of the PFP. a. Explain the process for expiration dating of the PFP as related to the data provided and proposed shelf life of the PFP vs. the potential for a (b) (4) month shelf life of the PFS, as the information provided is confusing on your process. (b) (4) Update section 3.2.P.3.3 of the PFP assembly process to address any requirements of the PFS used, e.g., specific age as well as the assessment of expiration dating considering the data available for the PFP may not be available to support its use for a PFS with longer shelf life. b. As relevant to your intended process, provide the protocol you propose to use for the extension of the shelf life of the PFP beyond 24 months. The protocol should, identify the functional attributes to be tested along with the acceptance criteria, and indicate the number of device lots that will be tested for the purpose of PFP shelf-life extension.	
Sponsor Response	a. Expiration dating of the PFP is based on the expiration date for the PFS; once assembled, the shelf life for the completed PFP is the same as that already assigned for the PFS, irrespective of the age of the PFS. No new expiration date is assigned to the PFP based on the date of manufacture of the PFP. The shelf life of the components used for the assembly of the PFP will not be limiting to the expiration date assigned for the PFP. In addition to the stability data in Section 3.2.P.8, this is supported by component and subassembly accelerated aging studies conducted during design verification to support an overall functional shelf life of (b) (4) for the device constituent at the long-term storage condition (2-8 °C) (results submitted in response to Question #2 of the information request, dated 2/27/2024, sequence 0022). The shelf life claim of 24 months for the PFP, as described in the response to Question #2 of the information request dated 2/27/2024, is based on stability data currently available for both the PFS and PFP. Any future extension of the shelf life would be based on appropriate results as they become available for the PFS, so long as results from stability testing of the PFP are also supportive. b. As shown in Section 3.2.P.8.1 Stability Summary and Conclusion (Prefilled Pen), the ongoing protocols also show that both PFP lots will be evaluated (b) (4). Any future extension of the shelf life will be based on submission of updated stability results for both the PFS (based on Section 3.2.P.8.1 Stability Summary and Conclusion	

	(Prefilled Syringe)) and the PFP in line with the ongoing stability protocols. The protocol duration is shown to be up to (b) (4) for both, which would allow any revision of the shelf-life post-approval, based on the ongoing protocols as presented in the 3.2.P.8.1 Stability Summary and Conclusion sections, alongside supportive data. The post-approval stability protocols presented in the respective 3.2.P.8.2 Post Approval Stability sections for the PFS and PFP are only to support the annual stability commitment of a minimum 1 lot being evaluated and is not intended to extend or revise the shelf life of the product. The definition of the date of manufacture of the PFS has been clarified and is provided in 3.2.P.8.1.7 of Section 3.2.P.8.1 Stability Summary and Conclusion (Prefilled Syringe).
Reviewer Comments	This strategy is not acceptable. To extend the shelf-life dating beyond 24-months,testing of the PFP EPRs will need to be submitted for review. In Seq. 0001 the sponsor has provided a post approval commitment for testing of the PFP EPRs each year. CDER will be reminded that the performance data from the PFP should be reviewed to ensure the performance data meets device specifications for extension of the shelf life beyond 24-months. **For the purpose of this review the stability testing provided is acceptable as the sponsor is only currently seeking a 24-month shelf-life and supporting data has been provided.**
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

8.3. Discipline Specific Sub-Consulted Review Summary

☑ No Additional Discipline Specific Sub-Consults were requested.
☐ The following additional Discipline Specific Sub-Consults were requested:

9. CLINICAL VALIDATION REVIEW

9.1. Review of Clinical Studies Clinical Studies

☑ There is no device related clinical studies for review.
☐ There are clinical studies for review.

10. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☑

11.FACILITIES & QUALITY SYSTEMS

11.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☑
CDRH Facilities Inspection Review was not conducted	☐

Facility Regulatory History Review	
Firm Name:	Pfizer Manufacturing
Address & FEI:	Belgium NV, Rijksweg 12 Puurs-Sint-Amands 2870 Belgium FEI# 1000654629
Responsibilities:	Assembly of prefilled pen, labeling, testing and secondary packaging. The firm is responsible for the following Quality management responsibility activities: • 21 CFR Part 210, 211, 600-680 • 21 CFR 4.4(b) • 21 CFR 820.20 Management responsibilities • 21 CFR 820.30 Design Controls • 21 CFR 820.50 Purchasing Controls • 21 CFR 820.100 Corrective and Preventive Action
Site Inspection Recommendation:	Choose an item..

Reviewer Comments:
Post approval inspection is recommended.

Facilities Review Conclusion		
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	☐ Yes	☑ No

11.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☑
CDRH Quality Systems Documentation Review was not conducted	☐

11.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s): **Pfizer**	(b) (4) [redacted]
21 CFR 820.170 Summary of Installation	Firm(s):	**Reviewer Discussion –** **NA**
21 CFR 820.200 Summary Servicing	Firm(s):	**Reviewer Discussion –** **NA**
Subpart F – Identification and Traceability	Firm(s):	**Reviewer Discussion –** **NA**
Subpart G – Production and Process Controls	Firm(s):	**Reviewer Discussion –** Reviewed in Section 12.3 NA
Subpart H – Acceptance Activities	Firm(s):	**Reviewer Discussion –** **NA**
Subpart I – Nonconforming Product	Firm(s):	**Reviewer Discussion –** **NA**
Subpart K – Labeling and Packaging Controls	Firm(s):	**Reviewer Discussion –** **NA**
Subpart L – Handling, Storage, Distribution	Firm(s):	**Reviewer Discussion –** NA

Subpart M – Records	Firm(s):	**Reviewer Discussion – NA**
Subpart O – Statistical Techniques	Firm(s):	**Reviewer Discussion – NA**

Reviewer Comments
The sponsor provided all elements of their streamlined GMP compliance activities.

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	☑ Yes	☐ No

11.2.3. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

The sponsor provided a high-level summary of their CAPA process; and a summary of their CAPA process at Midcycle.

The following table reflects whether the Sponsor addressed the required elements of corrective and preventive action controls:

CAPA Procedure Required Elements	**Present**
Procedures include requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.	YES
Procedures include review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.	YES
Procedures include appropriate statistical analysis of these quality data to detect recurring quality problems	YES
Investigations into the cause of nonconformities relating to product, processes, and the quality system	YES
Includes requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems	YES
Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device	YES
Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications	YES
Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems	YES
Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems	YES
Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review	YES
Requires documentation of all CAPA activities	YES

Reviewer Comments
Only high-level summary information was provided regarding the CAPA process. More description of the CAPA activities will be requested from the sponsor. [**Midcycle Deficiency #3]** The sponsor has provided a detailed

description/summary of their Deviation Management process CAPA process below. **[Midcycle Deficiency #3 RESOLVED]**

CAPA Conclusion		
The Sponsor provided adequate information for corrective and preventive actions.	☒Yes	☐No

11.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g., emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
EPR #1	Needle Extension (b) (4)	**Y**
EPR #2	Delivery time (b) (4)	**Y**
EPR #3	Delivered Volume ≥ 1.0 mL	**Y**

Reviewer Comments:
The release specifications identified by the sponsor are acceptable.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

11.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments A post approval device inspection has been recommended to CDER. CAPA information will be requested. **[Midcycle Deficiency #3]** The sponsor has provided a descriptive summary of their Deviation Management and CAPA process. This information is acceptable. **[Midcycle Deficiency #3 RESOLVED]**		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: 2/13/2024	**Date/Sequence Received: 2/27/2024**
Information Request #1 Question #3	In Seq. 0001 3.2.R 21CFR 4.4(b) Description, you provided a summary of the Quality System Regulation provision and a brief summary of your Corrective and Preventative Action (CAPA) procedures. However, insufficient information was provided to conclude that your CAPA procedures address all of the required elements per 21 CFR 820.100. Please provide additional information, including a summary response to how your CAPA procedures address the below specific considerations. This information is needed to ensure your CAPA procedures are meeting the elements of 21 CFR 820.100. a. Summarize your CAPA requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned	

	product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. b. Provide a summary of your CAPA procedures for review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use. c. Confirm that the procedures include appropriate statistical analysis of these quality data to detect recurring quality problems. d. Provide your process for investigation into the cause of nonconformities relating to product, processes, and the quality system as well as requirements for identification and implementation of actions needed to correct and prevent recurrence of non-conformities and other quality problems. e. Summarize the verification and validation activity process taken to ensure that the corrective and preventive actions taken are effective and do not adversely affect the finished device. f. Describe your established procedure for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications. g. Describe requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems. h. Confirm that your CAPA procedure ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems. i. Confirm that relevant information on identified quality problems, as well as corrective and preventive actions are submitted for management review and that all your CAPA activities requires documentation.
Sponsor Response	(b) (4)

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

	(b) (4)
Reviewer Comments	The sponsor has provided a summary of their CAPA processes. **The information provided is acceptable.**
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

<<END OF REVIEW>>

12. APPENDIX A (INFORMATION REQUESTS)

12.1. Filing/74-Day Information Requests

NONE

12.2. Mid-Cycle Information Requests

1. In 3.2.P.2.4 you state that a risk analysis was performed using multiple tools including hazard analysis, design failure mode and effects analysis (dFMEA), use failure mode and effects analysis (uFMEA) and process failure mode and effects analysis (pFMEA). However, your dFMEA and your pFMEA could not be located for review. This information is required to assess the overall risk of the subject Prefilled Pen (PFP). Please provide the dFMEA and the pFMEA documents for review

Firm Response:
See Section 7.7 for full response

2. We acknowledge that you have provided some device functionality testing for the subject Prefilled Pen (PFP) in Seq. 0001 of the submission. However, you have not provided adequate testing to demonstrate that the subject device will function as intended to the end of its proposed shelf life of 36 months. FDA has observed the following:
   a. In 3.2.P.8.3 you provided stability testing (accelerated aged) for two (2) devices lots, EC3195 and FR0508 to support your (b)(4) month shelf life. However, the testing did not meet the acceptance criteria at 3 and 6 months for time between clicks, delivery time, and the deliverable volume/dose accuracy for the 2 lots you presented.
   b. Only two (2) PFP lots were tested to the end of the proposed shelf-life. We generally recommend providing 3 GMP lots of the drug/device product to be tested to account for lot-to-lot variability.

   Please provide summary data and test reports for a total of 3 PFP lots for stability testing (either real time or accelerated aged testing). This testing should include cap removal torque, needle guard force (activation force), needle extension, time between clicks, delivery time and delivery volume that meet the acceptance criteria to demonstrate that the subject PFP can meet its performance specifications to the end of your proposed shelf life of (b)(4) months. Include the number of samples tested at each timepoint. Your sample size should be based on your risk assessment and should provide an adequate level of statistical assurance of 95% confidence with 95% reliability that your device will perform as intended to the end of its proposed shelf-life. This is important since device failure could lead to adverse events such as under or missed doses or accidental needle stick injury.

