CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761154Orig1s000

OTHER REVIEW(S)

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	3/14/2020		
To:	Kelly Ballard, OPQ/OPRO/DRBPMI/RBPMBI		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	Choose an item.
From	Suzanne Hudak OPEQ/OHT3/DHT3C		
Through (Team)	Rumi Young, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	BLA761154, Hulio (adalimumab) ICC1900614 (b) (4) Cases Numbers: Case 0001182 and Case 00011863		
Recommendation	**Filing Recommendation Date: 8/15/2019** ☐ 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)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761154
Sponsor	Mylan GmbH
Drug/Biologic	Adalimumab
Indications for Use	Indicated for the treatment of RA, juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), Plaque psoriasis (Ps), ankylosing spondylitis (AS), adult and pediatric CD, UC, (b) (4)
Device Constituent	Pre-Filled Syringe and Auto-Injector

Review Team	
Lead Device Reviewer	*Suzanne Hudak*

Important Dates	
Interim Due Dates	**Meeting/Due Date**
Filing Date	09/10/19
74-Day Letter Due to Applicant	09/24/2019
Mid-Cycle	1/17/2020
Primary Review	3/12/2020
PDUFA	5/12/2020

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	
Clinical Validation	x			
Human Factors Validation	x			
Facilities & Quality Systems	x			

1.1. 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:
The syringes used in the devices are plastic which are not siliconized. There are no device functionality issues, however take note when evaluating the CCI methods and results over time since plastic syringes are known for leakage/CCI issues.

Comment #2:
Differences in device essential performance parameters for the different product presentations (vial/PFS/AI) as well between the biosimilar and reference products are considered validated if the referenced studies FKB327-005 and FKB327-001 were adequate. We defer clinical outcome evaluation to CDER.

1.2. 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:

1.3. Recommended Post-Market Commitments/Requirements

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

2. PURPOSE/BACKGROUND

2.1. Scope

Mylan GmbH is requesting approval of FKB327 "Hulio" as a proposed biosimilar for Humira. The device constituents of the combination product are a Pre-Filled Syringe and an Autoinjector.

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

(b) (4) Case #00011862 Instructions: "Please provide a review for the device component for BLA 761154."
Case #00011863 Instructions: "Please provide a facilities review for the device component for BLA 761154."

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
- Biocompatibility of the patient contacting components
- Release Specifications for the device constituents
- Sterility of the device constituent if applicable
- Facilities inspection

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Human factors

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

2.2. Prior Interactions

2.2.1. Related Files

The sponsor provided a Statement of Right of Reference to:
MAF [redacted] (b) (4)
DMF

2.3. Indications for Use

Combination Product	Indications for Use
FKB327 "Hulio"	Indicated for the treatment of RA, juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), Plaque psoriasis (Ps), ankylosing spondylitis (AS), adult and pediatric CD, UC, [redacted] (b) (4)
Auto-Injector and Prefilled Syringe	Delivery of the Drug Product

2.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0001 (Original submission)	3.2.P.2.4 Pharmaceutical Development – Container Closure System, 20mg and 40 mg PS and 40 mg AI
	3.2.P.7 Container Closure System, 20mg and 40 mg PS and 40 mg AI
	3.2.P.5.1 Specifications, 20mg and 40 mg PS and 40 mg AI
	3.2.P.5.6 Justification of Specifications, 20mg and 40 mg PS and 40 mg AI
	3.2.P.8 Stability, 20mg and 40 mg PS and 40 mg AI
	3.2.P.3.3 Description of Manufacturing Process and Process Controls, 20mg and 40 mg PS and 40 mg AI
	3.2.P.2.3 Manufacturing Process Development
	3.2.P.3.5 Process Validation, 20mg and 40 mg PS and 40 mg AI
	1.14.1 Draft Labeling, 20mg and 40 mg PS and 40 mg AI
	3.2.P.1 Description and Composition of the Drug Product, 20mg and 40 mg PS and 40 mg AI
	5.3.5.1, 5.3.5.3, 5.3.5.4 Clinical studies and Usability studies
0003 (Response to interactive review)	1.11.1 Information Amendment Information not covered under Modules 2 to 5
0003	3.2.P.3 Manufacture

0014 (Response to interactive review)	1.11.1 Information Amendment Information not covered under Modules 2 to 5
0014	3.2.R Regional Information

3. DEVICE DESCRIPTION

3.1. Device Description

3.1.1. Prefilled Syringe

From 3.2.P.2 PharmDev

The container closure system (CCS) for FKB327 the Drug Product (DP) is a single-use PLAJEX™ plastic syringe (1 mL long), which is assembled into the safety device. The prefilled syringe (PFS) with safety device provides a delivery function for a single dose drug administration and safety function to protect from needle injury after administration. The PFS will be provided in 20 mg/0.4mL and 40 mg/0.8 mL presentations.

(b) (4)

The safety device used for FKB327 DP is (b) (4) The PFS with safety device provides a delivery function and safety function to protect needle injury after administration. No components of the safety device come into contact with the FKB327 DP solution and the safety device is not part of the fluid path. The safety device is also described in MAF (b) (4)

EPRs:

EPR Name (P.2.4)	Terminology from P.7 or P.5.1	Acceptance Criteria
Breakage force of lock mode	Same	(b) (4)
Gliding force	Same	
Deliverable Volume	Volume in container	

The following are tables from P.7:

Table 2: Primary Container Closure System Components, In-coming Testing Specifications

Component	Attribute	Test Method	Acceptance Criteria
PLAJEX™ (plastic syringe)	Material requirements	USP<85>	(b) (4)
		USP<661.2> Ph. Eur. 3.2.2.1	
	Outer diameter of needle	ISO9626	
	Inner diameter of needle	ISO9626	
PLAJEX™ (needle shield)	Material requirements	USP<381>, Ph. Eur. 3.2.9	
PLAJEX™ (b) (4) stopper)	Material requirements	USP<85>	
		USP<381>, Ph. Eur. 3.2.9	
Assembled PLAJEX™	Appearance	Visual inspection JP<7.02>	
	Puncture resistance	Physical force measurement [b]	
	Removal force of needle	Physical force measurement [c]	
	Removal force of needle shield	Physical force measurement [d]	
	Gliding force	Physical force measurement [e]	
	Liquid leakage	ISO11040-4	

a: Defect types include streak in barrel, scratch in barrel, bubble in barrel and other critical defects.
b: Puncture resistance is physical force to puncture rubber membrane by the needle and measured by compression/tension analyzer.
c: Removal force of needle is physical force to pull off the needle from the syringe barrel and measured by compression/tension analyzer.
d: Removal force of needle shield is physical force to pull off the needle shield from the syringe and measured by compression/tension analyzer.
e: Gliding force is physical force to push the stopper into the syringe barrel and measured by compression/tension analyzer.
Abbreviations: JP: Japanese Pharmacopoeia; Ph. Eur.: European Pharmacopoeia; USP: United States Pharmacopeia; ISO: International Organization for Standardization.

Table 4 Specification for the Safety Device Incoming Testing

Attribute	Test Method	Acceptance Criteria
Appearance	Visual inspection	(b) (4)
Capability of assembling with PLAJEX™	Visual inspection	
Activation force of lock mode	Physical force measurement [b]	
Breakage force of lock mode (push in)	Physical force measurement [c]	
Breakage of lock mode (pull out)	Visual inspection [d]	
Dimension [e]	Measurement	

a: Defect types include contamination and other critical defects.
b: The activation force of lock mode is physical force to push the plunger rod until initiating activation and measured by compression/tension analyzer.
c: Breakage force of lock mode (push in) is physical force to push the sleeve into body after activation and measured by compression/tension analyzer.
d: Breakage of lock mode by pulling out the sleeve manually is visually checked.
e: Measurement positions are described in Figure 4.

3.1.1.1.Steps for using the PFS

(b) (4)

Humira Prefilled Syringe

Below is a description of the proposed reference product

Instructions (from: https://www.humira.com/content/dam/humira/global/documents/pdf/humirasyringe_PIL.pdf
-Insert the needle into the squeezed skin at about a 45- degree angle
-Slowly push the plunger all the way in until all of the liquid is injected and the syringe is empty.

The available doses are 40 mg/0.8 mL syringe and 20 mg/0.4 mL syringe.
Device functionality is not included in the submission and is publicly available .

3.1.2. *Autoinjector*

From 3.2.P.2.4 Pharm Dev

The container closure system (CCS) for the FKB327 Drug Product (DP) is a single-use PLAJEX™ plastic syringe (1 mL long), which is assembled into an auto-injector (AI). The PLAJEX is a ready to fill plastic syringe assembled with a staked stainless-steel needle.

The AI provides a delivery function for a single dose administration of 40 mg/0.8 mL of FKB327 and a safety function to protect patients from needle injuries after administration.

EPRs:
Sponsor uses different terminology in different parts of the submission.

EPR Name (P.2.4)	Terminology from P.7 or P.5.1 or Verification Report	Acceptance Criteria
Injection depth	same	(b) (4)
Force to initiate injection	Push in resistance of cover sleeve, Initial force (verification report)	
Force to keep holding down device to skin during injection	Release force (verification report)	
Injection time	same	
Cover sleeve lock out force	Breakage force of lock mode	
Needle retraction after cover sleeve locks	same	
Dose accuracy	same	

The following table with specifications is from P.7

Table 4: Specification for the AI Incoming Testing

Attribute	Test Method	Acceptance Criteria
Appearance [a]	Visual inspection	(b) (4)
Elastic force of injection spring [a]	Physical force measurement [c]	
Capability of assembling with PLAJEX™	Visual inspection	
Dimension [d]	Measurement	
Removal force of cap remover	Physical force measurement [e]	
Push in resistance of cover sleeve	Physical force measurement [f]	
Functional testing for click sound	Sound inspection	
Injection depth	Measurement	
Capability of moving stopper to end position	Visual inspection	
Breakage force of lock mode	Physical force measurement [g]	

a: Test for pre-assembled unit.
b: Defect types include contamination and other critical defects.
c: The elastic force of injection spring is physical force of the spring during activation and measured by compression/tension analyzer.
d: Measurement positions are described in Figure 4.
e: Removal force of cap remover is physical force to pull off the cap remover from the housing and measured by compression/tension analyzer.
f: Push in resistance of cover sleeve is physical force to push the cover sleeve into the housing before activation and measured by compression/tension analyzer.
g: Breakage force of lock mode is physical force to push cover sleeve into the housing after activation and measured by compression/tension analyzer.

The following table with specifications is from P.5.1

Table 1: FKB327 40 mg AI Release and Shelf-life Specification

Attribute	Test Method	Acceptance Criteria
Appearance	Color and Clarity USP<631> Ph. Eur. 2.2.1, Ph. Eur. 2.2.2	(b) (4)
	Visible particles USP <790> Ph. Eur. 2.9.20 JP <6.06>	
pH	USP<791> Ph. Eur. 2.2.3	
Osmolality	USP <785> Ph. Eur. 2.2.35 JP<2.47>	
Particulate matter in injections	USP <788> Ph. Eur. 2.9.19	
Volume in container	USP <697> Ph. Eur. 2.9.17 JP <6.05>	
Device Functionality	Injection time	

Abbreviations: JP: Japanese Pharmacopoeia; Ph. Eur.: European Pharmacopoeia; USP: United States Pharmacopeia.

Figure 1: (b) (4)

Figure 2:

3.1.2.1. Steps for Using the Autoinjector

The first step of the operation of AI is pulling off the cap remover by a user. By taking off the cap remover, the rigid needle shield (including the needle shield) is also removed from the prefilled syringe which is assembled into the AI. A user pushes the AI's cover sleeve against the skin. By keeping pushing the device against the skin, the cover sleeve glides into the housing of the device and hence allows the needle to penetrate the subcutaneous tissue. The AI contains a pre-loaded spring which provides the power for controlled automated dose delivery. Dose delivery automatically starts once the cover sleeve has been pushed all the way to the stop. A click sound informs the user that dose delivery has started. Completion of the dose delivery is indicated by the second click sound. As a visual confirmation, the orange colored plunger rod becomes visible in the view window of the device. After the injection, the user removes the AI from the skin and the cover sleeve glides back to its initial position, completely covering the needle, where it is remained locked.

(b) (4)

Humira Auto-Injector

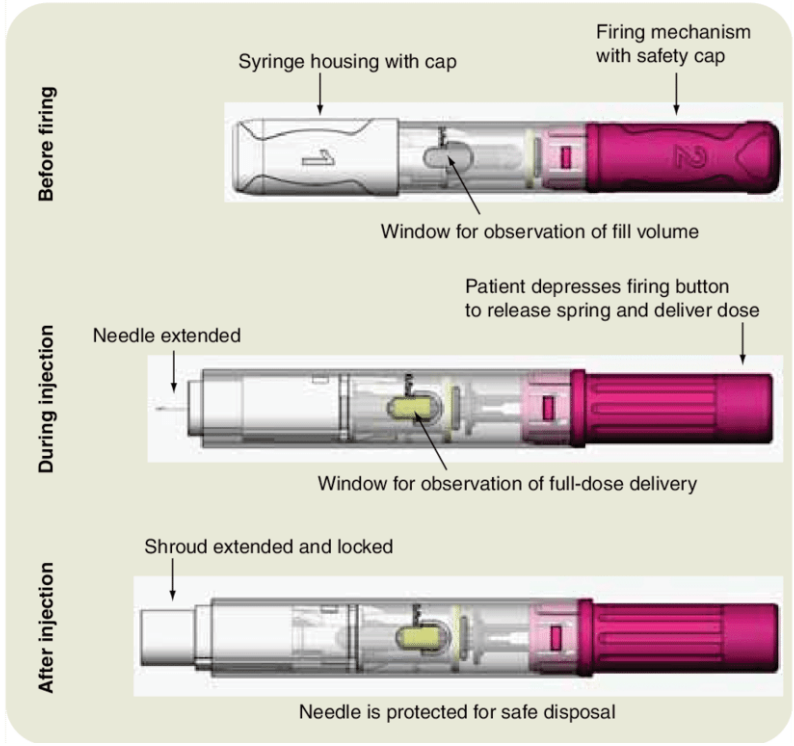

Image from publication: "HUMIRA (R) Pen: a novel autoinjection device for subcutaneous injection of the fully human monoclonal antibody adalimumab", Expert Review of Medical Devices 4(2) 109-16 April 2007.

Instructions (from: https://www.humira.com/content/dam/humira/global/documents/pdf/humirasyringe_PIL.pdf
-When the plum-colored button on the HUMIRA Pen is pressed to give your dose of HUMIRA, you will hear a loud "click."
-The loud "click" means the injection has started.
-You will know that the injection has finished when the yellow marker appears fully in the window view and stops moving

ICC1900614
IND 761154 , Adalimumab
Mylan GmbH
The autoinjector (referred to as a pen) is available in multiple strengths, including subject device strength of 40mg/0.8mL. Device functionality is not included in the submission and is not available online.

Reviewer Comment:
Dose strengths are the same as humira, and the devices are the same (prefilled syringe and autoinjector). Functional comparison was not provided by the sponsor. Clinical studies should be reviewed to validate any potential differences.

3.2. 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 Device Description is acceptable.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

4. FILING REVIEW

(b) (4)

[redacted]

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

(b) (4)

[redacted]

5. LABELING

5.1. 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

Labeling provided in section 1.14

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

(b) (4)

[redacted]

Reviewer Comments
Labeling contains relevant information and is acceptable.

5.2. 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 Labeling is adequate.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

6. DESIGN CONTROL SUMMARY

6.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product		**X (see comment)**	

Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)		**X (see comment)**	
Mitigations are adequate to reduce risk to health	**x**		
Version history demonstrates risk management throughout design / development activities		**X(see comment)**	
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
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 (see comment)	

Reviewer Comments

-Risk analysis approach provided for AI (P.2.4), however, data not provide. Risk analysis is not provided for PFS,

-P.2.4 PFS – references design FMEA, but it is not included. " Design verification testing was planned based on the functional requirements from the results of design FMEA."

- The traceability matrix was provided for the AI. The PFS essential performance was also reviewed and confirmed to be within specification.

Traceability was provided for the AI (3.2.P.2.4)

-The table provides adequate detail. User needs were linked to Product specifications. Below is an excerpt from the table.

User Requirement	Design Validation Set-up		Design Input Set-up	Design Output Set-u					Design Verification	Design Validation
Requirement	Confirmation Method	Criteria	Design Input (Product Specification)	Design Output (Product Specification)	Design Output (Reference Drawing)	EPRs	Verification Method	Criteria	Result	Result
The autoinjector allows users to inject the full volume of 0.8 mL FKB327 drug and to perceive the start and end of injections.	Usability engineering studies must confirm in a pass/fail-criterion whether users can operate the autoinjector properly in accordance with the intended use.	Patients or healthcare professionals can use the autoinjector appropriately and perceive the start and end of injections.	The duration of an injection must be (b) (4) seconds.	Product Requirement Specification (10090908)	9000126861, PQE-PF3512K3-00	X	Verification with Ypsomed verification report: Design Verification Summary Report (Doc# 10128133)	The duration of an injection must be (b) (4) seconds	Passed All the durations of an injection were within (b) (4) seconds.	Passed All the patients or healthcare professionals used the AI appropriately and perceived the start and end of injections.
			The inputs must meet Chapter 5.5h of ISO11608-1.	Product Requirement Specification (10090908)	N/A		Verification with Ypsomed verification report: Design Verification Summary Report (Doc# 10128133)	The inputs must meet Chapter 5.5h of ISO11608-1.	Passed The inputs of all tested autoinjectors met Chapter 5.5h of ISO11608-1.	
			A click sound must be audible at the end of injection.	Product Requirement Specification (10090908)	9000126861, PQE-PF3512K3-00		Verification with Ypsomed verification report: Design Verification Summary Report (Doc# 10128133)	A click sound must be audible at the end of injection.	Passed A click sound of all tested autoinjectors was audible at the end of injection.	

