

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761255Orig1s000

OTHER REVIEW(S)

Date	12/12/2022		
To:	Kelly Ballard		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	OPRO
From	Jake Lindstrom, Ph.D. OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	BLA 761255, ADALIMUMAB ICC2200071 00819273		
Recommendation	Filing Recommendation Date: Click or tap to enter a date. ☐ 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: 12/12/2022 ☒ 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)
Jake K. Lindstrom -S Digitally signed by Jake K. Lindstrom -S Date: 2022.12.12 09:53:04 -05'00'		 Alan M. Stevens -S3

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761255
Sponsor	Fresenius Kabi USA LLC.
Drug/Biologic	ADALIMUMAB
Indications for Use	• Rheumatoid arthritis (RA) • Juvenile idiopathic arthritis (JIA) (2 years of age and older) • Psoriatic arthritis (PsA) • Ankylosing spondylitis (AS) • Crohn's disease (CD) in adults and pediatric patients 6 years of age and older • Ulcerative Colitis (UC) in adult patients • Plaque Psoriasis (PsO)
Device Constituent	Pre-Filled Syringe and Auto-Injector
Related Files	N/A

Review Team		
Lead Device Reviewer	<i>Jake Lindstrom, PhD</i>	
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

- Approvable – the device constituent of the combination product is approvable for the proposed indication.
- Approvable with PMC or PMR, [See Section 2.3](#)
 - Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

Section	Adequate			Reviewer <u>Notes</u>
	Yes	No	NA	
Device Description	Y			
Labeling	Y			
Design Controls	Y			
Risk Analysis	Y			
Design Verification	Y			
Consultant Discipline Reviews			NA	
Clinical Validation	Y			
Human Factors Validation			NA	
Facilities & Quality Systems	Y			

2.1. **Comments to the Review Team**

- CDRH does not have any further comments to convey to the review team.
- CDRH has the following comments to convey to the review team:

2.2. **Complete Response Deficiencies**

- There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
- The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. **Recommended Post-Market Commitments/Requirements**

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

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3. PURPOSE/BACKGROUND

3.1. Scope

Fresenius Kabi is requesting approval of Adalimumab. The device constituent of the combination product is a Pre-Filled Syringe and Auto-Injector.

CDER/OPQ has requested the following [consult](#) for review of the device constituent of the combination product:

Autoinjector (AI), Prefilled Syringe (PFS), (b) (4)

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, device specific labeling, intact skin biocompatibility

This review will not cover the following review areas:

Human Factors

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

3.2. Prior Interactions

N/A

3.3. Indications for Use

Combination Product	Indications for Use
Pre-Filled Syringe	Delivery of the Drug Product
Auto-Injector	Delivery of the Drug Product

(b) (4)

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0001	1.1.2, 1.14, 1.5.2, 2.3.P, 3.2
0029	1.11.1, 3.2
(b) (4)	

4. DEVICE DESCRIPTION

4.1. Device Description

The device constituent is a prefilled syringe (PFS) and autoinjector (AI).

The PFS is depicted below. Note how the PFS has a needle safety device (b) (4). Further information about the plunger rod, finger flange, and safety device are included in MAF (b) (4)

4.2. Steps for Using the Device

1. Prepare for injection, including getting a device constituent from the refrigerator.
2. Wash hands
3. Check product for damage
4. Choose injection site (top of thighs or around “stomach-area”)
5. Clean injection site
6. Give injection (PFS between 45 and 90 degree angle)
7. Dispose of device constituent
8. Record injection

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
<u>Reviewer Comments</u> N/A		

CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: Yes No

5. FILING REVIEW

5.1. Facilities Information

Firm Name:	(b) (4)
Address:	(b) (4)
FEI:	(b) (4)
Responsibilities:	<u>Drug Substance QC Testing</u> <u>Drug Product QC and Stability Testing (PFS)</u> (b) (4)
<u>Inspectional History</u> An analysis of the firm's inspection history over the past 2 years: ☒ Inspection was conducted (b) (4). The inspection covered drug CGMP and was classified VAI. ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product	
<u>Inspection Recommendation:</u> ☐ A choose an item inspection is required because: The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, A recent medical device inspection of the firm Choose an item. ☒ An inspection is not required because A recent medical device inspection of the firm was acceptable.	

Firm Name:	(b) (4)
Address:	(b) (4)
FEI:	(b) (4)
Responsibilities:	<u>Drug Product Manufacture (PFS)</u> <u>Drug Product QC and Stability Testing (PFS)</u>
<u>Inspectional History</u> An analysis of the firm's inspection history over the past 2 years: ☒ Inspection was conducted (b) (4). The inspection covered drug CGMP and was classified VAI. ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product	
<u>Inspection Recommendation:</u> ☐ A choose an item inspection is required because: The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, A recent medical device inspection of the firm Choose an item. ☒ An inspection is not required because A recent medical device inspection of the firm was acceptable.	

Firm Name:	<u>Fresenius Kabi Austria GmbH-(FK-Werndorf)</u>
Address:	<u>Am Gewerbepark 6</u> <u>8402 Werndorf</u> <u>Austria</u>
FEI:	<u>3003708554</u>
Responsibilities:	<u>Device Assembly</u> <u>Labeling and Secondary Packaging (PFS (b) (4) and AI)</u>
Inspectional History An analysis of the firm's inspection history over the past 2 years: ☒ Inspection was conducted 01/27/2020 to 01/30/2020. The inspection covered drug CGMP and was classified VAI. ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product	
Inspection Recommendation: ☐ A choose an item inspection is required because: The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, A recent medical device inspection of the firm Choose an item. ☒ An inspection is not required because A recent medical device inspection of the firm was acceptable.	

5.2. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☒ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☒ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☒ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☒ Yes ☐ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☒ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☒ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☒ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☒ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment N/A

5.3. Filing Review Conclusion

FILING REVIEW CONCLUSION
Acceptable for Filing: ☒ Yes ☐ No (Convert to a RTF Memo) ☐ N/A
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☒ No Inspection ☐ N/A
Site(s) needing inspection:
<u>Reviewer Comments</u>
Refuse to File Deficiencies: ☐ Yes ☐ No ☒ N/A
74-Day Letter Deficiencies: ☐ Yes ☐ No ☒ N/A

6. LABELING

6.1. General Labeling Review

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

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
<u>MRI</u> Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments
 N/A

6.2. 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
<u>Reviewer Comments</u> N/A		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

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

Reviewer Comments
 N/A

7.2. Design Inputs and Outputs

Essential Performance Requirements

Pre-filled syringe

<u>Design Inputs</u> (Essential Performance Requirement)	<u>Design Outputs</u> (Specification)
Break loose force	(b) (4)

Glide force	(b) (4)
Cap removal force	
Delivered Volume	
Extra activation force	
Needle safety activation and locking	
Override force	

Autoinjector

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Cap removal force	(b) (4)
Activation force	
Injection time	
Delivered Volume	
Needle extension	

Reviewer Comments

Following IR29, the sponsor reduced the injection time EPR upper limit from (b) (4). They did not add a maximum volume EPR and are relying on the size of the syringe (1 mL with (b) (4) mL dead volume) to act as the upper limit. This is acceptable.

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Y
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
<u>Reviewer Comments</u> N/A		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

8. RISK ANALYSIS

8.1. Risk Management Plan

The sponsor separated the PFS and AI presentations but performed the same activities.

- Conduct risk analysis
 - Identify hazards/use errors and their severity (FMEA)
 - Determine the likelihood of occurrence

- Rate the risk based on severity and likelihood (see table below). Note the table uses 6 levels for severity and likelihood (instead of the more typical 5).

5.3 Risk Level Matrix

SEVERITY	Death	10	High Risk Level	High Risk Level	High Risk Level	High Risk Level	High Risk Level	High Risk Level
	Major Injury	8	Medium Risk Level	High Risk Level	High Risk Level	High Risk Level	High Risk Level	High Risk Level
	Serious Injury	6	Medium Risk Level	Medium Risk Level	Medium Risk Level	High Risk Level	High Risk Level	High Risk Level
	Minor Injury	4	Low Risk Level	Low Risk Level	Medium Risk Level	High Risk Level	High Risk Level	High Risk Level
	Delay	2	Low Risk Level	Low Risk Level	Low Risk Level	Medium Risk Level	Medium Risk Level	Medium Risk Level
	Inconvenience	1	Low Risk Level	Low Risk Level	Low Risk Level	Low Risk Level	Low Risk Level	Medium Risk Level
			1	2	3	4	5	6
			Improbable	Unlikely	Remote	Occasional	Probable	Frequent
			LIKELIHOOD					

■ Low Risk Level ■ Medium Risk Level ■ High Risk Level

- The sponsor conducts risk control activities until the risks are reduced as far as possible.
- The sponsor reevaluates hazard likelihood and iterates as needed
- Conduct benefit-risk analysis and an overall risk evaluation.
- Review and then verify risk management activities
- Review production and post-production information to identify issues and new risks and evaluate for information that alters pre-existing risk assessment

Reviewer Comments

The risk management plan is acceptable.

8.2. Hazard Analysis and Risk Summary Report

**PFS
Pre-mitigation**

SEVERITY	Death	10	High Risk Level	High Risk Level	High Risk Level	High Risk Level	High Risk Level	High Risk Level
	Major Injury	8	(b) (6)	High Risk Level	High Risk Level	High Risk Level	High Risk Level	High Risk Level
	Serious Injury	6	Medium Risk Level	(b) (6)	(b) (6)	High Risk Level	High Risk Level	High Risk Level
	Minor Injury	4	Low Risk Level	Low Risk Level	(b) (6)	Medium Risk Level	High Risk Level	High Risk Level
	Delay	2	Low Risk Level	Low Risk Level	(b) (6)	Medium Risk Level	Medium Risk Level	Medium Risk Level
	Inconvenience	1	Low Risk Level	Low Risk Level	Low Risk Level	Low Risk Level	Low Risk Level	Medium Risk Level
			1	2	3	4	5	6
			Improbable	Unlikely	Remote	Occasional	Probable	Frequent
			LIKELIHOOD					

■ Low Risk Level ■ Medium Risk Level ■ High Risk Level

Post-mitigation

SEVERITY	Death	10						
	Major Injury	8	(b) (6)					
	Serious Injury	6		(b) (6)				
	Minor Injury	4						
	Delay	2						
	Inconvenience	1						
			1	2	3	4	5	6
			Improbable	Unlikely	Remote	Occasional	Probable	Frequent
			LIKELIHOOD					
			Low Risk Level	Medium Risk Level	High Risk Level			

**Autoinjector
 Pre-mitigation**

SEVERITY	Death	10						
	Major Injury	8	(b) (6)					
	Serious Injury	6		(b) (6)				
	Minor Injury	4	(b) (6)					
	Delay	2			(b) (6)			
	Inconvenience	1						
			1	2	3	4	5	6
			Improbable	Unlikely	Remote	Occasional	Probable	Frequent
			LIKELIHOOD					
			Low Level Risk	Medium Level Risk	High Level Risk			

Post-mitigation

SEVERITY	Death	10	(b) (6)					
	Major Injury	8						
	Serious Injury	6						
	Minor Injury	4						
	Delay	2						
	Inconvenience	1						
			1	2	3	4	5	6
			Improbable	Unlikely	Remote	Occasional	Probable	Frequent
			LIKELIHOOD					
			Low Level Risk		Medium Level Risk		High Level Risk	

For both the PFS and AI, the sponsor then tabulates the residual risks by level (i.e., medium or low) and provides a “Risk Benefit Rationale” to show why the risk is acceptable. An example of which is shown below.

Hazardous situation	Hazards	Risk Benefit Rationale
Cross contamination Severity = 8 Likelihood = 1	Re- and/or cross-infection PFS-SS could be shared between patients / users / other persons. Lack of adequate determination for the end of life of the medical device. Improper disposal of used PFS (b) (4) Shelf life PFS (b) (4) failure can occur if it is used after its shelf life	The Hazards analysis shows that the risks associated with a cross contamination is mainly attributed to inappropriate disposal of the used PFS (b) (4) The following Risk Control Measures effectively mitigate the identified use error associated with the use of the MSB11022 PFS (b) (4) - Acetate Process C: - FNF-10.15 Safety system Intended users shall not be able to touch the needle of a fully activated PFS- (b) (4) - FNF-10.3 Passive safety system: The safety system shall be passively only activated at the end of a full injection - FNF-10.7 Safety system robustness: Intended users shall not be able to unintentionally override an activated safety system. (b) (4) - PLR_ADAM PFS-NF-0343 IFU shall depict both visually and in written content how to discard safely the device in a sharps container - PLR_ADAM PFS-NF-1055 IFU shall warn users not to share you're the device with another person. User may give another person an infection or get an infection from them The benefits of the MSB11022 PFS (b) (4) - Acetate Process C as designed are the following:

Reviewer Comments

The process and analysis are thorough and acceptable. The sponsor has demonstrated adequate risk mitigation.

8.3. 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		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: 10/19/2022	Date/Sequence Received: 9/27/2022
Information Request #29.5	You do not appear to have provided or referenced risk documentation for the final finished combination products (prefilled syringe and autoinjector). We need this information to assess the applicable risks and ensure risks have been mitigated adequately. Provide your risk management plan and risk analysis for the final finished combination products.	
Sponsor Response	(b) (4)	
Reviewer Comments	The sponsor continued by highlighted risk documentation specific to the PFS and AI presentations. The sponsor referenced all requested risk documentation was not readily accessible in the submission. Response and risk analysis are acceptable.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Autoinjector

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method <u>Acceptable</u> (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Cap Removal Force	(b) (4)	Y; n=60	Y; acceptable spec.	Y	Y
Activation Force		Y; n=60	Y; acceptable spec.	Y	Y
Injection Time		Y; n=60	Y; acceptable after upper limit reduced to (b) (4)	Y	Y

Delivered Volume	(b) (4)	Y; n=60	Y; acceptable spec.	Y	Y
Needle extension		Y; n=60	Y; acceptable spec.	Y	Y

PFS

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method <u>Acceptable</u> (Y/N)	<u>Validation</u> (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Break Loose Force	(b) (4)	Y; n=60; per ISO 7886-1 Annex E	Y; acceptable spec.	Y	Y
Mean Glide Force		Y; n=60; per ISO 7886-1 Annex E	Y; acceptable spec.	Y	Y
Cap Removal Force		Y; n=60	Y; acceptable spec.	Y	Y
Delivered Volume		Y; n=60	Y; acceptable spec.	Y	Y
Extra Activation Force		Y; n=60	Y; acceptable spec.	Y	Y
Needle Safety Activation and Locking		Y; n=453	Y; acceptable spec.	Y	Y
Override Force		Y; n=292	Y; acceptable spec.	Y	Y

Reviewer Comment

Shipping/transportation simulation per ASTM D4169-09 assurance level II and also a real time shipping study.

Biocompatibility was also evaluated for the intact skin contacting components. All components underwent and passed the following testing: ISO 10993-5 Cytotoxicity test, ISO 10993-10 Guinea Pig Maximization Sensitization Test, and ISO 10993-10 Irritation Intracutaneous Study in rabbits test. This information is acceptable, and the device does not pose intact skin biocompatibility concerns.

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments N/A		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent:	Date/Sequence Received:
	10/19/2022	9/27/2022
Information Request #29.1	The prefilled syringe and autoinjector device constituents both include a sharps injury prevention feature; however, it does not appear to have been adequately tested. FDA guidance "Medical Devices	

	with Sharps Injury Prevention Features” (available at https://www.fda.gov/files/medical%20devices/published/Medical-Devices-with-Sharps-Injury-Prevention-Features---Guidance-for-Industry-and-FDA-Staff-(PDF).pdf) outlines suitable sharps injury prevention feature testing. This testing is important to demonstrate that these components have adequately mitigated the sharps injury risk. Provide testing of the sharps injury protection features as indicated by this guidance, including a sample size of 500 with zero failures in a simulated use study.
Sponsor Response	The sponsor did not provide the requested test but provided other information to support the adequacy of the sharps injury prevention features. Namely, the sponsor conducted trials with healthcare providers and lay users where 1005 products were used without sharps injury which the sponsor estimates a true failure rate of at most 0.62%.
Reviewer Comments	This response was not what was requested but still fulfills the guidance and demonstrates adequate sharps injury prevention with the products.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

	Date Sent: 10/19/2022	Date/Sequence Received: 9/27/2022
Information Request #29.4	You provided specifications for your essential performance requirements, but the Delivered Volume for both the prefilled syringe and the autoinjector is unbounded and the Injection Time for the autoinjector is high. For the Delivered Volume, the device constituents can hold up to 1 mL of drug product, but you have not stated that 1 mL is an acceptable volume. Provide an upper specification for Delivered Volume. For Injection Time, your upper limit is high. Injection times over 10 s can increase the risk that users will remove the product prematurely, resulting in an incomplete injection. Your performance testing demonstrates that you could lower your Injection Time upper specification. Lower your Injection Time upper specification and justify the new upper limit.	
Sponsor Response	The sponsor lowered the injection time specification to (b) (4) and provided adequate data to support the change. The sponsor declined to add an upper limit to the delivered volume and referred to the maximum size of the syringe as a natural upper limit.	
Reviewer Comments	The reduction in the injection time specification is acceptable. It is (and was) supported by data, which is part of the reason the request was phrased as it was. (Namely, “Your performance testing demonstrates that you could lower your Injection Time upper specification.”) The lack of upper limit specification for injection volume is acceptable as it is bounded by the dimensions of the product.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

9.3. 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](#):

fks022-001-report-body.pdf

fks022-001-comp-drug-conc.pdf

Study Name	
Study Type	A PHASE I, RANDOMIZED, OPEN-LABEL, PARALLEL-GROUP STUDY TO DETERMINE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF MSB11022 (PROPOSED ADALIMUMAB BIOSIMILAR) FOLLOWING A SINGLE SUBCUTANEOUS INJECTION BY AN AUTO-INJECTOR OR BY A PREFILLED SYRINGE IN HEALTHY SUBJECTS

Objectives/Endpoints	Relevant secondary endpoint: • To compare the overall safety and local tolerability of MSB11022 administered by either an AI or a PFS after a single s.c. of 40 mg • Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • AESIs: hypersensitivity reactions • Local tolerability (injection site reactions [ISR]) • Vital signs • Clinical laboratory • 12-lead electrocardiogram (ECG)
Drug/Device Studied	Both the PFS and AI were studied
Number and Type of Subjects	A total of 216 subjects were randomized (108 subjects each to the AI and PFS treatment groups, respectively). There were 3 subjects who were randomized but did not receive study drug.
Brief description of protocol	9.1.1 Type of Study This was a Phase 1 randomized, open-label, two-arm, parallel-group, single-dose study (Study Design: Figure 1). Figure 1 Study Design AI = auto-injector; EOS = end-of-study visit; PFS = prefilled syringe; PK = pharmacokinetic. Overall 213 healthy volunteers were exposed to MSB11022 via PFS or AI. Each subject received a single dose of MSB11022 with either device. About half of the subjects in each treatment group received the injection in the lower abdomen. The second half received it in the thigh.