Firm Response:
See Section 8.2 for full response (IR#1 Q2)

3. In Seq. 0001 3.2.R 21CFR 4.4(b) Description, you provided a summary of the Quality System Regulation provision and a brief summary of your Corrective and Preventative Action (CAPA) procedures. However, insufficient information was provided to conclude that your CAPA procedures address all of the required elements per 21 CFR 820.100. Please provide additional information, including a summary response to how your CAPA procedures address the below specific considerations. This information is needed to ensure your CAPA procedures are meeting the elements of 21 CFR 820.100.
   a. Summarize your CAPA requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints,
   returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.

b. Provide a summary of your CAPA procedures for review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.
c. Confirm that the procedures include appropriate statistical analysis of these quality data to detect recurring quality problems.
d. Provide your process for investigation into the cause of nonconformities relating to product, processes, and the quality system as well as requirements for identification and implementation of actions needed to correct and prevent recurrence of non-conformities and other quality problems.
e. Summarize the verification and validation activity process taken to ensure that the corrective and preventive actions taken are effective and do not adversely affect the finished device.
f. Describe your established procedure for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications.
g. Describe requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems.
h. Confirm that your CAPA procedure ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems.
i. Confirm that relevant information on identified quality problems, as well as corrective and preventive actions are submitted for management review and that all your CAPA activities requires documentation.

Firm Response:
See Section 11.4 for full response.

12.3. Interactive Information Requests

12.3.1. Interactive Information Requests sent on Click or tap to enter a date.

1. In your response to Question #2 of the information request dated 2/27/2024 you state that a 24-month shelf life is being sought for the Prefilled Pen (PFP) at this time and you provided real time stability data for lot EC3195 at 5±3°C up to 36 month and up to 12 months for lot FR0508. In addition, you state that "additional stability data for lot FR0508 will be included during the ongoing assessment to further support the shelf life of 24 months". In Seq. 0022 Table 3.2.P.8.3-1 the PFP manufacture date is listed as NOV-2021. Therefore, provide the timeline for the 24-month functional testing assessment for lot FR0508 and indicate when that data would be available for review.

Firm Response:
See Section 8.2 for full response. (IR#2 Q#1)

2. In The initial requested shelf life for the marstacimab 150 mg/mL prefilled Syringe (PFS) is 24 months at 5±3 °C (section 3.2.P.8.1.1). A post approval stability protocol for the PFS drug product was provided (b) (4). If approved and supported by stability data, this would allow for an expiration dating that is (b) (4) from the date of sterile filtration of the PFS product. In section 3.2.P.8.1 you state that the overall shelf life for the PFP is based on the marstacimab prefilled syringe shelf life, while the response to Question #2 of the information request dated 2/27/2024 discusses a 24-month shelf life sought for the PFP, but does not address the fact that the extension of the PFS expiration dating is stated as also relevant to the PFP. No additional stability-extending protocols were included in section 3.2.P.8.2 of the PFP.

a. Explain the process for expiration dating of the PFP as related to the data provided and proposed shelf life of the PFP vs. the potential for a (b) (4) shelf life of the PFS, as the information provided is confusing

on your process. (b) (4) Update section 3.2.P.3.3 of the PFP assembly process to address any requirements of the PFS used, e.g., specific age as well as the assessment of expiration dating considering the data available for the PFP may not be available to support its use for a PFS with longer shelf life.

b. As relevant to your intended process, provide the protocol you propose to use for the extension of the shelf life of the PFP beyond 24 months. The protocol should, identify the functional attributes to be tested along with the acceptance criteria, and indicate the number of device lots that will be tested for the purpose of PFP shelf-life extension.

Firm Response:
See Section 8.2 for full response. (IR#1 Q#2)

13. APPENDIX B (CONSULTANT MEMOS)

NONE

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/s/

CARLEVEVA J THOMPSON
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 9, 2024

TO: Norman L. Stockbridge, M.D.
Director
Division of Cardiology and Nephrology (DCN)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Office of New Drugs (OND)

FROM: Xikui Chen, Ph.D.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun Julia Cho, Ph.D.
Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of Clinical Inspection at Pfizer Clinical Research Unit, Hopital Erasme, Brussels-Capital Region, 1070, Belgium

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of study B7841009 (BLA 761369, Marstacimab) conducted at Pfizer Clinical Research Unit, Hopital Erasme, Brussels-Capital Region, 1070, Belgium.

Form FDA 483 was not issued at the inspection close-out. There was one discussion item regarding sample processing. Based on the inspection finding and my review, I conclude the discussion item has no impact on reliability of the data and human subject protection for inspected study B7841009.

2. Inspected Study

BLA 761369
Study Number: B7841009
Study Title: "A Phase 1, Open-Label, Randomized, 4-Period, 2-Sequence, Crossover Study to Evaluate the Bioequivalence of Marstacimab (PF-06741086) Prefilled Syringe Device and Prefilled Pen Device

Following Subcutaneous Administration in Healthy Adult Male Participants"

Dates of study conduct: March 30 – November 22, 2021

Clinical site: Pfizer Clinical Research Unit, Hopital Erasme
Lennikse Baan 808 Anderlecht
Brussels-Capital Region, 1070, Belgium

Principal Investigator: Isabelle Huyghe, MD (FEI # 3030095682)

3. Inspectional Findings

3.1 Pfizer Clinical Research Unit, Hopital Erasme, Brussels-Capital Region, Belgium

ORA investigator Kristin M. Abaonza inspected Pfizer Clinical Research Unit, Hopital Erasme, Brussels-Capital Region, 1070, Belgium from May 27 - 30, 2024.

3.1.1 Previous Inspection

The previous Bioequivalence – Clinical inspection was conducted from April 8 to 12, 2019. No Form FDA 483 was issued, and no discussion items were addressed with the firm. The final classification was NAI.

3.1.2 Current Inspection

The current inspection included auditing the following items:
- Case report forms (CRFs)
- Informed consent process
- Protocol deviations
- Ethics committee approvals
- Randomization
- Test article accountability, and storage
- Adverse events

3.1.3 Inspection findings

At the conclusion of the inspection, investigators Kristin M. Abaonza did not issue Form FDA 483. One discussion item was communicated with management as the following:

Discussion item 1:
There were two out of window PK samples after samples were collected, centrifuged and transferred to storage (store at -70°C within 60 minutes after collection, per PCRU Laboratory

Manual).

Specifically for Subject (b) (6) (Period 3, Day 1, Hour 0): the PK sample was collected on June 23, 2021 at 08:21 am and was stored in the freezer at 09:24 am (3 minutes out of 60 min storage window). This deviation was not captured/reported in site's Phase I Management System (PIMS).

Specifically for Subject (b) (6) (Period 2, Day 1, Hour 480): the PK sample was collected on June 28, 2021 at 9:22 am and was stored in the freezer at 10:24 am (2 minutes out of 60 min storage window). This deviation was captured/reported in PIMS on June 28, 2021 at 14:45 because the sample was centrifuged 32 minutes (two minutes delay according to the protocol) after collection.

OSIS Evaluation:
Per PCRU Laboratory Manual, two PK samples were out of process specifications. One sample at period 3, day 1, hour 0 for subject 4 was not within the specification of 60 minutes from sample collection to storage at -70°C (the actual time was 62 minutes which is not within the specification of 60 minutes), and other at period 2, day 1, hour 480 for subject (b) (6) was not within the specification of 30 minutes from sample collection to centrifuge (the actual time was 32 minutes which is not within the specification of 30 minutes).

However, Ambient temperature matrix stability for 72 hours at room temperature was established in the Pfizer validation study No. B7849001 ((b) (6) Project No. 15-1536), titled "the validation of an ECL assay method for the determination of PF-06741086 in sodium citrate human plasma." Because the drug in human plasma is stable for 72 hours at ambient temperature, the three minutes later storage at room temperature or 2 minutes later centrifuge at ambient temperature is within the established 72 hours stability range. Thus, the discussion item does not impact reliability of the data for the inspected study.

Draft: XC 8/5/2024, 8/7/2024, 8/8/2024
Edit: MO 8/5/2024; JC 8/5/2024, 8/7/2024, 8/8/2024

OSIS File: BE 10096

eNSpect assignment ID: 238687
eNSpect operation ID: 277395
Site FEI #: 3007000232

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/s/

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SEONGEUN CHO
08/09/2024 10:57:04 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

PLLR Labeling Memorandum

Date: 8/8/2024 **Date consulted:** 7/5/2024

From: Katherine Kratz, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Non-Malignant Hematology (DNH)

Drug: Hympavzi (marstacimab-hncq) injection

BLA: 761369

Applicant: Pfizer

Subject: Labeling of Section 8

Indication(s):
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 (congenital factor VIII deficiency) without factor VIII inhibitors, or
- hemophilia B (congenital factor IX deficiency) without factor IX inhibitors

Materials Reviewed:

- DPMH consult request dated 7/5/2024. DARRTS Reference ID: 5408485
- Applicant's submitted background package and proposed labeling for BLA 761369, Sequence Number (SN) 0001, dated 10/11/2023

- [redacted] (b) (4)
- Pharmacology/Toxicology IND Assessment and Evaluation of IND 126734 for marstacimab by Fred Alavi, dated 8/11/2022, DARRTS Reference ID: 5028791
- United States Prescribing Information (USPI) for approved drug and biologic products to treat hemophilia: Hemlibra, Kovaltry, and Eloctate

Consult Question: "Please review draft labeling and provide recommendations for Section 8. We are specifically unsure whether this product should contain text regarding contraception recommendations. The Applicant did not conduct EFD [embryo-fetal development] studies in pregnant animals."

I. INTRODUCTION

On October 11, 2023, Pfizer submitted a Biologics Licensing Application (BLA) for a new molecular entity (NME), Hympavzi (marstacimab-hncq) injection. Marstacimab is a human monoclonal antibody of the G isotype, subclass 1 (IgG1), directed against Tissue Factor Pathway Inhibitor (TFPI) for routine prophylaxis to prevent or reduce the frequency of bleeding in patients with hemophilia A and hemophilia B treated with or without inhibitors.

In August 2022, the DNH Nonclinical Team wrote an IND evaluation and assessment[1] about the proposed product and noted that the Applicant proposed not to conduct female fertility and embryo fetal developmental (EFD) toxicity studies based on the low disease prevalence in women. FDA agreed with this proposal. Thus, female fertility and EFD toxicity studies were not conducted with marstacimab.

In terms of the prevalence of hemophilia in females, a 2021 study[2] reported that 1667 females who received care at U.S. Hematology Treatment Centers between January 2012 and September 2020 were diagnosed with severe (<1% of normal factor VIII (FVIII) or factor IX (FIX) activity), moderate (1-5% of FVIII or FIX activity), or mild hemophilia (>5 and <40% of normal FVIII or FIX activity). Among the 1667 females, 103 had moderate or severe hemophilia A and 27 had moderate or severe hemophilia B.