6.2. Applicable Standards and Guidance Documents

Generally Applicable Standards, Guidance Documents and Device-specific standards:

From 3.2.P.2.4 AI:

3.2.P.2.4.3.2. Applicable Regulations and Standards

Design controls of the AI were performed according to the applicable regulations and standards that include the following:

- 21CFR 820.30
- ISO 11608-1: Needle-based injection systems for medical use — Requirements and test methods — Part 1: Needle-based injection systems
- ISO 11608-5: Needle-based injection systems for medical use — Requirements and test methods — Part 5: Automated functions
- ISO23908: Sharps injury protection — Requirements and test methods — Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling
- ISO 13485: Quality management for medical devices
- ISO 10993-1: Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process
- ISO 10993-5: Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity
- ISO 10993-10: Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization
- ISO 14971: Medical devices — Application of risk management to medical devices

Design Verification complies with following standards:
ISO 11608-1:2014
ISO11608-5:2012
ISO 23908:2011

From 3.2.P.2.4 PFS:
Design requirements defined from the relevant regulatory standards:
ISO 23908:2011
ISO 14971:2007

Standard or Guidance	Conformance (Y/N/NA)

6.3. 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 Although there are no apparent design control IR, there are 74-Day letter IRs recommended for the design verification information. Refer to DV Section of this review memorandum.		

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

7. RISK ANALYSIS

7.1. Risk Analysis Attributes

Provided in Seq0001, P2.4

7.2. Summary of Risk Analysis

AI:

Risk analysis is included in P.2.4.
The sponsor states the following:
-Risk analysis and risk management followed ISO 14971:2007.
-Possible harms identified through available information and product profile
-Severity and risk assessment was conducted
-Control measures (mitigation) were reviewed
-Residual risks were reviewed to determine acceptability

Harms identified from:
-Ypsomate platform products and other AI products

****Reviewer note** – what are the harms? None listed. IR#1 was sent and was resolved after sponsor response.

-FMEA-based approach as a risk analysis method identified 108 harms. Likelihood and impacts were evaluated.
- The severity of each harm to patient's safety was classified by 5-qualitative severity scale and the result was as follows; Negligible (0), minor (11), moderate (55), major (40) and catastrophic (2).

Table 26: Severity of harms / hazardous situations to patients and their implications on GMP/QMS

Category	Negligible	Minor	Moderate	Major	Catastrophic
Patient's perspective	Minor injuries or discomfort	Requiring medical intervention	Requiring hospital admission	Leading to permanent impairment	Leading to patient's death
Result	0	11	55	40	2
GMP/QMS implications	Process is OK but production is affected such as the yield ratio while GMP/QMS requirements are met	Deviation report issued. GMP/QMS requirements are met. May lead to minor observation or recommendation	Customer complaint or quality investigation. May lead to moderate / major observation	Product recall, process shut-down, etc.	Product withdrawal, revocation of marketing authorization
Result	0	11	55	40	2

- The likelihood of each harm was classified by a semi-quantitative probability scale and the result was as follows; Rare (4), unlikely (63), possible (41), likely (0) and almost certain (0).

Table 27: Likelihood of each identified harm

Category	Rare	Unlikely	Possible	Likely	Almost certain
Description	Could happen but probably never will happen	Could occur theoretically	Occur under abnormal environment; outside the scope of specification	Use error; Occur due to fault condition.	Occurred in the past (real-life circumstances, including other products)
Result	4	63	41	0	0

-Each risk was classified as either Not acceptable (NA), As low as reasonably practicable (ALARP) or Broadly acceptable (BA) and the result was as follows; NA (0), ALARP (79) and BA (29). None of identified harms was judged as Not Acceptable

Table 28: Matrix of the severity and the likelihood

		Severity				
		1. Negligible	2. Minor	3. Moderate	4. Major	5. Catastrophic
Likelihood	5.Almost certain	ALARP (1)	ALARP	NA	NA	NA
	4. Likely	BA	ALARP (23)	ALARP (1)*	NA	NA
	3. Possible	BA	BA	ALARP (4)	ALARP	NA
	2. Unlikely	BA	BA	BA	ALARP	ALARP
	1. Rare	BA	BA	BA	BA	ALARP

NA: Not Acceptable [Pink]
ALARP: As Low As Reasonably Practicable [Yellow]
BA: Broadly Acceptable [Blue]

- Risk control measures (i.e., to reduce or mitigate unacceptable risks) were considered for identified risks through the following options; “Inherent safety by design,” “Protective measures in the medical device itself or in the manufacturing process” or “Safety information to patients/healthcare professionals”.

-Verification of the implementation of each risk control measure was mainly conducted by verification studies including various ISO tests or performance qualification or a human usability study.

****Reviewer note**: a table identifying control measures and how they were verified/validated would be useful. IR#1 was sent and resolved after sponsor response.

- Among the 79 ALARPs, the reduction of risks to the BA was achieved at 49 ALARPs by either “Inherent safety by design” or “Protective measures in the medical device itself or in the manufacturing process”, while 30 ALARPs were remained at “As low as reasonably practical” status.

-For all risks remained at an ALARP status, risk reduction measures were taken including additional descriptions at precautions, warning or instructions sections of IFU or Package Insert.

- Effectiveness of the risk reduction measures was, in part, verified by the usability studies (FKB Study ID HSS-1037-R1, HSS-3109-R and HSS-3102) as well as various validation studies.

- Benefit-risk analysis was conducted to all residual risks and the product itself.

- The majority of residual risks were at the periphery to BA (next to BA).

PFS:
Risk analysis approach was not provided for the PFS.

Reviewer Comments
The approach used for AI partially follows ISO 14971, however patient harms and control measures are not included. No risk information provided for the PFS IR#1: You have provided the overall plan used for risk analysis and control measures. However, the specific risks and control measures were not provided. For the PFS and AI products, identify the potential harms and provide the FMEA table which should include the risk control measures. **See Appendix A, IR for review of sponsor response. Resolved.**

7.3. 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 **See Appendix A, IR for review of sponsor response.**		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

8. DESIGN VERIFICATION REVIEW

8.1. Design Verification Evaluation 40 mg AI

The acceptance criteria defined in P.2.4 is as follows:

EPR Name (P.2.4)	Terminology from P.7 or P.5.1 or Verification Report	Acceptance Criteria
Injection depth	same	(b) (4)
Force to initiate injection	Push in resistance of cover sleeve, Initial force (verification report)	
Force to keep holding down device to skin during injection	Release force (verification report)	
Injection time	same	
Cover sleeve lock out force	Breakage force of lock mode	
Needle retraction after cover sleeve locks	same	
Dose accuracy	same	

Review of design verification report in Sequence 0014
Sponsor conformed to the following standards:
ISO 11608-1:2014 Needle based injection systems for medical use- Requirements and test methods
ISO 11608-5:2012 Needle based injection systems for medical use- Requirements and test methods- Part 5: Automated functions
ISO 23908:2011Sharps injury protection – Requirements and test methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling

Testing

1) Dose Accuracy:
- Subassembly units tested
- Conducted gravimetrically according to Terumo IFU
- Lower limit = (b) (4) mL, Upper limit = (b) (4)
- 60 samples tested under various conditions, including:
- 5C for >4 hours
- 23C for >4 hours
- 40C for >4 hours
- 23C for >4 hours & Free fall
- 40C for >96 hours
- 5C for >96 hours
- Vibration (n=20)
- Accelerated aging at 55C, 138 days
- Real time aging, 6 months & 2 years (note shelf life is 36 months, tested through 36 months on stability)
- K values range 2.371-2.396

High Level Summary: All results within specifications, no fails or outliers (lowest value=0.7994 mL after 2 years real time aging). With this k value range and sample numbers, reliability is 95-97.5%.

Midcycle IR#1: Subassembly units tested (not final device). See Midcycle IR #1 below. Resolved.

2) Lock force test:
- Subassembly units tested
- Description not provided
- 100 samples tested after 138 days accelerated aging (55C)
- Spec (b) (4)
- K value = 2.539

High Level Summary: All results well above (b) (4) (Avg=269 N), no fails or outliers. With this k value and sample number, reliability is >97.5%.

3) Specific needle hiding test:
- Subassembly units tested
- 100 samples tested after 138 days accelerated aging (55C)
- The needle retraction after the cover sleeve locks must be (b) (4) mm
- K value = 2.539

High Level Summary: All results well above (b) (4) mm, min of 5.9 mm, no fails or outliers. With this k value and sample number, reliability is >97.5%.

4) Injection depth
- Subassembly units tested
- 10 samples tested
- Specs: min of (b) (4) mm, max of (b) (4) mm
- K value = 3.87
- How were the specs selected? – not in JOS. Indicated for adult and pediatric. Reviewed the clinical section and patients are expected at age 2 or older (not <2 years old).
- No aging data – presented in another report

High Level Summary: All results within specifications, no fails or outliers. It is unclear how specs were set -will send IR. Only 10 samples were tested, but k value of 3.87 has a reliability probability of 97.5%, so this is ok. Data is tight min of 6.43 mm, max of 6.63 mm.

Midcycle IR#3: Unclear how specs were set. See IR below. Resolved

5) Needle hiding
- Subassembly units tested
- 100 samples tested
- Specs: needle retraction after the cover sleeve locks must be (b) (4) mm
- K value = 3.539

High Level Summary: All results well above (b) (4) mm, min of 5.49 mm, no fails or outliers. Its not clear how this is different from test #3 above, but a different lot was used. With this k value and sample number, reliability is >99.5%.

6) Lock force test:
- Subassembly units tested
- 100 samples tested after 138 days accelerated aging (55C)
- Spec (b) (4) N
- K value = 3.539
- Reviewer Comment: Unclear if lock force was tested after free fall. Issued IR#6: Per ISO 11608-5 4.1b, automated functions should be tested after free fall. We consider lock force to be an automated function and it is unclear if lock force was tested after free fall. Please clarify all testing that was conducted on the device after free fall. If the submitted verification summary report does not include lock force testing after free fall, provide the verification testing.
-

High Level Summary: All results well above (b) (4) N (Avg=260 N), no fails or outliers. With this k value and sample number, reliability is 99.9%. IR#4 issued. Resolved.

7) Removal force cap remover
- Subassembly units tested
- 10 samples tested
- Specs: (b) (4) N
- K value = 3.402

High Level Summary: All results within specifications, max value of 17.2 N. no fails or outliers. With this k value and sample number, reliability is 97.5%. This is acceptable.

8) Initial Force (activation)
- Subassembly units tested
- 10 samples tested
- No aging provided – provided in another report
- The initial force to initiate the axial movement of the cover sleeve (pressure point) during insertion is (b) (4) N
- Specs: (b) (4) N
- K value = 3.871

High Level Summary: All results within specifications, max value of 6.7 N, min value of 6.0 N. no fails or outliers. With this k value and sample number, reliability is 97.5%. This is acceptable.

8) Release Force
- Subassembly units tested
- 10 samples tested
- The force on the cover sleeve to initiate the injection process and during plunger movement is (b) (4) N
- Specs: (b) (4) N
- K value = 3.402

High Level Summary: All results within specifications, max value of 5.32 N. No fails or outliers. With this k value and sample number, reliability is 97.5%. This is acceptable.

9) Injection Time
- Subassembly units tested
- 10 samples tested
- The duration of an injection into air (with-out resistance) is (b) (4) seconds. Depending on drug / syringe. Unclear if drug was used, but this is included in midcycle IR#1 – RESOLVED (what was tested?)
- No aging provided – real time at 5C in another report
- Specs (b) (4) seconds
- K value = 3.39

High Level Summary: All results within specifications, 3.3-4.1 seconds. No fails or outliers. With this k value and sample number, reliability is 95%. This is acceptable.

9) Blocking Force Cap Remover
- Subassembly units tested
- 50 samples tested
- The attached cap remover blocks the injection to start. The cap remover withstands an proximal, axial force of at least (b) (4) N.
- Specs (b) (4) N
- K value = 2.86

High Level Summary: All results within specifications, min value of 391 N. No fails or outliers. With this k value and sample number, reliability is 99%. This is acceptable.

Sharps Injury Prevention

Conducted a simulated clinical use study in accordance with ISO 2390-1:2011, and exceded the requirements of number of devices to test, according to "Guidance for Industry and FDSA Staff – Medical Devices with Sharps Injury Prevention Features". There were 28 evaluators, each testing 20 devices, 560 devices total. There were no fails.

Review of Long term stability Testing for AI report, Sequence 0014

Three lots were tested (Lot: C15Y3A, C15Y4A and C15Y5A). Product with each external device was used for each stability study.
Timepoints: 6, 12, 18, 24, 36 months

Tests:
1) Volume in container,
-Criteria: (b) (4) mL
-Method: Weigh 5 samples gravimetrically to 4 decimal places. Measure density to calculate volume.
-One deviation where density results were not rounded to the 4 decimals, and used 6 decimals instead. They recalculated according to procedure (4 decimals) and results were essentially the same and passing (raw data was shown).
-All passed, but actual data not shown. According to the method description, each of the 5 samples were checked to determine whether each had sufficient volume. Results were recorded as pass.
-We probably do not need to see the raw data here since they state that each result is analyzed. Plus verification results showed acceptable data. . Are we ok that there is no upper limit?-Yes, there would not be a large overfill since this is not common practice from pharma companies due to monetary loss. Also, verification had an upper limit, and all data looked good.
-Conclusion: 3 lots demonstrate passing through 36 months.

2) Injection time
-Criteria: (b) (4) seconds
-5 samples

-measurement of solution discharge from start to finish using stopwatch
-Actual time shown to 2 decimal places. All passed, mean of 4 seconds.
-Conclusion: 3 lots demonstrate passing through 36 months.

Review of Force to Initiate Injection T=0 and Accelerated (6 years equivalent) reports, Sequence 0014

-For each study, 3 AI assembled lots were used, 13 samples tested on each lot.
-For the aging study, samples were aged 97C at 60C or 25 days at 60C. They state that this is equivalent to 3 years at 25C and 3 years at 5C, respectively.
-Criteria: (b) (4)
Shown below is a typical waveform and instructions for analysis. First peak is excluded from analysis (why?). Even if it was included, would pass. Issued in Midcycle IR#7. Resolved.
-why are there 2 patterns (what is the lower curve)?

Review of Injection Depth T=0 and Accelerated (6 years equivalent) reports, Sequence 0014

-For each study, 3 AI assembled lots were used, 13 samples tested on each lot.
-For the aging study, samples were aged 97C at 60C or 25 days at 60C. They state that this is equivalent to 3 years at 25C and 3 years at 5C, respectively.
- Upper limit= (b) (4) mm, Lower limit= (b) (4) mm

-All samples passed, with average ~6.5 mm

Review of Sequence 0001, Section 3.2.P.8.1
-Assays: volume in container, injection time
-Final product with external device tested
-Acceptance criteria not defined, report result only
-Values shown for injection time
-Values not shown for volume, results reported as: (b) (4) mL"

8.2. Design Verification Evaluation 20 mg & 40 mg PFS

Review of Sequence 0001, Section 3.2.P.8.1
-Assays: volume in container, gliding force
-Final product with external device tested
-Acceptance criteria not defined, report result only
-Values shown for gliding force
-Values not shown for volume, results reported as: (b) (4) mL"

Review of Long Term Stability Testing for 20 mg and 40 mg PFS reports, Sequence 0014
-3 lots tested
-Timepoints: 6, 12, 18, 24, 36 months
1)Volume in container:
-Criteria: (b) (4)
-Method: Weigh 5 samples gravimetrically to 4 decimal places. Measure density to calculate volume.
-All passed, but actual data not shown. According to the method description, each of the 5 samples were checked to determine whether each had sufficient volume. Results were recorded as pass.
-One deviation where density results were not rounded to the 4 decimals, and used 6 decimals instead. They recalculated according to procedure (4 decimals) and results were essentially the same and passing (raw data was shown).
-We probably do not need to see the raw data here since they state that each result is analyzed. Plus verification results showed acceptable data. .
-Conclusion: 3 lots demonstrate passing through 36 months.

2)Gliding force:
-Criteria: (b) (4)
-5 samples
-speed of 205 mm/min
-this is ~10 seconds, it seems like a reasonable rate
-No raw data provided
-All data pass criteria
-Conclusion: 3 lots demonstrate passing through 36 months for 20 mg and 40 mg configurations. In addition, 3 lots (20 mg and 40 mg) are ongoing and demonstrate passing results through 24 months.

Note: Breakloose force was not tested. The sponsor stated the following in the CMC response to the IR sent September 2019:
(b) (4) stopper used for PLAJEX syringe does not require break loose force because of the nature of the coating. Accordingly, the specification is only based on the extrusion force."
-This response seems acceptable, but would like to review raw data for confirmation. IR requesting it will be sent. See midcyle IR#8. Resolved.

8.3. Design Verification Essential Performance Requirement Evaluation Summary
Including only the major EPRs in table below:

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy (AI, PFS)	(b) (4)	N (MC#1-PFS, MC#6 PFS)	Y	N (MC#2)	Y, MC#5
Lock Force (AI)		N (MC#1)	Y	Y	Y, MC#5
Cap Removal Force (AI)		Y	Y	NA	NA
Injection depth (AI)		N (MC#1)	Y (MC #3)	Y (MC#3)	Y, MC#5
Initial force (activation) (AI)		N (MC#1, 7)	Y	N, (MC#4)	Y, MC#5
Injection time (AI)		N (MC#1)	Y	Y, (MC#2)	Y, MC#5
Gliding force (PFS)		N (MC #6, 8)	Y	Y (MC#2)	Y, MC#5

Reviewer Comments

The verification report and supporting studies may be suitable depending on the response to the IRs below. Midcycle IRs were sent to sponsor on 1/15/2019.

Midcycle #1: According to the AI Design Verification Summary Report, all of the verification testing was conducted on subassembly units and not the final finished combination product. Verification testing on EPR's should be conducted on the final finished combination product to account for the drug-device interactions and their impact on the EPR. In addition, we expect the following EPRs to be impacted by the drug product: Initial Force, Injection Time, Dose Accuracy. Provide a description of the subassembly product. Include details such as whether the syringe is filled with drug and a comparison of differences between the subassembly units and the final finished device. In addition, provide a justification for testing on the subassembly units instead of on the final finished devices. If there are impactful differences between the subassembly units and the final finished combination product, conduct verification testing on drug-filled final finished combination product for the following EPRs: Dose Accuracy, Injection Time, Initial Force, Injection Depth. Injection Depth can be conducted on devices that are not drug-filled but on the final assembled device.