Results	Table 8 Summary of TEAEs - Safety Analysis Set								
	Auto-Injector (N=106)			40 mg MSB11022 Prefilled Syringe (N=107)			Overall (N=213)		
	n	(%)	e	n	(%)	e	n	(%)	e
Number of subjects (%) with at least one TEAE and number of TEAEs	66	(62.3)	149	66	(61.7)	192	132	(62.0)	341
Subjects with worst grade of TEAE in each of the following category									
Mild TEAE	59	(55.7)	141	56	(52.3)	177	115	(54.0)	318
Moderate TEAE	6	(5.7)	7	10	(9.3)	15	16	(7.5)	22
Severe TEAE	1	(0.9)	1	0		0	1	(0.5)	1
Life Threatening TEAE	0		0	0		0	0		0
Death TEAE	0		0	0		0	0		0
Number of Subjects (%) with at Least One Study Drug Related TEAE	30	(28.3)	50	37	(34.6)	75	67	(31.5)	125
Number of Subjects (%) with at Least One TEAE Related to the Device	12	(11.3)	14	14	(13.1)	16	26	(12.2)	30
Number of Subjects (%) with at Least One SAE	0		0	0		0	0		0
Number of Subjects (%) with at Least One TEAE of Special Interest	0		0	0		0	0		0
Number of Subjects (%) with at Least One Study Drug Related TEAE Leading to Death	0		0	0		0	0		0
Number of Subjects (%) who Discontinued Study Due to a TEAE	0		0	0		0	0		0
TEAE=treatment-emergent adverse event; n=number of subjects; e=Number of Events. TEAEs of Special Interest are hypersensitivity reactions NCI-CTCAE Grade ≥3 or reported as serious events Subjects are counted only once under the category of their worst grade of TEAE - but all TEAE are counted as per their actual grade Source: Table 14.3.1.1									
Note: the one serious TEAE was a hand fracture, unrelated to the combination product.									
	Table 9 Total Subjects with at Least One Common Treatment-emergent Adverse Event by System Organ Class and Preferred Term – Safety Analysis Set								
	Auto-Injector (N=106)			40 mg MSB11022 Prefilled Syringe (N=107)			Overall (N=213)		
System Organ Class Preferred Term	n	(%)	e	n	(%)	e	n	(%)	e
Total subjects (%) with at least one common TEAE	66	(62.3)	149	66	(61.7)	192	132	(62.0)	341
Gastrointestinal Disorders									
Abdominal Pain	3	(2.8)	3	7	(6.5)	9	10	(4.7)	12
General Disorders And Administration Site Conditions									
Injection Site Erythema	7	(6.6)	7	7	(6.5)	7	14	(6.6)	14
Injection Site Pain	6	(5.7)	6	8	(7.5)	8	14	(6.6)	14
Infections And Infestations									
Upper Respiratory Tract Infection	24	(22.6)	26	20	(18.7)	21	44	(20.7)	47
Nervous System Disorders									
Headache	15	(14.2)	20	20	(18.7)	21	35	(16.4)	41
Respiratory, Thoracic And Mediastinal Disorders									
Oropharyngeal Pain	9	(8.5)	9	4	(3.7)	5	13	(6.1)	14
Nasal Congestion	6	(5.7)	6	3	(2.8)	3	9	(4.2)	9
TEAE = treatment-emergent adverse event. n = number of subjects. e = Number of Events. Adverse events are coded using the MedDRA version 22.0. A subject can experience multiple occurrences of an adverse event; but subject was counted once per system organ class and preferred term for each treatment. Source: Table 14.3.1.8									
Device Related Comments	There are few autoinjector related adverse events, namely injection site reactions, but none were serious or present an unexpected safety profile.								

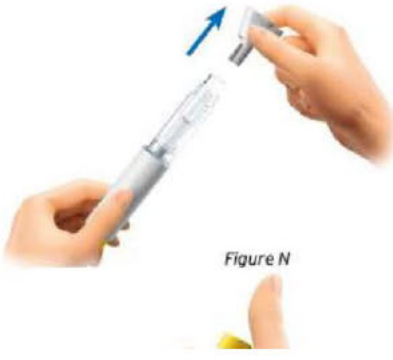
	There was one observed device failure. For subject (b) (6), a lower abdomen injection “UPON STARTING OF INJECTION, DEVICE STARTED MAKING A FIZZING/GURGLING SOUND AND TH [sic] IP STARTED TO BUBBLE OUT AROUND THE TOP OF THE NEEDLE.” Furthermore, “UNABLE TO ESTIMATE AMOUNT SUBJECT RECEIVED. WHEN THE DEVICE WAS RAISED FROM THE INJECTION SITE THE SUBJECT HAD A PUNCTURE WOUND FROM THE NEEDLE BUT THERE WAS POOLING OF IP AROUND THE SITE.” The sponsor should provide a root cause analysis. (Document: fks022-001-comp-drug-conc.pdf)
Reviewer Comments	Overall, the products presented similar and acceptable risk profiles. However, the root cause of the one observed device failure was not included in the report.
Reviewer Conclusion	Acceptable, see the IR discussion below in section 10.2.

Reviewer Comment
N/A

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

	Date Sent: 10/19/2022	Date/Sequence Received: 9/27/2022
Information Request #29.3	You conducted a phase I clinical study, “A PHASE I, RANDOMIZED, OPEN-LABEL, PARALLEL-GROUP STUDY TO DETERMINE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF MSB11022 (PROPOSED ADALIMUMAB BIOSIMILAR) FOLLOWING A SINGLE SUBCUTANEOUS INJECTION BY AN AUTOINJECTOR OR BY A PREFILLED SYRINGE IN HEALTHY SUBJECTS.” For one subject you noted a device failure where “UPON STARTING OF INJECTION, DEVICE STARTED MAKING A FIZZING/GURGLING SOUND AND TH [sic] IP STARTED TO BUBBLE OUT AROUND THE TOP OF THE NEEDLE.” Furthermore, you wrote, “UNABLE TO ESTIMATE AMOUNT SUBJECT RECEIVED. WHEN THE DEVICE WAS RAISED FROM THE INJECTION SITE THE SUBJECT HAD A PUNCTURE WOUND FROM THE NEEDLE BUT THERE WAS POOLING OF IP AROUND THE SITE.” You have not provided a root cause analysis of this failure. This failure may indicate device issues not otherwise noted that may suggest further mitigation activities. Provide a root cause analysis for this failure.	
Sponsor Response	The sponsor provided a long analysis but summarized it as follows: <i>The (b) (4) investigation (b) (4), clearly identified the root cause of the device failure, that is associated with the cap being twisted during usage. This is conclusive and aligns with the difficulties reported by the nurse to remove the cap. The nurse most probably twisted the cap during the attempt to remove the cap.</i> <i>The Idacio® Pre-Filled Pen’s instruction for use (IFU) clearly states that the cap must not be twisted. Therefore, the failure has been attributed to user mishandling. For the batch associated with the described complaint, there was no other complaint reported.</i>	
Reviewer Comments	The root cause was clearly identified and the sponsor provided adequate justification for lack of additional mitigation activities. The sponsor’s labeling clearly states “Do not twist the cap” (see below).	

	6.1 Remove the needle cap • Hold the pen upwards. • Remove the needle cap with your other hand by pulling the cap straight off (Figure N). Do not twist the cap. Do not insert your fingers into the opening of the safety guard You may see <u>a few</u> drops of liquid at the needle tip. This is normal • Dispose of the needle cap in your sharps disposal container.  Figure N Given the clarity of the instructions and rarity of occurrence, this response is acceptable. However, failures like this one should be monitored.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

HUMAN FACTORS VALIDATION REVIEW

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

11.FACILITIES & QUALITY SYSTEMS

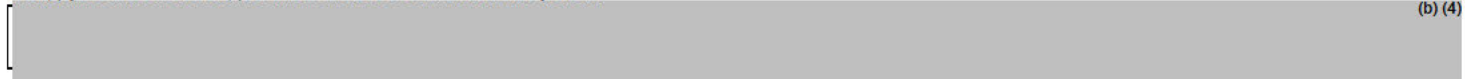
11.1. Quality Systems Documentation Review

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

11.1.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

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



(b) (4)

The Sponsor provided the following production/manufacturing flow diagram that identifies the steps involved in the manufacture of the finished combination product. The diagram includes all steps involved in the manufacturing and assembly of the device constituent parts of the combination product:



Reviewer Comments N/A

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒ Yes	☐ No

11.1.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:

- [Device](#) QSR-based
- X** Drug cGMP-Based Streamline – [Review Instructions](#)
- Stream-line Both ([no streamlined approach](#))

21 CFR 820.20 Summary of	Firm(s): Fresenius Kabi	Reviewer Discussion – Adequate. As described by the sponsor, “Fresenius Kabi has established a global Quality Management

Management Responsibility		(b) (4)
21 CFR 820.30 Summary of Design Controls	Firm(s): Fresenius Kabi	Reviewer Discussion – Reviewed in detail in Section 7
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): Fresenius Kabi	Reviewer Discussion – Adequate. As described by the sponsor, “The Purchasing Control System is generally defined in Fresenius Kabi’s Supplier Management Procedure (b) (4) The Supplier Management Process is covering all phases from selection, qualification, maintenance, development until discontinuation.”
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s): Fresenius Kabi	Reviewer Discussion – Reviewed in Section 12.2.3 .
Subpart G – Production and Process Controls	Firm(s): Fresenius Kabi	Reviewer Discussion – Reviewed in Section 12.3

Reviewer Comments
 N/A

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

11.1.3. Corrective and Preventive Action Review

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

(b) (4)

Reviewer Comments
 All CAPA activities are universal per the sponsor. Adequacy further supported by history of acceptable inspections.

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

11.2. 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)*

Autoinjector

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)
Cap removal force	Release testing	Y
Button activation force	Release testing	Y
Needle extensions	Release testing	Y
Injection time	Release testing	Y
Injection volume	Release testing	Y
Override force	Release testing	Y

Pre-filled Syringe

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)
Cap removal force	Release testing	Y
Break Loose Force	Release testing	Y
Glide Force	Release testing	Y
Extra Activation Force	Release testing	Y
Override force	Release testing	Y
Activation/locking of the safety system	Release testing	Y
Deliverable volume	Release testing	Y

Reviewer Comments

The sponsor added the PFS EPRs to their release testing protocol after IR55. They implemented the design specifications for break loose/glide force and extra activation force following IR 56.2.

Control Strategy Conclusion

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.

Yes

No

11.3. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION

Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments N/A		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: 10/19/2022	Date/Sequence Received: 9/27/2022
Information Request #29.5	You have indicated that you are implementing a drug based CGMP streamlined approach. Please provide the following information related to the medical device Quality System for the device: - Provide a summary of your management structure with executive responsibility for those who manage, perform, and assess work affecting quality of the product and related controls to ensure that your quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met, per 21 CFR 820.20. - Provide a summary of your design control system under 21 CFR 820.30 for the device constituent part and combination product. The design control information should include initial design, planning and development, design input, design output, design review, design transfer, design verification, design validation that meets the proposed intended use of the final combination product, design changes, and design history file. For changes made to the device constituent part of the combination product, the impact of the design changes on the overall combination product performance should be considered and documented. All the design control activities must be documented in the Design History File (DHF) and subjected for design reviews. In addition, identify the facility containing the DHF so that the Agency inspection planning activities are appropriately determined. - Provide a summary of your purchasing control system per 21 CFR 820.50 to demonstrate controls and documentation for components, products, or services (e.g., sterilization) received at your facility for use in the manufacture of the combination product. The summary should include your evaluation process of your suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes made by the suppliers should be considered in your Purchasing/Supplier agreement as changes to incoming specification that can impact the safety and effectiveness of the final combination product. - Provide a summary of your corrective and preventive actions (CAPA) system per 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions must be documented under your CAPA System as described in 21 CFR 820.100.	
Sponsor Response	The sponsor split the question into its four parts and responded individually to each. The sponsor provided the management structure outline, design control information, purchasing controls information, and CAPA information.	
Reviewer Comments	The responses are acceptable as detailed in the Section 11.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

	Date Sent: 12/8/2022	Date/Sequence Received: 12/9/2022
Information Request #55	In document 3.2.P.4 <i>control-critical-steps-pfs.pdf</i> , you provide "Autoinjector Assembly In-process Controls" in Table 2. However you have not included release testing for the pre-filled syringe presentation. Demonstrating each batch meets both the device and drug constituent specifications is	

	important for verifying the combination products' safety and effectiveness. We expect you to perform release testing for all essential performance requirements for the prefilled syringe and autoinjector presentations (i.e., prefilled syringe: break loose/glide force, cap removal force, delivered volume, extra activation force, needle safety activation/locking, override force; autoinjector: cap removal force, activation force, injection time, delivered volume, and needle extension). State all device constituent specifications tests you will perform at release.																																					
Sponsor Response	Sponsor reaffirmed commitment for AI release. Sponsor agreed to release testing for the PFS in stages in assembly. See table below. As noted in the table, they also commit to implementing release testing specifications for Break Loose/Glide force and Activation/Locking of the Safety System. Table 1 Control plan of the essential performance requirements for MSB11022 PFS (b) (4) presentation: <table border="1"> <thead> <tr> <th rowspan="2">Essential performance requirement</th> <th rowspan="2">Acceptance Criteria</th> <th colspan="3">Control plan</th> </tr> <tr> <th>Incoming control of the material (Release test from component supplier)</th> <th>Release Testing after filling</th> <th>Release Testing after assembly</th> </tr> </thead> <tbody> <tr> <td>Cap Removal Force</td> <td rowspan="8" style="background-color: #cccccc;">(b) (4)</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Break-Loose</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Glide Force</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Extra Activation Force</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Override Force</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Activation/locking of the safety system</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Deliverable Volume</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Essential performance requirement	Acceptance Criteria	Control plan			Incoming control of the material (Release test from component supplier)	Release Testing after filling	Release Testing after assembly	Cap Removal Force	(b) (4)				Break-Loose				Glide Force				Extra Activation Force				Override Force				Activation/locking of the safety system				Deliverable Volume			
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Glide Force																																						
Extra Activation Force																																						
Override Force																																						
Activation/locking of the safety system																																						
Deliverable Volume																																						
Reviewer Comments		AI release testing is acceptable, which it was prior to the IR. PFS release testing is acceptable, but it is unclear what specifications they plan to implement for Break Loose/Glide force and Activation/Locking of the Safety System. These specifications are the subject of the follow up IR 56.2.																																				
Response Adequate:	☐ Yes ☒ No, See IR 56.2 Sent on 12/9/2022																																					

	Date Sent: 12/9/2022	Date/Sequence Received: 12/12/2022
Information Request #56.2	In response to our December 8, 2022 information request, you stated you will submit the acceptance criteria for Break Loose/Glide Force and Extra Activation Force by June 2023. However, it is unclear why these acceptance criteria for Break Loose/Glide Force and Extra Activation Force cannot be implemented at this time given that the BLA contains design specifications for these essential performance requirements (EPRs). Clarify why the current design specifications, for example, could not be implemented at this time as your release acceptance criteria for these EPRs.	
Sponsor Response	The sponsor implemented the design specifications as the acceptance criteria for these EPRs.	
Reviewer Comments	This approach is acceptable.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

	Date Sent: 12/9/2022	Date/Sequence Received: 12/12/2022
Information Request #56.1	In 3.2.P.8.2 Post Approval Stability Protocol and Stability Commitment, you tabulated the long term stability plan for the prefilled syringe and autoinjector presentations. However, you have not included your device essential performance requirements (EPRs) in this stability protocol. You should include device EPRs in this stability protocol. Namely, the prefilled syringe should be evaluated for Break Loose/Glide Force, Delivered Volume, and Extra Activation Force, and the autoinjector should be	

	evaluated for Activation Force, Injection Time, and Delivered Volume. You also should place both the prefilled syringe and autoinjector presentations on the stability each year, instead of alternating between presentations every year. State that you will place both the prefilled syringe and autoinjector presentations on the stability protocol each year for each year that manufacturing occurs and evaluate the listed EPRs for both presentations for same duration as the drug product. Provide the updated Post Approval Stability Protocols and Commitments.
Sponsor Response	The sponsor added the requested EPRs to the stability protocol for the PFS and AI presentations.
Reviewer Comments	This approach is acceptable.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

<<END OF REVIEW>>

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/

SUSIE B CHOI

12/13/2022 08:36:07 AM

Finalized CDRH sent to RPM by RBPM to be archived in darrrts

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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: December 12, 2022
Requesting Office or Division: Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number: BLA 761255
Product Name and Strength: Idacio (adalimumab-aacf)^a injection, 40 mg/0.8 mL
Applicant/Sponsor Name: Fresenius Kabi USA, LLC. (Fresenius)
OSE RCM #: 2021-2398-2
DMEPA 1 Safety Evaluator: Damon Birkemeier, PharmD
DMEPA 1 Team Leader: Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 PURPOSE OF MEMORANDUM

Fresenius submitted revised instructions for use (IFU) for the Autoinjector (AI), AI starter pack, and prefilled syringe (PFS) received on December 6, 2022 for Idacio. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised instructions for use for Idacio (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 human factors results review.^b

2 DISCUSSION

Based on the Agency's recommendations, Fresenius updated the language in step 1.6 of the IFU to instruct users to let the pen sit at room temperature for (b) (4) 15-30 minutes (see Figure 1). We note that these updated instructions are not completely congruent with Figure H in Step 1.6 which states "Wait 30 minutes". However, in this case, we note that both the text instructions in Step 1.6 and the instructions in Figure H provide correct instructions to the end

^a The proprietary name for this BLA, Idacio, was found conditionally acceptable on March 7, 2022, and the nonproprietary name suffix for this BLA, adalimumab-aacf, was found conditionally acceptable on September 14, 2022.