II. BACKGROUND

Relevant Regulatory History

- There are no TFPI inhibitors that have been approved globally.
- Another TFPI inhibitor, [redacted] (b) (4) was reviewed by FDA [redacted] (b) (4)

[1] Pharmacology/Toxicology IND Assessment and Evaluation of IND 126734 for marstacimab by Fred Alavi, dated 8/11/2022, DARRTS Reference ID: 5028791

[2] Miller CH, Soucie JM, Byams VR, et al. Women and girls with haemophilia receiving care at specialized haemophilia treatment centres in the United States. Haemophilia. 2021;27(6):1037-1044. doi:10.1111/hae.14403

(b) (4)

- DPMH has not been consulted to review other drug and/or biologic products approved by FDA to prevent or reduce bleeding associated with hemophilia.
- The only monoclonal antibody approved by FDA's CDER to prevent or reduce the frequency of bleeding episodes associated with hemophilia is Hemlibra. Hemlibra (emcizumab-kxwh) is a humanized monoclonal modified immunoglobulin G4 (IgG4) that is a bispecific factor IXa- and factor X-directed antibody. Hemlibra bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective hemostasis.[7] Animal reproductive toxicity studies were not conducted for Hemlibra. Due to concern for placental transfer of Hemlibra, a recommendation for contraception was included in subsection 8.3 of labeling.[8] Hemlibra labeling includes a boxed warning for thrombotic microangiopathy and thrombotic events when administered with activated prothrombin complex concentrate. Of note, labeling for Hemlibra does not include a Warning and Precaution for embryofetal toxicity.

(b) (4)

8;123(19):2934-43. doi: 10.1182/blood-2013-11-512764. Epub 2014 Mar 11. PMID: 24620349; PMCID: PMC4014837.

[7] USPI, Hemlibra (emicizumab-kxwh), 1/2024.

[8] Internal email communication with Pharmacology/Toxicology reviewer Dr. Ramadevi Gudi, 7/19/24.

- DPMH conducted a literature search in PubMed using the search terms "Hemlibra" and "pregnancy" and found a single case report by Zharel et al.[9] in which a 29-year-old female with severe hemophilia was treated with emicizumab every 4 weeks throughout pregnancy. Emicizumab was detected in the cord blood at delivery at a concentration of 106 mcg/mL. The emicizumab concentration in maternal plasma during the third trimester was 49 mcg/mL. Therapeutic ranges for plasma emicizumab concentrations have not been established; however, trough plasma concentrations observed during clinical trials ranged between 35 and 55 mcg/mL. The FVIII activity in cord blood at the time of delivery was >400 IU/dL, with the normal reference range being between 50-150 IU/dL. Emicizumab was detected in breast milk at a concentration of 38 mcg/mL. Infant plasma was not tested for emicizumab concentrations following exposure via breast milk.

Reviewer comment:
The publication by Khamel et al. demonstrates that emicizumab was placentally transferred and that FVIII levels in cord blood were elevated. Although no adverse events related to blood clotting were reported in the infant by Khamel et al., increased FVIII activity in infant plasma following in-utero exposure has the potential to increase thrombotic events. Like emicizumab, marstacimab is an IgG that will be placentally transferred and may impact clotting factors in the infant who was exposed in utero.

- Other products approved by FDA's CBER to prevent or reduce bleeding episodes associated with hemophilia are coagulation factors, such as Kovaltry and Eloctate. Animal reproductive toxicity studies were not conducted for these coagulation factors. Coagulation factors VIII and IX do not cross the placenta.[10] Labelings for coagulation factors do not include a recommendation for contraception.

Drug Characteristics[11]

Drug class	Inhibitor of TFPI
Mechanism of action	Marstacimab targets the Kunitz domain 2 (K2) of TFPI, which is the primary inhibitor of the extrinsic coagulation cascade. TFPI initially binds to and inhibits the factor Xa active site via K2. Neutralizing the activity of TFPI may serve to enhance the extrinsic pathway and reduce or eliminate the need for replacement Factor VIII and Factor IX.
Dosage and Administration	• Day 1: Administer 300 mg (two 150 mg injections) by subcutaneous (SC) injection (loading dose)

[9] Kharel Z, Pruthi RK, Kouides P, Reid R. Transplacental transfer of emicizumab: Experience with emicizumab in a pregnant female with severe hemophilia A and an inhibitor. Haemophilia. 2024 May;30(3):868-871. doi: 10.1111/hae.15022. Epub 2024 Apr 22. PMID: 38650315.
[10] Davenport P, Sola-Visner M. Hemostatic Challenges in Neonates. Front Pediatr. 2021 Mar 2;9:627715. doi: 10.3389/fped.2021.627715. PMID: 33738269; PMCID: PMC7960661.
[11] BLA 761369, SN 0001, draft labeling, under review by DNH.

	• Day 8 and thereafter: Administer 150 mg every week by subcutaneous injection.
Molecular weight	145 kDa
Half-life	10-17 days
% protein bound	Not specified
Bioavailability	68%
Adverse Effects	Thromboembolic events

Reviewer comment:
DPMH discussed the half-life and the timeframe for continuation of contraception after the last dose of marstacimab with the DNH Clinical Pharmacology (CP) team. The DNH CP team recommended using the half-life of 17 days and multiplying by 5 and 6 to determine the time needed for clearance of the proposed drug from the maternal circulation. Based on these calculations (17 days x 5 = 85 days; 2.8 months) and (17 days x 6 = 102 days; 3.4 months), the DNH CP team stated that it would be reasonable to state in labeling that contraception is needed for 3 months after the last dose of marstacimab.

III. REVIEW

PREGNANCY

Hemophilia and Pregnancy[12,13,14]
Hemophilia A and B are X-linked recessive bleeding disorders caused by deficiency of factor VIII and factor IX, respectively. These hemophilias predominantly affect males, but females who are heterozygous carriers may be affected as well. Heterozygous carriers may have varying expression ranging from asymptomatic to symptomatic. In rare instances, severe factor deficiency may occur in heterozygous carriers, and these patients have an increased risk of bleeding during pregnancy and/or delivery. Pregnancy in females with severe hemophilia is exceedingly rare and limited to a few case reports. Female carriers of hemophilia do not have an increased risk of miscarriage. Treatment of pregnancy and delivery in patients with decreased factor levels includes use of replacement coagulation factors, desmopressin (DDAVP), and coordinated care with a multidisciplinary team.

Nonclinical Experience[15,16]
Per the Applicant's submission package, the assessment of the reproductive and developmental toxicity potential of marstacimab was limited to a male fertility and an early embryonic development study in rats. Marstacimab was administered to male rats at doses of 0, 60, 180, or 1000 mg/kg/week via IV injection once weekly for a minimum of 4 weeks prior to mating, throughout mating, and continuing until euthanasia (11 total doses). The no observed adverse

[12] Hoots WK, Malec L. Clinical manifestations and diagnosis of hemophilia. UpToDate. Topic 1310, Version 43.0.
[13] Sharma V, Khalid A, Cohen A. Management of pregnancy in a patient with severe Hemophilia type A. Am J Perinatol Rep. 2012;03(01):029-032. doi:10.1055/s-0032-1331376
[14] Bodrozic JN, Miljic PS, Lekovic DR, et al. Pregnancy and delivery in a woman with severe haemophilia A. Blood Coagul Fibrinolysis.
2017;28(6):496-499. doi:10.1097/MBC.0000000000000630
[15] BLA 761369, Module 2.4, Nonclinical Overview, p.47.
[16] BLA 761369, Module 2.6.6. Toxicology Written Summary, p. 13.

effect level (NOAEL) for male systemic and reproductive toxicity and early embryonic toxicity was 1000 mg/kg/week, approximately 200 times the clinical dose of 300 mg based on the AUC, based on the absence of test article-related clinical observations, or effects on body weight, body weight gain, food consumption, male reproductive performance, spermatogenesis endpoints, embryonic survival in naïve females, or changes in organ weights or macroscopic findings.

The reader is referred to the Pharmacology/Toxicology by Dr. Fred Alavi for this BLA.

Reviewer comment:
DPMH discussed the absence of nonclinical female fertility and EFD toxicity data with the DNH Pharmacology/Toxicology (P/T) team. The P/T team stated that neither pre- nor post-marketing animal reproduction studies in females are likely to provide useful information for the following reasons: 1) Males are the target patient population. 2) Females are very rarely affected by hemophilia A or B. 3) Animal reproduction studies are conducted in healthy animals and not in animal models of the disease. Marstacimab is not a potent drug, and it has minimal potency in healthy animals. In repeat-dose toxicity studies in healthy animals, coagulation markers (i.e. PT, APTT, fibrinogen) were either unchanged or contradictory to marstacimab's expected pharmacology. Based on marstacimab being an IgG1 monoclonal antibody that has the potential to be increasingly transferred across the placenta as pregnancy progresses and due to its mechanism of action, marstacimab could, hypothetically, induce thrombotic events in the fetus. Nonclinical studies related to the inhibition of TFPI have been conducted in TFPI knock-out mice.[4,5,17] In these mice, the TFPI gene is inactivated, and TFPI activity is completely absent. The TFPI knock-out studies in mice showed embryofetal lethality and suggested that TFPI is required for cerebrovascular development. Although these findings in TFPI knock-out mice are concerning, the findings do not likely represent the effects of marstacimab in humans because marstacimab will not completely inhibit TFPI as was the case in the knock-out mice. Based on preclinical studies, one would expect that decreased TFPI levels in humans could be associated with increased rates of thrombus formation. In the case of thrombus formation related to coronary artery disease, however, the majority of clinical trials, though mostly retrospective in nature, show increased plasma TFPI activity levels.[18] On the other hand, low plasma TFPI levels have been reported in patients with ischemic stroke,[19] thrombotic thrombocytopenic purpura,[20] and with taking combined oral contraceptives (COCs).[21] Although the clinical data related to TFPI activity in humans are limited and conflicting in nature, it is biologically plausible that

[17] Maroney SA, Westrick RJ, Cleuren AC, Martinez ND, Siebert AE, Zogg M, Ginsburg D, Weiler H, Mast AE. Tissue factor pathway inhibitor is required for cerebrovascular development in mice. Blood. 2021 Jan 14;137(2):258-268. doi: 10.1182/blood.2020006054. PMID: 32735640; PMCID: PMC7820871.
[18] Winckers K, ten Cate H, Hackeng TM. The role of tissue factor pathway inhibitor in atherosclerosis and arterial thrombosis. Blood Rev. 2013 May;27(3):119-32. doi: 10.1016/j.blre.2013.03.001. Epub 2013 Apr 28. PMID: 23631910.
[19] Abumiya T, Yamaguchi T, Terasaki T, Kokawa T, Kario K, Kato H. Decreased plasma tissue factor pathway inhibitor activity in stroke patients. Thromb Haemost 1995;74:1050.
[20] Kobayashi M, Wada H, Wakita Y, Shimura M, Nakase T, Hiyoyama K, Nagaya S, Minami N, Nakano T, Shiku H. Decreased plasma tissue factor pathway inhibitor levels in patients with thrombotic thrombocytopenic purpura. Thromb Haemost 1995;73:10.
[21] Harris GM, Stendt CL, Vollenhoven BJ, Gan TE, Tipping PG. Decreased plasma tissue factor pathway inhibitor in women taking combined oral contraceptives. Am J Hematol. 1999 Mar;60(3):175-80. doi: 10.1002/(sici)1096-8652(199903)60:3<175::aid-ajh1>3.0.co;2-x. PMID: 10072106.

reduced TFPI activity could contribute to thrombus formation and adversely affect embryofetal development.