Midcycle #2: You have included the following device tests on stability:

- Dose Accuracy for PFS and AI
- Injection Time for AI
- Gliding Force for PFS

You did not set acceptance criteria for any of the device tests (results are 'Report Only'). Acceptance criteria is necessary to ensure that the product remains within specifications and an investigation is launched if product falls out of specifications. Include acceptance criteria for the device tests. In addition, AI initial force is not being tested in the stability studies. The AI initial force should also be added to the stability testing program since it may change over time, and you should add defined acceptance criteria as well.

Midcycle #3: In the Verification Summary Report, you provided specifications for the AI injection depth. The data collected is within the acceptance criteria, however it is unclear how the specifications were set. Since the AI may be

used in a pediatric population, specifications should be validated to ensure that pediatric patients will receive the dose in the subcutaneous space. Provide evidence that you validated the specification for the pediatric patient population.

Micycle #4: For the AI, you provided initial force test results in the Design Verification Summary Report, but you did not provide real time aging data through shelf life. This test is also not included in the stability study. In order to ensure acceptable force results through end of shelf life, include initial force testing, with acceptance criteria, on the stability study. Alternatively, provide design verification testing demonstrating acceptable results through end of shelf life (36 months).

Midcycle#5: In your Design Verification Summary Report, you have referenced transport verification results, however you did not provide the reports or data. In order to ensure acceptable design study and results, provide the test reports with data after shipping for both the AI and PFS.

Midcycle #6: You provided PFS stability study results for 3 lots through shelf life. However, it is unclear if the stability study adequately evaluated PFS EPRs to the appropriate confidence and reliability limits. Additionally, you did not provide design verification test reports for gliding force and dose accuracy. Provide verifications reports supporting the acceptance criteria for gliding force and dose accuracy. Alternatively, provide a justification of how the PFS stability data supports target reliability of 95% or greater with 95% confidence.

Midcycle#7: You provided AI waveform data with instructions of selecting the maximum point between (b) (4) mm and the point where cover sleeve was blocked. It is noted that the graph has a defined peak between (b) (4) mm. Provide explanation of what the peak represents and why it is not monitored during testing. Since it is a real force that will be experienced by users, it should be included in the acceptance criteria.

Midcycle#8: You have provided PFS results for gliding force summarizing the results. Provide criteria for determining the gliding force and a representative injection force curve illustrating the region that is measured to determine gliding force.

All Midcycle deficiencies are Resolved. See Section 13.3 for review.

8.4. Biocompatibility - PFS

"The components are or can be in contact with the patient or the user as surface contacting can be for less than 24 hours duration. Biocompatibility testing has been performed including cytotoxicity, irritation and sensitization and the results demonstrate that the product meets ISO 10993-5 and ISO 10993-10 requirements. More detailed information are provided in MAF# (b) (4) ."

Review of the drug contact parts of the PFS are in the scope of CMC review and are not covered in this memo.

The user will come in direct contact with the outer materials of the PFS. Contact is limited to skin of hands and injection site. Components that may potentially have contact with skin are: Body, Plunger, EFF, needle shield. Materials of components are shown below.

From P.7:

Table 1: Primary Container Closure System Components for FKB327 Drug Product

Component	Description	DMF Type and No	Supplier	Quality Standard
PLAJEX™ (plastic syringe)	Syringe barrel (1 mL Long) (b) (4)	NA	Terumo Yamaguchi D&D Corporation 3-22, Azamurayama, Sayama, Yamaguchi, Yamaguchi 754-0894, Japan	USP<661.2> USP<85> USP<87> Ph. Eur. 3.2.2.1 JP<7.02> ISO10993 ISO9626 [a] Ph. Eur. 3.1.8 [b]
	Needle (29G (b) (4) Stainless Steel (Needle) (b) (4)			
PLAJEX™ (needle shield)	Needle shield (b) (4)			USP<381> USP<87> Ph. Eur. 3.2.9 ISO10993
	Rigid needle shield			NA
PLAJEX™ (b) (4) stopper)	(b) (4) rubber	Type III (b) (4)	Terumo Corporation 818 Misonodaira, Fujinomiya, Shizuoka, 418-0004, Japan	USP<381> USP<85> USP<87> Ph. Eur. 3.2.9 ISO10993

a: This quality standard is applied to Needle.
b: This quality standard is applied to 360 medical fluid 12500 and 360 medical fluid 1000.
Abbreviations: JP: Japanese Pharmacopoeia; Ph. Eur.: European Pharmacopoeia; USP: United States Pharmacopeia; ISO: International Organization for Standardization; NA: Not Applicable.

Table 3: Container Closure Components for FKB327 Drug Product

Component	Description		Device master file, MAF No.	Supplier
Safety device	(b) (4) Sub-assembly	Body	(b) (4)	(b) (4)
		Sleeve		
		Spring		
		Cone		
	Plunger rod			
	Extended finger flange			

Abbreviations: (b) (4)

-Reviewed MAF# (b) (4). Sponsor conducted cytotoxicity, irritation and sensitization on the plajex syringe with EFF.
High Level Summary:
Cytotoxicity – extracted in MEM. Conclusion - no cytotoxic effect.
Irritation – polar and nonpolar extraction. Biological reaction not greater than control.

Sensitization - polar and nonpolar extraction. Conclusion – test articles classified as nonsensitizer or weak sensitizer (grade 1 reaction). Grade 1 reaction is not considered significant and meets the requirements of ISO-10993 guidelines.

The contact materials have passed biocompatibility testing and comply with the applicable sections of ISO 10993-5 and 10992-10.

8.5. Biocompatibility - AI

Some AI components (marked as X in the table below) may have a contact with a patient or user's skin while others may not. The duration of skin contact is expected to be less than 24 hours. Biocompatibility testing that included the assessment of cytotoxicity, irritation and sensitization demonstrated that the product meets the ISO standard requirements (ISO 10993-1, 5 and 10).

Table 29: AI components that may make contact with skin

	Part name	Material	Skin contact
Syringe Unit	Cap Remover	(b) (4)	X
	Cover Sleeve		X
	Housing		X
	Syringe Holder		-
Drive Unit	Telescopic Lock Sleeve (TLS)		—
	Cover Sleeve Spring		—
	Plunger Rod		—
	Injection Spring		—
	Mechanic Holder		—
	Click Sleeve		—
	Holding Pin		—
	End Cap		X

Not enough info to review. Issued IR#2. Resolved.

Reviewer Comments
IR#2: You stated that AI biocompatibility testing demonstrates that the product meets the appropriate ISO standard requirements, however verification reports were not provided. Provide biocompatibility verification reports for the skin-contacting components of the device. The reports should describe the test methods, data and conclusions. Resolved.

8.6. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION

Filing Deficiencies:	Mid-Cycle Deficiencies:	Final Deficiencies:
☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A

Reviewer Comments
Requests for the sponsor to identify the location of DV and stability testing were issued interactively during the filing period (IR#1, below). Based on the responses, adequate information was provided for filing; however, the sponsor should provide complete test reports. See 74-Day Letter IRs # 2 and 3 below. Mid-cycle IR's (#1-8) were sent, all were Resolved. See section 13.3 for review. An additional IR (#4) was sent and response is pending.

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

	Date Sent: 7/30/2019	Date/Sequence Received: 8/2/2019
Filing Information Request #1	Can you please tell me where the reviewers can locate the following in the BLA submission: • Prefilled syringe and autoinjector combination product design verification test reports • Control strategy for essential performance requirements (EPR) • Device stability for the combination product: o Prefilled syringe EPR for the combination product on stability o Gliding force and injection time are included in the stability testing in 32p8 but could not locate the stability testing for the other EPRs. The sponsor should identify the location of stability testing for the PFS with safety device and the autoinjector EPRs for the combination product. • Biocompatibility testing	
Sponsor Response	• Prefilled syringe and autoinjector combination product design verification test reports *The summary results are located at:* • ***20mg PFS**: 3.2.P.2.4.3.1.1. Design Requirement and Design Verification (page 11 of 12)* • ***40mg PFS**: 3.2.P.2.4.3.1.1. Design Requirement and Design Verification (page 11 of 13)* • ***40mg PFP (autoinjector):** 3.2.P.2.4.3.4.2. Design Verification (page 25 of 62)* • Control strategy for essential performance requirements (EPR) *The control strategy for EPR is located at:* • ***20mg PFS:** 3.2.P.2.4.3.1.2 Essential performance requirements (page 11 of 12)* • ***40mg PFS**: 3.2.P.2.4.3.1.2 Essential performance requirements (page 11 of 13)* • ***40mg PFP (autoinjector):** 3.2.P.2.4.3.4.1.Essential performance requirements (page 23 of 62)* • Device stability for the combination product: o Prefilled syringe EPR for the combination product on stability o Gliding force and injection time are included in the stability testing in 32p8 but could not locate the stability testing for the other EPRs. The sponsor should identify the location of stability testing for the PFS with safety device and the autoinjector EPRs for the combination product. *The EPRs related to the combination product are included as part of stability testing in 3.2.P.8. This includes injection time and dose accuracy for autoinjector and deliverable volume and gliding force for prefilled syringe.* *The EPRs related specially to the device are evaluated in the stability testing in the design verification. Accelerated aging tests result is located at:* • ***20mg PFS:** refer to MAF#* (b) (4) • ***40mg PFS:** refer to MAF*	

	• ***40mg PFP (autoinjector)**: 3.2.P.2.4.3.4.2. Design Verification - Accelerated Aging Test of the AI device (page 42 of 62)* *This includes force to initiate injection, force to keep holding down the device to the skin during injection, cover sleeve lock-out force, injection depth, needle retraction after cover sleeve locks for autoinjector and breakage force of lock mode for prefilled syringe.* *Injection depth and Needle retraction are not evaluated the stability because these EPRs are not changed during storage.* • Biocompatibility testing *Biocompatibility testing is located at:* • ***20mg PFS:** 3.2.P.2.4.2.1.2 Biological Reactivity (page 6 of 12)* • ***40mg PFS**: 3.2.P.2.4.2.1.2 Biological Reactivity (page 6 of 13)* • ***40mg PFP (autoinjector):** 3.2.P.2.4.1.2. Biological Reactivity (page 8 of 62)* *Compatibility information is located at:* • ***20mg PFS:** 3.2.P.2.4.3.1.3. Compatibility (page 12 of 12)* • ***40mg PFS**: 3.2.P.2.4.3.1.3. Compatibility (page 12 of 13)* • ***40mg PFP (autoinjector):** 3.2.P.2.4.3.6 Compatibility (page 62 of 62)*
Reviewer Comments	The sponsor identified the location in the submission where the requested information was provided. Based on their response, it appears that the submission contains only summary results for the design verification testing. The sponsor will be asked to provide complete test reports during the 74-day letter. Additionally, incomplete stability testing has been performed, as only some of the device constituent EPRs were evaluated for the combination product on stability. However, because some of the stability testing was provided, this will not result in a refuse to file recommendation. The sponsor will be asked to provide the complete EPR testing on stability in the 74-day letter.
Response Adequate:	☐ **Yes** ☐ **No, See IR # 2 and 3 Sent in 74-Day Letter**

	Date Sent: **74-Day Letter**	**Date/Sequence Received:** Click or tap to enter a date.
74-day Information Request #2	*You provided summary design verification results in 3.2.P.2.4.3.1.1 for the 20 mg PFS and 40 mg PFS and in Section 3.2.P.2.4.3.4.2 for the autoinjector. However, you did not provide the complete test reports for the prefilled syringe and autoinjector design verification testing. Provide the design verification test reports for the autoinjector and prefilled syringe. Ensure the test reports include the acceptance criteria, deviations, statistical summary and data.*	
Sponsor Response	Sequence 00014, Refer to Section 8 for review.	
Reviewer Comments	Sponsor provided the requested information. **See Appendix A, Mid-Cycle IR #1-8 issued after review of sponsors response**	
Response Adequate:	☐ **Yes** ☐ **No,**	

	Date Sent: **74-Day Letter**	**Date/Sequence Received:** Click or tap to enter a date.
74- day letter Information Request #3	*You provided stability data for injection time and dose accuracy for the autoinjector and deliverable volume and gliding force for the prefilled syringe in Section 3.2.P.8; however, you did not include all of the relevant EPRs on stability for each device type. To support the*	

	intended shelf- life, provide stability testing of the EPRs for the autoinjector and prefilled syringe. For the autoinjector, stability testing should include delivered volume accuracy, activation force, injection time, and extended needle length. For the prefilled syringe, stability testing should include delivered volume, break loose force, and extrusion force.
Sponsor Response	Sequence 00014, Refer to Section 8 for review.
Reviewer Comments	Sponsor provided the requested information. **See Appendix A, Mid-Cycle IR #1-8 issued after review of sponsors response**
Response Adequate:	☐ **Yes** ☐ **No, See IR Sent on** Click or tap to enter a date.

9. 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)
Dose Accuracy	(b) (4)	Y
Initial Force		Y
Force to keep holding down during injection		Y
Glide Force		Y
Injection Time		Y
Other		

(b) (4)

(b) (4)

[redacted]

Reviewer Comments

The sponsor provided all of the appropriate control strategies. All but injection force are tested at release and during stability. The injection force is tested on subassembly units, and sponsor has shown that the results (accelerated and real time) are similar to the final product with drug. They provide reasoning why drug product does not affect the injection force (it is the force of cover sleeve spring required to initiate sliding), which is acceptable reasoning.

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

9.1. Control Strategy Review Conclusion

CONTROL STRATEGY REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments Mid-cycle IR's 2 & 7 were sent, all were Resolved. See section 13.3 for review.		
CDRH sent Control Strategy Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

9.2. Discipline Specific Sub-Consulted Review Summary

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

10.CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

☐ There is no device related clinical studies for review
☐ There are clinical studies for review
This information was obtained from the following **documents**:

Study Name	A Phase I, Randomised, Open-Label, Single-Dose Study to Assess the Relative Bioavailability of a Subcutaneous Dose of FKB327 When Administered Using Either a Pre-Filled Syringe, a Pre-Filled Auto-Injector or a Vial with Disposable Syringe in Healthy Subjects
Study Type	Ph 1 Open-label
Objectives/Endpoints	Assess Bioavailability when administered with PFS, AI or vial and syringe
Drug/Device Studied	40 mg FKB327 SC with vial/syringe, PFS or AI, 1:1:1 ratio
Number and Type of Subjects	200, Men and Women
Brief description of protocol	Patients receive dose every 2 weeks. The dose (40 mg) is same as in an ongoing Ph. 3. This is a bridging PK study to compare the intended commercial finished products, PFS and AI with the vial used in a Ph 3 study to support using the results for licensure.
Device Related Comments	Its not clear if final commercial devices are used.
Reviewer Comments	Will send an IR to get clarity on device used (ie, final finished product?)
Reviewer Conclusion	**Devices used in clinical study are comparable to final commercial devices. See Appendix A, IR#3 for review of sponsor response.**

Study Name	A randomized, double-blind, single-dose study to compare pharmacokinetic characteristics and safety of FKB327 with those of Humira® in healthy subjects.
Study Type	Ph 1 randomized, FKB327-001
Objectives/Endpoints	Comparison of FKB327 to Humira (RLD), EU and US versions.
Drug/Device Studied	FKB327 seems to be not supplied as a device, though not specified. It is stated that Humira is available as PFS and AI, but device used in study is not stated.
Number and Type of Subjects	180 men and women
Brief description of protocol	To compare the safety and pharmacokinetics (PK) of FKB327 and European Union (EU)-approved and United States (US)-licensed Humira after single doses, by subcutaneous (sc) injection in healthy volunteers.
Results	Safety profile similar
Device Related Comments	From Natlaie Pica, clinical reviewer: "Its my understanding that Humira was provided in a prefilled syringe. FKB327 was provided in vials, but was placed then in a syringe identical to that of Humira PFS prior to administration in order to maintain blind."
Reviewer Comments	No comments
Reviewer Conclusion	**Comparison study between biosimilar and reference product deferred to CDER.**

Reviewer Comment

IR#3: It is unclear whether the final commercial design for the PFS and AI devices were used in the clinical studies. Provide a comparison of the devices validated in the clinical studies against the commercial design, and explain why any identified differences would not impact the clinical study outcomes. Resolved.

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A

Reviewer Comments

This application is for a biosimilar to humira PFS and AI. The clinical studies propose Pk bridging between the vial/PFS/AI biosimilar configurations and between the biosimilar and referenced product using pfs and biosimilar from vial transferred to PFS. Assuming the data is adequate (defer to CDER), the sponsor adequately validated any differences in device EPRs that could impact clinical outcomes through this clinical data. See comment to CDER #2 (Section 1.1) .Mid-Cycle IR#3 (resolved) was sent to clarify differences between commercial and clinical devices. Noted differences were acceptable, see Mid-cycle IR #3 for review of sponsor response.

CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐

Human Factors deferred to DMEPA	☐

Reviewed validation studies to determine whether there were usability issues.
Study: 1037 – Usability Validation for RA AI
High level summary – there were no usability issues from a device functionality perspective. Few participants had a problem removing the cap and administering full dose. According to the sponsor, *The use errors seen in this validation study are consistent with those seen in studies of other AI devices available.*

Reviewer Comment: Few participants had a problem removing the cap and administering the full dose. Cap removal force is ≤29 N, and result average is 17.2 N (see Section 8.1). The specification should be acceptable for use with hand-impaired patients.

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

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

Facility Regulatory History Review	
Firm Name:	Terumo Yamaguchi D&D Corporation
Address & FEI:	3013611763
Responsibilities:	Manufacture combination product.
Site Inspection Recommendation:	NAI.

Reviewer Comments

This is the initial inspection. The inspection was conducted February 2020. As of 3/13/2020, the EIR is not available. According to Lindsey Fleischman from ORA, result for device inspection "was NAI". The report will be sent to me when it is completed.