^b Birkemeier D. Human Factors Study Results Review Memo for Idacio (BLA 761255). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 DEC 1. OSE RCM No.: 2021-2398-1.

user. We do not believe this minor difference will lead to medication errors. Therefore, we find this acceptable at this time.

Figure 1. Proposed Updates to Step 1.6 of the Instructions for Use for the Autoinjector

1.7.6 Let the ~~Idacio~~IDACIO ~~pre-filled~~prefilled pen sit at room temperature for ^{(b) (4)} ~~15~~-30 minutes before use to allow the medicine to reach room temperature (Figure H).	
Do not warm the pen in any other way, such as in a microwave, hot water, or direct sunlight.	
Do not remove the needle cap until you are ready to inject.	

3 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

APPENDIX A. LABELING RECEIVED ON DECEMBER 6, 2022

- Instructions for use for the autoinjector are available via <\\CDSESUB1\EVSPROD\bla761255\0053\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-ai-pfp-tracked-changes.docx>
- Instructions for use for the autoinjector starter pack are available via <\\CDSESUB1\EVSPROD\bla761255\0053\m1\us\114-labeling\114a-draft-label\draft-labeling-text-starter-pack-ifu-tracked-changes.docx>
- Instructions for use for the prefilled syringe are available via <\\CDSESUB1\EVSPROD\bla761255\0053\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-pfs-tracked-changes.docx>

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/

DAMON A BIRKEMEIER
12/12/2022 08:32:56 AM

OLUWAMUREWA OGUNTIMEIN
12/12/2022 11:22:48 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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: December 6, 2022
Requesting Office or Division: Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number: BLA 761255
Product Name and Strength: Idacio (adalimumab-aacf)^a Injection, 40 mg/0.8 mL
Applicant/Sponsor Name: Fresenius Kabi USA, LLC
TTT ID #: 2021-2397-3
DMEPA 1 Safety Evaluator: Teresa McMillan, PharmD
DMEPA 1 Team Leader: Idalia Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on December 6, 2022 for Idacio. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised carton labeling for Idacio (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

2 CONCLUSION

The Applicant implemented all of our recommendations and stated that the QR code will refer to the website www.idacio.com. We have no additional recommendations at this time.

^a The proposed nonproprietary name, "adalimumab-aacf", was found conditionally acceptable on September 19, 2022. We therefore refer to the proposed product as "adalimumab-aacf" throughout this review in place of the nonproprietary name for this product.

^b McMillan, T. Label and Labeling Review for Idacio (BLA 761255). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Dec 02. TTT ID No.: 2022-2397-3.

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TERESA S MCMILLAN
12/06/2022 04:00:35 PM

IDALIA E RYCHLIK
12/06/2022 04:08:00 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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: December 2, 2022
Requesting Office or Division: Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number: BLA 761255
Product Name and Strength: Idacio (adalimumab-aacf)^a Injection, 40 mg/0.8 mL
Applicant/Sponsor Name: Fresenius Kabi USA, LLC
TTT ID #: 2021-2394-2
DMEPA 1 Safety Evaluator: Teresa McMillan, PharmD
DMEPA 1 Team Leader: Idalia Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on November 29, 2022 for Idacio. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised carton labeling for Idacio (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

2 CONCLUSION

The revised carton labeling is unacceptable from a medication error perspective. We provide recommendations to the Applicant in Section 3.

^a The proposed nonproprietary name, "adalimumab-aacf", was found conditionally acceptable on September 19, 2022. We therefore refer to the proposed product as "adalimumab-aacf" throughout this review in place of the nonproprietary name for this product.

^b McMillan, T. Label and Labeling Review for Idacio (BLA 761255). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 NOV 17. TTT ID No.: 2021-2397-1.

3 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC

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

A. Carton Labeling

1. The 4 pack and 6 pack starter carton labeling lacks differentiation due to the similarity of [REDACTED] ^{(b) (4)} color appearance. A lack of differentiation between the AI starter packs may lead to dispensing errors. Implement the following:
 - 4-pack and 6-pack AI starter packs-utilize distinctly different color blocking to increase the difference between the cartons and bring prominence to the different AI counts within each carton.
2. There is a QR code present on all of the carton labeling presentations that states, "SCAN FOR ADDITIONAL INFORMATION". Clarify what additional information the QR code contains once scanned.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 29, 2022

Carton labeling

Prefilled syringe

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

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TERESA S MCMILLAN
12/02/2022 08:51:24 AM

IDALIA E RYCHLIK
12/02/2022 02:22:05 PM

MEMORANDUM
HUMAN FACTORS STUDY RESULTS REVIEW MEMO
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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: December 1, 2022
Requesting Office or Division: Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number: BLA 761255
Product Name and Strength: Idacio (adalimumab-aacf)^a injection, 40 mg/0.8 mL
Applicant/Sponsor Name: Fresenius Kabi USA, LLC. (Fresenius)
TTT ID #: 2021-2398-1
DMEPA 1 Safety Evaluator: Damon Birkemeier, PharmD
DMEPA 1 Team Leader: Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 PURPOSE OF MEMORANDUM

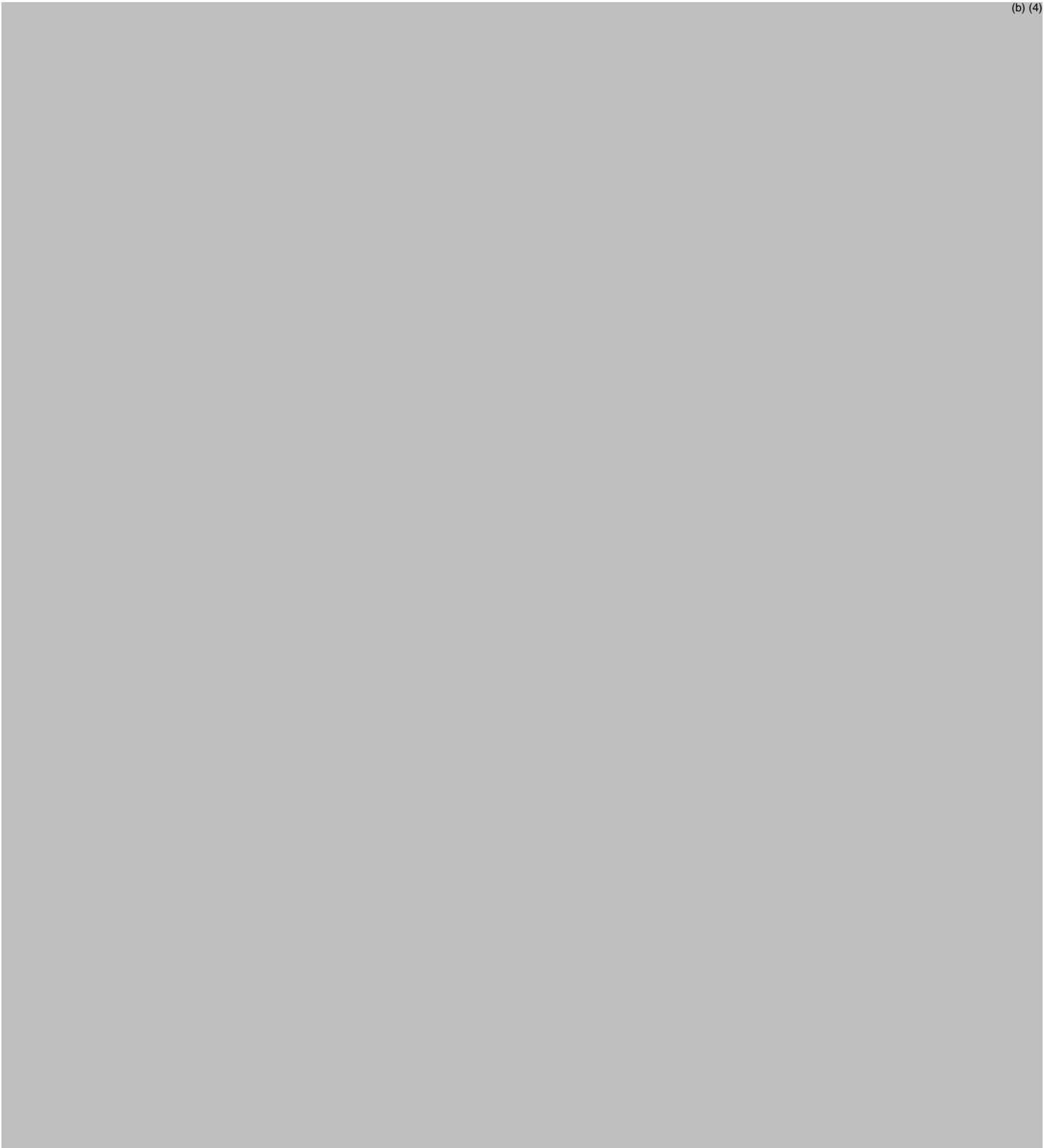
Fresenius submitted revised carton labeling and instructions for use (IFU) on November 29, 2022 for Idacio. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised carton labeling and instructions for use (IFU) for Idacio (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous human factors results review.^b

2 DISCUSSION

The Applicant implemented most of our recommendations. However, we recommended Fresenius consider revising the four autoinjector (AI) starter pack so that the AI for the second and third doses are in separate trays underneath the first dose. Alternatively, Fresenius proposes to add additional information on a card and place the card above the bottom tray containing the AIs for the second and third doses in the four AI starter pack (b) (4)

^a The proprietary name for this BLA, Idacio, was found conditionally acceptable on March 7, 2022, and the nonproprietary name for this BLA, adalimumab-aacf, was approved on September 14, 2022.

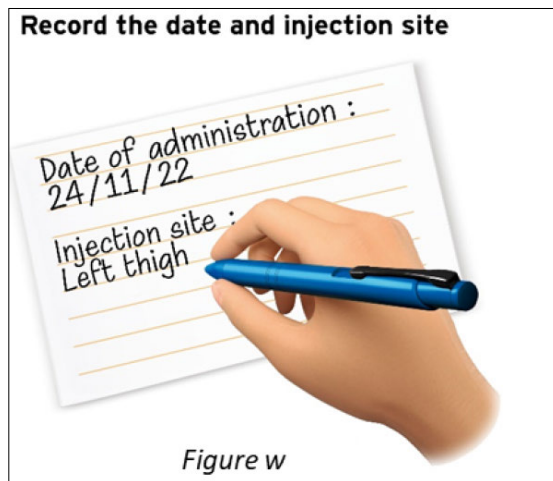
^b Birkemeier D. Human Factors Study Report Review for Idacio (BLA 761255). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 OCT 27. OSE RCM No.: 2021-2398.



Additionally, Fresenius accepted our recommendation to “revise Figure V to include the ‘Date of Administration’ and ‘Injection Site’ and consider including example date(s) and site(s) for users to reference.” However, Fresenius includes an example date in DD/MM/YY format (see

Figure 4). We recommend Fresenius update the example date to be in United States standard date format (MM/DD/YY).

Figure 4. Proposed Revised Figure V [now Figure W]



3 CONCLUSION

The Applicant implemented most of our recommendations and we find their proposal to add an additional information card to the four AI starter pack acceptable. However, Fresenius includes an example date in DD/MM/YY format. We recommend Fresenius update the example date to be in United States standard date format (MM/DD/YY).

4 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC.

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

- A. You accepted our recommendation to revise Figure V [now Figure W] to include the 'Date of Administration' and 'Injection Site' and consider including example date(s) and site(s) for users to reference." However, you included an example date in DD/MM/YY format. We recommend you update the example date to be in United States standard date format (MM/DD/YY).

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 29, 2022

- The AI IFU can be accessed via: <\\CDSESUB1\EVSPROD\bla761255\0051\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-ai-tracked-changes.docx>
- The AI starter pack IFU can be accessed via:
<\\CDSESUB1\EVSPROD\bla761255\0051\m1\us\114-labeling\114a-draft-label\draft-labeling-text-starter-pack-ifu-tracked-changes.docx>

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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: November 29, 2022

To: Susie Choi, PharmD
Regulatory Health Project Manager
Division of Rheumatology and Transplant Medicine (DRTM)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Mary Carroll, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kyle Snyder, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (nonproprietary name): IDACIO (adalimumab-aacf)¹

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761255

Applicant: Fresenius Kabi USA, LLC

¹ MSB11022 has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). The proprietary name for this BLA, Idacio, was found conditionally acceptable on March 7, 2022. The nonproprietary name, adalimumab-aacf, was found conditionally acceptable on September 19, 2022.

1 INTRODUCTION

On December 13, 2021, Fresenius Kabi USA, LLC submitted for the Agency's review an original Biologics License Application (BLA) 761255 for IDACIO (adalimumab-aacf) injection, for subcutaneous use. Fresenius Kabi USA, LLC seeks approval for IDACIO (adalimumab-aacf) as a biosimilar to US-licensed HUMIRA (adalimumab) injection, for subcutaneous use, licensed under BLA 125057 by AbbVie, Inc.

The Applicant has proposed IDACIO (adalimumab-aacf) injection, for subcutaneous use to be licensed for the same indications as US-licensed HUMIRA (with exception of those indications under orphan drug exclusivity), for the treatment of the following:

- **Rheumatoid Arthritis (RA):** Reducing signs and symptoms, including major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active R.A.
- **Juvenile Idiopathic Arthritis (JIA):** Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 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.
- **Crohn's Disease (CD):** Treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.
- **Ulcerative Colitis (UC):** Treatment of moderately to severely active ulcerative colitis in adult patients.
- **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.

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 Rheumatology and Transplant Medicine (DRTM) on March 3, 2022 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for IDACIO (adalimumab-aacf) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft IDACIO (adalimumab-aacf) MG and IFU received on March 3, 2022 received by DMPP and OPDP on November 8, 2022.
- Draft IDACIO (adalimumab-aacf) Prescribing Information (PI) received on March 3, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 8, 2022.
- Approved US-licensed HUMIRA (adalimumab) comparator labeling dated February 24, 2021.

3 REVIEW METHODS

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

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

In our collaborative review of the MG and IFUs we:

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

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

MARY E CARROLL
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KYLE SNYDER
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MARCIA B WILLIAMS
11/29/2022 02:32:30 PM

LASHAWN M GRIFFITHS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1) Hey Davo
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: November 17, 2022
Requesting Office or Division: Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number: BLA 761255
Product Name and Strength: Idacio (adalimumab-aacf)^a Injection, (b) (4)
Applicant/Sponsor Name: Fresenius Kabi USA, LLC*
TTT ID #: 2021-2397-1
DMEPA 1 Safety Evaluator: Teresa McMillan, PharmD
DMEPA 1 Team Leader: Idalia Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 4, 2022 for Idacio. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container label and carton labeling for Idacio (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

2 CONCLUSION

The Applicant implemented most of our recommendations. However, the revised carton labeling is unacceptable from a medication error perspective and we provide recommendations to the Applicant in Section 3.

^a The proposed nonproprietary name, "adalimumab-aacf", was found conditionally acceptable on September 19, 2022. We therefore refer to the proposed product as "adalimumab-aacf" throughout this review in place of the nonproprietary name for this product.

^b McMillan, T. Label and Labeling Review for Idacio (BLA). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 SEPT 29. OSE RCM No.: 2021-2397.

3 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC*

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

A. Carton Labeling (all)

1. The carton labeling lacks differentiation. A lack of differentiation between the prefilled syringe (PFS) , autoinjector (AI), AI starter packs (b) (4) may lead to dispensing errors.