Clinical Trial Experience
Females were not enrolled in the drug development clinical trials with marstacimab.

Review of Literature
Applicant's review:
The Applicant did not provide a literature search.

DPMH review:
DPMH conducted a search of published human studies in PubMed, using the search terms "tissue factor pathway inhibitor" OR "TFPI" AND "pregnancy," "pregnancy outcomes," "birth defects," "malformations," "stillbirth," and "spontaneous abortion." DPMH retrieved the publications previously cited on page 3 of this review by Martinuzzo et al.[22] and Gardiner et al.[23] In addition, DPMH retrieved a publication that suggests that high concentrations of TFPI are associated with pre-eclampsia as follows:

- Erez et al.[24] conducted a cross-sectional study that included the following groups: 1) women with normal pregnancies (n = 86); 2) patients who delivered small for gestational age (SGA) neonates (n = 61) and 3) women with pre-eclampsia (n = 133). Maternal plasma concentrations of tissue factor (TF) and TFPI were measured by a sensitive immunoassay. TFPI concentrations were higher in patients with pre-eclampsia than in patients with normal pregnancy (median: 87.5 ng/mL; range 25.4-165.1 vs. median: 66.1 ng/mL; range: 14.3-86.5; $p < 0.0001$, respectively).

Reviewer comment:
Available publications suggest that low maternal concentrations of TFPI may be associated with the adverse pregnancy outcome of recurrent pregnancy loss when combined with Activated Protein C (APC) resistance or antiphospholipid antibodies (aPL).[9,10] Conversely, the publication by Erez et al. suggests that high maternal concentrations of TFPI may be associated with the adverse pregnancy outcome of pre-eclampsia. Based on the limited and conflicting information in the clinical literature related to pregnancy, the impact of inhibition of TFPI with a monoclonal antibody, such as marstacimab, on pregnancy outcomes is unknown.

LACTATION

[22] Martinuzzo M, Iglesias Varela ML, Adamczuk Y, Broze GJ, Forastiero R. Antiphospholipid antibodies and antibodies to tissue factor pathway inhibitor in women with implantation failures or early and late pregnancy losses. J Thromb Haemost. 2005 Nov;3(11):2587-9. doi: 10.1111/j.1538-7836.2005.01612.x. PMID: 16241962.
[23] Gardiner, C, H Cohen, SK Austin, SJ Machin, and IJ Mackie, 2006, Pregnancy loss, tissue factor pathway inhibitor deficiency and resistance to activated protein C, J Thromb Haemost, 4(12):2724-2726.
[24] Erez O, Romero R, Hoppensteadt D, Than NG, Fareed J, Mazaki-Tovi S, Espinoza J, Chaiworapongsa T, Kim SS, Yoon BH, Hassan SS, Gotsch F, Friel L, Vaisbuch E, Kusanovic JP. Tissue factor and its natural inhibitor in pre-eclampsia and SGA. J Matern Fetal Neonatal Med. 2008 Dec;21(12):855-69. doi: 10.1080/14767050802361872. PMID: 19065458; PMCID: PMC3171292.

There are no nonclinical data related to the presence of marstacimab in milk. There were no females enrolled in the drug development clinical trials with marstacimab.
The Applicant did not provide a literature search related to TFPI inhibitor use during lactation. DPMH conducted a literature search in PubMed using the search terms "tissue factor pathway inhibitor" OR "TFPI" AND "lactation" and "breastfeeding." No relevant publications were found.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical studies related to female fertility were not conducted. Nonclinical studies related to male fertility did not demonstrate adverse effects on fertility parameters (see *PREGNANCY* section above). The Applicant did not provide a literature search related to TFPI inhibitors and fertility. DPMH conducted a literature search in PubMed using the search terms "tissue factor pathway inhibitor" OR "TFPI" AND "fertility," "infertility," contraception," and "oral contraceptives." One publication was found as follows:

- Thyzel et al.[25] measured TFPI levels in ovarian follicular fluid from 70 women undergoing in vitro fertilization stimulated to induce superovulation and in seminal plasma of 28 healthy ejaculate donors and 23 infertile patients with oligozoospermia, asthenozoospermia, or teratozoospermia. TFPI concentrations in seminal plasma samples of infertile men were significantly reduced (median 2.20 ng/ml, 90% range 0.28–6.02 ng/ml, $p<0.07$) in comparison to healthy donors (median 3.55 ng/ml, 90% range 0.93–7.90 ng/ml). The authors concluded that the high TFPI levels measured in the ovarian follicular fluid underline the physiological importance of this inhibitor for maintaining the hypocoagulable state. They also concluded that the decreased TFPI concentrations in seminal plasma of infertile men support the possible correlation between the coagulation properties of ejaculated semen and male fertility.

Reviewer comment:
The publication by Thyzel et al. suggests that low TFPI concentrations in seminal plasma may be associated with male infertility in humans. With this limited information from the published literature that contrasts with the lack of effect on fertility parameters in male rats observed in the nonclinical studies conducted during the marstacimab development program, it is not possible to draw conclusions about the effects of inhibition of TFPI or the effects of marstacimab on human fertility.

IV. DISCUSSION/CONCLUSIONS
In the absence of nonclinical female fertility and EFD toxicity studies and clinical data from drug development, the effects of marstacimab on embryofetal development are theoretical. Some clinical publications suggest that TFPI deficiency may result in thrombotic events. Thrombotic events in a developing fetus could potentially cause fetal harm, including worse-case scenarios of myocardial infarction, stroke and death. Thus, given that marstacimab is an IgG1 and IgG1 is

[25] Thyzel E, Siegling S, Götting C, Tinneberg HR, Brinkmann T, Kleesiek K. Quantification of tissue factor pathway inhibitor in human seminal plasma and in human follicular fluid. Thromb Res. 2003 Mar 15;109(5-6):329-32. doi: 10.1016/s0049-3848(03)00210-x. PMID: 12818258.

known to cross the placenta efficiently,[26] it is possible that marstacimab, through its mechanism of action involving inhibition of TFPI, may cause embryofetal harm. For this reason, DPMH recommends an embryofetal toxicity warning in labeling. See the specific recommendations below. Due to the potential for fetal harm , DPMH recommends use of contraception to prevent pregnancy and pregnancy testing to limit in-utero exposure of the fetus to marstacimab, which should appear in subsection 8.3 of labeling.

There are no nonclinical or clinical data to inform marstacimab lactation labeling; however, given that marstacimab is a monoclonal antibody, general information related to monoclonal antibodies in milk should be included in the labeling of subsection 8.2.

Given that utilization of marstacimab is likely to be very low in females of reproductive potential and pregnancy is rare in this population, DPMH does not recommend issuing postmarketing studies to assess pregnancy safety as enrollment in these studies is likely to be very low to absent. DPMH discussed the possibility of issuing a postmarketing requirement (PMR) for an animal reproduction study with the DHN P/T team. The DHN P/T team does not plan to issue a PMR for an animal reproduction study based on the rationale presented in the reviewer comment on page six of this review. Finally, DPMH does not recommend issuing a PMR for a lactation study given that systemic exposure in the infant is expected to be low with exposure via breast milk and since use of this product in females is likely to be low.

V. RECOMMENDATIONS

DPMH recommends labeling as shown below in the Highlights of Prescribing Information, section 2, 5, subsections 8.1, 8.2, and 8.3, and section 17, which were discussed with the DNH team on 8/5/2024. DPMH refers to the final BLA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

---------- WARNINGS AND PRECAUTIONS ----------

- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.X, 8.1, 8.3)

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

Pregnancy Testing

Verify that females of reproductive potential are not pregnant prior to initiating DRUG-X *[see Warnings and Precautions (5.X), Use in Specific Populations (8.1, 8.3)]*.

5.X Embryo-Fetal Toxicity

Based on its mechanism of action, HYMPAVZI may cause fetal harm when administered

[26] Clements T, Rice TF, Vamvakas G, Barnett S, Barnes M, Donaldson B, Jones CE, Kampmann B, Holder B. Update on Transplacental Transfer of IgG Subclasses: Impact of Maternal and Fetal Factors. Front Immunol. 2020 Sep 11;11:1920. doi: 10.3389/fimmu.2020.01920. PMID: 33013843; PMCID: PMC7516031.

to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with HYMPAVZI and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, HYMPAVZI may cause fetal harm when administered a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on HYMPAVZI use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Female animal reproduction studies have not been conducted with marstacimab-hncq. Although there are no data on marstacimab-hncq, monoclonal antibodies can be actively transported across the placenta, and marstacimab-hncq may cause fetal harm.

The background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of marstacimab-hncq in either human or animal milk, the effects on the breastfed child, or the effects on milk production. Endogenous maternal IgG and monoclonal antibodies are transferred into human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed childt to marstacimab-hncq are unknown.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HYMPAVZI and any potential adverse effects on the breastfed child from HYMPAVZI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

HYMPAVZI may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating HYMPAVZI treatment.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with HYMPAVZI and for 3 months after the final dose.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise female patients of reproductive potential to use effective contraception during treatment with HYMPAVZI and for 3 months after the final dose *[see Warnings and Precautions (5.x) and Use in Specific Populations (8.1, 8.3)]*.

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CLINICAL INSPECTION SUMMARY

Date	August 1, 2024
From	Anthony Orencia, M.D., Ph.D., F.A.C.P., Senior Physician Min Lu, M.D., M.P.H., Medical Team Leader Jenn Sellers, M.D., Ph.D., F.A.A.P., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Saleh Ayache, M.D., Clinical Reviewer Margaret Thompson, M.D. Clinical Team Leader Courtney Hamilton, Pharm.D., Senior Regulatory Health Project Manager Carleveva Thompson, MSc., Senior Regulatory Health Project Manager Ann Farrell, M.D., Director Division of Nonmalignant Hematology (DNH) Office of Cardiology, Hematology, Endocrinology and Nephrology Drugs
BLA	BLA 761369
Applicant	Pfizer Inc.
Drug	Hympavzi™ (marstacimab)
NME	Yes
Classification	Human monoclonal immunoglobulin
Proposed Indications	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years of age with hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors or hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.
Review Type	Priority Review
Consultation Request Date	January 22, 2024
Summary Goal Date	August 5, 2024
Action Goal Date	September 11, 2024
PDUFA Date	October 11, 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study B7841005 were submitted to the Agency in support of a Biologics License Application, for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years of age and older with: (a) hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or (b) hemophilia B (congenital factor IX deficiency) without factor IX inhibitor.