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

12.2. Quality Systems Documentation Review

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

Facilities:
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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:	June 29, 2020
To:	Elaine Sit, PharmD Regulatory Project Manager **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams MSN, BSN, RN Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, Pharm.D., MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFUs), and Quick Reference Guide (QRGs)
Drug Name (nonproprietary name):	HULIO (adalimumab-xxxx)[1]
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761154
Applicant:	Mylan GmbH

[1]The proposed proprietary name (HULIO) for this proposed product has been conditionally accepted. A four letter suffix for the nonproprietary name for HULIO has been conditionally accepted until such time that the application is approved.

1 INTRODUCTION

On July 11, 2019, Mylan GmbH submitted for the Agency's review a Biologics License Application (BLA) 761154 for FKB327 (adalimumab-xxxx), a proposed biosimilar to HUMIRA (adalimumab).

Mylan GmbH is seeking approval of HULIO (adalimumab-xxxx) injection, for subcutaneous use for the following indications:

- **Rheumatoid Arthritis (RA)**: Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- **Juvenile Idiopathic Arthritis (JIA)**: Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.
- **Psoriatic Arthritis (PsA)**: Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- **Ankylosing Spondylitis (AS)**: Reducing signs and symptoms in adult patients with active AS.
- **Adult Crohn's Disease (CD)**: Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab products.
- **Ulcerative Colitis (UC)**: Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of adalimumab products has not been established in patients who have lost response to or were intolerant to TNF blockers.
- **Plaque Psoriasis (Ps)**: The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

Mylan GmbH is seeking approval for three HULIO presentations: 40 mg/0.8 mL and 20 mg/0.4 mL in single-dose pre-filled syringes and 40 mg/0.8 mL in a single-dose prefilled pen.

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 Pulmonary, Allergy, and Rheumatology Products (DPARP) on August 26, 2019 , for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for HULIO (adalimumab-xxxx) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft HULIO (adalimumab-xxxx) MG and IFUs received on July 11, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 5, 2020.
- Draft HULIO (adalimumab-xxxx) Prescribing Information (PI) received on July 11, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 5, 2020.
- Approved HYRIMOZ (adalimumab-adaz) injection MG and IFUs dated October 30, 2018.
- Approved CYLTEZO (adalimumab-adbm) injection MG and IFUs dated September 13, 2019.

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%.

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.

In our collaborative review of the MG, IFUs, and QRGs we:

- simplified wording and clarified concepts where possible
- ensured that the MG, IFUs, and QRGs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG, IFUs, and QRGs are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG, IFUs, and QRGs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG, IFUs, and QRGs are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG, IFUs, and QRGs 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 MG, IFUs, and QRGs 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 MG, IFUs, and QRGs.

Please let us know if you have any questions.

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	June 1, 2020
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Bruce Huang, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research II
Application:	BLA 761154
Applicant:	Mylan GmbH
Submission Date:	July 12, 2019
Product:	Hulio (adalimumab-fkjp)
Dosage form(s):	injection
Strength and Container-Closure:	40 mg/0.8 mL in a single-dose prefilled pen (HULIO Pen) 40 mg/0.8 mL in a single-dose prefilled syringe 20 mg/0.4 mL in a single-dose prefilled syringe
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The Prescribing Information, Medication Guide, Instructions for Use, Quick Reference Guide, container labels, and carton labeling submitted on May 28, 2020 are acceptable from an OBP labeling perspective.

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

n/a = not applicable for this assessment

DISCUSSION

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

CONCLUSION

The Prescribing Information, Medication Guide, Instructions for Use, Quick Reference Guide, container labels, and carton labeling submitted on May 28, 2020 are acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on July 12, 2019 \\cdsesub1\evsprod\bla761154\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-marked-up-word.doc)

Medication Guide (submitted on July 12, 2019 \\cdsesub1\evsprod\bla761154\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-medication-guide-clean-word.docx)

Instructions for Use (submitted on July 12, 2019 \\cdsesub1\evsprod\bla761154\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-pfs-clean-word.docx and \\cdsesub1\evsprod\bla761154\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-pen-clean-word.docx)

Quick Reference Guide (submitted on July 12, 2019 \\cdsesub1\evsprod\bla761154\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-quick-reference-guide-pfs-word.docx and \\cdsesub1\evsprod\bla761154\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-quick-reference-guide-pen-word.docx)

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

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

Comment/Recommendation: Labeling submitted on July 12, 2019 had the correct manufacturer's name, address, and US license number which corresponds to the manufacturer listed on FDA form 356h. Labeling submitted on March 26, 2020 was revised incorrectly to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No 2062". Revised to the licensed applicant (manufacturer) as provided on Form FDA 356h ("Manufactured by: Mylan GmbH, Turmstrasse 24, 6312 Steinhausen, Switzerland US license No 2062").
Applicant's response: Mylan acknowledges the Agency's comment…Mylan submitted an administrative update to the application on April 17, 2020 to transfer ownership/licensure of this application from Mylan GmbH to Mylan Pharmaceuticals Inc…Given the minor nature of the change in applicant name, it is our understanding that the currently assigned U.S. License Number 2062 will be reissued to Mylan Pharmaceuticals Inc. as part of the revocation and reissuance process. Accordingly, we wish to retain reference to Mylan Pharmaceuticals Inc. on all proposed labeling components so that this product will reflect the correct applicant at the time final regulatory action is taken.

OBP labeling's response: We acknowledge the transfer of ownership submission but also understand that the revocation and reissuance process is not yet complete. At this time, it is not certain that the process will assign the U.S. License Number 2062 to Mylan Pharmaceuticals Inc. as such, we ask that a placeholder be used for the US license number. The U.S license number is provided the approval letter and can be applied to the final labels and labeling. Please revise to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No XXXX".
The Applicant revised as requested

[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

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

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

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

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

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

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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

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

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

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	☐ Yes ☐ No ☒ N/A

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

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

Applicant's response: Mylan acknowledges the Agency's request and confirms that placement of the labels (once affixed) will allow for visual inspection by the patient. The syringe label is clear and allows full length and circumference visibility. See the 'Viewing Window' in Figure A.

(b) (4)

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

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

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

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

Comment/Recommendation: space considerations

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

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

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

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

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

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

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

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

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

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

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

Package[6] Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: Labeling submitted on July 12, 2019 had the correct manufacturer's name, address, and US license number which corresponds to the manufacturer listed on FDA form 356h. Labeling submitted on March 26, 2020 was revised incorrectly to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No 2062". Revised to the licensed applicant (manufacturer) as provided on Form FDA 356h ("Manufactured by: Mylan GmbH, Turmstrasse 24, 6312 Steinhausen, Switzerland US license No 2062").
Applicant's response: Mylan acknowledges the Agency's comment…Mylan submitted an administrative update to the application on April 17, 2020 to transfer ownership/licensure of this application from Mylan GmbH to Mylan Pharmaceuticals Inc…Given the minor nature of the change in applicant name, it is our understanding that the currently assigned U.S. License Number 2062 will be reissued to Mylan Pharmaceuticals Inc. as part of the revocation and reissuance process. Accordingly, we wish to retain reference to Mylan Pharmaceuticals Inc. on all proposed labeling components so that this product will reflect the correct applicant at the time final regulatory action is taken.

OBP labeling's response: We acknowledge the transfer of ownership submission but also understand that the revocation and reissuance process is not yet complete. At this time, it is not certain that the process will assign the U.S. License Number 2062 to Mylan Pharmaceuticals Inc. as such, we ask that a placeholder be used for the US license number. The U.S license number

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

is provided the approval letter and can be applied to the final labels and labeling. Please revise to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No XXXX". The Applicant revised as requested

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

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

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

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

Comment/Recommendation: Add the statement "No preservative" to all tray labeling per 21 CFR 610.61(e) *The Applicant revised as requested*

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

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

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

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

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

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

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

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

Comment/Recommendation: Revise the ingredient list appearing on all carton labeling to read as follows: "Each 0.8 mL [or 0.4 mL] single-dose prefilled syringe [or prefilled pen] contains 40 mg [or 20 mg] of adalimumab-xxxx, methionine (xx mg), monosodium glutamate (xx mg), polysorbate 80 (xx mg), sorbitol (xx mg) and Water for Injection, USP. Hydrochloric acid is added as necessary to adjust pH."
The Applicant revised as requested

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

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

Comment/Recommendation: Add the statement "No U.S. Standard of potency" to all tray labeling per 21 CFR 610.61(r)
The Applicant revised as requested

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

Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	☐ N/A

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

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

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

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

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

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A

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

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

Comment/Recommendation: Consider deleting the redundant statement "Prefilled pen [syringe] for Single Dose Only" appearing on all tray labeling or consider revising to read "Prefilled pen [syringe] is for one time use only".

We acknowledge that tray labeling submitted on March 26, 2020 revised from "Prefilled pen [syringe] for Single Dose Only" to read "Prefilled pen [syringe] is for one time use only", however, the carton labeling submitted on March 26, 2020 should also be revised for consistency. The Applicant revised as requested

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

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

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

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

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

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

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

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

Comment/Recommendation: Consider revising the statement of dosage from "See package insert for full prescribing information" to read "Dosage: See Prescribing Information"
The Applicant revised as requested

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

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

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

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

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

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products	☐ Yes ☐ No ☒ N/A

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

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

Comment/Recommendation: We combined the ingredient paragraphs into one paragraph to reduce clutter.
The Applicant revised as requested

Full Prescribing Information	
15 Cytotoxic Drug reference	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) xxxx is a cytotoxic drug. Follow applicable special handling and disposal procedures.1 1.OSHA Hazardous Drugs. OSHA. [Accessed on June 9, 2017, from http://www.osha.gov/SLTC/hazardousdrugs/index.html	☐ Yes ☐ No ☒ N/A

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

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

Comment/Recommendation: Per 21 CFR 201.1 and 21 CFR 201.100(e), the name and location of business listed here (street address, city, state, and zip code) is required in labeling and should be located after the Patient Counseling Information section, at the end of the PI. If the product has FDA-approved patient labeling that is not a separate document from the PI, the manufacturer information should be located at the end of labeling, after the FDA-approved patient labeling. If the FDA-approved patient labeling is a separate document, or is to be detached and distributed to patients, the manufacturer information should be located both after the Patient Counseling Information section and after the FDA-approved patient labeling.
The Applicant informed that the Medication Guide will not be a separate document and deleted the information appearing after the Patient Counseling Information.
This is acceptable.

Applicant's response: Mylan acknowledges the Agency's comment…Mylan submitted an administrative update to the application on April 17, 2020 to transfer ownership/licensure of

this application from Mylan GmbH to Mylan Pharmaceuticals Inc…Given the minor nature of the change in applicant name, it is our understanding that the currently assigned U.S. License Number 2062 will be reissued to Mylan Pharmaceuticals Inc. as part of the revocation and reissuance process. Accordingly, we wish to retain reference to Mylan Pharmaceuticals Inc. on all proposed labeling components so that this product will reflect the correct applicant at the time final regulatory action is taken. *OBP labeling's response: We acknowledge the transfer of ownership submission but also understand that the revocation and reissuance process is not yet complete. At this time, it is not certain that the process will assign the U.S. License Number 2062 to Mylan Pharmaceuticals Inc. as such, we ask that a placeholder be used for the US license number. The U.S license number is provided the approval letter and can be applied to the final labels and labeling. Please revise to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No XXXX". See Applicant's response for Medication guide.*

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

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

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

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

Comment/Recommendation: Labeling submitted on July 12, 2019 had the correct manufacturer's name, address, and US license number which corresponds to the manufacturer listed on FDA form 356h. Labeling submitted on March 26, 2020 was revised incorrectly to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No 2062". Revised to the licensed applicant (manufacturer) as provided on Form FDA 356h ("Manufactured by: Mylan GmbH, Turmstrasse 24, 6312 Steinhausen, Switzerland US license No 2062").

Applicant's response: Mylan acknowledges the Agency's comment…Mylan submitted an administrative update to the application on April 17, 2020 to transfer ownership/licensure of this application from Mylan GmbH to Mylan Pharmaceuticals Inc…Given the minor nature of the change in applicant name, it is our understanding that the currently assigned U.S. License Number 2062 will be reissued to Mylan Pharmaceuticals Inc. as part of the revocation and reissuance process. Accordingly, we wish to retain reference to Mylan Pharmaceuticals Inc. on all proposed labeling components so that this product will reflect the correct applicant at the time final regulatory action is taken.

OBP labeling's response: We acknowledge the transfer of ownership submission but also understand that the revocation and reissuance process is not yet complete. At this time, it is not certain that the process will assign the U.S. License Number 2062 to Mylan Pharmaceuticals Inc. as such, we ask that a placeholder be used for the US license number. The U.S license number is provided the approval letter and can be applied to the final labels and labeling. Please revise to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No XXXX".
The Applicant revised as requested

Patient Information Labeling Evaluation (N/A)

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add in the dosage form (see Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019)
The Applicant revised as requested

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for IFU: Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	✓ Yes ☐ No ☐ N/A

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

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019).	✓ Yes ☐ No

21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	☐ N/A

Comment/Recommendation: Add in the name and place of business of the manufacturer (see Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019)

Labeling submitted on July 12, 2019 had the correct manufacturer's name, address, and US license number which corresponds to the manufacturer listed on FDA form 356h. Labeling submitted on March 26, 2020 was revised incorrectly to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No 2062". Revised to the licensed applicant (manufacturer) as provided on Form FDA 356h ("Manufactured by: Mylan GmbH, Turmstrasse 24, 6312 Steinhausen, Switzerland US license No 2062").
Applicant's response: Mylan acknowledges the Agency's comment…Mylan submitted an administrative update to the application on April 17, 2020 to transfer ownership/licensure of this application from Mylan GmbH to Mylan Pharmaceuticals Inc…Given the minor nature of the change in applicant name, it is our understanding that the currently assigned U.S. License Number 2062 will be reissued to Mylan Pharmaceuticals Inc. as part of the revocation and reissuance process. Accordingly, we wish to retain reference to Mylan Pharmaceuticals Inc. on all proposed labeling components so that this product will reflect the correct applicant at the time final regulatory action is taken.

OBP labeling's response: We acknowledge the transfer of ownership submission but also understand that the revocation and reissuance process is not yet complete. At this time, it is not certain that the process will assign the U.S. License Number 2062 to Mylan Pharmaceuticals Inc. as such, we ask that a placeholder be used for the US license number. The U.S license number is provided the approval letter and can be applied to the final labels and labeling. Please revise to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No XXXX".
The Applicant revised as requested

APPENDIX C. Acceptable Labels and Labeling
Prescribing Information/Medication Guide (submitted on May 28, 2020 \\cdsesub1\evsprod\bla761154\0048\m1\us\114-labeling\draft\labeling\draft-labeling-text-clean-pdf.pdf)

Instructions for Use (submitted on May 28, 2020 \\cdsesub1\evsprod\bla761154\0048\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-syringe-clean-pdf.pdf and \\cdsesub1\evsprod\bla761154\0048\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-pen-clean-pdf.pdf)

Quick reference guide (submitted on May 28, 2020 \\cdsesub1\evsprod\bla761154\0048\m1\us\114-labeling\draft\labeling\draft-labeling-text-quick-reference-guide-syringe-clean-pdf.pdf and \\cdsesub1\evsprod\bla761154\0048\m1\us\114-labeling\draft\labeling\draft-labeling-text-quick-reference-guide-pen-clean-pdf.pdf)

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

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 6/01/2020 01:09:43PM
GUID: 50814c7000007a3d59329f660d8ddf02

Bruce Huang

Digitally signed by Bruce Huang
Date: 6/01/2020 05:06:29PM
GUID: 5621444a001ab2c406ce890a591799dd
Comments: Thanks very much Vicky!

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: April 14, 2020

TO: Julia Beaver, M.D.
Director
Division of Oncology I
Office Oncologic Diseases
Office of New Drugs

Nikolay Nikolov, M.D.
Director (Acting)
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Office of New Drugs

FROM: Amanda Lewin, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

Melkamu Getie Kebtie, Ph.D., R. Ph.
Division of Generic Drug Study Integrity (DGDSI)
OSIS

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI/OSIS

SUBJECT: Surveillance inspection of Kyowa Hakko Kirin California Inc., La Jolla, CA

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion of [redacted] (b) (4) conducted at Kyowa Hakko Kirin California Inc., La Jolla, CA.

We observed objectionable conditions and issued Form FDA 483 at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

1.1. Recommendation

Based on our review of the objectionable conditions and the firm's response to Form FDA 483, we conclude the objectionable

conditions have no impact on the data from the audited studies (see Section 3). Thus, data from the audited studies are reliable to support a regulatory decision.

2. Inspected Studies

(b) (4)

FKB327-001 (BLA 761154)
"A randomized, double-blind, single-dose study to compare pharmacokinetic characteristics and safety of FKB327 with those of Humira® in healthy subjects"

Sample Analysis Period: 05/13/2013 – 12/11/2013 (PK)

3. Scope of Inspection
OSIS scientists Amanda Lewin, Pharmacologist and Melkamu Getie Kebtie, Pharmacologist, along with ORA Investigator Sherri Rohlf, audited the analytical portion of the above studies at Kyowa Hakko Kirin California Inc., La Jolla, CA from 03/02/2020 to 03/06/2020.

Kyowa Hakko Kirin California Inc. ceased their bioanalytical operations in 2015. Therefore, the inspection covered study records for laboratory equipment, method validation, and sample analysis. Study personnel were no longer available at the firm, however, Katsuhiko Yamamoto, director of the analytical laboratory at the time of the studies, was available via teleconference during the inspection.

4. Inspectional Findings

At the conclusion of the inspection, we observed objectionable conditions. We issued Form FDA 483 to Kyowa Hakko Kirin California Inc. Our evaluation of the Form FDA 483 observation (**Attachment 1**) and the firm's response dated 03/26/2020 (**Attachment 2**) are presented below.

4.1. FDA 483 Observations

4.1.1. Observation 1

The firm did not report all precision and accuracy data from method validations (b) (4) 327-PK12-001 (FKB-327) and 327-PK12-002 (Humira EU) associated with studies (b) (4) and FKB327-001. Specifically, precision and accuracy data generated in the following runs of their respective method validations were not reported:

(b) (4)

Firm's Response:
The firm acknowledged the observation and agreed the data was omitted from the method validation reports. The firm generated addendums for each of the method validation reports to include the omitted data, rationale for omission, and the impact on the validation. These addendums are included in the firm's response. The firm ceased their bioanalytical operations in 2015, therefore, no corrective actions were proposed for future studies. Additionally, the firm noted that (b) (4) and FKB327-001 were the only bioequivalence study samples analyzed at the firm.