Implement the following:

- 2-pack AI and PFS-utilize different color blocking and/or boxing around the terms 'prefilled syringe and prefilled pens' to increase the difference between the cartons and bring prominence to the different devices within each carton.
- 4-pack and 6-pack AI starter packs-utilize different color blocking and/or boxing around the numbers '4' and '6' to increase the difference between the cartons and bring prominence to the different AI counts within each carton.

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11/18/2022 11:14:15 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: November 17, 2022

To: Susie Choi, Regulatory Project Manager
Division of Rheumatology and Transplant Medicine

From: Kyle Snyder, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for IDACIO® (adalimumab-aacf) injection, for subcutaneous use (Idacio)

BLA: 761255

Background:

In response to DRTM's consult request dated March 3, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and Instructions for Use (IFU) for the original BLA submission for Idacio.

PI/Medication Guide/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 8, 2022, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide and IFU, and comments will be sent under separate cover.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on November 17, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at 240-402-8792 or kyle.snyder@fda.hhs.gov.

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/s/

KYLE SNYDER
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Clinical Inspection Summary

Date	November 1, 2022
From	Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	K. Dev Verma, M.D., Clinical Reviewer Melinda McCord, M.D., Team Leader Susie Choi, PharmD, Regulatory Project Manager Division of Rheumatology and Transplant Medicine (DRTM)
BLA #	761255
Applicant	Fresenius Kabi USA, LLC
Drug	Idacio (adalimumab biosimilar-aacf)
NME (Yes/No)	No
Proposed Indication	Treatment of plaque psoriasis
Consultation Request Date	February 1, 2022
Summary Goal Date	November 13, 2022
Action Goal Date	November 13, 2022
BsUFA Date	December 13, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Charles Lynde and Efren Sanchez Campos were inspected in support of BLA 761255 (a biosimilar application for adalimumab for the treatment of plaque psoriasis) covering one clinical study, Protocol EMR200588-002. The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

BLA 761255 was submitted in support of the use of MSB11022 as a biosimilar to Humira (adalimumab) for the treatment of plaque psoriasis. The sponsor submitted one study. The following briefly describes the protocol:

EMR2000588-002, “A randomized, double-blind, confirmatory trial to evaluate the efficacy, safety and immunogenicity of MSB11022 compared with European Union-Approved Humira in subjects with moderate to severe chronic plaque psoriasis.”

Protocol EMR2000588-002 was a Phase 3, randomized, double-blind trial to demonstrate equivalency in efficacy with European Union-approved Humira in subjects with moderate to severe chronic plaque psoriasis. The primary objective was to demonstrate equivalence in efficacy of MSB11022, compared to the European Union (EU)-approved Humira, both

administered subcutaneously, in subjects with moderate to severe chronic plaque psoriasis.

Sites: The study was conducted at 76 centers in North America, South America, and Europe.

Subjects: 443 subjects were randomized (i.e., 222 subjects received MSB11022 and 221 received EU-approved Humira) and 374 subjects completed the study (i.e., 95 subjects in the MSB11022 group and 179 subjects in the EU-approved Humira group).

Study initiation and completion dates: February 16, 2016 (first patient, first visit); 21 September 21, 2017 (last patient, last 4-week follow-up visit)

Week 24 partial database lock date: April 7, 2017

Week 54 partial database lock date: November 9, 2017

Week 66 final database lock date: February 9, 2019

The study consisted of the following periods:

- **Screening period:** 28 days to 3 days prior to investigational product administration
- **Double-blind core treatment period (Weeks 1-16):** Subjects were randomized to receive either MSB11022 or EU-approved Humira at an initial dose of 80 mg, followed by 40 mg every other week starting at Week 2.
- **Double-blind extension treatment period:** Subjects who achieved Psoriasis Area and Severity Index score reduction of $\geq 50\%$ (PASI 50) at Week 16 were entered into a 37-week double-blind extension period. Subjects who were initially randomized to the EU-approved Humira arm would be re-randomized 1:1 to receive either MSB11022 or EU-approved Humira for an additional 37 weeks to allow collection of long-term comparative immunogenicity, efficacy, and safety data. Subjects who were initially randomized to the MSB11022 arm were to remain on MSB11022 throughout the entire trial. During the double-blind extension period, subjects were to receive 40 mg investigational product (IP) every other week from Week 16 up to and including Week 50. Subjects who achieved less than PASI 50 at or after Week 16 (non-responders) were to be discontinued from the trial.
- **Safety evaluation period of 4 months.**

Primary Efficacy Endpoint: Psoriasis Area and Severity Index score reduction of $\geq 75\%$ from Baseline (PASI 75) at Week 16.

The primary analysis was to be performed after all randomized subjects had reached Week 24 or discontinued from the study. Final analyses were performed at Week 54. For the primary analysis, the 90% CI of the risk difference between the biosimilar and the reference group should have been bounded by $\pm 18\%$.

Rationale for Site Selection

The clinical investigators Drs. Elzbieta Krolikowska and Grazyna Pulka in Poland were originally selected for GCP inspections primarily based on risk ranking in the site selection tool, taking into account numbers of enrolled subjects, treatment effect, and prior inspectional history. Due to the Russian military invasion of Ukraine, these two inspections were cancelled and replaced with Dr. Charles Lynde in Canada and Dr. Efren Sanchez Campos in Mexico based on the same factors mentioned above.

III. RESULTS (by site):

1. Dr. Charles Lynde

Site #206

The Lynde Institute for Dermatology
25 Main Street North
Markham, Ontario
Canada

BsUFA Inspection dates: May 16-19, 2022

At this site, 15 subjects were screened, 5 were randomized, and all 5 subjects completed the study.

Records were reviewed for all 5 randomized subjects. Records reviewed included, but were not limited to, protocol versions, subject eligibility, randomization, blinding, required procedures and evaluations, investigational product handling, and dosing, Institutional Review Board approvals and correspondence, financial disclosures, site training activities, subject records, sponsor correspondence and monitoring activities, and efficacy endpoint source records. Source records were in paper format except for the quality-of-life questionnaires, which were completed on a tablet.

Efficacy endpoint data for the components of the PASI score at visits Week 1 (Baseline), Week 16, Week 24, and Week 52 as documented in the source records were compared with the data line listings submitted by the sponsor for all five randomized subjects. No discrepancies were noted. There were no unreported adverse events or protocol deviations.

2. Dr. Efren Sanchez Campos

Site #707

Calle 3 Numero 299 entre calle 8 y calle 10
Fraccionamiento San Carlos
Merida, Yucatan, 97130
Mexico

BsUFA Inspection dates: May 16-19, 2022

At this site, 18 subjects were screened, 16 were randomized, and 10 subjects completed the

study. Per the sponsor's data line listings, two subjects withdrew consent from the study. Subject #'s (b) (6) (randomized to MSB11022), (b) (6) (randomized to MSB11022), and (b) (6) (randomized to MSB11022) were discontinued due to latent tuberculosis. Subject (b) (6) (randomized to Humira) was discontinued due to the serious adverse event of hypertensive cardiomyopathy and mitral valve disorder. The narrative for this SAE was included in the clinical study report.

Records were reviewed for all 10 randomized subjects. Records reviewed included, but were not limited to, overall control and administration of the clinical trial, adherence to the study protocols, informed consents, protocol versions, Form FDA 1572s, financial disclosure statements, IRB submissions and correspondence, adverse event reporting, efficacy endpoint source records, study test article accountability, concomitant medication, and sponsor monitoring activities. Source records were in a hospital electronic medical record database, with the exception of paper forms for blood draws and ECGs.

Efficacy endpoint data for components of the PASI score at visits Week 1 (Baseline), Week 16, Week 24, and Week 52 as documented in the source records were compared with the data listings submitted by the sponsor for all 10 randomized subjects. No discrepancies were noted. There were no unreported adverse events or protocol deviations.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Jenn Sellers, M.D., Ph.D.,
Acting Branch Chief
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CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/

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HUMAN FACTORS STUDY REPORT REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	October 27, 2022
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761255
Drug Constituent Name and Strength	Idacio [MSB11022] ^a (adalimumab-xxxx) ^b Injection, 40 mg/0.8 mL
Product Type:	Combination Product (Biologic-Device)
Device Constituents:	Autoinjector (AI); (b) (4)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fresenius Kabi USA, LLC. (Fresenius Kabi)
FDA Received Date:	December 13, 2021; January 3, 2022; February 22, 2022; March 11, 2022; March 25, 2022; May 5, 2022; May 17, 2022; May 18, 2022; May 23, 2022
OSE RCM #:	2021-2398
DMEPA 1 Human Factors Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader (Acting):	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

^a MSB11022 has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). The proprietary name for this BLA, Idacio, was found conditionally acceptable on March 7, 2022. Idacio is referred to as MSB11022 throughout this review.

^b The nonproprietary name suffix for this BLA has not yet been determined, therefore, the placeholder "adalimumab-xxxx" is used throughout this review to refer to the non-proprietary name for this product and is not intended to be included in the final labels and labeling.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study reports submitted under BLA 761255 for MSB11022 (adalimumab-xxxx) 40 mg/0.8 mL Autoinjector (AI), four- and six- AI starter packs, (b) (4)

1.1 PRODUCT DESCRIPTION

MSB11022 is a proposed biosimilar to US-licensed Humira (adalimumab). MSB11022 is a tumor necrosis factor (TNF) blocker that is intended to treat Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) in patients ≥ 2 years of age, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease (CD) in adults and pediatric patients ≥ 6 years of age, adult Ulcerative Colitis (UC), Plaque Psoriasis (Ps), and Hidradenitis Suppurativa (HS). MSB11022 will be supplied (b) (4)

- a single-dose prefilled syringe (PFS)
- a single-dose prefilled autoinjector (AI)

(b) (4)

Each MSB11022 40 mg/0.8 mL PFS and AI will be supplied in one-count, two-count, four-count, and six-count cartons. The MSB11022 40 mg/0.8 mL AI will also be supplied in a four-count starter pack for Psoriasis and in a six-count starter pack for Crohn's Disease, Ulcerative Colitis,

(b) (4)

or additional product information, see Table 8 in [Appendix A](#).

(b) (4)

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

- On January 23, 2019, Fresenius Kabi submitted human factors (HF) validation study protocols for their proposed MSB11022 40 mg/0.8 mL PFS (b) (4) under IND 124098.
- On January 24, 2019, Fresenius Kabi submitted a human factors (HF) validation study protocol for their proposed MSB11022 40 mg/0.8 mL AI under IND 124098.
- On March 22, 2019, we provided HF validation study protocol recommendations for (b) (4) proposed configurations. Additionally, we recommended the Sponsor submit a

use-related risk analysis (URRA) and threshold analysis for the MSB11022 40 mg/0.8 mL PFS as HF validation study results for the PFS configuration may not need to be submitted for review.^c

- On May 28, 2019, Fresenius Kabi submitted a threshold analysis and URRA for the PFS configuration.
- On September 5, 2019, we determined that results of a HF validation study for the PFS configuration were not required to be submitted for Agency review as part of the marketing application.^d
- On December 13, 2021, Fresenius Kabi submitted MSB11022 AI Starter Pack HF Validation Test Protocol and AI and PFS HF summary reports, assessment reports, and risk management reports to support the 351(k) BLA for MSB11022 40 mg/0.8 mL as a biosimilar to US-licensed Humira 40 mg/0.8 mL (BLA 125057).
- On December 23, 2021, we issued an information request (IR) to clarify if Fresenius Kabi would be able to conduct an additional HF validation study for their AI configuration.^e
- On January 3, 2022, Fresenius Kabi responded to our IR dated December 23, 2021, stating they wrongly submitted the report of a HF validation study that was conducted for the European Marketing Authorization Application, and they resubmitted the correct AI HF validation study results report intended to support the US BLA submission which is the subject of this review.^f
- On February 17, 2022, we issued another IR requesting Fresenius Kabi resubmit their MSB11022 Starter Pack HF Validation Test Protocol under IND 124098 and clarify if they had already conducted the study or provide their planned timeline for completion of the study. Additionally, (b) (4)
[REDACTED]
- On February 22, 2022, Fresenius Kabi responded to our IR dated February 17, 2022, stating their human factors validation study has been initiated and is ongoing to demonstrate safe and effective use of the starter packs. Fresenius Kabi conveyed their plan to submit the study results report in May 2022. (b) (4)
[REDACTED]

^c Barlow M. Human Factors Validation Study Protocol Review for MSB11022 (IND 124098). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 22. RCM No.: 2019-177, 2019-178, and 2019-179.

^d Barlow M. Threshold Analysis and Use-Related Risk Analysis Review for MSB11022 (IND 124098). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 5. RCM No.: 2019-1209.

^e Rashid N. FDA Communication: Human Factors Information Request – BLA 761255 – MSB11022. Silver Spring (MD): FDA, CDER, OSE. 2021 DEC 23. BLA 761255.

^f Response to HF Information Request for MSB11022 (BLA 761255). Lake Zurich (IL): Fresenius Kabi, USA, LLC. 2022 JAN 3. Available from: <\\CDSESUB1\evsprod\bla761255\0002\m1\us\111-info-amend\response-to-hf-information-request.pdf>

(b) (4)

- On May 23, 2022, Fresenius Kabi submitted their four- and six-count AI starter packs HF validation study results report, which is also the subject of this review.¹

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

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
Labels and Labeling	F

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study designs for the AI, AI starter pack, (b) (4) use errors, close calls, and use difficulties observed; and our analysis to determine if the results indicate that the user interface has been optimized to support the safe and effective use of the proposed product as a biosimilar to US-licensed Humira 40 mg/0.8 mL.

3 SUMMARY OF HUMAN FACTORS VALIDATION STUDY METHODOLOGY

3.1 SUMMARY OF AUTOINJECTOR HUMAN FACTORS VALIDATION STUDY METHODOLOGY

Table 2 presents a summary of the HF validation study design.

¹ Submission of Starter Pack Human Factors Validation Report for MSB11022 (BLA 761255). Lake Zurich (IL): Fresenius Kabi, USA, LLC. 2022 May 23. Available from: <\\CDSESUB1\evsprod\bla761255\0022\m1\us\12-cover-letter\cover-letter.pdf>

Table 2. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details																																						
Participants	<table border="1"> <thead> <tr> <th data-bbox="391 363 727 537" rowspan="2">User Groups</th> <th colspan="3" data-bbox="727 363 1424 436">Number of Users</th> </tr> <tr> <th data-bbox="727 436 992 537">Injection Experienced</th> <th data-bbox="992 436 1224 537">Injection Naïve</th> <th data-bbox="1224 436 1424 537">Total</th> </tr> </thead> <tbody> <tr> <td data-bbox="391 537 727 590">Trained Adult Patients</td> <td data-bbox="727 537 992 590">10</td> <td data-bbox="992 537 1224 590">5</td> <td data-bbox="1224 537 1424 590">15</td> </tr> <tr> <td data-bbox="391 590 727 642">Trained Caregivers</td> <td data-bbox="727 590 992 642">10</td> <td data-bbox="992 590 1224 642">5</td> <td data-bbox="1224 590 1424 642">15</td> </tr> <tr> <td data-bbox="391 642 727 737">Untrained Adult Patients</td> <td data-bbox="727 642 992 737">6</td> <td data-bbox="992 642 1224 737">9</td> <td data-bbox="1224 642 1424 737">15</td> </tr> <tr> <td data-bbox="391 737 727 789">Untrained Caregivers</td> <td data-bbox="727 737 992 789">10</td> <td data-bbox="992 737 1224 789">5</td> <td data-bbox="1224 737 1424 789">15</td> </tr> <tr> <td data-bbox="391 789 727 884">Untrained Adolescent Patients</td> <td data-bbox="727 789 992 884">13</td> <td data-bbox="992 789 1224 884">2</td> <td data-bbox="1224 789 1424 884">15</td> </tr> <tr> <td data-bbox="391 884 727 978">Untrained Healthcare Professionals (HCPs)</td> <td data-bbox="727 884 992 978">15</td> <td data-bbox="992 884 1224 978">n/a</td> <td data-bbox="1224 884 1424 978">15</td> </tr> <tr> <td data-bbox="391 978 727 1050">Total</td> <td data-bbox="727 978 992 1050">64</td> <td data-bbox="992 978 1224 1050">26</td> <td data-bbox="1224 978 1424 1050">90</td> </tr> </tbody> </table>	User Groups	Number of Users			Injection Experienced	Injection Naïve	Total	Trained Adult Patients	10	5	15	Trained Caregivers	10	5	15	Untrained Adult Patients	6	9	15	Untrained Caregivers	10	5	15	Untrained Adolescent Patients	13	2	15	Untrained Healthcare Professionals (HCPs)	15	n/a	15	Total	64	26	90			
User Groups	Number of Users																																						
	Injection Experienced	Injection Naïve	Total																																				
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Untrained Caregivers	10	5	15																																				
Untrained Adolescent Patients	13	2	15																																				
Untrained Healthcare Professionals (HCPs)	15	n/a	15																																				
Total	64	26	90																																				
Training	<u>Trained Participants:</u> The trained participants received a 45-minute training session a week prior to the 1-hour testing session. The training included a brief description of the function of the device and a hands-on demonstration of use, including review of the instructions for use (IFU) and answering user questions about the device. <u>Untrained Participants:</u> The untrained participants did not receive any training prior to completing the 1-hour testing session.																																						
Test Environment	Simulated the intended use environment for each user group.																																						