Four foreign clinical investigators were inspected for the study: Nirmal Kumar Choraria, M.D. (Gujarat, India), Young Shil Park, M.D. (Seoul, South Korea), Javier Morales Adrian, M.D. (Yucatan, Mexico) and Laurent Frenzel, M.D, Ph.D. (Paris, France).

Based on the inspection results, Study B7841005 in BLA 761369 appears to have been conducted adequately and the study data derived from the above clinical investigator sites are considered acceptable.

In general, the clinical data submitted to the Agency for assessment are acceptable in support of the proposed indication.

II. BACKGROUND

Marstacimab is a human monoclonal immunoglobulin of the G isotype, subclass 1 (IgG1) and a potential first in class treatment utilizing the extrinsic coagulation pathway. Marstacimab (PF-06741086) targets the Kunitz 2 domain of tissue factor pathway inhibitor (TFPI), a natural anticoagulation protein that functions to prevent the formation of blood clots.

The Sponsor proposes the indication of marstacimab for 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 (congenital factor VIII deficiency) without factor VIII inhibitors, or
• hemophilia B (congenital factor IX deficiency) without factor IX inhibitor

Study B7841005
Study B7841005 was a one-way, cross-over, open-label, multi-center study planned for approximately 145 adolescent and adult participants between ages 12 to less than 75 years with severe hemophilia A or moderately severe to severe hemophilia B (defined as FVIII activity less than 1% or factor IX activity less than 2%, respectively) with or without inhibitor, with approximately 20% of participants as adolescents (ages between 12 to <18 years old). Additional participants (approximately 20%) could have been recruited for this study in order to account for attrition of enrolled participants and to provide for sufficient representation into regions which have experienced recruitment delays due to the COVID-19 (coronavirus disease 2019) pandemic.

This study compared treatment with the participant's prescribed factor replacement therapy or bypass therapy during an Observational Phase with a 12-month Active Treatment Phase, during which participants were to receive marstacimab prophylaxis (defined as treatment by subcutaneous injection of marstacimab). The dosing regimen was marstacimab 300 mg subcutaneously for the initial loading dose followed by 150 mg subcutaneously once a week (QW). Individual participants who met protocol-specified dose escalation criteria based upon breakthrough bleeding, may have had their dose increased to 300 mg subcutaneously QW.

Participants were to be enrolled into one of two cohorts:

1) Inhibitor Cohort – individuals with inhibitors who were receiving prior on-demand treatment (at least 45 participants, with at least 35 hemophilia A and 10 hemophilia B participants).

2) Non-Inhibitor Cohort – individuals without inhibitors who were receiving regimens of either prior on-demand or prior prophylaxis factor-based therapy at least 100 participants, with at least 80 hemophilia A and 20 hemophilia B participants).

The primary objective for this study was to demonstrate the efficacy and safety of marstacimab (PF-06741086) for routine prophylaxis in severe hemophilia A or moderately severe to severe hemophilia B (Factor VIII [FVIII] activity less than 1% or Factor IX [FIX] activity less than 2%, respectively) participants 12 to less than 75 years of age with or without inhibitors.

The primary efficacy endpoint is the annualized bleeding rate (ABR) of treated bleeding events. It will be analyzed in the following measures:

1) Inhibitor Cohort (participants with prior on-demand therapy): the population summary for the ratio of the mean annualized bleeding rate (marstacimab prophylaxis vs. on-demand treatment) based on adult and adolescent participants meeting the entry criteria with prior on-demand therapy.

2) Non-Inhibitor Cohort for regions outside the European Union: the population summary for the ratio of the mean annualized bleeding rate (marstacimab prophylaxis versus on-demand treatment) based on adult and adolescent participants meeting the entry criteria with prior on-demand therapy.

3) Non-Inhibitor Cohort for the EU: the population summary for the mean annualized bleeding rate difference (marstacimab prophylaxis – prior prophylactic treatment) based on adult and adolescent participants meeting the entry criteria.

The safety endpoints involved the following measured events: adverse events and serious adverse events; incidence and severity of thrombotic events; incidence and severity of thrombotic microangiopathy; disseminated intravascular; coagulation/consumption coagulopathy; immunogenicity (incidence of antidrug antibody [ADA] and clinically significant persistent neutralizing antibody [NAb] against PF-06741086; incidence and severity of injection site reaction; changes in physical examination and vital signs; incidence of clinically significant laboratory value abnormalities, or incidence of severe hypersensitivity and anaphylactic reactions.

This study was conducted at 52 sites in 19 countries. The study period ranged from March 9, 2020, to April 17, 2023.

III. RESULTS

1. Nirmal Kumar Choraria, M.D./Site 1123
Nirmal Hospital Pvt, Ltd, Abhishek Market Ring Road
Surat, Gujarat 395002
India

Inspection dates: April 29-May 3, 2024

There were 21 study subjects who were screened, 18 subjects were enrolled, and 17 study subjects received investigational drug during the treatment phase.

FDA inspection comprised evaluation of these documents: independent ethics committee initial and continuing review, protocol compliance agreements, financial disclosure forms, training, delegation of authority, subject eligibility, informed consent, monitoring, investigational product accountability, adverse events, protocol deviations, record retention, electronic records, case report forms, protocol compliance, and source document verification.

Clinical trial utilized electronic diaries for subjects to record study events, such as infusion history, bleeding events, and investigational product treatments. Information is automatically transmitted from the electronic diary to the TrialManager platform, and then to the Sponsor in the electronic CRF.

The primary efficacy endpoint, annualized bleeding rate data, was not verifiable directly. The bleeding events were collected using subject electronic diaries. The study site does not create nor maintain efficacy endpoint data. However, supportive elements for the primary efficacy were evaluable at the site during the FDA inspection. For instance, FDA inspection confirmed that the electronic diary access was limited to the subject; the site has read-only access to data. No one on site had the ability to edit data in TrialMaster. Once the subject completed the last visit, the electronic diary was de-activated for this protocol and the subject was rolled over into the extension study. The site confirmed that sponsor's Secure Access Manager for electronic CRFs had audit trail capabilities. FDA confirmed that changes in data required a reason for change, date entered, and entered by. User access was restricted. Unique identifiers to database users were assigned.

No discrepancies were noted after a comprehensive review to all reported adverse events and serious adverse events. There was no evidence of under-reporting of adverse events.

The study data derived from Dr. Choraria's site are considered acceptable.

2. Young Shil Park, M.D./Site 1035
Kyung Hee University Hospital at Gangdong, 892, Dongnam-ro
Gangdong, Seoul, 05278
South Korea

Inspection dates: April 15 – 19, 2024

The site screened 8 subjects and enrolled 7 subjects. Five study subjects completed the treatment phase. Subject records were reviewed for these enrolled subjects.

Records reviewed for the study comprised study protocol and amendments, institutional review board and regulatory authority approvals/acknowledgments, correspondence, regulatory documents, investigational product accountability records, informed consent forms, the electronic medical record, and subject binders. FDA verified the number of treated bleed events for Observation Phase and Active Treatment Phase of the study diary data, concomitant medications, physical examinations, ECG results, adverse events and serious adverse events.

The primary efficacy study endpoint, annualized bleeding rate, could not be verified since this was a derived or calculated value. However, composite of the efficacy data that supported the annualized bleeding rate as the study endpoint were assessed.
No discrepancies were noted after a comprehensive review to all reported adverse events and serious adverse events. There was no evidence of under-reporting of adverse events.

At the inspection close-out, discussion items which involved a six-day lapse in IRB approval, delayed reporting to the IRB of subject (b) (6) not meeting eligibility criteria and enrolling in the study, and one concomitant medication not recorded in the electronic CRF and not submitted in the data line listings.

Reviewer's comments: These inspectional discussion items were not deemed significant. The above FDA discussions with the clinical study site did not have a significant impact on patients' safety outcomes, human subject protection or the primary efficacy endpoint for this study,

In general, this clinical study site appeared acceptable.

3. Javier Morales Adrian, M.D./Site 1127
Entre Calle 8 Y Calle 10, Fraccionamiento, Calle 3 No. 299; Fracc.
San Carlos, Merida
Merida, Yucatan 97130
Mexico

Inspection dates: May 13-16, 2024

There were 11 subjects who were screened, 9 study subjects enrolled and 7 subjects received treatment. A single subject remains active in the study. All 9 enrolled subjects' records were reviewed.

FDA site inspection involved document review of the study protocol, Ethics Committee approvals and correspondence, financial disclosures, site training activities, subject records, informed consent forms and assents, receipt, storage, and disposition of investigational product, sponsor correspondence and monitoring activities, electronic case report forms to determine compliance and the electronic diary platform, adverse events and serious adverse events.

For evaluable inspection documents and data at the site including data line listings, no major discrepancies were observed.

Annualized bleeding rate, the primary efficacy endpoint was not evaluable directly at the clinical site since this was a derived measure. Supportive composite data to the primary efficacy endpoint were assessed.

No discrepancies were noted after a comprehensive review to all reported adverse events and serious adverse events. There was no evidence of under-reporting of adverse events.

In general, this clinical study site appeared reliable.

4. Laurent Frenzel, M.D., Ph.D./ Site 1013
Hôpital Necker Enfants Malades
149 rue de Sèvres
Paris 75015 France

Inspection dates: March 25-28, 2024

There were five study participants who were screened. These five study subjects enrolled and received treatment during the study phase.

FDA inspection at this site comprised a review of available documents. Source documents and case report forms (where applicable) were comparable to sponsor line listings with respect to reported adverse events (no serious adverse events or deaths noted), registered protocol deviations, reported concomitant medications (relevant to screening, enrollment and protocol deviations), and subject study status (all subjects initially screen-failed and re-screened; no discontinuations registered).

The primary efficacy study endpoint, that is, annualized bleeding rate, could not be verified directly. The electronic diary data were automatically transferred to the TrialMax database for study staff to review and confirm on site. The marketing applicant revoked the site's access to electronic systems around the time of study completion.

There was no underreporting of nonserious or serious adverse events.