OSIS Evaluation:
The firm excluded precision and accuracy data from method validations (b) (4) 327-PK12-001 (FKB-327) and 327-PK12-002 (Humira EU) without any assignable cause. The firm did not provide an acceptable reason for excluding the results for the low-quality control (b) (4) report. In method validation reports MV 327-PK12-001 (FKB-327) and MV 327-PK12-002 (Humira EU), all data from Runs (b) (4) were rejected for no valid reason.

However, the global precision and accuracy was less than 20% for all three method validations when excluded results were included. Therefore, this observation does not impact the precision and accuracy of the method used to analyze samples in studies (b) (4) and FKB327-001. Since the firm's bioanalytical operations are no longer functional, no

preventative actions are necessary and the firm's response is adequate.

Conclusion

We conclude the data from the (b) (4) and FKB327-001 (BLA 761154, adalimumab)) are reliable.

Final Classification:

VAI- Kyowa Hakko Kirin California Inc
La Jolla, CA
FEI#: 3008076127

cc: OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/ Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/Lewin
OTS/OSIS/DGDSI/Cho/Choi/Skelly/Au/Getie Kebtie
ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: AL 4/6/2020
Edit: MG 4/7/2020; GB 04/12/2020, 4/13/2020; AD 04/13/2020; 04/14/2020

ECMS:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881cf5384

OSIS File #: (b) (4) and BE 8695 (BLA 761154)

FACTS: 11952960

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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/

AMANDA E LEWIN
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MELKAMU GETIE KEBTIE
04/14/2020 11:33:52 AM

GOPA BISWAS
04/14/2020 11:40:14 AM

ARINDAM DASGUPTA
04/14/2020 11:59:31 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	April 3, 2020
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA-761154
Product Name and Strength:	Hulio (adalimumab-fkjp) Injection, 20 mg/0.4 mL and 40 mg/0.8 mL
Applicant/Sponsor Name:	Mylan
OSE RCM #:	2019-1495-1
DMEPA Safety Evaluator:	Teresa McMillan, PharmD
DMEPA Team Leader:	Millie Shah, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, carton labeling, Instructions for Use (IFU), and Quick Reference Guide (QRG) received on March 26, 2020 for Hulio. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container labels and carton labeling for Hulio (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.[a]

2 CONCLUSION

The revised prefilled Pen IFU and QRG and all carton labeling and container labels are unacceptable from a medication error perspective.

[a] Flint J. and McMillan T. HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW for Hulio (BLA-761154). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 12. RCM No.2019-1495 and 2019-1497.

3 RECOMMENDATIONS FOR MYLAN

We recommend the following be implemented prior to approval of this BLA:

A. Instructions for Use (IFU) and Quick Reference Guide (QRG) for Pen

1. We refer to your Information Request Response dated March 26, 2020. We also acknowledge your inclusion of 'and' after the first two bulleted statements and revising the heading for Step 4 (QRG) Step 5 (IFU) to include all three cues of the proposed IFU and QRG. However, we note the figure in Step 4 (QRG) and 5 (IFU) presents the cues in a different order (i.e. 2nd click, orange indicator, and 10 seconds) than what is written (2nd click, 10 seconds, and orange indicator). In addition, for Step 5 (IFU), remove the heading "click, 10 seconds, and orange indicator" and place it as a subheading under Step 5. For consistency, present both (written cues and depiction in the figure), and headings/subheadings for both the Pen IFU and QRG in the same order to prevent confusion.
2. You also state that the revised Pen images in the proposed IFU and QRG reflect the band around the needle end (b) (4). However, this is not reflected in the Pen IFU and QRG submitted on March 26, 2020. Revise the labeling to accurately depict the actual needle end. In addition, we note the words "needle end" have been removed from the description of parts of the Pen as well as all other images of the Pen throughout the IFU/QRG. Retain the words "needle end" on all Pen images displayed throughout the IFU/QRG because this is how the IFU/QRG was tested in the supplemental human factors validation studies.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 26, 2020

IFU and QRG (all)

\\cdsesub1\evsprod\bla761154\0042\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-pfs-clean-pdf.pdf

\\cdsesub1\evsprod\bla761154\0042\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-pen-clean-pdf.pdf

\\cdsesub1\evsprod\bla761154\0042\m1\us\114-labeling\draft\labeling\draft-labeling-text-quick-reference-guide-pfs-pdf.pdf

\\cdsesub1\evsprod\bla761154\0042\m1\us\114-labeling\draft\labeling\draft-labeling-text-quick-reference-guide-pen-pdf.pdf

Container labels and Carton labeling (all)

\\cdsesub1\evsprod\bla761154\0042\m1\us\114-labeling\draft\carton-and-container\draft-carton-and-container-label-pdf.pdf

APPEARS THIS WAY ON ORIGINAL

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/

TERESA S MCMILLAN
04/03/2020 05:38:35 PM

MILLIE B SHAH
04/06/2020 08:33:45 AM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
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:	March 12, 2020
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA-761154
Product Type:	Combination Product
Drug Constituent Name and Strength	Hulio (FKB327)[1]-injection 20 mg/0.4 mL and 40 mg/0.8 mL
Device Constituent:	Pre-filled Syringe and Pen
Rx or OTC:	Rx
Applicant/Sponsor Name:	Mylan
Submission Date:	July 12, 2019
OSE RCM #:	2019-1495 2019-1497
DMEPA Safety Evaluator (Human Factors):	Jason Flint, MBA, PMP
DMEPA Safety Evaluator:	Teresa McMillan, PharmD
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Associate Director	Mishale Mistry, PharmD, MPH

[1] Hulio has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). Since the proper name for Hulio has not yet been determined, the descriptor, FKB327 is used throughout this review as the nonproprietary name for this product

1. REASON FOR REVIEW

This report reviews two human factors (HF) validation study reports and labels and labeling submitted under BLA 761154 for FKB327. These are combination products with proposed Pen and Pre-filled syringe (PFS) device constituent parts that are intended to treat rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Adult Crohn's Disease (CD) and ulcerative colitis (UC), plaque psoriasis (Ps), and juvenile idiopathic arthritis (JIA) in patients age 4 and older.

1.1 PRODUCT DESCRIPTION

Pen –

As described in the HF validation study report, the FKB327-Pen device is a single-dose disposable Auto-Injector (Figure 1). FKB327-Pen is used to deliver a single 40 mg (0.8 mL) subcutaneous dose of FKB327. The FKB327-Pen device design includes a viewing window, which allows the end-user to inspect the amount of liquid (i.e. liquid is at or close to the fill marker seen through the window) and that the liquid is clear and colorless.

An initial auditory click informs the user that the injection has started, and a second click indicates the injection has completed. The device also includes a visual confirmation that the injection is complete, when the orange indicator becomes fully visible in the viewing window.

Figure 1: FKB327 Autoinjector

Pre-filled Syringe -

As described in the HF validation study report, the FKB327-PFS device (Figure 2) user interface includes a needle safety feature, transparent syringe barrel, fill marker and protective needle cap that prevents accidental activation of the device and protects the needle prior to injection.

Figure 2: FKB327 Pre-filled Syringe

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

We reviewed an HF validation study protocol[2] for the Pen presentation study HDD-1037 in November 2015 under IND 116471. Additionally, the Agency held a BPD2 meeting with Mylan on July 30, 2019. The meeting minutes[3] detail that the Agency asked Mylan to submit their HF data pertaining to JIA patients, and to validate proposed design modifications. The additional data that Mylan submitted is addressed in this review.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Reports	D
Information Requests Issued During the Review	E

[2] McMillan, T. Human Factors Protocol Review for FKB327 (proposed adalimumab biosimilar) IND 116471. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015NOV09. RCM No: 2015-2239.

[3] Nabavian, S. Meeting Minutes for FKB327 IND 116471, Silver Spring (MD): FDA, CDER, ODEII, DPARP (US); 2018 SEP 26.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Labels and Labeling	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed (Table 2), and our analysis to determine if the results support the safe and effective use of the proposed product. The findings are presented in two sections, one for the Pen presentation, and one for the pre-filled syringe presentation.

3.1 SUMMARY OF STUDY DESIGN

Pen HF Validation Studies

We reviewed the HF validation study protocol for study HSS-1037 in November 2015, and Mylan incorporated our recommendations in all the studies submitted. Mylan submitted results from three HF validation studies for the Pen presentation; *Usability Validation of a Rheumatoid Arthritis Auto-Injector* (HSS-1037), *Focused Needle Stick Risk Mitigation Study* (HSS-3109), and *Usability Validation of an Auto-Injector for Juvenile Idiopathic Arthritis* (HSS-1055).

It is important to note that study HSS-1055 was conducted prior to supplemental study HSS-3109, which means that the final Pen with labeling identifying the needle end was not assessed in JIA patients. In response to an information request, the applicant noted that even without the additional needle-end labeling, no JIA patients experienced a use-error related to orientation of the Pen.

Table 2 shows a summary of the user groups for the three studies.

Table 2. Pen HF Validation Study User Groups		
Study	**User Groups**	**Number of Participants**
HSS-1037	Untrained Adult Patients	30
	Untrained Caregivers	30
	Trained Adult Patients	30
	Trained Caregivers	30

	Untrained Healthcare Providers	15
HSS-3109	Untrained Adult Patients	30
	Untrained Caregivers	30
HSS-1055	Untrained Pediatric JIA Patients	15

Pre-filled Syringe HF Validation Study

Mylan did not submit the HF validation protocol for the pre-filled syringe presentation for our review; however, the study methodology was consistent with the protocol that we reviewed for the Pen presentation, except that there was no pediatric user group despite the indication for juvenile idiopathic arthritis. We provide a recommendation in Section 4, but defer to the Division of Pulmonary, Allergy, and Rheumatology Products on addressing this data gap and determine appropriate labeling for this user group. Mylan submitted results from one HF validation study for the PFS presentation; *Usability Validation of a Rheumatoid Arthritis Auto-Injector* (HSS-1075). Table 3 shows a summary of the user groups for the study.

Table 3. Pre-filled Syringe HF Validation Study User Groups

Study	User Groups	Number of Participants
HSS-1075	Untrained Adult Patients	30
	Untrained Caregivers	30
	Trained Adult Patients	30
	Trained Caregivers	30

	Untrained Healthcare Providers	16

3.2 **RESULTS AND ANALYSES**

Table 2 describes the study results, Mylan's analysis of the results, and DMEPA's analyses and recommendations.

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Check expiration date	71 Participants failed to check the expiration date.	1 participant had difficulty locating the expiration date.	"I actually did forget to do that." • "I wasn't sure if there was any. Never done it before." • "Whenever I get medication directly from pharmacy I don't check it, it doesn't occur to me to check expiration date of new medication. If it had been in cabinet for a while I would	• forgetting; • it not occurring for them to check; • assuming they would be provided unexpired medication; • a mistake; • checking the expiration date when receiving the product, not just before use; and • a close call where they recovered but almost did not check the expiration date due to having difficulty finding it.	The dimensions of the Pen allow for a prominent label on the device to display the expiration date. The on-device label and carton display the expiration date. Information for use clearly states that the user should check the	Based on the Applicant's use-related risk analysis (URRA), the harm associated with failure to check the expiration date is potentially receiving degraded product, which could reduce the product's effectiveness. We agree that there were several root causes that may have led to the use errors. However, we confirmed that the instructions to check the expiration date are displayed in the Instructions for Use (IFU). Our review didn't identify any recommendations to further optimize the IFU, and we find the residual risks acceptable.

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			check" • "Yeah, I didn't look at it." "I glanced at this [box] but didn't look at the syringe." • "You're correct. You would absolutely want to check the date of expiration, probably before you put it in there [refrigerator]". • "I don't know why I was		expiration date prior to use. Images provided supplement the description of checking the expiration date.	

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			looking at the box. It was right here [on the front]."			
Check medication in viewing window	68 Participants failed to check the medication window.	0	[Unprompted] "I forgot to look in that window to make sure to the line." • "Didn't occur to me. [I] was more focused on checking [the] window during [the injection] to see if it moved." • "I didn't, no. I assumed it was in sealed box so	• forgetting; • checking the viewing window after the injection but not prior; • it did not occur to them to check the medication window; • assuming they would not be provided defective medication; • being unsure why they did not; • checking the	The Pen has a large window to view the contents of the syringe housed in the device and therefore look for product degradation and medication level. The on-device label has a fill marker to	Based on the Applicant's use-related risk analysis (URRA), the harm associated with failure to check the medication in the viewing window is potentially receiving degraded product, which could reduce the product's effectiveness. We agree that there were several root causes that may have led to the use error; however, after our review, we confirmed that the instructions to check the medication are displayed in the IFU. Our review didn't identify

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			I didn't look at condition." • Unprompted, the participant stated, "I think I would check that [expiration date] and the medication when I got it." • "I did after, where orange indicator is, but I did not prior." • "I'm nervous." • "That is also true. For doing it for 10 years, I guess I got out	medication window when receiving the product, not just before use; • being nervous; • personal habits.	indicate the necessary amount of medication within the device for complete dose administration. Information for use clearly states that the user should inspect the biosimilar product through the viewing window to look for product	any recommendations to further optimize the IFU, and we find the residual risks acceptable.

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			of the habit of doing [it]." • "I'm not sure why I didn't. Looked like it was full, so I went with it. Looked like there was medication in it."		degradation and medication level. Images provided supplement the description of inspecting the medication.	
Select correct injection site	19 Participants selected the wrong injection site.	0	[Injected into the left arm] "Most patients prefer it if it can go in their arm. In my experience, people don't	• their professional opinion (Healthcare Professionals only); • choosing the injection site based on accessibility to the site;	Information for use clearly states the recommended injection sites are the thighs and the abdomen.	Based on the Applicant's use-related risk analysis (URRA), the harm associated with failure to select the correct injection site is intradermal or intramuscular injection, which could impact the effectiveness of the dose.

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			like the thighs, so I wouldn't choose that as first option." • [1] [Injected into the left forearm.] "It's just the easiest place for me to inject, and if I was going to have a skin reaction, it would be very visible." • [Injected into the left arm] "The medication we do use now, we	• previous knowledge; and • an assumption that the injection needed to be administered to the afflicted area.	Images provided supplement the verbiage and highlight the correct injection sites.	We agree that there were several root causes that may have led to the use error; however, after our review, we confirmed that the instructions for selecting the correct injection site are displayed in the IFU. Our review didn't identify any recommendations to further optimize the IFU, and we find the residual risks acceptable.

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			use the arm. He used another one where could use thigh or abdomen, but he said those were more painful. His current one arm is an option." • [Injected into the left wrist [confirmed from video review]. Participant injected into arm where she stated she			

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			usually had flare-ups and she would have talked to her doctor about where to inject.] "That's where I've had my flare ups from my RA."			
Remove Auto-Injector cap* *The Applicant categorized the cap removal task as critical; however, we find that this is not a critical task because failure to	1 participant did not remove the cap.	5 participants had difficulty removing the cap.	• "I was mainly concerned with getting him his medicine." • "I didn't remember if the cap came off or not, but it was very clear." "[I'm] not sure	•being focused on administering the medication; •difficulties with the cap; •misunderstanding the instructional materials; and	No risk mitigation information was provided. Mylan notes that the use error and the close calls documented with respect to	Since there were some users that had difficulty with cap removal, we consulted with the Centers for Devices and Radiological Health (CDRH) and they determined that the forces for cap removal were within an acceptable range. We find the

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
remove the cap will not result in harm for this specific product.			what happened there. I don't know if I was trying to twist it off or just not put enough pressure going forward." • "I had difficulty taking the cap off." • "That thing is hard to come off. It doesn't tell you exactly how to remove it." • "Oh, surely I didn't. I missed that step."	• missing that step.	removing the Pen cap are consistent with use of other auto injection devices.	residual risk acceptable and have no recommendations.

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Squeeze injection site to create a raised area	79 Participants failed to pinch the injection site.	1 participant almost failed to pinch the injection site, but recovered before they made the error.	• "The only thing I forgot was to pinch the little area." • "It didn't occur to me. Had this been real injection I think I would've been more aware of that." • "In the past, squeezing injection site creates rash on the outside or the area that I inject, so I don't do that." • "I need to aim	• not knowing to squeeze the injection site; • personal habits; • forgetting because of previous knowledge or experience; • misunderstanding what area to squeeze; and • knowing to squeeze the injection site but did not.	Information for use clearly states to squeeze the injection site and images provided supplement the description.	Based on the Applicant's use-related risk analysis (URRA), the harm associated with failure to squeeze the injection site is intramuscular injection, which may impact effectiveness. We agree that there were several root causes that may have led to the use error; however, after our review, we confirmed that the instructions for squeezing the skin at the injection site are displayed in the IFU. Our review didn't identify any recommendations to further optimize the IFU, and we find the residual risks acceptable.

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			for the meaty part of the back of my palm. I'm not a good patient. It's not really a pinching kind of thing, I've never done that before." • "I did squeeze it. I don't think you saw me. I did squeeze it." [Study staff confirmed by video review participant did not squeeze injection site].			