Table 2. Study Methodology for Human Factors (HF) Validation Study

	
Sequence of Study	1. Session Introduction – review and signage of the informed consent document 2. Background Questions and Administration of RAPID3 Questionnaire 3. Explanation of Overall Testing Procedure 4. For those <u>undergoing training</u>, 45-minute training session followed by a week decay period prior to study participation <u>Three Test Phases</u> 5. Test Phase 1 – Simulated Injection with IFU optional 6. Root Cause Analysis and Debrief for Test Phase 1 7. Test Phase 2 – Simulated Injection with IFU required 8. Root Cause Analysis and Debrief for Test Phase 2 9. Test Phase 3 – IFU Comprehension 10. Root Cause Analysis and Debrief for Test Phase 3

3.2 SUMMARY OF AUTOINJECTOR STARTER PACK HUMAN FACTORS VALIDATION STUDY METHODOLOGY

Table 3 presents a summary of the HF validation study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details

Table 3. Study Methodology for Human Factors (HF) Validation Study

Participants	User Groups	Number of Users*
	Adult patients with one of the indicated conditions	15
	Caregivers who provide care for patients with one of the indicated conditions	15
	HCPs (licensed pharmacists who dispense medication for patients with one of the indicated conditions or nurses who have experience training patients with one of the indicated conditions on how to administer injections)	15
	Adolescents with either hidradenitis suppurativa or Crohn’s disease	15
	Total	60
	* Participants were randomly assigned to the four AI starter pack or the six AI starter pack, such that at the end of the study about half of all users within each intended user group will have used the four AI starter pack or the six AI starter pack during the evaluation activities.	
Training	No training	
Test Environment	Room represented basic characteristics of the intended use environment (clinical offices, home environment). The room was equipped with all materials required to facilitate the hands-on use scenarios. The average lighting level at table level was in the range of 400-750 Lux. The test room was representative of the intended use environments. The room was relatively quiet, comparable to a library reading room. The average sound at desktop level was about 45 dB (the sound pressure level in a quiet room). Test personnel introduced one distraction (sound of a phone ringing for a couple of seconds) when the participant performed use scenario 2.	
Sequence of Study	Scenario 1: Retrieve starter pack and prepare for first day of treatment Scenario 2: Prepare for second day of treatment Scenario 3: Prepare for third day of treatment (four pack only)	

(b) (4)

4 RESULTS AND ANALYSES

4.1 SUMMARY OF AUTOINJECTOR HUMAN FACTORS VALIDATION STUDY RESULTS

Table 5 describes the AI study results, Fresenius Kabi’s analyses of the results, and DMEPA 1’s analyses and recommendations. Section 4.1.1 describes use errors, close calls and use difficulties with non-critical tasks associated with the use of the AI in the HF validation study.

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

Please note the following:

Test Phases:

- Test Phase 1 – Simulated Injection with IFU optional
- Test Phase 2 – Simulated Injection with IFU required
- Test Phase 3 – IFU Comprehension

Participant ID Acronyms:

- A##T – trained adult patient
- C##T – trained caregiver
- A##UT – untrained adult patient
- C##UT – untrained caregiver
- T##UT – untrained adolescent patient
- H##UT – untrained HCP

	Identified Issue and Rationale for Concern	DMEPA’s Analysis and Findings						
1.	For the “collect necessary supplies to prepare the injection site (alcohol pads included in the box)” task, see the table and list below for a summary of participant performance. <table border="1"> <thead> <tr> <th>Total number of use errors (UE), close calls (CC), and use difficulties (UD)</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UD (n=1)</td> <td>AUT = 1</td> <td>1</td> </tr> </tbody> </table>	Total number of use errors (UE), close calls (CC), and use difficulties (UD)	Type of Participants	Test Phase	UD (n=1)	AUT = 1	1	Our review of the study results identified subjective feedback that indicated a participant misunderstood the IFU instructions and images and thought the instructions were telling him to get cotton balls from the refrigerator.
Total number of use errors (UE), close calls (CC), and use difficulties (UD)	Type of Participants	Test Phase						
UD (n=1)	AUT = 1	1						

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: - Unclear IFU image grouping (1) – one participant stated he was using the instructions and thought the instructions were telling him to get cotton balls from the refrigerator. Based on the URRRA, if this task is omitted or not performed correctly there is risk of non-sterile injection technique. Fresenius Kabi proposed the following mitigation strategy in response to participant performance for this task: - Increase the IFU font size to 10 pt. bold of all sub-step numbers (e.g., 1.1, 1.2 ... 8.1)	(b) (4) We acknowledge Fresenius Kabi’s proposed mitigation strategy, and our review of the revised labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.						
2.	For the “set autoinjector on a flat clean surface and allows it to acclimate to room temperature” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 1101 1329 1338"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=22)</td> <td>AUT = 5 CT = 1 CUT = 2 HUT = 7 TUT = 7</td> <td>1</td> </tr> </tbody> </table>	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=22)	AUT = 5 CT = 1 CUT = 2 HUT = 7 TUT = 7	1	Our review of the study results identified subjective feedback that indicated participants thought the first part of IFU step 1.7 lacked salience compared with the information around it (i.e., the bolding in step 1.6 and the next two points under step 1.7). Additionally, participants overlooked these steps since they were separate from the header “Step 1 Prepare for your injection.”
Total number of UE, CC, and UD	Type of Participants	Test Phase						
UE (n=22)	AUT = 5 CT = 1 CUT = 2 HUT = 7 TUT = 7	1						

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

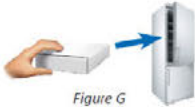
UE (n=4)	AUT = 1 CUT = 2 HUT = 1	2	Subjective feedback also indicated that other participants incorrectly thought the IFU step 1.6 Figure G and step 1.7 Figure H collectively indicated to store their AI in the refrigerator for 30 minutes prior to use. Additionally, other participants stated that the monochromatic appearance of Figure H caused it to be overlooked and that Figure H did not clearly indicate what they were supposed to do for “30 minutes”. We acknowledge Fresenius Kabi’s proposed mitigation strategy, however, the image in Figure H is monochromatic, difficult to read, and does not clearly explain why users need to “wait for 30 minutes”. Based on our overall assessment we find that the user interface can be improved to further mitigate risk of failure to set the autoinjector on a flat clean surface and allow it to acclimate to room temperature. We provide recommendations in the Identified Issues and Recommendations Table to address these concerns. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.
Participant performance includes: - Not allowing the medication to reach room temperature before use Fresenius Kabi provided the following RCA and supportive evidence: - Unclear IFU (Figure G and Figure H) (10) – some participants interpreted Figures G and H as saying that the prefilled pens needed to be put into the refrigerator for 30 minutes because of the pictures’ proximity to each other. Additionally, some participants missed Figure H due to the monochromatic color scheme (i.e., black and white) on the white background and the words “30 minutes” did not indicate participants were supposed to allow the AI to warm to room temperature for 30 minutes prior to use. One participant stated the image in Figure H was too small and she missed it. 1.6 Return the remaining pen in its original carton to the refrigerator (Figure G). See “Storing Idacio pre-filled pens” for information on how to store your unused pen  1.7 Let the Idacio pre-filled pen sit at room temperature for (b) (4) 30 minutes before use to allow the medicine to reach room temperature (Figure H). Do not warm the pen in any other way, such as in a microwave, hot water, or direct sunlight. Do not remove the needle cap until you are ready to inject.  - Negative transfer (12) – relied on previous injection experience and did not read the IFU when performing this task. - Insufficient salience of IFU text for step 1.7 (9) – participants did not read the instruction because it did not contain bolded information.			

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	- IFU design (steps 1.5-1.7) (2) – participants did not see these step(s) because they were on a different pane not associated with the header “Step 1 Prepare for your injection”. Based on the URRRA, if this task is omitted or not performed correctly there is risk of chronic underdosing or administration of expired/degraded drug. Fresenius Kabi proposed the following mitigation strategy in response to participant performance for this task: - Change the directive information in Figure H from “30 minutes” to “wait 30 minutes”.										
3.	For the “clean hands” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 748 1329 948"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=3)</td> <td>AUT = 1 CUT = 1 TUT = 1</td> <td>1</td> </tr> <tr> <td>UE (n=1)</td> <td>TUT = 1</td> <td>2</td> </tr> </tbody> </table> Participant performance includes: - Not washing their hands prior to handling the autoinjector - Wearing gloves instead of washing hands prior to handling the autoinjector Fresenius Kabi provided the following RCA and supportive evidence: - Negative transfer (3) – relied on previous AI use experience when performing this task; wore gloves instead of washing hands.	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=3)	AUT = 1 CUT = 1 TUT = 1	1	UE (n=1)	TUT = 1	2	Our review of the study results identified subjective feedback that indicated the majority of these use errors were due to negative transfer and test artifact. We acknowledge Fresenius Kabi’s proposed mitigation strategy, and our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
Total number of UE, CC, and UD	Type of Participants	Test Phase									
UE (n=3)	AUT = 1 CUT = 1 TUT = 1	1									
UE (n=1)	TUT = 1	2									

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	• Test artifact (2) – one participant was nervous about giving the injection since he had never given an injection; one participant stated since she was not actually letting the AI sit for 30 minutes (verbally stating she would let it sit) she washed her hands before instead of after. • Insufficient salience of IFU text for step 2.1 (1) – one participant stated he did not see the instructions in step 2.1. Based on the URRRA, if this task is omitted or not performed correctly there is risk of bacterial contamination and local infection. Fresenius Kabi proposed the following mitigation strategy in response to participant performance for this task: • Increase the font size to 10 pt. bold of all sub-steps numbers (e.g., 1.1, 1.2 ... 8.1)	(b) (4)						
4.	For the “check product name on the autoinjector” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 1024 1329 1260"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=11)</td> <td>AT = 1 AUT = 3 CUT = 3 HUT = 1 TUT = 3</td> <td>1</td> </tr> </tbody> </table> Participant performance includes: • Not checking product name on pen label before use	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=11)	AT = 1 AUT = 3 CUT = 3 HUT = 1 TUT = 3	1	Our review of the study results identified subjective feedback that indicated the majority of these use errors were due to negative transfer and test artifact. Our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task.
Total number of UE, CC, and UD	Type of Participants	Test Phase						
UE (n=11)	AT = 1 AUT = 3 CUT = 3 HUT = 1 TUT = 3	1						

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Fresenius Kabi provided the following RCA and supportive evidence: • Negative transfer (8) – relied on previous medication experience when performing this task; participants stated they often check the name of the carton when receiving it and not the actual product inside. • Test artifact (2) – in a testing environment; one participant stated she focused on how to administer the medication rather than how to prepare it because that is how she interpreted the study prompt. • Inconspicuous IFU figure (1) – one participant stated she was focused on the step headings and did not notice step 3.2 or Figure K because it was further from the step 3 heading than Figure J. • First time use (1) – one participant stated they were injection naïve, did not know they needed to check the label for the product name and did not read the IFU. Based on the URRRA, if this task is omitted or not performed correctly there is risk of erroneous drug administration. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.	We did not identify areas of improvement and have no recommendations at this time.						
5.	For the “check the autoinjector integrity” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 1260 1329 1377"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=3)</td> <td>AUT = 1 TUT = 2</td> <td>1</td> </tr> </tbody> </table>	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=3)	AUT = 1 TUT = 2	1	Our review of the study results identified subjective feedback that indicated the majority of these use errors were due to negative transfer.
Total number of UE, CC, and UD	Type of Participants	Test Phase						
UE (n=3)	AUT = 1 TUT = 2	1						

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	UE (n=1)	TUT = 1	2	
	Participant performance includes: • Not checking the pen for damage before use Fresenius Kabi provided the following RCA and supportive evidence: • Negative transfer (2) – relied on previous medication experience when performing this task. • Insufficient IFU image (Figure J) (1) – one patient stated that the image in Figure J does not say what to check for. • Insufficient IFU step (step 3.1) (1) – one participant stated she expected to check the needle for damage, but she could not check the needle because it was not visible, and she did not check the device for damage because she did not know what a damaged device would look like. • First time use (1) – one participant stated they were injection naïve, did not know they needed to check the prefilled pen for damage and did not read the IFU. Based on the URRR, if this task is omitted or not performed correctly there is risk of drug product coming in contact with skin or delayed treatment. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.			Our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
6.	For the “check the drug product integrity” task, see the table and list below for a summary of participant performance.			Our review of the study results identified subjective feedback that indicated the

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

Total number of use errors, close calls, and use difficulties	Type of Participants	Test Phase	
Use errors (n=7)	AUT = 1 CT = 1 CUT = 1 HUT = 1 TUT = 3	1	majority of these use errors were due to negative transfer. We acknowledge Fresenius Kabi’s proposed mitigation strategy, and our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
Participant performance includes: • Not checking the integrity of the liquid before use Fresenius Kabi provided the following RCA and supportive evidence: • Negative transfer (5) – relied on previous medication experience when performing this task. • Test artifact (1) – one participant stated she did not check because she was in a testing environment and typically relies on the hospital pharmacy to check the medication. • Insufficient IFU image (Figure J) (1) – one participant stated that the image in Figure J does not say what to check for. • IFU design/ambiguous step text/lack of visual salience of sub-steps (3.1 and 3.2) (1) – one participant stated she interpreted the word “check” in the step header to mean check the expiration date and she only read the header for step 3, not the sub-steps, because the header was colored and stood out more.			

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	• First time use (1) – one participant stated they were injection naïve, did not know they needed to check the medication and did not read the IFU. Based on the URRRA, if this task is omitted or not performed correctly there is risk of degraded drug being administered. Fresenius Kabi proposed one mitigation strategy in response to participant performance for this task: • Increase the font size to 10 pt. bold of all sub-step numbers (e.g., 1.1, 1.2 ... 8.1)													
7.	For the “select an injection site (must be different from the previous injection site)” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 789 1329 1182"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE(n=6)</td> <td>AUT = 4 CT = 1 CUT = 1</td> <td>1</td> </tr> <tr> <td>UE (n=12)</td> <td>AT= 1 AUT = 2 CUT = 2 HUT = 1 TUT = 6</td> <td>2</td> </tr> <tr> <td>CC (n=1)</td> <td>TUT = 1</td> <td>1</td> </tr> </tbody> </table> Participant performance includes: • No rotation of injection site • Selection of inappropriate injection site Fresenius Kabi provided the following RCA and supportive evidence:	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE(n=6)	AUT = 4 CT = 1 CUT = 1	1	UE (n=12)	AT= 1 AUT = 2 CUT = 2 HUT = 1 TUT = 6	2	CC (n=1)	TUT = 1	1	Our review of the study results identified subjective feedback that indicated the majority of these use errors were due to insufficient salience of the instructions for the first line of step 4.2 and the inconspicuous location of step 4.2 as it was located on a separate page away from the rest of step 4. Additionally, a few participants did not clearly understand the instructions to only inject into the front of the thigh or stomach area. We acknowledge Fresenius Kabi’s proposed mitigation strategy, however, our review of the labels and labeling (user interface, etc.) indicates that the wording of step 4.1 could be improved to better portray to only inject in the front of the thighs or stomach area. We provide recommendations in the
Total number of UE, CC, and UD	Type of Participants	Test Phase												
UE(n=6)	AUT = 4 CT = 1 CUT = 1	1												
UE (n=12)	AT= 1 AUT = 2 CUT = 2 HUT = 1 TUT = 6	2												
CC (n=1)	TUT = 1	1												

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

- Negative transfer (6) – relied on previous injection experience when performing this task. Participants often injected into the arm or forearm.
- Insufficient salience of instructions (5) – participants stated that the first line of step 4.2 is the only line in that step that does not include a bolded, “do not,” statement.
- IFU design (inconspicuous location for step 4.2) (5) – participants did not see step 4.2 because it was located at the top of the second page without a header.
- Ambiguous IFU (3) – one participant stated he interpreted the word “choose” in the header of step four meant he could choose his injection site; another participant stated she interpreted the text “the front of your thigh or stomach-area” to mean inject into a fatty area.
- Test artifact (2) – one participant stated he changed the injection site from his knee because the injection pad would not fit there.
- Insufficient training (1) – one participant stated she did not know she needed to change injection sites because she only used one autoinjector during training.
- Mental model (1) – one participant stated he expected to administer the medication where he was experiencing pain.

Step 4 Choose the injection site

- 4.1 Choose an injection site (Figure L). You can use:
- the front of your thighs or
 - your stomach-area. If you choose your stomach - area, do not use the area 2 inches around your belly button (navel). (See Figure L)



Only inject into injection sites shown (Figure L)

- 4.2 Choose a different site (at least one inch away from your last injection site) for each injection to reduce redness, irritation or other skin problems.
Do not inject into an area that is sore (tender), bruised, red, hard, scarred or where you have stretch marks or tattoos.
 If you have psoriasis, do not inject into any lesions or red, thick, raised or scaly patches.
Do not inject through your clothes.

Identified Issues and Recommendations Table to address this concern.