In general, this clinical study site appeared reliable.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D., F.A.C.P.
FDA Senior Physician
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Min Lu, M.D., M.P.H.
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Good Clinical Practice Assessment Branch
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CONCURRENCE:

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Jenn Sellers, M.D., Ph.D., F.A.A.P.
Branch Chief
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Office of Scientific Investigations

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JENN W SELLERS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 15, 2024

To: Carleveva Thompson, Senior Regulatory Project Manager, Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, Associate Director for Labeling, DNH

From: Melissa Khashei, Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for HYMPAVZI (marstacimab-hncq) injection, for subcutaneous use

BLA: 761369

Background:

In response to DNH's consult request dated October 26, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI)/Instructions for Use (IFU) and carton and container labeling for the original BLA submission for HYMPAVZI (marstacimab-hncq) injection, for subcutaneous use.

PI/PPI/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on July 2, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI and IFU, and comments were sent under separate cover on July 12, 2024.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on July 12, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or melissa.khashei@fda.hhs.gov.

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/s/

MELISSA KHASHEI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 12, 2024
To:	Carleveva Thompson, MS Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, MSN, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Helen Young, MSN, MPH, CRRN, PHN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Melissa Khashei, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	HYMPAVZI (marstacimab-hncq)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761369
Applicant:	Pfizer, Inc.

1 INTRODUCTION

On October 11, 2023, Pfizer, Inc. submitted for the Agency's review an original Biologics Application (BLA) 761369 for HYMPAVZI (marstacimab-hncq) injection. The proposed indication is for 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 (congenital factor VIII deficiency) without factor VIII inhibitors, or
- hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on October 26, 2023 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for HYMPAVZI (marstacimab-hncq) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a DMEPA review of the IFUs was completed on April 15, 2024.

2 MATERIAL REVIEWED

- Draft HYMPAVZI (marstacimab-hncq) injection PPI and IFUs received on October 11, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 2, 2024.
- Draft HYMPAVZI (marstacimab-hncq) injection Prescribing Information (PI) received on October 11, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 2, 2024.
- DMEPA review of HYMPAVZI (marstacimab-hncq) injection Human Factors Study Report and Label and Label Review dated April 15, 2024.
- Approved HEMLIBRA (emicizumab-kxwh) injection comparator labeling dated January 31, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFUs document using the Arial font, size 10.

In our collaborative review of the PPI and IFUs we:

- simplified wording and clarified concepts where possible

- ensured that the PPI and IFUs are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFUs meet the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFUs are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFUs.

Please let us know if you have any questions.

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/s/

HELEN K YOUNG
07/12/2024 01:37:22 PM

MELISSA KHASHEI
07/12/2024 01:58:46 PM

BARBARA A FULLER
07/12/2024 02:16:47 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 12, 2024
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761369
Product Name, Dosage Form, and Strength:	Hympavzi (marstacimab-hncq) Injection, 150 mg/mL
Applicant Name:	Pfizer Inc.
FDA Received Date:	July 3, 2024
TTT ID #:	2023-6697-2
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader (Acting):	Millie Shah, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Pfizer Inc. submitted revised container labels and carton labeling received on July 3, 2024 for Hympavzi. We reviewed the revised container labels and carton labeling for Hympavzi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to our Nonproprietary Name Suffix Advice letter.[a]

2 CONCLUSION

Pfizer Inc. implemented all of our recommendations and we have no additional recommendations at this time.

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

[a] Corbie, C. Nonproprietary Name Suffix Advice for Hympavzi. Silver Spring (MD): FDA, CDER, DNH (US); 2024 JUN 21. BLA 761369.

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/s/

JODY K KUNDRESKAS
07/12/2024 03:52:50 PM

MILLIE B SHAH
07/12/2024 03:56:26 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	May 10, 2024
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761369
Product Name, Dosage Form, and Strength:	Hympavzi (marstacimab-xxxx)[a] Injection, 150 mg/mL
Applicant Name:	Pfizer, Inc.
FDA Received Date:	April 30, 2024
TTT ID #:	2023-6697-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader (Acting):	Millie Shah, PharmD, BCPS

[a] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder established name-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

1 PURPOSE OF MEMORANDUM

Pfizer, Inc. submitted revised container labels and carton labeling received on April 30, 2024 for Hympavzi. We reviewed the revised container labels and carton labeling for Hympavzi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

Pfizer, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

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

[b] Kundreskas, J. Human Factors Study Report and Label and Labeling Review for Hympavzi (BLA 761369). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 APR 15. TTT ID: 2023-6697.

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JODY K KUNDRESKAS
05/10/2024 01:53:16 PM

MILLIE B SHAH
05/10/2024 03:17:42 PM

HUMAN FACTORS STUDY REPORT AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 15, 2024
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761369
Product Type:	Combination Product (Biologic-Device)
Product, Name, Dosage Form and Strength:	Hympavzi (marstacimab-xxxx)[a] injection, 150 mg/mL
Device Constituents:	Prefilled syringe and prefilled pen
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer, Inc.
FDA Received Date:	October 11, 2023, December 14, 2023, January 31, 2024, and March 7, 2024
TTT ID #:	2023-6697 and 2023-6698
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader (Acting):	Millie Shah, PharmD, BCPS
DMEPA 2 Associate Director for Human Factors:	Lolita Sterrett, PharmD
DMEPA 2 Associate Director for Nomenclature and Labeling:	Hina Mehta, PharmD

REASON FOR REVIEW

[a] The nonproprietary name for this BLA has not yet been determined thus, the nonproprietary name placeholder, marstacimab-xxxx, is used throughout this review to refer to the non-proprietary name for this product.

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under BLA 761369 for Hympavzi (marstacimab-xxxx) injection.

1.1 PRODUCT INFORMATION

Table 1 presents relevant product information for Hympavzi that Pfizer, Inc. submitted on October 11, 2023.

Table 1. Relevant Product Information for Hympavzi	
Initial Approval Date	N/A
Active Ingredient	Marstacimab-xxxx
Indication	For the routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with: • Hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or • Hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	150 mg/mL
Dose and Frequency	Day 1: 300 mg (two 150 mg injections) by subcutaneous injection (loading dose) Day 8 and thereafter: 150 mg every week by subcutaneous injection <u>Dose Adjustment During Treatment:</u> A dose adjustment to 300 mg subcutaneous injection weekly can be considered in patients weighing 50 kg or more when control of bleeding events is judged to be inadequate by the healthcare provider.
How Supplied	• Prefilled Syringe o 150 mg/mL o Carton of 1 single-dose prefilled syringe • Prefilled Pen o 150 mg/mL o Carton of 1 single-dose prefilled pen
Storage	• Store refrigerated between 36°F and 46°F (2°C to 8°C) in the original carton to protect from light. • The product may be removed from refrigerated storage and stored in its original carton for one

	single period of maximum 7 days at room temperature [up to 86°F (30°C)]. The product must not be returned to refrigerated storage. Prior to the end of this period of room temperature storage, the product must be used or discarded. • Do not freeze. • Do not shake.
Container Closure/Device Constituent (including figure)	• Prefilled Syringe (PFS) o [redacted] (b) (4) 1 mL Syringe made of Type I [redacted] (b) (4) glass with staked needle, plunger rod, and finger grip. o Placed in a paperboard inlay within a paperboard carton. Each carton contains a single syringe as well as Prescribing Information and Instructions for Use. The carton has tamper evident perforations. 

	(b) (4)
	• Prefilled Pen o (b) (4) o Placed in a paperboard inlay within a paperboard carton. Each carton contains a single pen as well as Prescribing Information and Instructions for Use. The carton has tamper evident perforations.

	(b) (4)
Intended Users	By patients and their lay caregivers. Additionally, Healthcare Professionals may administer.
Intended Use Environment	Home or other non-clinical settings. Additionally, may be administered in clinical settings.

1.2 RELEVANT REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On December 8, 2023, we searched for previous DMEPA reviews and FDA/Applicant interactions relevant to this current review using the terms, 'marstacimab', '761369', and '126734'. The identified reviews and FDA/Applicant interactions are provided below.

- On November 1, 2021, the Sponsor submitted a Use-Related Risk Analysis (URRA) to present justification not to submit human factors validation study (HFVS) results for the proposed 150 mg/mL prefilled syringe (PFS) and a HFVS protocol for the proposed 150 mg/mL prefilled pen under IND 126734.

- On July 7, 2022, we informed the Sponsor that we agreed with the Sponsor's plan not to submit the HFVS results for the proposed prefilled syringe.[b]
- On July 7, 2022, we communicated our recommendations for the HFVS protocol for the prefilled pen to the Sponsor.[c]

- On October 11, 2023, the Applicant submitted a Human Factors Risk Assessment – Justification for not performing Human Factors Validation for the proposed prefilled syringe, and a HFVS report for the proposed prefilled pen, as well as labels and labeling for both the prefilled syringe and the prefilled pen, which are the subject of this review. Since we previously determined that no HF validation study data needed to be submitted for the marketing application for the proposed PFS[d], only the HFVS results for the proposed 150 mg/mL prefilled pen are the subject of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2. Materials Considered for this Review

Material Reviewed	Section/Appendix
Product information	Section 1.1
Background Information Previous DMEPA HF Reviews	Section 1.2
Human Factors (HF) Validation Study Report and HF-Related Supporting Documents	Appendix A
Information Requests Issued During the Review	Appendix B
Product Sample, Labels, Labeling, and Packaging	Appendix C

N/A=not applicable for this review

OVERALL ASSESSMENT OF HUMAN FACTORS STUDY DESIGN AND METHODOLOGY

The sections below provide a summary of the study design, and our evaluation of the study methodology to determine if study has been appropriately designed to support the safe and effective use of the proposed product.

1.4 SUMMARY OF STUDY DESIGN

[b] Wu, L. Human Factors General Advice Letter for Marstacimab. Silver Spring (MD): FDA, CDER, DNH (US); 2022 JUL 07. IND 126734.

[c] Wu, L. Human Factors Validation Study Protocol Advice Letter for Marstacimab. Silver Spring (MD): FDA, CDER, DNH (US); 2022 JUL 07. IND 126734.

[d] White, L. Use Related Risk Analysis and Comparative Analysis Review for Marstacimab (IND 126734). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUN 15. OSE RCM No.: 2021-2209.