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Orient orange-activator end toward the injection site	3 participants failed to orient the pen correctly.	2 participants initially oriented the pen incorrectly, but made a correction prior to delivering the medication.	• "I was looking at thumb area being the orange area. For some reason looked at that area as area you pushed down. [It] was an oversight." • "I was thinking about other things, mother is sick/dying and concerned about what to do."	• misinterpretation of the user interface; and • a distraction that was independent of the task.	Mylan added labeling to the Pen cap and conducted a focused study HSS-3109 to assess whether the mitigation was effective.	Based on the Applicant's use-related risk analysis (URRA), the harm associated with failure to orient the orange end of the activator toward the injection site is administration of the dose into the patient's thumb. We note that the applicant made a labeling change to the activator end of the Pen by adding a "needle end" label to mitigate the risk of this use error. The applicant then conducted a focused HF validation study (HSS-3109) to assess whether this change was an effective risk mitigation strategy. We note that there were no use errors and one close call in the focused HF study, which indicates that the labeling

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Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
						change was effective at mitigating this use error in adult patients. We also note that the focused study did not include JIA patients; however, we don't expect that the mitigation strategy of adding a "needle end" label to the Pen will increase the incidence of this use error in JIA patients. Thus, based on the totality of the information provided, we find the residual risk acceptable and have no additional recommendations.
Place Auto-Injector at 90 degree angle to the injection site	2 failed to place the autoinjector at a 90	1 failed to place the autoinjector at a 90 degree	[1] "I thought that I did it, I wasn't sure if I did it or not. Probably	Test Artifact Misconception	No risk mitigation information was provided.	Based on the Applicant's use-related risk analysis (URRA), the harm associated with failure to place the pen at a 90 degree

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	degree angle	angle, but recovered from the error before giving the injection	because of the way he's sitting [mannequin], would be easier laying down." [2] "I thought I did, was trying to hold at a 90^{o} angle." 002-095 PT EX [1] [Moderator observed participant place AI at angle, while he was viewing the medication window. No drug loss			angle is administration of the dose intradermally. The root causes identified were test artifact and "misconception", or the participant misjudging the angle of the pen. Our review didn't identify any recommendations to further optimize the IFU, and we find the residual risks acceptable.

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			occurred.] "It's supposed to be at 90° angle. I did it as close to a 90° angle as I could." [Close Call] [2] [Participant started holding the injector at a 45° and then adjusted to 90° prior to inserting] "I didn't notice that. I thought it was at 90°"			
Push Auto-Injector down	5 activated the	0	"I shouldn't have pushed it	• One (1) end-user activated the	No risk mitigation	Based on the Applicant's use-related risk analysis (URRA), the

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
against injection site, so first "click" is heard	autoinjector prematurely		before. I should have pushed it down against my [injection site], the pad." "You're supposed to hear the click. I pushed it down, but I had messed it up from the beginning." "I thought I heard it [first click]. If it did, it wasn't very loud. I was waiting for the second click."	device by recapping and held it down to the site due to a mistake. • One (1) end-user mis-oriented the pen and did not push the Pen down against the injection site due a mistake. (Mistake) • One (1) end-user did not remove the cap and did not push the Pen down against the injection site due a misunderstanding. (Misunderstanding) • One (1) end-user	information was provided.	harm associated with failure to push the Pen down so the first click is heard is underdose. We agree that there were several root causes that may have led to the use error; however, after our review, we confirmed that the instructions to press down to begin the injection are located in the IFU. Our review didn't identify any recommendations to further optimize the IFU, and we find the residual risks acceptable.

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			"I was thinking about other things, mother is sick/dying and concerned about what to do."	mis-oriented the pen and did not push the Pen down against the injection site due to their mind being distracted by occurrences independent of the study. (Distracted)		
Administer a full dose	15 - Delivered a partial dose	0	• "No, it pushed in and popped out, maybe because my thumb wasn't on top. It popped and surprised me, didn't think	• an insecure grip on the device; • being unsure when the injection was complete or how long to hold it; • previous knowledge obtained regarding	Two prominent feedback mechanisms indicate the injection is complete – an audible second click and visual	Based on the Applicant's use-related risk analysis (URRA), the harm associated with failure to administer a full dose is under dose. Based on the participant feedback, it appears that while some errors were related to

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			could push down again. I don't think I had a good grip." • "I blew it, I jumped the gun. I didn't wait for second click. I'm used to epi-pen. One click. I knew I made a mistake when I lifted up and saw stuff still coming out." • "No. I definitely didn't. Didn't	use of other injection devices; • a mistake; • being startled by the first click; • having forgotten to do a previous step; • being anxious.	confirmation by the orange plunger blocking the viewing window. Information for use states that users should do the following to complete the injection – hold the Pen to the site for a count of ten seconds, listen for the second audible click, and look for	negative transfer from the participant's previous experience, in some cases, elements of the device design, IFU, and QRG appear to have contributed to this use error. For example, some participants failed to hear the second click, and one participant experienced difficulty with maintaining his grip on the device. In response to an information request, the applicant provided data to show that this use error was less prevalent in a second injection scenario, which occurred two weeks later. Therefore, we find it reasonable to expect users to become aware of the injection duration and

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			realize it had to be held in as long as it did." • "like I said I was kind of gun shy I should have held it steady I flinched, I don't know." • "Yes. I kind of backed off a little bit at first a bit gun shy, but I did get it." • The participant stated she forgot to wipe injection site.		the orange indicator blocking the viewing window. Images provided depict the feedback mechanisms along a time line of ten seconds.	need to place the thumb over the top of the Pen to prevent slipping after first time use and then apply that knowledge for subsequent use. However, after review of the IFU and QRG, we identified one section that may contribute to this use error. We provide a recommendation in section 4 to include "AND" statements in some of the bulleted statements to ensure consistency with the image associated with the step. This change would not require additional HF data.

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			She then stated she was going to pretend to do it correctly, which she did. • "I realized halfway through, I didn't use the alcohol wipe." • "I didn't read the instructions completely and that's why I goofed up." • "No, I only listened for the first click and the liquid was coming out."			

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			• 1st Injection "I was a little anxious about doing this, just should've left it there longer." "No, I pulled it up too early, the medicine was squirting." • 2nd Injection "No, some fluid was still squirting so I think it was not a full dose, some didn't go into the patient when I lifted it up. I thought I			

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			was finished, thought the push part was at the bottom."			
Failure to administer one Pen for one dose	5 participants would have attempted to deliver a second injection if they were concerned about partial dose delivery.	0	"Heard the first click, realized didn't use alcohol and deliberately stopped it." • "I'm not sure [if a full dose was administered] but it did move, the indicator. I didn't hold for 10 seconds and I didn't hear 2nd click." In	No root cause analysis information was provided.	The Pens are provided individually packaged in blister packs within the carton. Information for use and the packaging clearly state to use one auto-injector for one dose.	Based on the Applicant's use-related risk analysis (URRA), the harm associated with failure to administer one Pen for one dose is over dose. No root cause analysis is presented by the applicant. However, from the participant's subjective feedback, we identify three potential root causes; the participant relying on their previous experience with a Pen (negative transfer of learning), rather than the IFU, lack of understanding that one Pen

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			regards to the 2nd injection, the participant stated, "I think so, I held it down. But I didn't hear 2nd click. I'm not sure if it's noticeable." • "It appears two are a single dose." "That's what I was looking for [points to the back of the box]. The box says, '2 single-use pre-filled			contains 40 mg, and lack of knowledge about what to do if the participant delivers an incomplete dose. Our review didn't identify any recommendations to further optimize the IFU, and we find the residual risks acceptable.

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			auto injectors (one dose) " "If I was out in the field I would have called the physician to confirm the order." "It [2nd injection] was easier. It comes with 2, so I gave 2. At home the dose is cut in half into Pen, so give 2 at home."			

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Dispose of Auto-Injector in a sharps container* *The Applicant categorized the disposal task as critical; however, we find that this is not a critical task because failure to dispose in a sharps container will not result in harm.	21 participants failed to dispose of the Pen in a sharps container.	5 participants	• "I saw it there, but just completely forgot. That was just an omission." • "I didn't, you're right. This is my first time and I didn't even see that there. I didn't realize that [hazard bin] was there." • "I'm sorry I started talking and whatever. Honestly I got really nervous	• forgetting to dispose of the Pen in a sharps container; • not knowing to dispose of the device in the sharps container or did not see the sharps container; • being distracted; • a mistake; and • knowing to depose of the device into the sharps container but did not.	No mitigation steps discussed.	We note that there were several participants that failed to dispose of the Pen in a sharps container; however, we note the IFU includes disposal instructions. Our review didn't identify any recommendations to further optimize the IFU, and we find the residual risks acceptable.

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			with the cough attack; that really threw me off." • "I put it back in here [packaging], but I put the cover on it." • "That should've gone in the sharps, just threw it in this pail [trash can] because closer."			
Troubleshooting an incomplete dose.	14 participants gave incorrect		Not Provided	Not Provided	When asked what the instructions (QRG or IFU)	There were several errors related to the knowledge task for troubleshooting an incomplete dose. We are unable to comment

Table 2: Summary and Analyses of Study Results Pen						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	information for the knowledge task.				had to say about that topic, all fourteen participants responded correctly (e.g. do not take a 2nd dose, or contact your healthcare provider).	on potential root causes because no subjective feedback was provided; however, participants that responded incorrectly were able to find the information when directed to the IFU. Since the participants were able to use the IFU to locate the correct information, we find the residual risk acceptable and have no additional recommendations.
Troubleshooting a device with particles floating in the medication.	5 participants gave incorrect information for the		Not Provided	• Slip – Attentional failure (3) • Assumption – Accepting something to be true without evidence (2) • Information	The participants later located and understood the instruction to not use the Pen if the	There were several errors related to the knowledge task for troubleshooting a device with particles floating in the medication. We are unable to comment on potential root causes because no subjective feedback was provided; however,

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Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	knowledge task.			Oversight – Unaware of the instruction (5) • Mistake – Omission (1) • Not UE as determined by study staff (1)	device has particles floating in it.	participants that responded incorrectly were able to find the information when directed to the IFU. This indicates that some participants may have answered based on their experience or mental model. Since the participants were able to use the IFU to locate the correct information, we find the residual risk acceptable and have no additional recommendations.

Analysis of non-critical tasks – PEN

We observed use errors/close calls/use difficulties with the following non-critical tasks:

- Rotate injection site
- Wash hands (or puts on gloves)
- Wipe injection site with alcohol prep
- Kept auto-injector still (not moved, twisted or rotated) during the injection
- Pull Auto-Injector straight away from injection site

After evaluating the errors pertaining to these use-related events, we found that for the task "Rotate injection site", some participants referenced an instruction that indicated that they should use the same injection site they had previously used. The attribution of this use-error to an instruction in the IFU may be associated with a choice-supportive bias, because upon review of the IFU we note that it contains the instructions, "You should rotate and change your injection site each time. "and "Stay at least 1 inch from a previous site used." Based on this information, we find the residual risk acceptable and have no additional recommendations.

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe

Critical Tasks Evaluated	Number and Description of Use Errors	Number and Description of Close Calls	Participant's Subjective Feedback on Use Errors and Close Calls	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Check expiration date	78 participants failed to check the expiration date prior to administering	0	I sure didn't you've got to make sure the expiration date is up to par - it's up	• They forgot to check the expiration date. (Lapse) • It did not occur to them to	The Pre-Filled Syringe label and the carton clearly state the expiration date.	Based on the Applicant's use-related risk analysis (URRA), the harm associated with failure to check the expiration date is potentially receiving degraded product, which could reduce the product's effectiveness.

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	the medication.		to date. I forgot all about that. I am prob a little too trusting and I need to be better about that. I didn't even think about it. Good question. I never when I receive the product from my pharmacy - I never check the expiration date on the	check the expiration date. (Slip) • They assumed that the medication provided would not be expired. (Assumption) • They had difficulty locating it or did not know they were supposed to check it. (Information Oversight) • They acted	Information for use clearly states that the user should check the expiration date. Images are provided aid the description of how to check the expiration date.	We agree that there were several root causes that may have led to the use errors. However, after our review, we confirmed that the instructions to check the expiration date are displayed in the Instructions for Use (IFU). Our review didn't identify any recommendations to further optimize the IFU, and we find the residual risks acceptable.

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			box. I assume that they're doing that themselves. I assume I'm receiving a product within the right time. It wasn't visible on here. Is it supposed to be on the plastic part of the needle? [looks at syringe] Oh I see it now. Yeah I guess I	based on previous experiences or habits. (Mental Model) • Inquiry was not performed to find root cause for three (3) use errors.		

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			probably should have done that, but I'm known for taking medications when they're out of date, that's probably why.			
Check medication	54 participants failed to check the medication prior to administering	0	It was an oversight, and I just didn't do it. Because this is new to me I think I did a couple of mistakes	• They forgot to check the medication. (Lapse) • They did not think to check the medication. (Slip)	The Pre-Filled Syringe has a transparent barrel to show the contents of the medication vial housed by the device.	Based on the Applicant's use-related risk analysis (URRA), the harm associated with failure to check the medication is potentially receiving degraded product, which could reduce the product's effectiveness. We agree that there were several potential root causes; however, after our review, we

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
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	the medication.		being new to injections. These are things I would have to make myself aware of. I just thought the medication was already in the syringe, instead of me having to put it in there. I guess that's why I didn't check the date on it	• They assumed the medication would not be defective. (Assumption) • They did not know they needed to check the medication or did not know what to look for while checking the medication. (Information Oversight) • They did not check	The Pre-Filled Syringe label has a fill marker to indicate the correct amount of medication within the device. Information for use clearly states that the user should inspect the biosimilar product through the viewing window to look for	confirmed that the instructions to check the viewing window are located in the IFU. Our review didn't identify any recommendations to further optimize the IFU, and we find the residual risks acceptable.

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			either. I'm used to having to filled the syringe myself. I didn't check the medication. So when you check the medication do you just have to check that it's full? If you're not an experienced person you won't know the	the medication due to personal habit or previous experience. (Mental Model) • They made a mistake. (Mistake) • Root cause inquiry was not performed for three (3) end-users.	product degradation and medication level. Images are provided aid the description of how to inspect the medication.	

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			difference. I'm used to one dose application that everything is pre-measured. With any of the medications I give to my wife so there's no need to measure it. Everything comes pre-measured - it's a matter of boom,			

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			stick it in. You're right I didn't do it; I failed to do that.			
Select correct injection site	12 participants failed to select the correct injection site.	3 participants initially selected the wrong injection site, but made the appropriate correction prior to delivering the medication.	[Right belly, <2 inches from belly button, Injected too close to belly button]. As I got used to it I would move more to the side. I don't really know why. That's just the first place that came to	• They chose an incorrect site due to previous experience. (Mental Model) • They did not understand the instructions concerning injection site. (Information	Information for use clearly states the recommended injection sites are the thighs and the abdomen. Images are provided to aid the description of the correct injection sites.	Based on the Applicant's use-related risk analysis (URRA), the harm associated with failure to select the correct injection site is intradermal or intramuscular injection, which could impact the effectiveness of the dose. We agree that there were use errors that appear to be related to the participant's mental model or previous experience, however; after our review, we confirmed that the instructions include a section for "Choosing & Preparing Injection Site." Our review didn't identify any recommendations to further optimize the

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			mind. I would automatically think the arm would be the most common place. [The injection was not 2 inches away from the belly button]. Sometimes I do it on the right, sometimes on the left (belly), sometimes on my thigh, it depends	Oversight) • They made a mistake. (Mistake) • Root cause inquiry was not performed for one (1) use error.		IFU, and we find the residual risks acceptable.

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			how I feel that day.			
Remove cap* *The Applicant categorized the cap removal task as critical; however, we find that this is not a critical task because failure to remove the cap will not result in harm for this specific product.	9 participants did not remove the cap from the syringe.	11 participants either did not think they had to remove the cap, or had difficulty removing the cap, but eventually recovered.	I didn't? Where is it? I thought it was already removed. Where is it? That's interesting. I still don't see. I didn't think it had a cap on it because I wasn't able to get it off. I tried tugging on it, and I didn't think it needed to	• They did not know that the needed to remove the cap. (Information Oversight), • They made a mistake. (Mistake) • They had difficulty removing it. (Physical Limitation) • Root cause was not performed	The design of the Pre-Filled Syringe cap allows the user to securely grip when pulling the cap off. Information for use clearly describes the cap as a protective part of the device and during use steps, states to remove the	Since there were some users that had difficulty with cap removal, we consulted with the Centers for Devices and Radiological Health (CDRH) and they determined that the forces for cap removal were within an acceptable range. We find the residual risk acceptable and have no recommendations from a medication error perspective.

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
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			come off. So if there was a cap on there, it was a little difficult to get it off. I suppose that was a mistake. I should have removed the cap. That's why it was so difficult to inject. That's why it dripped out. That's my mistake.	for three (3) use errors.		
Squeeze injection site to	51 participants	0	I forgot, I'm so sorry - but	• They forgot.	Information for use clearly	Based on the Applicant's use-related risk analysis (URRA), the harm associated with

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create a raised area	did not squeeze the injection site prior to delivering the injection.		I was supposed to pinch it. I missed that I didn't. I wiped the area and put the syringe in that area. I didn't know to do that. That was probably lack of training or lack of knowledge. Yeah I probably missed, but usually my friend	(Lapse) • They did not think to squeeze the site. (Slip) • They did not know they needed to squeeze the site. (Information Oversight) • They made a mistake. (Mistake) • They followed their personal experience. (Mental Model) • Root cause	states to squeeze the injection site and provides images to aid the description of how to squeeze.	failure to squeeze the injection site is intramuscular injection, which may impact effectiveness. We agree that that there were use errors that appear to be related to the participants' mental model or previous experience; however, after our review, we confirmed that the instructions state to "Gently squeeze the injection site to create a raised area, and hold that area firmly", and have an accompanying image. Our review didn't identify any recommendations to further optimize the IFU, and we find the residual risks acceptable.

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Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			doesn't have to do all that. I remember reading that in here [QRG], I just didn't do it.	inquiry was not performed for three (3) end users who did not squeeze the injection site.		
Insert needle at a 45° angle	22 participants failed to insert the needle at a 45 degree angle.	0	I think I was supposed to put it up a little more. I almost went straight in. I have problems with my right hand. It was easier if I go straight down. I don't	• They did not insert the needle at a 45-degree angle due to habit or personal experience. (Mental Model) • They had a physical limitation.	Information for use clearly states to insert the needle at a 45-degree angle to the injection site and provides images to aid the description of	Based on the Applicant's use-related risk analysis (URRA), the harm associated with failure to insert the needle at a 45 degree angle is intradermal injection. We agree that that there were use errors that appear to be related to the participants' mental model or previous experience; however, after our review, we confirmed that the instructions state "At a 45° angle to the injection site, use a quick dart-like motion to insert the needle into the site", and include an associated image.