We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Based on the URRRA, if this task is omitted or not performed correctly there is risk of injection site reaction, too shallow injection might be performed, or the injection site might be contaminated. Fresenius Kabi proposed one mitigation strategy in response to participant performance for this task: The two sub-steps 4.1 and 4.2 are joined in the same page and the same column													
8.	For the “clean the skin at the selected injection site” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 630 1329 1024"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=9)</td> <td>AT = 2 AUT = 3 CT = 1 CUT = 1 HUT = 2</td> <td>1</td> </tr> <tr> <td>UE (n=5)</td> <td>AT= 2 AUT = 3</td> <td>2</td> </tr> <tr> <td>CC (n=2)</td> <td>AUT = 1 CT = 1</td> <td>2</td> </tr> </tbody> </table> Participant performance includes: - Not cleaning site before administering medication - Blowing on injection site after cleaning the site - Cleaning with a cotton ball instead of alcohol pad - Drying the injection site with a cotton ball after cleaning with an alcohol pad - Initially forgetting to clean the injection site but self-correcting Fresenius Kabi provided the following RCA and supportive evidence:	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=9)	AT = 2 AUT = 3 CT = 1 CUT = 1 HUT = 2	1	UE (n=5)	AT= 2 AUT = 3	2	CC (n=2)	AUT = 1 CT = 1	2	Our review of the study results identified subjective feedback that indicated many participants had difficulty locating the alcohol swabs within the package. Participants stated that they did not see the alcohol swabs in the packaging because the IFU was covering them. Some participants stated the image in Figure M did not clearly depict the injection site. We acknowledge Fresenius Kabi’s proposed mitigation strategy, however, our review of the labels and labeling (user interface, etc.) indicates that Figure M could be improved to better depict the injection site. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.
Total number of UE, CC, and UD	Type of Participants	Test Phase												
UE (n=9)	AT = 2 AUT = 3 CT = 1 CUT = 1 HUT = 2	1												
UE (n=5)	AT= 2 AUT = 3	2												
CC (n=2)	AUT = 1 CT = 1	2												

Table 5: Identified Issues and DMEPA's Findings – AI Configuration

- Inconspicuous alcohol swab location (4) – participants stated they did not see the alcohol swabs in the packaging because the IFU was covering them.
- Ambiguous figure in step 5.1 (Figure M) (2) – two participants stated the image in Figure M did not clearly depict the injection site.



- IFU design (step 5 header placement) (1) – one participant stated he overlooked step 5 since the step 5 header was not at the top of page 3 and was placed between step 4.2 and 5.1.
- IFU design (1) – one participant stated it was his first time giving an injection and that he did not know there was a back to the instructions because he did not notice the line at the bottom of the instructions saying to Continue on the other side.



- IFU design (lack of step 1 instruction) (2) – one participant stated steps 1.1 through 1.7 did not indicate to remove the alcohol swabs; one patient expected to find information about where the alcohol swabs were stored in step 5 and did not see the information during step 1.

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	• Test artifact (1) – one participant stated she expected to find the alcohol swabs on the table because the moderator provided the other study supplies. Based on the URRRA, if this task is omitted or not performed correctly there is risk of injection site contamination. Fresenius Kabi proposed one mitigation strategy in response to participant performance for this task: • Increase the font size to 10 pt. bold of all sub-step numbers (e.g., 1.1, 1.2 ... 8.1)										
9.	For the “remove cap of the device” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 748 1329 911"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=2)</td> <td>AUT = 1 HUT = 1</td> <td>1</td> </tr> <tr> <td>CC (n=1)</td> <td>HUT = 1</td> <td>1</td> </tr> </tbody> </table> Participant performance includes: • Removing the cap [too early] before cleaning the injection site • Twisting the cap off instead of pulling • Discarding cap into the trashcan instead of the sharps container Fresenius Kabi provided the following RCA and supportive evidence: • Negative transfer (3) – two participants stated they discarded the needle cap in the trash because that is what they normally do with other injections. One participant stated he typically removes the cap of his syringe (b) (4) immediately.	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=2)	AUT = 1 HUT = 1	1	CC (n=1)	HUT = 1	1	Our review of the study results identified subjective feedback that indicated the majority of these use errors were due to negative transfer. We acknowledge Fresenius Kabi’s proposed mitigation strategies, and our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. However, we note Fresenius Kabi proposes to change the last sentence of Step 1.5 to “Put the pen on a clean flat surface and do not remove the cap.” We consider the phrase “do not remove the cap” may be made more prominent, and therefore we provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern.
Total number of UE, CC, and UD	Type of Participants	Test Phase									
UE (n=2)	AUT = 1 HUT = 1	1									
CC (n=1)	HUT = 1	1									

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

- IFU design (inconspicuous footer, ambiguous arrow icon in footer) (1) – one participant stated he did not see the “Continue on the other side” text or the image of the orange triangle icon.
- IFU design (step 1.5) – one participant interpreted the word “packaging” in the second bullet point in step 1.5 to mean remove the needle cap from the prefilled pen because she thought the prefilled pen was encased in an external package, and she thought the prefilled pen was an external package. She heard the click sound after removing the needle cap and therefore attempted to recap the needle.



- Device design (force required to remove needle cap) (1) – one participant stated he twisted the cap off because the force required to pull it off was too great.
- Device design (arrows on needle cap, needle cap size and shape) (1) – one participant interpreted the arrows on the needle cap to mean “remove” and she removed the needle cap too early, immediately after removing the pen from the carton.

Based on the URRRA, if this task is omitted or not performed correctly there is risk of the autoinjector being unable to be used, the needle might be contaminated, or a drop might appear at the tip of the needle leading to limited underdosing.

Fresenius Kabi proposed the following mitigation strategies in response to participant performance for this task:

We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	• Change the last sentence of step 1.5 to: “Put the pen on a clean flat surface and do not remove the cap” • Increase the font size to 10 pt. bold of all sub-steps numbers (e.g., 1.1, 1.2 ... 8.1) • Improve the structuring of step 6 by reducing the white space between sub-steps • Improve visibility of the third bullet point on step 6.1 by bolding “Throw away” • Increase the visibility of the blue arrows in the figures, and the call for actions, by using a bigger line thickness							
10.	For the “press the autoinjector against the skin at a 90 degree angle. (b) (4) [redacted]” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 756 1329 837"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=1)</td> <td>CUT = 1</td> <td>1</td> </tr> </tbody> </table> Participant performance includes: • Attempt to hold the pen a few inches above the injection site and press the injection button Fresenius Kabi provided the following RCA and supportive evidence: • IFU design (ambiguous step 6.1 text and figure O) – one participant stated she held the pen over the injection site because she interpreted the text in step 6.1 “you may see drops of liquid at the needle tip” and Figure O to mean she needed to prime the prefilled pen. Based on the URRR, if this task is omitted or not performed correctly there is risk of the injection site contamination, the autoinjector not activating, the injection not being triggered, or the injection not starting (delays in treatment).	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=1)	CUT = 1	1	Our review of the study results identified subjective feedback that indicated this error was due to misinterpretation of the text in step 6.1 and Figure O. We acknowledge Fresenius Kabi’s proposed mitigation strategies, and our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
Total number of UE, CC, and UD	Type of Participants	Test Phase						
UE (n=1)	CUT = 1	1						

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Fresenius Kabi proposed the following mitigation strategies in response to participant performance for this task: • Reduce spacing between sub-steps 6.1 and 6.2 and within sub-step 6.2 • Increase visibility of the third bullet point of step 6.1 by using bold appearance of “Throw away” • Increase the visibility of the blue arrows in the figures, and the call for actions, by using a bigger line thickness										
11.	For the “maintain pressure on injection site until plunger has moved all the way down” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 906 1329 1144"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=18)</td> <td>AUT = 6 CUT = 3 HUT = 4 TUT = 5</td> <td>1</td> </tr> <tr> <td>UE (n=2)</td> <td>AUT = 2</td> <td>2</td> </tr> </tbody> </table> Participant performance includes: • Preemptive lifting of pen from injection site often resulting in wet injection Fresenius Kabi provided the following RCA and supportive evidence:	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=18)	AUT = 6 CUT = 3 HUT = 4 TUT = 5	1	UE (n=2)	AUT = 2	2	Our review of the study results identified subjective feedback that indicated many of these use errors were due to negative transfer. Subjective feedback also indicated that the placement of step 6.3 and 6.4 was inconspicuous and may have been overlooked until after the administration was complete or overlooked entirely. Additionally, some participants indicated that they interpreted the “click” sound to mean the injection was complete. Other participants misunderstood the instructions to mean “hold the prefilled pen down for 5 seconds after pressing the injection button”
Total number of UE, CC, and UD	Type of Participants	Test Phase									
UE (n=18)	AUT = 6 CUT = 3 HUT = 4 TUT = 5	1									
UE (n=2)	AUT = 2	2									

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

- Negative transfer (8) – relied on previous injection experience when performing this task.
- Device design (lack of auditory feedback and clear plunger area) (12) – one participant stated it was unclear when the device was empty due to a lack of indicator; one participant stated he did not know when the pre-filled syringe was successfully delivering medication; two participants stated they lifted the prefilled pen after hearing the clicking sound because it scared/startled them; one participant stated the safety guard can be interpreted as a mechanism indicating the injection was completed; two participants stated the spring of the syringe plunger can be interpreted as a quick release; one participant stated she interpreted the design of the safety guard to mean that she had to lift the pre-filled pen from the injection site after pressing the injection button and the medication would be administered as soon as she lifted up the prefilled pen; three participants stated they did not realize the medication was in the clear part of the device; one participant stated she did not expect to have to hold the device down that long while injecting.
- Ambiguous text (step 6.2 and step 6.3) (2) – one participant stated she gave herself the injection during step 6.2 and did not read step 6.3 Administer the Injection until afterwards; three participants stated they held the prefilled pen down for 5 seconds after pressing the injection button; three participants stated they thought the click sound meant the injection was completed; two participants stated they did not notice

or “hold the prefilled pen down for 5 seconds after hearing the click” instead of holding for 5 seconds after the plunger has moved all the way down.

We acknowledge Fresenius Kabi’s proposed mitigation strategies, however, there is inadequate instruction denoting when the injection is complete. Our review of the labels and labeling (user interface, etc.) indicates that the images in Figures Q and R may be confusing and do not clearly indicate how long users are to hold the injection button/prefilled pen down. Additionally, Figures Q, R, and S do not intuitively depict the process of pressing the button, hearing a click, holding and watching the plunger move to the base, and holding an additional 5 seconds. Based on our overall assessment we find that the user interface can be improved to further mitigate risk of failure to maintain pressure on injection site until plunger has moved all the way down. **We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address these concerns.**

We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.

Table 5: Identified Issues and DMEPA's Findings – AI Configuration

	the phrase “after the plunger has reached the bottom” because it was not in bold font. • IFU design (figures R and S) (2) – one participant stated the blue arrows in the images in Figure R and S could be misinterpreted to mean push the autoinjector down and then lift it back up and did not depict a waiting action; one participant stated the phrase “watch” in the image in Figure R did not clearly indicate to watch the plunger come down to ensure the injection as completed. • IFU design (step 6.3 and 6.4) (1) – one participant stated they did not see step 6.3 or step 6.4 because they were at the top right of the IFU and did not have their own step headers. • Dexterity issue (1) – one participant stated they had difficulty keeping the syringe down due to her arthritis. • IFU design (footer) (1) – one participant stated he did not see the “Continue on other side” text and the orange triangle because the font size was too small and did not look like an arrow. • Slip (1) – one participant unknowingly adjusted the injection angle while she was rereading the IFU and while the injection was being administered. • Test artifact (2) – one participant stated they were nervous in the testing environment; one participant stated they administered the second prefilled pen (limited overdose) because the first attempt resulted in a partial dose, and they were administering a manikin.	(b) (4)

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

Based on the URRRA, if this task is omitted or not performed correctly there is risk of chronic underdosing or limited overdosing. Fresenius Kabi stated that acceptance criteria for the injection is between (b) (4) seconds, and that the maximum injection time measured during design verification was 10 seconds. Fresenius Kabi further stated that when the syringe plunger reaches the bottom of the syringe barrel, the injection is considered complete. Therefore, the syringe plunger provides visual feedback of the completion of the injection. Fresenius Kabi stated they included the instruction “Continue holding the pen for 5 seconds after the syringe plunger has reached the bottom of the transparent housing” as a reasonable risk mitigation measure to prevent underdosing. Additionally, Fresenius Kabi stated that the average hold time for all participants was 8.1 seconds (minimum 1 second, maximum 30 seconds) during test phase 1 and 9.5 seconds (minimum 1 second, maximum 48 seconds) during test phase 2. Fresenius Kabi noted that 18 use errors were observed related to not holding the AI to the injection site long enough resulting in the loss of some medication during test phase 1 and two use errors were observed related to not holding the AI to the injection site long enough resulting in the loss of some medication during test phase 2. Fresenius Kabi proposed the following mitigation strategies in response to participant performance for this task. • Increase the font size to 10 pt. bold of all sub-step numbers (e.g., 1.1, 1.2 ... 8.1) • Improve the design of step 6.3 and Figure R and provide further guidance by changing the caption of the call out in Figure R from “watch” to “watch plunger and hold” • Increase the font size and improve the visibility of the “continue on other side” and “continue” note at the bottom of the front page and the top of the back page	

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

12. For the “^{(b) (4)} pressing a cotton ball or gauze on the injection site” task, see the table and list below for a summary of participant performance.

Total number of UE, CC, and UD	Type of Participants	Test Phase
UE (n=3)	AUT = 2 CUT = 1	1

Participant performance includes:

- Not treating the injection site with a cotton ball after injection
- Wiping the site with an alcohol pad after injection

Fresenius Kabi provided the following RCA and supportive evidence:

- IFU design (step 6.4) (2) – one participant stated he did not notice step 6.4 because he interpreted step 6.3 Figure S to mean the injection was complete and read step 7 and discarded the prefilled pen; one participant stated he did not see this step because he did not know the IFU had a back page
- Test artifact (1) – one participant stated he did not treat the injection site with a cotton ball because there was no blood at the injection site.
- Negative transfer (1) – one participant stated she used a cotton ball but then recleaned the injection site because she typically does this before putting a bandage on it.

Our review of the study results identified subjective feedback that indicated these use errors were due to negative transfer and IFU design.

We acknowledge Fresenius Kabi’s proposed mitigation strategy, and our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Based on the URRRA, if this task is omitted or not performed correctly there is risk of drug product coming in contact with the skin or injection site contamination. Fresenius Kabi proposed the following mitigation strategy in response to participants performance for this task: • Increase the font size and improve the visibility of the “continue on other side” and “continue” note at the bottom of the front page and the top of the back page													
13.	For the “Discard the autoinjector into a sharps container” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 670 1329 870"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=4)</td> <td>AUT = 3 TUT = 1</td> <td>1</td> </tr> <tr> <td>CC (n=1)</td> <td>TUT = 1</td> <td>1</td> </tr> <tr> <td>CC (n=1)</td> <td>AUT = 1</td> <td>2</td> </tr> </tbody> </table> Participant performance includes: • Discarding the pen in the trashcan instead of the sharps container • Discarding or almost discarding in the trashcan and then self-correcting Fresenius Kabi provided the following RCA and supportive evidence: • Unclear IFU wording (4) – two participants stated they interpreted the heading of step 7 “throw away” to mean throw away in the trash, but they then read the phrase “do not throw away pre-filled pens in your household trash” and corrected their mistake; one participant stated he interpreted the heading of step 7 “throw away” to mean throw away in the trash; one participant stated he read the bolded text in step 3.2 “throw away used prefilled pens”; two participants did not see the	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=4)	AUT = 3 TUT = 1	1	CC (n=1)	TUT = 1	1	CC (n=1)	AUT = 1	2	Our review of the study results identified subjective feedback that indicated these use errors were due to misinterpretation of the header of step 7 and association of the phrase “throw away” with “trash”. We acknowledge Fresenius Kabi’s proposed mitigation strategy, however, our review of the labels and labeling (user interface, etc.) indicates that the header of step 7 could instruct users more clearly how to discard their used prefilled pens. Based on our overall assessment we find that the user interface can be improved to further mitigate risk of third parties being injured or contaminated. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern.
Total number of UE, CC, and UD	Type of Participants	Test Phase												
UE (n=4)	AUT = 3 TUT = 1	1												
CC (n=1)	TUT = 1	1												
CC (n=1)	AUT = 1	2												

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	instructions in step 7 because they were not aware there was a back to the instructions. • Test artifact (2) – one participant stated he saw the red sharps container in Figure and did not think he could use the green sharps container provided on the table; one participant stated she did not notice the sharps container because she was nervous. • Negative transfer (2) – two participants stated they typically throw away items in the trash. Based on the URRR, if this task is omitted or not performed correctly there is risk of third parties being injured or contaminated. Fresenius Kabi proposed the following mitigation strategy in response to participant performance for this task. • Increase the font size and improve the visibility of the “continue on other side” and “continue” note at the bottom of the front page and the top of the back page	(b) (4) We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.						
14.	For the “Record injection” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 1377 1329 1412"> <thead> <tr> <th data-bbox="317 1377 768 1412">Total number of UE, CC, and UD</th> <th data-bbox="768 1377 1079 1412">Type of Participants</th> <th data-bbox="1079 1377 1329 1412">Test Phase</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Total number of UE, CC, and UD	Type of Participants	Test Phase				Our review of the study results identified subjective feedback that indicated the
Total number of UE, CC, and UD	Type of Participants	Test Phase						