Table 3 presents a summary of the HF validation study design for the pen. See Appendix A for more details on the study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study of Prefilled Pen	
Study Design Elements	Details
Participants	• Patients (Adolescent aged 12-17 years) o n=15 o Diagnosed with hemophilia A or B (with or without inhibitors) or surrogate condition including Von Willebrand, Factor II, V, VII, X, or XII deficiency, syringe medicated diabetic patients, or bleeding disorders. o 10/15 had injection experience • Caregivers (Adults aged 18+ years) o n=15 o Who care for a patient diagnosed with hemophilia A or B (with or without inhibitors) or approved surrogate condition including Von Willebrand, Factor II, V, VII, X, or XII deficiency, syringe medicated diabetic patients, or bleeding disorders. o 12/15 had injection experience • Healthcare Professionals (Adults aged 18+ years) o n=15 o Medical professionals with at least one year of experience who administer injections to patients.
Training	All participants attended a single simulated use testing session to assess the use of the product without training, representing the worst-case scenario.
Test Environment & Materials	• Both the home environment simulation (for patients and caregivers) and the clinical environment simulation (for healthcare professionals) had minimal background noise, normal indoor temperature, humidity, and light conditions. • The pen used in this study was representative of the 150 mg/mL dose strength and filled with surrogate drug solution, devoid of active drug. The pen, labeling, packaging and all user interface materials supplied were

	representative of the commercial intent in terms of size, shape, and functionality, however, did not include the final commercial branding. • Additional supplies present in all study environments include: A pre-opened sharps container, paper towels, cotton balls, gauze pads, Band-Aids, hand sanitizer, alcohol wipe, gloves, injection pad/strap, manikin (for healthcare providers and caregivers), and a household trash can. • The home environment simulation consisted of a large, well-lit room containing typical home furnishings (e.g., table, chairs, lamps, bookshelves, etc.). The room also had either a refrigerator or a simulated refrigerator where the drug product was stored. A fully functional or simulated sink was also present. • The clinical environment simulation consisted of a quiet, well-lit room containing typical clinical equipment and supplies (e.g., gloves, sharps container, cotton balls).
Sequence of Study	1. Introduction and informed consent. Participants were asked to simulate up to 3 injections representative of marstacimab-xxxx 150 mg/mL to themselves (patients) or someone else (caregivers/healthcare professionals). 2. Participants were introduced to the study environment and received a brief introduction to the scenario. 3. Participants were asked which injection site they wished to choose. If injecting themselves, the participant injected into an injection pad worn on their own body. When injecting someone else, they injected into an injection pad attached to a manikin. 4. First simulated injection. 5. Study participants asked how they believe they did and were given an opportunity to comment on their performance. 6. An hour of learning decay consisting of a 40 minute break where participants left the simulation room, followed by 20 minutes of distraction tasks before starting the next simulated-use injection. During the distraction tasks, a

	REALM[e] or REALM Teen health literacy assessment, Snellen visual acuity test, a Cochin assessment to evaluate hand dexterity, hand measurements, grip strength, pinch strength, and hand size measurements were assessed. 7. Second simulated injection. 8. Study participants asked how they believe they did and were given an opportunity to comment on their performance. 9. Third simulated injection (if needed). 10. Study participants asked how they believe they did and were given an opportunity to comment on their performance (if third simulated injection performed). 11. Follow up questions to determine root cause for any use events. 12. Knowledge questions assessing IFU and subjective feedback. 13. Compensation and dismissal.

1.5 DISCUSSION OF METHODOLOGY

We acknowledge the Applicant has indicated that the caregiver cohort represents both caregivers and patients 18 years and older in terms of cognitive and physical ability since hemophilia does not inhibit the ability of patients to use the PFP. We find that this approach provides for a lack of data from the adult patient user group who may self-inject.

We further considered the identified user groups to determine if the methodology precludes our ability to review the HFVS data. We find that HFVS study data from the adolescent patient user aged 12-17 who may self-inject is a higher risk use scenario when compared to the adult patient who may self-inject in this specific instance. We find that patients do not have any physical or cognitive limitations that would impact use of the product based on this disease. As such, we find that the Applicant's proposal in this specific instance that the caregiver cohort represents both adult lay caregivers and adult patients in this particular instance does not preclude our ability to review the HFVS results to support that the proposed product is safe and effective when used as intended.

RESULTS AND ANALYSIS

We have carefully reviewed each reported issue (i.e., use error, close call, use difficulty), the Applicant's URRA, the participants' subjective feedback, the Applicant's RCA, and the Applicant's comments and proposed mitigations (if applicable) to determine if the results indicate that the user interface has been appropriately designed to support the safe and

[e] The Rapid Estimate of Adult Literacy in Medicine (REALM) is a word recognition test to provide an assessment of patient health literacy.

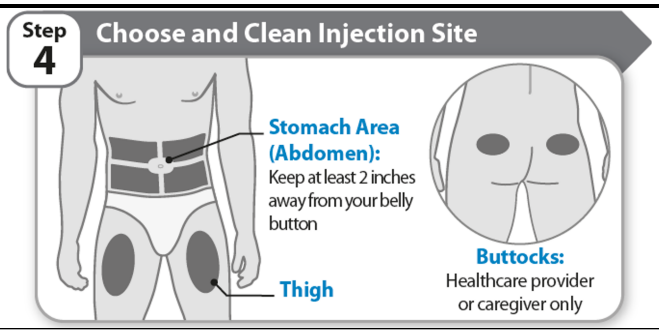
effective use of the proposed product. In Table 4 below, we provide a summary of the use-related events supplied by the Applicant along with our detailed analysis of use-related events that resulted in recommendations and document our points of dissent with the Applicant's findings.

Table 4. Focused Analysis of Reported Issues and DMEPA's Recommendations

Legend: **UE** = use error; **CC** = close call; **UD** = use difficulty; **URRA** = use-related risk analysis; **RCA** = root cause analysis; **HFVS** = Human Factors Validation Study; **CE** = injection experienced caregiver; **CN** = injection naïve caregiver; **H** = healthcare practitioner; **PE** = injection experienced patient; **PN** = injection naïve patient

<table>
<tr><th>Summary of Information Supplied by Applicant</th><th>DMEPA's Identified Areas of Dissent and Recommendations</th></tr>
<tr><td>Task: Select injection site
Scenario: Simulated use
<table>
<tr><td>Reported Issues:</td><td colspan="3">Participant Type(s):</td></tr>
<tr><td></td><td>1st Injection</td><td>2nd Injection</td><td>3rd Injection</td></tr>
<tr><td>UE (n=9)</td><td>PE (n=1)
PN (n=2)
CE (n=1)</td><td>PE (n=1)
PN (n=2)
CE (n=1)
CN (n=1)</td><td></td></tr>
<tr><td>CC (n=1)</td><td>H (n=1)</td><td></td><td></td></tr>
<tr><td>UD (n=0)</td><td></td><td></td><td></td></tr>
</table></td><td></td></tr>
<tr><td>Observed event(s):
Observed using an unsuitable injection site.</td><td></td></tr>
<tr><td>Relevant RCA/Subjective Feedback:
One participant chose a correct injection site in the abdomen in simulation 1, then selected an incorrect site in the abdomen in scenario 2. The participant stated they chose to inject over the center of the abdomen during scenario 2 because they saw in the IFU to inject into the abdomen, and they wanted to avoid injecting into the ribcage or intestines.
Two participants chose an area in the forearm in both first and second scenarios due to prior experience. Of these two participants, one did not read the IFU at all prior to injecting and the other did but chose to ignore them.
One participant chose an area in the upper forearm, disregarding the IFU prompts for the correct injection site due to their prior experience and a simulated use environment.
One caregiver participant chose an area in the lower arm during the first simulation and the forearm during the second injection due to this being the standard injection site for their child and more comfortable position for administration. Their healthcare provider had instructed them to not inject their child anywhere else and so they remained in</td><td></td></tr>
</table>

that area. Additionally, they stated after reviewing Step 4 of the IFU they thought any soft tissue was acceptable. • The healthcare provider initially chose the wrong injection site to the upper arm but corrected themselves prior to administering the dose. They stated a lot of injections can be administered in the upper arm so they assumed the appropriate location would be there.	
Based on the Applicant's URRA, performing this task incorrectly or not at all may result in: • Subcutaneous injection not achieved. Injection is intradermal leading to loss of therapeutic effect, injection site reaction. • Subcutaneous injection not achieved. Injection is intramuscular leading to loss of therapeutic effect, injection site reaction. • Injection at unsuitable injection sites leading to loss of therapeutic effect, injection site reaction, internal bleed episode and/or inflammation and/or local infection. • Potential contamination with biological agents (CCI maintained) leading to local infection, inflammation. • Injection at unsuitable injection sites leading to loss of therapeutic effect, injection site reaction, internal bleed episode. • Subcutaneous Injection not achieved. Injection is intravenous leading to bleeding and/or bruising.	
Applicant's Comments and Proposed Post- HFVS Mitigations: • The majority (40/45) participants completed this task successfully in the simulated testing. The arm was chosen by 4/5 participants as a result of an incorrect mental model or prior experience overriding the IFU. Two of these participants did not read or skim read the IFU. • During the post test interview, 44/45 participants correctly stated where to give an injection and 1/45 stated that the pen can be injected into the abdomen, thigh, and buttocks, but did not clarify that only healthcare providers or caregivers can inject into the buttocks. Due to the nature of the root causes and post test interview results, no further mitigations are required.	We note that the text of Step 4 in the IFU instructs users to choose one of three injection sites – stomach area (abdomen), thigh, or buttocks and specifies if choosing the stomach area to keep at least 2 inches away from the belly button. However, the corresponding image has a solid black line and terminal black dot visually directing the user to the area around the belly button where they should not inject (see figure below). We find this graphic can be improved to direct the reader to where they should inject (grey areas), instead. As such, we provide a recommendation in Table 6 below. We find this recommendation can be implemented without the submission of additional HFVS data.

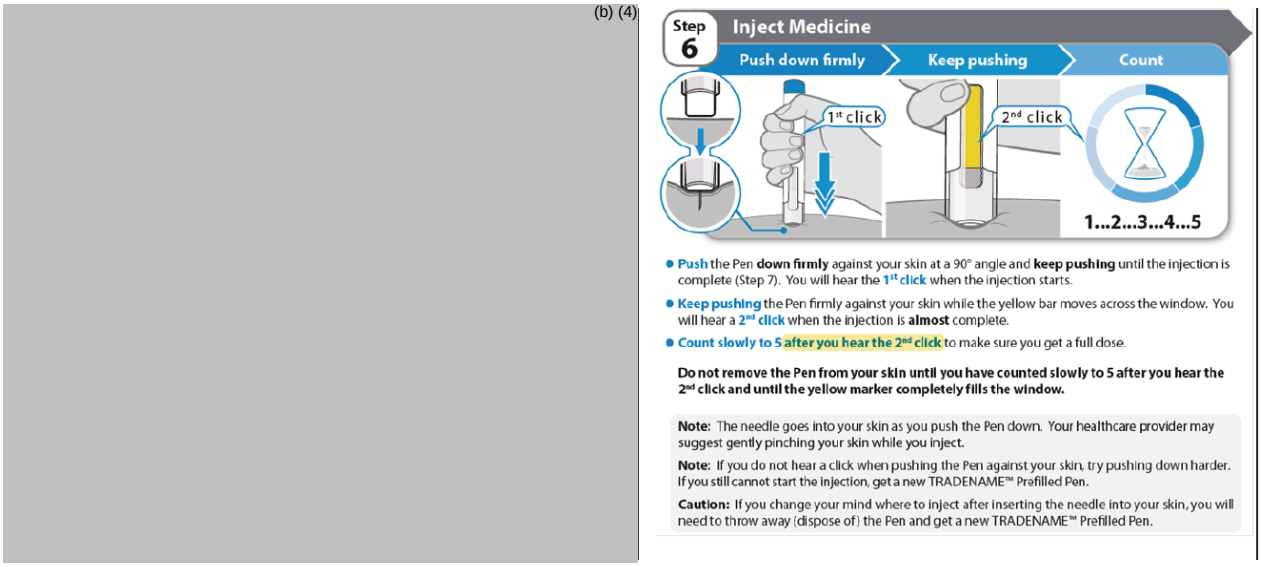
1.6 ANALYSIS OF THE REMAINING IDENTIFIED ISSUES