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			want the needle to break. Good question, I didn't give that any thought. It's supposed to be at a 90-degree angle, I think. I suppose I should have read the directions on it. I guess I'd have to read the instructions better.	(Physical Limitation) • They forgot. (Lapse) • They did not think to insert the needle at a 45-degree angle. (Slip) • They did not know how to insert the needle at a 45-degree angle. (Information Oversight) • They made a mistake or	how to squeeze.	Our review didn't identify any recommendations to further optimize the IFU, and we find the residual risks acceptable.

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			[participant went back and looked at the instructions] Oh, a 45-degree angle, not 90. I guess I didn't do that. I didn't read the instructions well enough. I thought I knew it, but I didn't. That's how I always do it, straightwards in.	did not realize they did not do the task correctly. (Mistake)		

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			In this case I'm glad that I saw this. It is normal to see the drip. Since I'm left handed, I'm going to say it's at an angle.			
Administer a full dose	16 participants failed to deliver a full dose	0	[Substantial amount of drug leakage - pulled plunger out and medication leaked out the back of the syringe]. I kind of	• They did not know to fully depress the plunger. (Information Oversight), • They made a mistake. (Mistake) • Root cause was not	Information for use indicates that users should fully depress the plunger to administer the safety feature.	Based on the Applicant's use-related risk analysis (URRA), the harm associated with failure to administer a full dose is under dose. We agree that there were use errors that appear to be related to the participants' mental model or previous experience, however, after our review, we confirmed that the instruction "Slowly push the plunger all the way until all the medication

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			spilled a bit, but yes. Usually I tap all the bubbles out, usually put in a little more than what I need to compensate for the air. I look at it then go ahead and administer the full dose. [Substantial amount of drug leakage] Because I put my finger on	performed for one (1) use errors.		is injected and the syringe is empty." is located in the IFU. Our review didn't identify any recommendations to further optimize the IFU, and we find the residual risks acceptable.

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			the plunger. I should have just been holding it around the orange piece.			
Dispose of syringe in a sharps container* *The Applicant categorized the disposal task as critical; however, we find that this is not a critical task because failure to dispose in a sharps	18 participants did not dispose of the syringe in a sharps container.	4 participants almost didn't dispose of the PFS in a sharps container, but recovered before the end of the scenario.	Didn't know there was one. I probably would have known if I had read the manual. I saw that. It says to hold it as you take the needle out and then release your thumb after	• They did not know they needed to dispose of the syringe in the sharps container. (Information Oversight) • They forgot to discard the syringe in the sharps container. (Lapse)	The Pre-Filled Syringe design causes the needle guard to lock in place, preventing access to the needle after the plunger is fully depressed and released, and the needle guard inner	We note that there were several participants that failed to dispose of the PFS in a sharps container; however, we note the IFU includes disposal instructions. Our review didn't identify any recommendations to further optimize the IFU, and we find the residual risks acceptable.

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
container will not result in harm.			you take the needle out. I think I released my thumb before I should have. It was an oversight. I have one of these things at home. It didn't seem to be a sharps. It retracted back into the syringe, into itself. It didn't seem to be, from	• Root cause was not performed for three (3) use errors.	diameter is sufficiently small to prevent most fingers from fitting inside of it and reaching the needle tip. Information for use clearly states to dispose the Pre-Filled Syringe in a sharps container and provides additional information regarding	

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			my perspective a sharps.		what containers can be used as a sharps container.	
Storage	4 participants indicated the wrong storage location for the PFS.	0	Not Provided	Not Provided	When asked what the instructions (QRG or IFU) had to say about that topic, all of the participants responded correctly (e.g. in the refrigerator).	There were several errors related to the knowledge tasks: Storage, Troubleshooting a device with an expired date, Troubleshooting a device with particles floating in the medication, Troubleshooting a device with medication not at or near the fill marker, and Keeping device out of the reach of children. We are unable to comment on potential root causes because no subjective feedback was provided; however, participants that responded incorrectly were able to find the

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Troubleshooting a device with an expired date	1 participants gave incorrect information for the knowledge task.	0	Not Provided	Not Provided	The remaining one (1) participant was able to locate the instruction in the IFU and provide a correct response.	information when directed to the IFU. This indicates that some participants may have answered based on their previous experience or mental model. Since the participants were able to use the IFU to locate the correct information, we have no additional recommendations.
Troubleshooting a device with particles floating in the medication	3 participants gave incorrect information for the knowledge task.	0	Not Provided	Not Provided	All of the remaining three (3) participants responded correctly (e.g. do not use medication) when asked what the instructions	

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
					(QRG or IFU) had to say about that topic.	
Troubleshooting a device with medication not at or near the fill marker	11 participants gave incorrect information for the knowledge task.	0	Not Provided		All of the remaining seven (7) participants responded correctly (e.g. do not use medication) when asked what the instructions (QRG or IFU) had to say about that topic.	

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Keeping device out of the reach of children	8 participants provided an incorrect response to the knowledge task.	0	Not Provided	Not Provided	When asked what the instructions (QRG or IFU) had to say about that topic, seven (7) of the remaining eight (8) participants responded correctly (e.g. out of the reach of children)	
Troubleshooting an incomplete dose	33 participants gave incorrect information	0	Not Provided	Not Provided	When asked what the instructions (QRG or IFU) had to say	We note that there were use errors associated with troubleshooting an incomplete dose, and that 9 participants

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	for the knowledge task.				about that topic, twenty-two (22) of the remaining participants found the correct answer. Nine (9) participants did not find the answer in the instructional materials, and two (2) healthcare providers that gave incorrect answers were not asked to	were unable to locate the correct information in the IFU. The IFU includes instructions accompanied by a caution statement that included the information on what to do if the injection is incomplete. ⚠ **CAUTION:** If the needle did not retract or you do not think you received the full dose, **Do not** take another dose. Contact your healthcare provider for assistance. Thus, based on the totality of the information provided, we find the residual risk acceptable and have no additional recommendations.

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
					find the correct answer in the instructional materials.	
Unexpected Interruptions during product use* * The Applicant categorized the unexpected interruptions task as critical; however, we find that this is not a critical task because failure to complete this	13 participants gave incorrect information for the knowledge task.	0	Not Provided		After consulting the instructions (QRG or IFU), eight (8) of the remaining users provided the correct answer, while five (5) users were unable to locate this topic in the instructions.	We note that there were use errors associated with how to handle unexpected interruptions, and that 5 participants were unable to locate the correct information in the IFU. The IFU includes instructions accompanied by a caution statement that included the correct information. ⚠ **CAUTION:** Injection process must be completed without interruption. Read all steps first before beginning injection. Our review didn't identify any recommendations to further optimize the

Table 3: Summary and Analyses of Study Results – Pre-filled Syringe						
Critical Tasks Evaluated	**Number and Description of Use Errors**	**Number and Description of Close Calls**	**Participant's Subjective Feedback on Use Errors and Close Calls**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
task will not result in harm.						IFU, and we find the residual risks acceptable.

ANALYSIS OF NON-CRITICAL TASKS PRE-FILLED SYRINGE

We observed use errors/close calls/use difficulties with the following non-critical tasks: Rotate injection site

- Wash hands
- Wipe injection site
- Remove device cap
- Keep syringe uncapped
- Activate safety feature
- Keep syringe still
- Pull syringe straight away

After evaluating the errors pertaining to these use-related events, we agree with the Applicant that no additional mitigation strategies are necessary, and we determined that the residual risk is acceptable.

3.3 LABELS AND LABELING

Tables 3 and 4 below include the identified medication error issues with the submitted product samples, packaging, label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 4: Identified Issues and Recommendations for Mylan (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Instructions for Use (IFU) and Quick Reference Guide (QRG) for Pen			
1.	*While there appeared to be a learning effect and participants demonstrated improved performance in administration of a full dose in the second injection scenario, we note that some users had difficulty with delivering a full dose of the medication.*	*We identified that the instructions for step 4 in the QRG, and step 5 in the IFU may be confusing because bulleted statements do not include an "AND" statement between them. Thus, a user may rely on only one statement as an indicator that the full dose has been administered. Additionally, the heading for Step 5 ('Hold Down for 2nd "CLICK" & 10 Seconds') does not include the third cue of the orange indicator. This is inconsistent with the graphic and the caution statement in Step 5 which indicates that all three cues (2nd click, 10 seconds has passed, orange indicator blocks window) must occur to ensure that all medication was delivered.*	*For consistency with the graphic and caution statement in Step 5, we recommend adding the word "AND" between each of the bulleted statements. For example:* *• A Second "CLICK" was heard,* *AND* *• 10 seconds has passed,* *AND* *• Orange Indicator has stopped and completely blocked the Viewing Window.* *Additionally, we recommend revising the heading for Step 5 to include all three cues (click, 10 seconds, orange indicator).* *Based on the nature of these changes, we have determined that additional HF validation data is not needed at this time.*

2.	*The statements '[redacted] (b) (4) are misleading.*	*Use of this product may require more than one Pen for a complete dose. Thus, these statements may lead to under doses.*	*We note that some of your proposed indications require administration of more than one Pen for a complete dose. Thus, the proposed statements [redacted] (b) (4) are misleading and could lead to under dosing. We recommend that you delete these statements.*
3.	*The depiction of the needle end for the prefilled Pen in the IFU is labeled blue. However, in the samples sent to the Agency and in Quick Reference Guide (QRG) the needle end is labeled black.*	*Inconsistency between the actual color of the device needle end and the depictions of the device needle end in the QRG and IFU may lead to confusion of which end houses the needle.*	*Ensure that the figures and labeling in the QRG and the IFU accurately depict the actual needle end (e.g. colors , wording, etc.).*
4.	*There is a discrepancy between the description of the drug product in Section 3 Dosage Forms and Strengths in the Prescribing Information and in the IFU/QRG.*	*Inconsistency of drug product appearance statements throughout the labels/labeling may lead to confusion.*	*Section 3 of the Prescribing Information lists this drug product as a clear to slightly opalescent, colorless to pale brownish-yellow solution. However, the IFU and QRG states that the medication is clear, colorless and has no particles.* *Clarify the appearance of the drug product and ensure it is consistently stated throughout the labels and labeling.*
Instructions for Use (IFU) and Quick Reference Guide (QRG) for Pre-filled Syringe			

1.	*The statements* [redacted] *are misleading.*	*Use of this product may require more than one syringe for a complete dose. Thus, these statements may lead to under doses.*	*We note that some of your proposed indications require administration of more than one syringe for a complete dose. Thus, the proposed statements* [redacted] *are misleading and could lead to under dosing. We recommend that you delete these statements.*
2.	*There is a discrepancy between the description of the drug product in Section 3 Dosage Forms and Strengths in the Prescribing Information and in the IFU/ QRG.*	*Inconsistency of drug product appearance statements throughout the labels/labeling may lead to confusion.*	*Section 3 of the Prescribing Information lists this drug product as a clear to slightly opalescent, colorless to pale brownish-yellow solution. However, the IFU and QRG states that the medication is clear, colorless and has no particles.* *Clarify the appearance of the drug product and ensure it is consistently stated throughout the labels and labeling.*
Container Labels and Carton Labeling (All)			
1.	*The expiration date format has not been defined on the labels and labeling.*	*We are unable to evaluate the format of the expiration date for risk of medication error.*	*As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to*

			represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	*The dosage form has been omitted from the principal display panel.*	*Omission of the dosage from may lead to confusion.*	*Revise to the following:* *Proprietary name* *Proper name* *Injection* *Strength* *For Subcutaneous Use Only*
3.	*The middle digits of the NDC numbers are not adequately differentiated or non-sequential.*	*Similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., 6666, 6667, and 6668), nor is using the identical product code for injectable products containing the same concentration of drug but different total volumes.*	*Ensure the middle digits of the proposed NDC numbers are non-sequential and adequately differentiated.* *Draft Guidance: Container and Carton, April 2013 (lines 521-525)* *FDA National Drug Code Directory* *https://www.fda.gov/drugs/informationondrugs/ucm142438.htm*
Container Label (prefilled syringe and pen)			

1.	*As proposed, we are unsure if the linear barcode is scannable.*	*If the linear barcode is presented in horizontal position, then the barcode may wrap around the curvature of a pen or syringe, and will not be scannable and will prevent drug product identification.*	*Consider reorienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.*[4]
Carton Labeling (prefilled syringe and pen)			
1.	*The serial number is missing from the carton labeling.*	*The serial number is part of the human-readable product identifier and if omitted may prevent drug product identification.*	*FDA draft guidance recommends this format for the human-readable product identifier:* *NDC: [insert product's NDC]* *SERIAL: [insert product's serial number]* *LOT: [insert product's lot number]* *EXP: [insert product's expiration date]* ***Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers*, September 2018**
Tray Labels and Carton Labeling (prefilled syringe and pen)			
1.	*The recommended usual dosage statement is not consistent with the Prescribing Information.*	*Inconsistency with the presentation of the recommended dosage statement may lead to wrong dose errors.*	*To ensure consistency with the Prescribing Information, revise the statement, "See package insert for full prescribing information" to read "Dosage: See Prescribing Information."*

[4] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

4. CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm to the patient. We found that based on the root cause analysis and subjective feedback for most of these use errors/close calls/difficulties, we did not identify any areas to further optimize the user interface, and found that the residual risks were acceptable. However, we identified one risk area from the HF validation study that warranted a change to the IFU, and we included that recommendation in table 4.

Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. In this particular instance, we have determined that that these changes can be implemented without additional validation testing to be submitted for review. Above, we have provided recommendations in Table 4 for the Applicant. We ask that the Division convey Table 4 in its entirety to the applicant so that recommendations are implemented prior to approval of this BLA.

For the pre-filled syringe presentation, we note that the applicant did not conduct an HF validation study with pediatric/adolescent JIA patients as a distinct user group and recommend that the following statement be added to Section 2 of the PI: “Hulio pre-filled syringe is for adult self-administration or caregiver administration only. Self-administration of Hulio pre-filled syringe in pediatric patients has not been tested.” We defer to the Division of Pulmonary, Allergy, and Rheumatology Products on addressing this data gap and determine appropriate labeling for this user group.

4.1 RECOMMENDATIONS FOR MYLAN

Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4 and we recommend that you implement these recommendations prior to approval of this BLA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for FKB-327 that Mylan submitted on July 16, 2019 and the reference product US-licensed Humira.

Table 5. Relevant Product Information	**FKB-327**	**US-licensed Humira**
Initial Approval Date	N/A	12/30/2002
Therapeutic Drug Class or New Drug Class	tumor necrosis factor (TNF) blocker	
Nonproprietary or Proper Name	Adalimumab-xxxx	adalimumab
Indication	rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Adult Crohn's Disease (CD) andulcerative colitis (UC), plaque psoriasis (Ps), and juvenile idiopathic arthritis (JIA) in patients age 4 and older	RA, PsA, AS, CD, UC, Ps, JIA in patients age 2 and older, Hidradenitis Suppurativa, Pediatric Crohn's Disease, and Uveitis
Route of Administration	Subcutaneous	
Dosage Form	Injection	
Strength	Injection: 40 mg/0.8 mL in a single-dose prefilled pen (HULIO Pen) (3) Injection: 40 mg/0.8 mL in a single-dose prefilled plastic syringe (3) Injection: 20 mg/0.4 mL in a single-dose prefilled plastic syringe (3)	**Pen (HUMIRA Pen)** Injection: 80 mg/0.8 mL in a single-dose pen. Injection: 40 mg/0.8 mL in a single-dose pen. Injection: 40 mg/0.4 mL in a single-dose pen. **Prefilled Syringe** Injection: 80 mg/0.8 mL in a single-dose prefilled glass syringe. Injection: 40 mg/0.8 mL in a single-dose prefilled glass syringe. Injection: 40 mg/0.4 mL in a single-dose prefilled glass syringe. Injection: 20 mg/0.4 mL in a single-dose prefilled glass syringe. Injection: 20 mg/0.2 mL in a single-dose prefilled glass syringe. Injection: 10 mg/0.2 mL in a single-dose prefilled glass syringe. Injection: 10 mg/0.1 mL in a single-dose prefilled glass syringe. **Single-Dose Institutional Use Vial** Injection: 40 mg/0.8 mL in a single-dose, glass vial for institutional use only.

Dose and Frequency	**Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis (2.1):** • 40 mg every other week. • Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week. **Juvenile Idiopathic Arthritis (2.2):** • 15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg every other week • ≥ 30 kg (66 lbs): 40 mg every other week **Adult Crohn's Disease and Ulcerative Colitis (2.3, 2.4):** • Initial dose (Day 1): 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days) • Second dose two weeks later (Day 15): 80 mg • Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week. • For patients with Ulcerative Colitis only: Only continue HULIO in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy. **Plaque Psoriasis (2.5):** • 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.	**Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis (2.1):** • 40 mg every other week. • Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week. **Juvenile Idiopathic Arthritis or Pediatric Uveitis (2.2):** • 10 kg (22 lbs) to <15 kg (33 lbs): 10 mg every other week • 15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg every other week • ≥ 30 kg (66 lbs): 40 mg every other week **Adult Crohn's Disease and Ulcerative Colitis (2.3, 2.5):** • Initial dose (Day 1): 160 mg • Second dose two weeks later (Day 15): 80 mg • Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week. • For patients with Ulcerative Colitis only: Only continue HUMIRA in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy. **Pediatric Crohn's Disease (2.4):** • 17 kg (37 lbs) to < 40 kg (88 lbs): • Initial dose (Day 1): 80 mg • Second dose two weeks later (Day 15): 40 mg • Two weeks later (Day 29): Begin a maintenance dose of 20 mg every other week. • ≥ 40 kg (88 lbs): • Initial dose (Day 1): 160 mg • Second dose two weeks later (Day 15): 80 mg • Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week. **Plaque Psoriasis or Adult Uveitis (2.6):**

		• 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose. **Hidradenitis Suppurativa (2.7):** **Adults:** Initial dose (Day 1): 160 mg Second dose two weeks later (Day 15): 80 mg Third (Day 29) and subsequent doses: 40 mg every week. Adolescents (12 years and older) ≥60 kg (132 lbs): Initial dose (Day 1): 160 mg Second dose two weeks later (Day 15): 80 mg Third (Day 29) and subsequent doses: 40 mg every week. Adolescents (12 years and older) 30 kg (66 lbs) to <60 kg (132 lbs): Initial dose (Day 1): 80 mg Second (Day 8) and subsequent doses: 40 mg every other week.
Storage	Do not use beyond the expiration date on the container. HULIO must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. Store in original carton until time of administration to protect from light. If needed, for example when traveling, HULIO may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days, with protection from light. HULIO should be discarded if not used within the 14-day period. Record the date when HULIO is first removed from the refrigerator in the spaces provided on the carton and dose tray. Do not store HULIO in extreme heat or cold.	Do not use beyond the expiration date on the container. HUMIRA must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. Store in original carton until time of administration to protect from light. If needed, for example when traveling, HUMIRA may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days, with protection from light. HUMIRA should be discarded if not used within the 14-day period. Record the date when HUMIRA is first removed from the refrigerator in the spaces provided on the carton and dose tray. Do not store HUMIRA in extreme heat or cold.