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

UE (n=27)	AT = 3 AUT = 8 CT = 2 CUT = 6 HUT = 2 TUT = 6	1	majority of these use errors occurred due to negative transfer. Subjective feedback also indicated ambiguity in step 8.1. Participants stated they interpreted the wording of the header and step 8.1 to mean to only record the date, and some participants stated they misinterpreted the word “site” to mean physical location of injection (e.g., at home). We acknowledge Fresenius Kabi’s proposed mitigation strategy, however, our review of the labels and labeling (user interface, etc.) indicates that the step 7 heading, text in step 8.1 and the image in Figure V could instruct users more clearly what to record. Based on our overall assessment we find that the user interface can be improved to further mitigate risk of failure to record the injection. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.
UE (n=4)	AUT = 1 CT = 1 CUT = 1 TUT = 1	2	

Participant performance includes:

- Did not record the injection site location
- Did not record the injection date
- Did not record injection site location or injection date

Fresenius Kabi provided the following RCA and supportive evidence:

- Negative transfer (14) – relied on previous injection experience when performing this task.
- IFU design (ambiguous text in step 8.1) (12) – one participant stated she typically only records the injection date and the phrase “remember when” indicated a timeframe, therefore she recorded the injection date but not the injection location; two participants stated they interpreted the phrase “record your injection” in step 8 header to mean record the injection date and did not record the location; two participants stated they interpreted the word “site” to mean physical location and did not think it was necessary to record the physical location of the study environment; two participants stated they expected to find this information in the Important Information section; four participants

Table 5: Identified Issues and DMEPA's Findings – AI Configuration

	stated the instructions blended in with the extra text at the bottom of the page and they would have followed this step if the items that needed to be recorded were separated by bullets like the other steps in the instructions; one participant stated she thought the word record referred to recording the injection with a camera, and she thought that the phrase “next injection” told her to record the date for the next injection. • IFU design (ambiguous step 7) (3) – three participants read step 7 (Throw away your pre-filled pens) but not step 8 (Record your injection) interpreting step 7 as the last step in the administration process. • IFU design (inconspicuous footer) (1) – one participant stated he did not read step 8.1 because he did not know there were instructions on the other side of the IFU. • IFU design (Figure V) (1) – one participant stated she uses the computer to record this information and assumed these instructions were for the home setting. • Test artifact (3) – one participant stated she read and understood the step instruction but disregarded it because she did not know if she could use the pen and paper provided; one participant stated she did not record the injection information because she was nervous since she did not successfully administer the medication; one participant stated she did not record the injection information because she was not in her normal work environment and did not have an electronic health record system.	(b) (4)

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Based on the URRRA, if this task is omitted or not performed correctly there is risk of limited overdosing or inadequate injection technique (lack of injection site rotation). Fresenius Kabi proposed the following mitigation strategy in response to participant performance for this task. Increase the font size to 10 pt. bold of all sub-step numbers (e.g., 1.1, 1.2 ... 8.1)					
15.	For the knowledge-based question “what should you not do when using the pre-filled pen?” see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 634 1335 829"> <thead> <tr> <th>Total number of “incorrect answers”</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>Incorrect answers (n=8)</td> <td>AT = 4 CT = 1 CUT = 2 TUT = 1</td> </tr> </tbody> </table> The subjective data and Fresenius Kabi’s root cause analysis indicated: - Unclear IFU wording (2) – one participant stated she was unsure whether the opening to the safety guard was referring to an opening on the box or something on the device; one participant stated if the pen cannot be frozen it should say do not place the pen in a freezer, as opposed to do not freeze. - Negative transfer (2) – one participant stated she thought that “safety guard” was referring to the tamper seal on her medications at home; one participant stated she only used the instructions to use the device and therefore did not expect to find information in the important information section. - Font size (2) – two participants stated the font size was too small and they were having difficulty reading the instructions.	Total number of “incorrect answers”	Type of Participants	Incorrect answers (n=8)	AT = 4 CT = 1 CUT = 2 TUT = 1	Our review of the study results identified subjective feedback that indicated the participants did not notice the relevant information in the IFU. Our review of the label and labeling (user interface, etc.) finds that the “Important Information” section of the IFU states: “Idacio pre-filled pen is for single-dose (one-time) use only” and “Do not try to reuse the Idacio pre-filled pen” “Do not insert your fingers into the opening of the safety guard” “Do not freeze Idacio” and “Do not use an Idacio pre-filled pen that has been frozen or left in direct sunlight” However, our review of the labels and labeling (user interface, etc.) indicates that Step 6.1 Remove the needle cap could be improved to remind users “Do not insert your fingers into the opening of the safety guard.”
Total number of “incorrect answers”	Type of Participants					
Incorrect answers (n=8)	AT = 4 CT = 1 CUT = 2 TUT = 1					

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	• Inconspicuous step location (2) – one participant stated she did not see the second to last bullet point (“Do not use an Idacio pre-filled pen that has been frozen or left in direct sunlight”) in the Using the Idacio Pre-filled Pen section of the IFU because she expected this information to be grouped or be placed after the third bullet point; one participant stated he expected the bullet stating “do not insert your fingers into the opening of the safety guard” to be located in step 6 because the step 6 text pertains to using the prefilled pen while the safety guard was exposed. • Insufficient salience (“read this instructions for use”) (1) – one participant stated he did not read the “Important Information” section because it did not stand out to him, and other instructions have “important information” that he does not perceive as important therefore he does not read. • Training artifact (1) – one participant stated during training he was told during traveling he could put the pen on ice in a cooler and he interpreted this to mean the pen could be frozen and thawed. Based on the URRRA, if this task is omitted or not performed correctly there is risk of needle stick injury or expired/degraded drug product. Fresenius Kabi did not propose any risk mitigation strategies for these “incorrect responses.”	Based on our overall assessment we find that the user interface can be improved to further mitigate risk of needle stick injury or expired/degraded drug product. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.								
16.	For the knowledge-based question “what additional supplies are needed beside the pre-filled pen?” see the table and list below for a summary of participant performance. <table border="1" data-bbox="310 1255 1335 1408"> <thead> <tr> <th data-bbox="310 1255 1045 1295">Total number of “incorrect answers”</th> <th data-bbox="1045 1255 1335 1295">Type of Participants</th> </tr> </thead> <tbody> <tr> <td data-bbox="310 1295 1045 1336">Incorrect answers (n=5)</td> <td data-bbox="1045 1295 1335 1336">AT = 1</td> </tr> <tr> <td></td> <td data-bbox="1045 1336 1335 1377">CT = 2</td> </tr> <tr> <td></td> <td data-bbox="1045 1377 1335 1408">CUT = 1</td> </tr> </tbody> </table>	Total number of “incorrect answers”	Type of Participants	Incorrect answers (n=5)	AT = 1		CT = 2		CUT = 1	Our review of the study results identified subjective feedback that indicated the participants did not see the information immediately under step 1 because it was in paragraph format.
Total number of “incorrect answers”	Type of Participants									
Incorrect answers (n=5)	AT = 1									
	CT = 2									
	CUT = 1									

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	<table border="1" style="width: 100%;"> <tr> <td style="width: 50%;"></td> <td style="width: 50%; text-align: right;">TUT = 1</td> </tr> </table> The subjective data and Fresenius Kabi’s root cause analysis indicated: Insufficient salience of instructions (step 1) (5) – four participants stated they did not see the paragraph mentioning the alcohol pads at the top of the step because it was not bulleted or numbered; one participant did not provide subjective feedback. Based on the URRR, if this task is omitted or not performed correctly there is risk of non-sterile injection technique. Fresenius Kabi did not propose any risk mitigation strategies for these “incorrect responses.”		TUT = 1	Our review of the label and labeling (user interface, etc.) finds that the IFU includes information about the alcohol swabs directly beneath step 1. These instructions are separated from step 1.2 which states users will need additional items that are not included in the carton (cotton ball or gauze and a sharps container). We agree this is the appropriate location for this information, however, based on our overall assessment we find that the user interface can be improved to further mitigate risk of failure to gather the supplies necessary for a sterile injection. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.		
	TUT = 1					
17.	For the knowledge-based question “How can you tell that the pre-filled pen device itself is okay to use?” see the table and list below for a summary of participant performance. <table border="1" style="width: 100%;"> <tr> <td style="width: 50%;">Total number of “incorrect answers”</td> <td style="width: 50%;">Type of Participants</td> </tr> <tr> <td>Incorrect answers (n=1)</td> <td>AT = 1</td> </tr> </table> The subjective data and Fresenius Kabi’s root cause analysis indicated: Insufficient salience of step 3.1 (1) – the moderator noted she did not use the IFU	Total number of “incorrect answers”	Type of Participants	Incorrect answers (n=1)	AT = 1	Our review of the study results identified moderator feedback that indicated the participant did not use the IFU. Our review of the label and labeling (user interface, etc.) finds that the IFU includes instructions to check the prefilled pen to make sure it is not cracked or damaged in step 3.1. Based on our review of the user
Total number of “incorrect answers”	Type of Participants					
Incorrect answers (n=1)	AT = 1					

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Based on the URRRA, if this task is omitted or not performed correctly there is risk of drug product coming in contact with skin or delayed treatment. Fresenius Kabi did not propose any risk mitigation strategies for this “incorrect response.”	interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.				
18.	For the knowledge-based question “What are the circumstances under which you should not use the pre-filled pen anymore?” see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 591 1335 672"> <tr> <td>Total number of “incorrect answers”</td> <td>Type of Participants</td> </tr> <tr> <td>Incorrect answers (n=1)</td> <td>AT = 1</td> </tr> </table> The subjective data and Fresenius Kabi’s root cause analysis indicated: • Insufficient salience of step 3.1 (1) – the moderator noted she did not use the IFU Based on the URRRA, if this task is omitted or not performed correctly there is risk of non-sterile injection technique. Fresenius Kabi did not propose any risk mitigation strategies for these “incorrect responses.”	Total number of “incorrect answers”	Type of Participants	Incorrect answers (n=1)	AT = 1	Our review of the study results identified moderator feedback that indicated the participant did not use the IFU. Our review of the label and labeling (user interface, etc.) finds that the IFU includes instructions “Do not use the pen if the liquid is cloudy or colored, if it has particles or flakes in it or shows any sign of damage” in step 3.1. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
Total number of “incorrect answers”	Type of Participants					
Incorrect answers (n=1)	AT = 1					
19.	For the knowledge-based question “Which sites are okay to inject into?” see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 1143 1335 1224"> <tr> <td>Total number of “incorrect answers”</td> <td>Type of Participants</td> </tr> <tr> <td>Incorrect answers (n=1)</td> <td>AT = 1</td> </tr> </table> The subjective data and Fresenius Kabi’s root cause analysis indicated:	Total number of “incorrect answers”	Type of Participants	Incorrect answers (n=1)	AT = 1	Our review of the study results identified subjective feedback that indicated the participant misinterpreted the image in Figure L. Our review of the label and labeling (user interface, etc.) finds that the IFU includes images and the instructions “You can use: the front of your thighs or your stomach-area. If
Total number of “incorrect answers”	Type of Participants					
Incorrect answers (n=1)	AT = 1					

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	• Unclear IFU image (1) – one participant stated the injection could be given in the middle of the stomach while pointing to her belly button and referencing the picture in the IFU. Based on the URRRA, if this task is omitted or not performed correctly there is risk of inadequate injection technique (injection site reaction), too shall injection, or non-sterile technique. Fresenius Kabi did not propose any risk mitigation strategies for these “incorrect responses.”	 Figure L	you choose your stomach-area, do not use the area 2 inches around your belly button (navel)” in step 4.1. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.

4.1.1 ANALYSES OF AUTOINJECTOR HUMAN FACTORS VALIDATION STUDY NON-CRITICAL TASK ERRORS

The AI HF validation study showed use errors and use difficulties with the following non-critical tasks; however, based on our review of the available participants’ subjective feedback, Fresenius Kabi’s root cause analysis, and Fresenius Kabi’s proposed risk mitigation strategies, we determined the residual risk is acceptable. Specifically, we find that the labeling mitigations in place include information that is prominently placed within the labels and labeling to address the non-critical tasks below. We also find the labels and labeling are in alignment with labeling best practices. In addition, we considered the use tasks of the proposed product as compared with the use tasks in similar marketed products with the same user groups to determine if there are any known concerns of vulnerability to use error and did not identify any concerns. Subsequently, we did not identify further need to implement additional risk mitigation strategies at this time to address the use errors and use difficulties related to the following non-critical tasks:

- Open the carton
- Place the remaining prefilled pen in its original carton back in the refrigerator
- Check the prefilled pen to make sure that the glass syringe or other parts are not cracked or damaged
- Push and hold the prefilled pen firmly against your skin until the safety guard is fully depressed

4.2 SUMMARY OF AUTOINJECTOR STARTER PACK HUMAN FACTORS VALIDATION STUDY RESULTS

Table 6 describes the AI starter pack study results, Fresenius Kabi’s analyses of the results, and DMEPA 1’s analyses and recommendations.

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs						
<u>Please note the following:</u> <u>Scenarios:</u> Scenario 1: Retrieve starter pack and prepare for first day of treatment Scenario 2: Prepare for second day of treatment Scenario 3: Prepare for third day of treatment (4-pack only) <u>Participant ID Acronyms:</u> A##: Adult patients T##: Adolescent patients C##: Caregivers P##: Pharmacists						
	Identified Issue and Rationale for Concern	DMEPA’s Analysis and Findings				
Scenario 1: Retrieve starter pack and prepare for first day of treatment						
1.	For the “Open the box” task, see the table and list below for a summary of participant performance. <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 50%;">Total number of UE, CC, and UD</th> <th style="width: 50%;">Type of Participants</th> </tr> </thead> <tbody> <tr> <td>UE (n=1)</td> <td>C = 1</td> </tr> </tbody> </table> Participant performance includes: • Tearing the cardboard flap slightly while opening the box Fresenius Kabi provided the following RCA and supportive evidence: • Unintended action (1): one participant pulled the cardboard flap at an angle in the process of lifting it up, causing it to tear, but this did not obscure Important Information or Starter Schedule sections	Total number of UE, CC, and UD	Type of Participants	UE (n=1)	C = 1	We note that Fresenius Kabi’s RCA was incomplete because it did not identify why the participant pulled the cardboard flap at an angle in the process of lifting it up, causing it to tear. Our review of the labels and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule contains instructions and/or images to support this task. Based on our review of the user interface, we find the residual risk acceptable for this task. We did
Total number of UE, CC, and UD	Type of Participants					
UE (n=1)	C = 1					

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	Based on the URRRA, if this task is omitted or not performed correctly there is risk of non-sterile injection technique. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.	not identify areas of improvement and have no recommendations at this time.						
2.	For the “Determine the correct number of injections” and “Remove correct number of autoinjectors from the blister” tasks, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 553 1325 792"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>UE (n=8)</td> <td>T = 5 A = 3</td> </tr> <tr> <td>UD (n=4)</td> <td>T = 2 A = 1 C = 1</td> </tr> </tbody> </table> Participant performance includes: • Two participants selected 2 AIs instead of 4 AIs (six-pack) because the blue second treatment day box attracted their attention more than the yellow first treatment day box and they did not find the number in the IFU • One participant selected 1 AI instead of 4 AIs (six-pack) because it was not clear the small and large colored boxes for each treatment day on the carton lid were related to one another • Two participants selected of 1 AI instead of 2 AIs (four-pack) because the IFU only showed one AI • One participant selected 4 AIs instead of 2 AIs (four-pack) • Two participants selected the wrong number of AI because they made assumptions about the number of AI rather than referencing the on-carton directions	Total number of UE, CC, and UD	Type of Participants	UE (n=8)	T = 5 A = 3	UD (n=4)	T = 2 A = 1 C = 1	Our review of the study results identified subjective feedback that indicated some participants expected to find the number of AIs needed in the IFU and some participants stated they would have had help from their parents at home. We acknowledge Fresenius Kabi’s proposed mitigation strategies, and our review of the labels and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
Total number of UE, CC, and UD	Type of Participants							
UE (n=8)	T = 5 A = 3							
UD (n=4)	T = 2 A = 1 C = 1							

Table 6: Identified Issues and DMEPA's Findings – AI Configuration Starter Packs

- One participant selected 1 AI instead of 2 AIs (four-pack) before reviewing on-carton instructions, noting the on-carton phrase “ (b) (4) ” led her to think the correct number of AI could vary
- One participant read the instructions and selected 1 AI instead of 4 AIs (six-pack) before reviewing the on-carton labeling and selecting 3 more because the IFU only showed 1 AI
- One participant initially referred to the IFU and selected 1 AI instead of 4 (six-pack) before correctly selecting 4 AI, based on previous experience
- One participant initially removed all 6 AIs before correctly putting 2 AIs back (six-pack) noting they misheard the moderator prompt

Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence:

- Inconspicuous packaging illustration (1) – inconspicuous yellow color of box with AI needed for first treatment day relative to blue color of second treatment day
- Insufficient IFU (2) – two participants expected to find required number of AI needed in the IFU
- Test artifact (2) – two participants would have adult assistance reading directions at home

Based on the URRRA, if these tasks are omitted or not performed correctly there is risk of underdose or overdose.