The HF validation study reported issues with the tasks listed below that impact delivering a full dose:

- Push the pen firmly down against the skin to start injection (first click):
  - One participant stated they felt their hand was not very steady when pressing the pen against the skin. They clarified that they do not typically self-inject. Two participants pushed down on the blue end of the pen with their thumb before pressing the pen down at the injection site. The blue end of the pen inferred it was a button. The Applicant stated these use events were not repeated on subsequent injections, demonstrating that participants learned from their mistakes committed during an initial injection in a subsequent injection. Therefore, no further mitigations are required.
- Keep pushing the pen firmly against skin whilst yellow bar moves across the window:
  - Three participants did not push the pen firmly against the skin while the yellow bar moved across the window during the first scenario. One participant released pressure slightly while holding the pen against the skin, one participant lifted the pen slightly before the second click but corrected to holding firmly until the second click during the second scenario, and one participant depressed the pen against the injection pad with such force that it caused the pad to deform, preventing the liquid from escaping the pen during both the second and third injections. Participants thought the injection was complete prior to the second click due to not reading the IFU, thinking the first click was the second click, assuming the medication was delivered as soon as the pen made contact with the skin, and believing the mechanism of the plunger pushing down was the second click. All resulted in a wet injection and all three participants realized they had not delivered a full dose of medicine, recognized that they would need to hold the pen longer, and were successful when giving either a second or third dose. The Applicant made updates to Step 6 of the IFU to better emphasize the need to continue

to hold the pen in place until you hear the second click and count slowly to five by changing “after you hear the 2nd click” to bold and blue text (see figure below).

- Hold the pen in place for 0.6 seconds post second click (count to 5 after the second click): (According to the Applicant, “A minimum hold time of 0.6 seconds post 2nd click is required to ensure a full dose of medicine is delivered. This is referred to as the ‘clinically relevant hold time’. The IFU instructs users to count slowly to five after the second click to ensure the pen is held in place for the required 0.6 seconds after the second click.”)
    - Two participants did not hold the pen in place for 0.6 seconds post second click and removed the pen from the injection site immediately after the second click. One participant counted to 5 after the first click due to misreading IFU and one participant thought the second click indicated the injection was complete. One participant experienced a close call due to negative transfer from previous experience because they began counting to five after the first click, reached “four” and the second click occurred so then corrected and recounted to five after the second click. Three participants experienced a use difficulty holding the pen in place after the second click due to not recognizing the first click and misinterpreting the first click (were unable to hear the clicks and held the pen in place longer than necessary) or negative transfer from previous experience. Additionally, one participant recognized they did not administer a full dose as they did not hear a second click to prompt them to count to five. In this case, when the pen was removed from the injection pad, the liquid started flowing again. The Applicant made updates to Step 6 of the IFU to better emphasize the need to continue to hold the pen in place until you hear the second click and count slowly to five by changing “after you hear the 2nd click” to bold and blue text (see figure below).



Applicant's updates to Step 6 of the IFU Original (left) and Revised (right).

Based on our review of the available assessment of these identified issues, the available participants' subjective feedback, the Applicant's root cause analysis, and post-HFVS changes to the user interface, we find the proposed user interface has been appropriately designed to address the identified issues and we did not identify further need for risk mitigation strategies at this time. Additionally, in this instance, we determined the Applicant's proposed post-HFVS changes to Step 6 of the IFU do not require submission of additional HF data.

LABELS AND LABELING

Tables 5 and 6 below include the identified medication error issues with the submitted product samples, packaging, label and labeling, our rationale for concern, and our proposed recommendations to minimize the risk for medication error.

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	As currently presented, the text in the second bullet under Dosage and Administration does not specify all possible injection sites such as the upper arm (prefilled	Providing only partial information may lead to users missing important information, leading to wrong injection site selection.	We recommend removing this bullet.

Table 5. Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	syringe only) or buttocks (prefilled pen only) by a caregiver or healthcare professional.		
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, the error prone symbol "≥" is utilized in section 2.3.	Error prone symbols may lead to misinterpretation and medication error.	We recommend replacing the symbol with its intended meaning. Revise "≥50 kg" to "greater than or equal to 50 kg".
2.	The instructions describing what to do when a dose is missed is confusing.	Confusing instructions may contribute to medication error.	We recommend revising "(b) (4) [redacted] to "If more than 13 days have passed since the last dose was administered, a loading dose of 300 mg by subcutaneous injection should be administered, followed by a resumption of 150 mg by subcutaneous injection once weekly thereafter.".

Table 6. Identified Issues and Recommendations for Pfizer, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			

Table 6. Identified Issues and Recommendations for Pfizer, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	As currently presented, the proprietary name is denoted by the placeholder "Trade name".	We are unable to assess the prominence and readability of the intended presentation of the proprietary name.	We reference our April 3, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Hympavzi, was found conditionally acceptable. We recommend replacing the placeholder "Trade name" with the conditionally acceptable proprietary name, Hympavzi, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
Container Labels			
1.	On the prefilled syringe, the "Rx only" statement competes for prominence with other more critical information (e.g., proprietary name, proper name, strength, route of administration) on the principal display panel.	The "Rx only" statement should not compete in size and prominence with critical information on the principal display panel.	We recommend the "Rx only" statement does not compete in prominence with critical information on the principal display panel. We recommend debolding "Rx only" to reduce the prominence of this statement. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
Carton Labeling			
1.	The statement (b) (4) " may be misinterpreted.	This statement is boxed and prominently located above the "Store refrigerated…" message and may be misinterpreted as the carton providing sufficient	We recommend removing this statement.

Table 6. Identified Issues and Recommendations for Pfizer, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		refrigerated controls, leading to inadvertent storage at room temperature, and deteriorated drug medication errors.	
Instructions for Use			
1.	In both the prefilled syringe and prefilled pen IFUs, the image for Step 4 is not consistent with the written instructions for choosing an injection site in the stomach area (abdomen). Specifically, (b) (4) "Keep at least 2 inches away from your belly button".	Inconsistency between the image and the text in Step 4 of the IFU may lead to wrong site medication errors.	Revise this image to be consistent with the written instructions (for example, consider removing (b) (4)).
2.	In the IFU for the prefilled syringe, the image for Step 6 is not consistent with the written instructions. Specifically, the image depicts a needle visible outside of the skin while the written instructions state "Insert the needle to its full depth into your	Inconsistent use of diagrams may lead to medication errors.	Revise this image to be consistent with the written instructions.

Table 6. Identified Issues and Recommendations for Pfizer, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	skin, at a 45° angle, as shown.”.		

CONCLUSION AND RECOMMENDATIONS

The results of the HFVS identified use errors, close calls, and use difficulties with critical tasks. However, based on our review of the available participants' subjective feedback, and the Applicant's URRA, RCA, and proposed mitigations (including any post-HFVS changes to the user interface), we find the residual risks are acceptable or can be further mitigated via additional labeling revisions for those use-related events. Thus, in this specific instance, we find the simulated use HFVS results are acceptable provided our recommendations are implemented.

Additionally, our evaluation of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. We provide recommendations for the Division in Table 5 and for the Applicant in Table 6, above. These changes can be implemented without submitting additional HF validation testing results for Agency review.

APPENDICES:

APPENDIX A. HUMAN FACTORS (HF) VALIDATION STUDY REPORT AND HF-RELATED SUPPORTING DOCUMENTS

- The HF study results report and background information can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761369\0001\m3\32-body-data\32r-reg-info\dp-prefilled-pen-human-factors-engineering-report.pdf
- The use-related risk analysis can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761369\0001\m3\32-body-data\32r-reg-info\dp-prefilled-pen-hfer-appendix-1-human-factors-summative.pdf

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On 12/7/2023, we issued an Information Request (IR) to request a red lined and annotated version of the HFVS protocol that identifies the changes made after Agency feedback as well as any Agency recommendations that were not implemented, and justification. Additionally, 5 placebo only intend-to-market samples of both the prefilled pen and prefilled syringe were requested. On 12/14/2023, the Applicant notified the Agency that samples are currently unavailable and would be provided by the end of January 2024. Additionally the Applicant provided an annotated HFVS protocol that can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761369\0013\m1\us\resp-cmc-ir-07dec2023-qqr1.pdf

On 1/25/2024, we issued an IR to request rationale for the use of the verb "pushing" after the injection begins (throughout Step 6 of IFU) rather than the word "holding". On 1/31/2024, the Applicant provided an acceptable response. The Applicant stated that during early formative studies of the platform delivery system, the word "hold" was utilized throughout Step 6 of the IFU. However, it was found that the use of the verb "hold" resulted in a number of participants failing to maintain downward force against the skin for the duration of the injection, and therefore the verb was changed to "pushing". Further formative work showed this change in wording to be effective in reducing the number of incomplete injections due to failure to maintain downward force for the duration of the injection. The Applicant's full response can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761369\0018\m1\us\response-25jan2024.pdf

APPENDIX C. PRODUCT SAMPLE, LABELS, LABELING, AND PACKAGING

C.1 Product Sample

The product samples were submitted for our review, and we did not identify any recommendations for improvement at this time.

C.2 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error experiences with similar products, we reviewed the following Hympavzi labels and labeling submitted by Pfizer, Inc.

- Container label(s) received on October 11, 2023
- Carton labeling received on October 11, 2023
- Instructions for Use received on October 11, 2023, available from \\CDSESUB1\EVSPROD\bla761369\0001\m1\us\uspi-lab-1556-0-1-clean.pdf
- Prescribing Information and Patient Prescribing Information (Image not shown) received on October 11, 2023, available from \\CDSESUB1\EVSPROD\bla761369\0001\m1\us\uspi-lab-1556-0-1-clean.pdf

C.3 Label and Labeling and Packaging Images

Container Labels:

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

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/s/

JODY K KUNDRESKAS
04/15/2024 07:14:36 AM

MILLIE B SHAH
04/15/2024 07:22:30 AM

LOLITA G STERRETT
04/15/2024 04:31:16 PM

HINA S MEHTA
04/17/2024 01:09:24 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 1/9/2024

TO: Division of Cardiology and Nephrology (DCN)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761369

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4) The RRA was conducted under the following submissions: (b) (4)

OSIS concluded that the data from the reviewed studies were reliable.

Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

WENDY NG
01/09/2024 06:11:19 PM