Container Closure/Device Constituent	1 Carton Containing: • Two (2) FKB327-Pens in sealed blister trays OR • Two (2) FKB327-PFS in sealed blister trays AND • Two (2) alcohol preps • One (1) US Prescribing Information insert (USPI) which includes Medication Guide (MG) • One (1) Medication Guide (MG) • One (1) Product Instructions-for-Use (IFU) • One (1) Quick-Reference-Guide (QRG)	HUMIRA Pen Carton - 40 mg/0.8 mL HUMIRA Pen Carton - 40 mg/0.4 mL HUMIRA Pen 40 mg/0.8 mL - Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa HUMIRA Pen 40 mg/0.4 mL - Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa HUMIRA Pen 80 mg/0.8 mL - Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa HUMIRA Pen 40 mg/0.8 mL - Psoriasis, Uveitis or Adolescent Hidradenitis Suppurativa Starter Package HUMIRA Pen 40 mg/0.4 mL - Psoriasis, Uveitis or Adolescent Hidradenitis Suppurativa Starter Package HUMIRA Pen 80 mg/0.8 mL and 40 mg/0.4 mL - Psoriasis, Uveitis or Adolescent Hidradenitis Suppurativa Starter Package Prefilled Syringe Carton - 40 mg/0.8 mL Prefilled Syringe Carton - 40 mg/0.4 mL Prefilled Syringe Carton - 20 mg/0.4 mL Prefilled Syringe Carton - 20 mg/0.2 mL Prefilled Syringe Carton - 10 mg/0.2 mL Prefilled Syringe Carton

		- 10 mg/0.1 mL HUMIRA Prefilled Syringe 40 mg/0.8 mL - Pediatric Crohn's Disease Starter Package (6 count) HUMIRA Prefilled Syringe 80 mg/0.8 mL - Pediatric Crohn's Disease Starter Package (3 count) HUMIRA Prefilled Syringe 40 mg/0.8 mL - Pediatric Crohn's Disease Starter Package (3 count) HUMIRA Prefilled Syringe 80 mg/0.8 mL and 40 mg/0.4 mL - Pediatric Crohn's Disease Starter Package (2 count) Single-Dose Institutional Use Vial Carton - 40 mg/0.8 mL
Intended Users	Lay Users	
Intended Use Environment	Home Environments	

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On January 30, 2020, we searched the L:drive and AIMS using the terms "761154" and "FKB327" to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified one previous review[5] of an HF validation protocol for the Pen protocol, and we confirmed that our previous recommendations were implemented or considered for the Pen HF validation studies. The HF validation study for the pre-filled syringe presentation closely followed the approach used for the Pen HF validation study, but did not include pediatric JIA patients as a user group.

[5] McMillan, Teresa. Human Factors Protocol Review for FKB327 IND 116471. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Nov 09. RCM No: 2015-2239.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

N/A

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

HF Report- RA Pen Late Formative	\\cdsesub1\evsprod\bla761154\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ra\5354-other-stud-rep\hss-1037\hss-1037-report-body.pdf
RA PFS Report	\\cdsesub1\evsprod\bla761154\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ra\5354-other-stud-rep\hss-1075\hss-1075-report-body.pdf
HF Report JIA Pen Summative	\\cdsesub1\evsprod\bla761154\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ra\5354-other-stud-rep\hss-1055\hss-1055-report-body.pdf
Pen for Needle End Labeling Needle Stick Risk Mitigation	\\cdsesub1\evsprod\bla761154\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ra\5354-other-stud-rep\hss-3109\hss-3109-report-body.pdf
Pen HFE UE Report	\\cdsesub1\evsprod\bla761154\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ra\5354-other-stud-rep\rep-2986\rep-2986-report-body.pdf
Summary Report for Adult PFS	\\cdsesub1\evsprod\bla761154\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ra\5354-other-stud-rep\rep-2987\rep-2987-report-body.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

IR Cover Letter	\\cdsesub1\evsprod\bla761154\0025\m1\us\12-cover-letters\cover-letter-0025-response-to-information-request-dated-janu.pdf
IR Response	\\cdsesub1\evsprod\bla761154\0025\m1\us\111-information-amendment\quality-response-to-information-request-dated-january-15-202.pdf

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

[6] E.2 Label and Labeling Images

Prescribing Information (image not available)

\\cdsesub1\evsprod\bla761154\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-clean-pdf.pdf

Instructions for Use (image not available)

\\cdsesub1\evsprod\bla761154\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-pfs-clean-pdf.pdf

\\cdsesub1\evsprod\bla761154\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-pen-clean-pdf.pdf

Quick Reference Guide (Image not available)

\\cdsesub1\evsprod\bla761154\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-quick-reference-guide-pfs-pdf.pdf

\\cdsesub1\evsprod\bla761154\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-quick-reference-guide-pen-pdf.pdf

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

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

(b) (4)

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/

JASON A FLINT
03/12/2020 03:16:15 PM

TERESA S MCMILLAN
03/12/2020 03:18:46 PM

MILLIE B SHAH
03/13/2020 09:12:20 AM

QUYNHNHU T NGUYEN
03/13/2020 10:31:27 AM

MISHALE P MISTRY
03/13/2020 11:10:56 AM

Clinical Inspection Summary

Date	February10th, 2019
From	Tina Chang, M.D., Reviewer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Natalie Pica, MD, Ph.D., Clinical Reviewer Miya Paternitit, M.D., Clinical Team Leader Nikolay Nikolov, M.D., Associate Director Elaine Sit, Pharm.D., Regulatory Project Manager Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
NDA/BLA #	761154/0001
Applicant	Mylan GmbH / Fujifilm Kyowa Kirin Biologics Co., Ltd. (FKB)
Drug	Hulio (FKB327), proposed biosimilar to Humira (adalimumab)
NME (Yes/No)	Yes
Therapeutic Classification	Recombinant human immunoglobulin (Ig)G1 monoclonal antibody specific for tumor necrosis factor (TNF)-α
Proposed Indication(s)	Treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), crohn's disease (CD), ulcerative colitis (UC), and plaque psoriasis (Ps) in adults, as well as juvenile idiopathic arthritis (JIA) in patients 4 years of age and older.
Consultation Request Date	August 29, 2019
Summary Goal Date	June 12, 2020
Action Goal Date	July 12, 2020
PDUFA Date	July 12, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The sponsor conducted a Phase 3 study, (FKB327-002), to compare the efficacy, safety, immunogenicity, and PK of US-licensed Humira with FKB327 in patients with rheumatoid arthritis (RA) taking concomitant methotrexate. Two clinical investigators Dr. Maria Greenwald (Site# 0104), and Dr. Elias Chalouhi El Khouri (Site# 0702) were selected for clinical site inspections.

Based on the results of these inspections, the data generated by these clinical investigators sites submitted by the Sponsor appear acceptable and in support of this BLA.

II. BACKGROUND

FKB327 is a proposed biosimilar to the US-licensed Humira (adalimumab) which was first approved in 2002. Adalimumab binds specifically to human tumor necrosis factor alpha (TNF-α) and neutralizes the biological function of TNF by blocking its interaction with TNFR1 and TNFR2 cell surface TNF receptors. The sponsor Mylan is seeking all the indications for which Humira is licensed for in the US: rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps) in adult patients and juvenile idiopathic arthritis (JIA) in patients 4 years of age and older and is requesting approval for the 40 mg/0.8mL pre-filled syringe (PFS), 20 mg/0.4mL PFS and the 40 mg/0.8mL pre-filled pen (PFP). FKB327 is a combination product – a biological product delivered via a PFS or PFP.

The Phase 3 study, Protocol FKB327-002, with a PK study and a long-term safety study will form the basis for the regulatory decision-making process for this application. The efficacy of FKB327 for other indications will be based upon extrapolation.

Study FKB327-002

Study Title: A Randomized, Blinded, Active-Controlled Study to Compare FKB327 Efficacy and Safety with the Comparator Humira® in Rheumatoid Arthritis Patients Inadequately Controlled on Methotrexate (ARABESC)

This was a Phase 3 multi-center, randomized, double-blinded equivalence study of FKB327 at a dose of 40 mg by subcutaneous injection every other week for 24 weeks conducted in patients with RA taking concomitant methotrexate (MTX) to assess the efficacy of FKB327 with Humira when each is administered in combination with MTX.

The primary efficacy endpoint was the American College of Rheumatology (ACR) 20 response rate (ACR20), based on testing the equivalence of FKB327 and Humira using the difference in proportion of patients achieving an ACR20 response at Week 24. An ACR 20 response is defined as:

1. ≥20% improvement from baseline in both swollen joint count (66 joints) and tender joint count (68 joints),

AND

2. ≥20% improvement from baseline in 3 of the following 5 assessments:
    - Patient's assessment of pain Visual Analogue Scale (VAS)
    - Patient's Global Assessment of Disease Activity (arthritis, VAS)
    - Physician's Global Assessment of Disease Activity (VAS)
    - Patient's assessment of physical function as measured by HAQ-DI
    - CRP

The first patient was enrolled on 05 January 2015 and the last patient completed the study on 12 July 2016. 730 patients were enrolled in 109 sites in 12 countries in 3 geographical regions: North America (Canada [3 sites] and the United States (US) [19 sites]); Europe (Bulgaria [4 sites] , Czech Republic [6 sites], Germany [7 sites], Poland [10 sites], Romania [9 sites] and Spain [6 sites]); Rest of World (Chile [5 sites], Peru [8 sites], Russia [18 sites] and the Ukraine [14 sites]). Overall, 279 patients (38.2%) were recruited from Europe, 85 patients (11.6%) from North America and 366 patients (50.1%) from the Rest of World, with the proportion of patients recruited in each region being similar for the FKB327 and Humira treatment groups.

Rationale for Site Selection

Two clinical investigator sites were selected for clinical inspections: Dr. Maria Greenwald (Site# 0104), and Dr. Elias Chalouhi El Khouri (Site# 0702). Site 0104 had the highest enrollment in the United States and previously had a for-cause inspection. Site 0702 also had a high enrollment of subjects as well as a high participant discontinuation and a serious adverse event during the conduct of study FKB327-002.

III. RESULTS (by site):

1. **Dr. Maria Greenwald, Site # 0104 (72855 Fred Waring Dr, Suite A6, Palm Desert, CA, 92260-9369); Inspection dates: October 28 – November 11, 2019.**

   For Protocol FKB327-002, this site screened 53 subjects and enrolled 33 subjects. Among the 33 enrolled subjects, 12 completed the study treatment. Seventeen (17) of the 33 enrolled subjects were reviewed comprehensively during the inspection.

   The inspection evaluated the following documents: the protocol FKB327-002, IRB approvals, FDA 1572s, financial disclosures, training records, monitoring letters, informed consent forms, subjects' research charts, electronic case report forms, x-rays and test article accountability records.

   The primary efficacy endpoint was verifiable for the following subject level line listings:
   - Listing 5-4 Tender and Swollen Joints Data
   - Listing 5-5 CRP Values
   - Listing 5-6 ESR Values

   No under-reporting of adverse events was noted.

   There was one inspectional observation reported which led to a Form FDA 483 being issued to Dr. Greenwald on November 1, 2019, at the end of the inspection. This observation was a failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

   Specifically:

a. Protocol Section 6.1.2 Procedures for the Screening Visit (Visit 1) required chest x-rays to be performed within the last 12 weeks. Ten (10) subjects' screening chest x-rays were not available for review during the inspection. Dr. Greenwald explained that storage and space were an issue for excess x-rays and were maintained in Dr. Gary Greenwald's archive storage facility for 7-10 years. Dr. Greenwald provided a memo describing the incident. Dr. Greenwald admitted that she never considered the x- ray films as original source data, but verbally stated that she understood the relevance and the requirements.

Reviewer's Comments: The protocol for the study does not require that the X-rays be made available. The reports for the X-rays were available for review and audit.

b. Investigational Product Administration Log listed Subject (b) (6) as randomized to FKB-327 although according to the electronic Case Report Form, the subject was reported as randomized to Humira. Subject (b) (6) was documented by (b) (6) as receiving FKB327 40 mg/0.8mL and Adalimumab 40mg in 0.8mL was crossed out on the Investigational Product Administration Log. According to the sponsor data listings, this subject was randomized to Humira (Adalimumab) 40 mg/0.8mL. There were no interactive web response system (IWRS) confirmation records to verify this (b) (6) stated she is certain that she dispensed to the subject the correctly identified kit numbers with the correctly randomized and allocated treatment. She stated that she merely inadvertently crossed Adalimumab out and added FKB327 in error. Additional verification of what the subject was randomized was provided from a Medidata Balance List Export record which revealed that the subject was randomized to Humira 40 mg. (b) (6) provided a written memo documenting that Subject (b) (6) was randomized to the Humira arm of the study drug and that she erroneously crossed out Humira and wrote in that the patient received FKB-327 study drug. Dr. Greenwald and (b) (6) stated they will consider a process to retain the IWRS real-time report of the treatment allocation to support a transcribed entry record.

In general, this clinical site appeared to be in compliance with Good Clinical Practices except the items described as above. Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Dr. Elias Chalouhi El-Khouri, Site #0702 (Clinica Investigacion Consultorios, Avenida Garcilaso De La Vega 1420, Lima, Peru); Inspection dates: 12/2-12/6/2019.

For Protocol FKB327-002, this site screened 56 subjects and enrolled 36 subjects. Among the 36 enrolled subjects, 31 subjects completed the study. Thirteen subject records were comprehensively reviewed during this inspection.

The inspection evaluated the following documents: IRB records, signed Form FDA 1572s, study protocol/amendments, subject eligibility, enrollment/screening records, drug accountability records, adverse events documents, case report forms, training and duty

delegation records, monitoring reports, correspondence and signed informed consent documents.

The raw data used to assess the primary efficacy endpoint was verifiable, except for the following discrepancies in the swollen joint count for one subject. The swollen joint count for one Subject (b) (6) receiving Humira for visit 2 (the baseline visit) was listed in the source data as zero (0) and on the same day, the source data value of zero (0) was corrected to eight (8) per a handwritten note because the ePRO tablet used to capture the data ran out of battery, but it is documented as four (4) in the background data listings which still does not match the corrected source value of eight (8). Dr. Chalouhi and Ms. (b) (6) could not explain these discrepancies.

Reviewer's Comment: In this reviewer's opinion, since this is an isolated incident, this discrepancy in the swollen joint count for Subject (b) (6) receiving Humira may not have an impact on efficacy.

At the conclusion of the inspection, the following items were discussed with the clinical investigator at the close-out meeting:

a. Source data from the Health Assessment Questionnaire Disability Index (HAQ-DI) values did not match those in data listings for two subjects.
   i. Subject (b) (6) (Visit 2, 12/17/2015), Source data = 1.3; Data listings = 1.5
   ii. Subject (b) (6) (Visit 8, 3/21/2016), Source data = 1.1; Data listings = 1.25

b. For Subject (b) (6) receiving Humira, per source records at Visit 2 (baseline), the tender/swollen joint 68/66 count was 8 and 0 respectively. Since the baseline value for swollen is below six, the subject did not meet protocol inclusion criteria #3 which required subjects to have active RA, as confirmed by ≥6 tender and ≥6 swollen joint counts out of 68/66 respectively, at screening and baseline. A protocol deviation is documented and reported to the sponsor. Additionally, the subject's baseline visit, 12/29/2015 swollen joint count source data value of zero (0) was corrected to eight (8) on the same day. Per (b) (6) statement, hand-written notes, and a database query created on 3/2/2016, the ePRO tablet used to capture the data ran out of battery before electronic capture of the swollen joint data value. However, per the background data listings, the subject's Visit 2 swollen joint (66) value is four (4) which did not match the corrected source value of eight (8).

c. Subject source records did not document whether blinding was maintained on each dosing occasion as required in Section 3.6.2 of the protocol. However, all study staff members affirmed that blinding was maintained throughout the study and review of the records did not reveal any indication that blinding was broken at any time. It was reiterated to management that that protocol required data capture specifications should be reflected in the source data records.

d. For Subject (b) (6) Serious Adverse Event (SAE) of latent TB was not reported to the sponsor within 24 hours as required by the protocol. The subject returned a positive QuantiFERON laboratory results on 5/17/2016. The laboratory report is signed by the investigator on 5/20/2016. The subject had a normal chest X-ray result. Per section 16.4 of the protocol, this is defined as possible latent TB or extra-pulmonary TB. The SAE was documented as a protocol deviation and reported to the ethics committee and the sponsor 10 days later on 5/30/2016. The subject was discontinued from the study on 6/7/2016. Dr. Chalouhi and (b) (6) explained that the reporting delay was likely due to the follow-up investigations that were conducted to ruled out the presence of active TB.

Reviewer's Comments: The clinical investigator failed to report an SAE (latent TB) to the sponsor within 24 hours. Although, the clinical investigator failed to assure timeliness of reporting of an SAE (development of latent TB) to the sponsor, the finding has been reported to the sponsor and appears in the application. The clinical investigator also discontinued administration of the investigational product to the subject appropriately after the patient developed latent TB. As such, this finding is unlikely to impact data reliability or patient safety.

In general, this clinical site appeared to be in compliance with Good Clinical Practices except the items described as above. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

{See appended electronic signature page}

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/s/

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