Fresenius Kabi proposed the following mitigation strategies in response to participants performance for this task:

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	- The sentence in the starter schedule “ (b) (4) ” may be misunderstood as a necessary preliminary request to the physician to ask about each injection. This information is redundant and not necessary in this box (removal of statement depicted below) - The boxes depicting number of pens and injection date are merged to better associate those information - Before Change: (b) (4) - After Change:  STARTING DAY 2 weeks later same week day Administer 4 prefilled pens one after the other on the same day					
3.	For the “Remove correct number of alcohol swabs” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 1279 1325 1395"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>UE (n=9)</td> <td>T = 7 A = 2</td> </tr> </tbody> </table>	Total number of UE, CC, and UD	Type of Participants	UE (n=9)	T = 7 A = 2	Our review of the study results identified subjective feedback that indicated some participants did not see the alcohol swabs folded on top of each tray because they were folded together between trays.
Total number of UE, CC, and UD	Type of Participants					
UE (n=9)	T = 7 A = 2					

Table 6: Identified Issues and DMEPA's Findings – AI Configuration Starter Packs

Participant performance includes: • One participant selected one alcohol swab instead of two because she missed seeing the swabs that were folded together between trays • One participant did not remove any alcohol swabs instead of two because she missed seeing the other swabs that were folded together between the trays, and she explained she would not use them anyways because she washes her hands and injects her current medication into her palm • One participant selected four alcohol swabs instead of two because the IFU did not state how many to use • Six participants removed the incorrect number of alcohol swabs because of a use event on the prior task Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: • Inconspicuous packaging design (2) – folded over alcohol swabs led participants to think the box only provided the 2 alcohol swabs on the top tray • Incorrect mental model (1) – participant assumed injection site would be the same as her current site (palm) and thought washing hands was sufficient • Insufficient IFU (1) – IFU does not state number of alcohol swabs are required for the first day of treatment Based on the URRRA, if these tasks are omitted or not performed correctly there is risk non-sterile injection technique. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.	Our review of the label and labeling (user interface, etc.) finds that the IFU includes information about the alcohol swabs directly beneath step 1, instructing users “You will need 1 alcohol swab and 1 Idacio pre-filled pen for each injection.” Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

Scenario 2: Prepare for second day of treatment

1. For the “Determine the correct number of injections” task, see the table and list below for a summary of participant performance.

Total number of UE, CC, and UD	Type of Participants
UE (n=3)	T = 2 A = 1
UD (n=1)	C = 1

Participant performance includes:

- One participant removed two AIs instead of one (four-pack). He explained seeing two AIs in the tray together led him to think they were for a single day
- One participant removed two AIs instead of one (four-pack). She explained the phrase “(b) (4)” made her think her physician would repeat the same instructions for the second treatment day
- One participant removed one AI instead of two (six-pack) because they assumed the number of AIs needed was one instead of referencing the on-carton instructions
- One participant had difficulty determining the correct number of AIs because of the unclear visual hierarchy and low visual importance of the phrase “2 weeks later”

Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence:

- Misleading package design (1) – layout of 2 AIs grouped together in each layer signaled they should be administered together
- Insufficient labeling (1) – ambiguous instruction “(b) (4)” leading participant to think the dose was dependent on the individual patient’s dosage

Our review of the study results identified subjective feedback that indicated one participant associated a tray of two AI as one dose and one participant assumed the dose was the same as the first treatment dose.

Our review of the labels and labeling (user interface, etc.) indicates that the packaging of the AIs could be improved to more clearly indicate that users only need to administer one AI for the second and third doses. **We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern.**

We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	• Test artifact (1) – protocol deviation in which “treatment day” was replaced by “dose” in moderator prompts might have led participant to think the number of AI would be the same as first treatment • Incorrect mental model (1) – participant made assumptions rather than referring to on-carton instructions • Inconspicuous packaging design (1) – unclear visual hierarchy and low visual salience of the phrase “2 weeks later” Based on the URRRA, if these tasks are omitted or not performed correctly there is risk of underdose or overdose. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.									
2.	For the “States correct date of second treatment day” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 829 1325 1146"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>UE (n=5)</td> <td>T = 1 A = 2 C = 2</td> </tr> <tr> <td>CC (n=2)</td> <td>C = 1 P = 1</td> </tr> <tr> <td>UD (n=3)</td> <td>A = 2 C = 1</td> </tr> </tbody> </table> Participant performance includes: • One participant stated the second treatment day would take place 24 hours instead of 2 weeks after (six-pack) because of the low visual salience of the phrase “2 weeks later” relative to the surrounding information	Total number of UE, CC, and UD	Type of Participants	UE (n=5)	T = 1 A = 2 C = 2	CC (n=2)	C = 1 P = 1	UD (n=3)	A = 2 C = 1	Our review of the study results identified subjective feedback that indicated there was low salience around the “2 weeks later” statement (six-pack) and more emphasis between the blue and purple boxes as compared to the yellow and blue boxes. We acknowledge that Fresenius Kabi removed the statement “(b) (4)” from the on-carton starter schedule. Our review of the labels and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this
Total number of UE, CC, and UD	Type of Participants									
UE (n=5)	T = 1 A = 2 C = 2									
CC (n=2)	C = 1 P = 1									
UD (n=3)	A = 2 C = 1									

Table 6: Identified Issues and DMEPA's Findings – AI Configuration Starter Packs

	● One participant stated the second treatment day would take place 2 weeks instead of 1 week after (four-pack) because the information for a single treatment day was not contained in its own square on the on-carton label ● One participant stated the second treatment day would happen 2 weeks instead of 1 week (four-pack) after the first treatment day because she assumed it was the same as her current medication ● One participant stated the second treatment day would take place 2 weeks instead of 1 week after (four-pack) because she skipped ahead when reading on the carton labeling ● One participant stated the second treatment day would happen the day after instead of 1 week after (four-pack) because he could not read, and his mom would help him at home ● Two participants stated the second treatment day would occur two weeks after and correctly changed to 1 week after. ○ One participant stated the layout divides the yellow box from the blue and purple boxes, which emphasizes “2 weeks later” ○ One participant stated the blue and purple boxes stood out more, which emphasizes “2 weeks later” ● Three participants had difficulty determining the correct date ○ One participant stated the “tue” in “Tuesday” and “2 weeks” caused her to initially misspeak ○ Two participants stated an incorrect date before reflecting and responding with the correct date because the simulated environment caused them to behave differently Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence:	task. We did not identify areas of improvement and have no recommendations at this time.

Table 6: Identified Issues and DMEPA's Findings – AI Configuration Starter Packs

- Inconspicuous packaging illustration – low visual importance of “2 weeks later”
- Insufficient labeling – information for a single treatment day is divided across different boxes within the on-carton label
- Incorrect mental model – participant’s experience caring for daughter with diabetes led her to pay more attention to amount of medication than to the treatment day
- Incorrect mental model – assumed the timing of treatment days would be the same as her current medication
- User state – participant might have experienced brain fog due to multiple sclerosis
- User state – participant did not know how to read
- Test artifact – participant would have adult assistance in reading directions at home
- Inconspicuous packaging illustration – blue and purple colors of the second and third treatment day boxes stand out more than the yellow starting day box and caused “2 weeks later” to stand out more than “1 week later”
- Slip – stated the correct time between doses but misspoke the date after saying the day of the week
- Test artifact – simulated environment caused participant to behave differently than at home

Based on the URRR, if these tasks are omitted or not performed correctly there is risk of user taking the next dose too soon, too late, or not at all.

Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

3.	For the “Remove correct number of autoinjectors form the blister” task, see the table and list below for a summary of participant performance.		Our review of the study results identified subjective feedback that indicated one participant misunderstood the moderator instructions. Our review of the labels and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
	Total number of UE, CC, and UD	Type of Participants	
	UE (n=1)	T = 1	
	N/A ^j (n=4)	T = 2 A = 2	

Participant performance includes:

- One participant removed two AIs instead of 1 because they removed the supplies for both the second and third treatment days in response to the moderator prompt
- Three participants removed the incorrect number of AIs from the blister because of a use event on a previous task
- One participant’s performance could not be assessed because she selected all 4 AIs instead of 2 on the first treatment day and therefore did not have any available AIs for the second treatment day

Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence:

- Test artifact (1) – simulated environment caused the participant to behave differently form how they would at home

Based on the URRRA, if these tasks are omitted or not performed correctly there is risk of underdose or overdose.

^j Fresenius Kabi noted that the coding “N/A” used throughout Table 6 indicates that the participant did not complete the step because of a previous error on a previous task.

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.							
4.	For the “Remove correct number of alcohol swabs” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 396 1323 672"> <thead> <tr> <th data-bbox="317 396 905 435">Total number of UE, CC, and UD</th> <th data-bbox="905 396 1323 435">Type of Participants</th> </tr> </thead> <tbody> <tr> <td data-bbox="317 435 905 594">UE (n=6)</td> <td data-bbox="905 435 1323 594"> T = 3 A = 1 C = 1 P = 1 </td> </tr> <tr> <td data-bbox="317 594 905 672">N/A (n=4)</td> <td data-bbox="905 594 1323 672"> T = 3 A = 1 </td> </tr> </tbody> </table> Participant performance includes: • One participant removed two alcohol swabs instead of one alcohol swab (four pack) explaining he saw the tray with two AIs and two alcohol swabs and assumed they were for one day • One participant removed two alcohol swabs instead of one alcohol swab (four-pack) explaining she did not think to unfold the swabs and did not realize they were connected • One participant selected two alcohol swabs instead of 1 alcohol swab (four-pack) explaining she did not notice the two alcohol swabs were connected because they were folded together to look like there was one • Three participants did not select any alcohol swabs because they were not performing an injection • Three participants removed the incorrect number of AIs from the blister because of a use event on a previous task • One participant’s performance could not be assessed because she selected all 4 AIs instead of 2 on the first treatment day and therefore did not have any available AIs for the second treatment day	Total number of UE, CC, and UD	Type of Participants	UE (n=6)	T = 3 A = 1 C = 1 P = 1	N/A (n=4)	T = 3 A = 1	Our review of the study results identified subjective feedback that indicated the majority of these use errors occurred due to test artifact. Our review of the label and labeling (user interface, etc.) finds that the IFU includes information about the alcohol swabs directly beneath step 1, instructing users “You will need 1 alcohol swab and 1 Idacio pre-filled pen for each injection.” However, based on our overall assessment we find that the user interface can be improved to further mitigate risk of failure to remove correct number of alcohol swabs. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.
Total number of UE, CC, and UD	Type of Participants							
UE (n=6)	T = 3 A = 1 C = 1 P = 1							
N/A (n=4)	T = 3 A = 1							

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: • Misleading package design – layout of 2 alcohol swabs and 2 AIs grouped together in each layer signaled they should be administered together • Test artifact (2) – participant removed two alcohol swabs instead of one because they were folded together • Test artifact (3) – simulated environment caused the participant to behave differently from how they would at home					
Scenario 3: Prepare for third day of treatment (4-pack only)						
1.	For the “Determine correct number of injections” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 764 1325 883"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>N/A (n=2)</td> <td>T = 1 A = 1</td> </tr> </tbody> </table> Participant performance includes: • Two participants determined the incorrect number of injections because of a use event on the prior task Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: • These use events were attributed to previous use events when participants determined the number of injections required. The participants being N/A for the following use scenarios is due to them determining the incorrect number of injections from the pack from the beginning and start of the use scenario	Total number of UE, CC, and UD	Type of Participants	N/A (n=2)	T = 1 A = 1	Our review of the labels and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule contains instructions and/or images to support this task. Based on our review of the user interface, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
Total number of UE, CC, and UD	Type of Participants					
N/A (n=2)	T = 1 A = 1					

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	Based on the URRRA, if these tasks are omitted or not performed correctly there is risk of underdose or overdose. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.									
2.	For the “States correct date of third treatment day” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 513 1325 711"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>UE (n=4)</td> <td>T = 1 A = 3</td> </tr> <tr> <td>CC (n=1)</td> <td>T = 1</td> </tr> <tr> <td>UD (n=2)</td> <td>C = 2</td> </tr> </tbody> </table> Participant performance includes: • Two participants stated the third treatment day would take place 2 weeks after the first treatment day instead of 2 weeks after the second treatment day because the phrase “2 weeks later same weekday” was ambiguous about which treatment day to count from • One participant stated the third treatment day would take place 28 days instead of 2 weeks after the second treatment day because she expected to find the dosage instructions in the IFU • One participant did not check the starter pack and stated the third treatment day would happen on Saturday (the day after the first treatment day) because he could not read • One participant stated the treatment day would occur 1 week after the first treatment day before self-correcting because the phrase “2 weeks later same weekday” was ambiguous • Two participants had difficulty determining the correct date of the third treatment day. They expressed uncertainty about which day the third	Total number of UE, CC, and UD	Type of Participants	UE (n=4)	T = 1 A = 3	CC (n=1)	T = 1	UD (n=2)	C = 2	Our review of the study results identified subjective feedback that indicated some participants thought the third treatment day would occur 2 weeks after the first treatment day instead of 2 weeks after the second treatment day. Our review of the label and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule does not clearly indicate when the third treatment day occurs. Based on our overall assessment we find that the user interface can be improved to further mitigate risk of users taking the next dose too soon, too late, or not at all. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.
Total number of UE, CC, and UD	Type of Participants									
UE (n=4)	T = 1 A = 3									
CC (n=1)	T = 1									
UD (n=2)	C = 2									

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	treatment day was 2 weeks from (i.e., 2 weeks after the first treatment day or after the second treatment day) Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: • Insufficient labeling (2) – ambiguous instruction “2 weeks later same weekday” led participant to think the third treatment day should occur 2 weeks after the first treatment day instead of two weeks after the second treatment day • Insufficient IFU (1) – the participant expected to find the dosage instructions in the IFU • User state (1) – the participant did not know how to read Based on the URRRA, if these tasks are omitted or not performed correctly there is risk of users taking the next dose too soon, too late, or not at all. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.							
3.	For the “Remove correct number of autoinjectors from the blister” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 1024 1325 1182"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>UD (n=1)</td> <td>T = 1</td> </tr> <tr> <td>N/A (n=3)</td> <td>T = 1 A = 2</td> </tr> </tbody> </table> Participant performance includes: • One participant removed one of the AIs from the plastic tray and the cap detached from the AI body. He explained he had no idea what happened, but he removed the AI in the same way he removed the	Total number of UE, CC, and UD	Type of Participants	UD (n=1)	T = 1	N/A (n=3)	T = 1 A = 2	Our review of the study results identified subjective feedback that indicated one participant had the cap pop off while removing the AI from the tray, this might have occurred because the AIs were dropped prior to the session, which might have caused the AI cap to become loose. Our review of the labels and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule contains instructions and/or images to support this task. Based on
Total number of UE, CC, and UD	Type of Participants							
UD (n=1)	T = 1							
N/A (n=3)	T = 1 A = 2							

Table 6: Identified Issues and DMEPA's Findings – AI Configuration Starter Packs

	others, by holding the AI in the middle. He explained he was removing the AI normally when he heard a popping noise • Three participants performance could not be assessed because of previous use events Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: • Test artifact – the AIs were dropped prior to the session, which might have caused the AI cap to become loose • Previous use event – determined incorrect number of AIs for the second treatment day • Misleading packaging design – layout of 2 AIs grouped together in each layer implied they should be administered together • Previous use event – determined incorrect number of AIs for the first treatment day or the second treatment day • Previous user state – the participant might have experienced brain fog due to multiple sclerosis • Labeling – ambiguous instruction “ (b) (4) ” led participant to think the number of AIs needed for the first dose depended upon the individual patient’s dosage • Test artifact – protocol deviation in which “treatment day” was replaced by “dose” in moderator prompts might have led participant to think the number of AIs for subsequent treatments would be the same as the first treatment Based on the URRRA, if these tasks are omitted or not performed correctly there is risk of underdose or overdose.	our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.							
4.	For the “Remove correct number of alcohol swabs” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 396 1325 594"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>UE (n=2)</td> <td>T = 1 A = 1</td> </tr> <tr> <td>N/A (n=4)</td> <td>T = 3 A = 1</td> </tr> </tbody> </table> Participant performance includes: • One participant removed the correct supplies for both the second and third treatment days on the second treatment day but indicated she would not use the swabs because she washes her hands and injects her current medication into her palm • One participant did not select any alcohol swabs for the third treatment day because she was not performing an injection • Four participants removed the incorrect number of alcohol swabs because of a use event on the prior task Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: • Incorrect mental model – would not use alcohol swabs because she assumed the injection site would be the same as her current medication • Test artifact – simulated environment caused participant to behave differently from how they would at home • Previous use event – remove incorrect number of alcohol swabs for the second treatment day • Inconspicuous packaging design – participant removed 2 alcohol swabs instead of 1 because they were folded together to appear as one	Total number of UE, CC, and UD	Type of Participants	UE (n=2)	T = 1 A = 1	N/A (n=4)	T = 3 A = 1	Our review of the study results identified subjective feedback that indicated the majority of these use errors occurred due to test artifact. Our review of the label and labeling (user interface, etc.) finds that the IFU includes information about the alcohol swabs directly beneath step 1, instructing users “You will need 1 alcohol swab and 1 Idacio pre-filled pen for each injection.” However, based on our overall assessment we find that the user interface can be improved to further mitigate risk of failure to remove correct number of alcohol swabs. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.
Total number of UE, CC, and UD	Type of Participants							
UE (n=2)	T = 1 A = 1							
N/A (n=4)	T = 3 A = 1							

Table 6: Identified Issues and DMEPA's Findings – AI Configuration Starter Packs

- Previous use event – removed incorrect number of alcohol swabs for the first treatment day
- Insufficient IFU – paper instructions do not state how many alcohol swabs are required for the first day of treatment
- Misleading packaging design – layout of 2 alcohol swabs and 2 AIs grouped together in each layer signaled they should be administered together

Based on the URRRA, if these tasks are omitted or not performed correctly there is risk non-sterile injection technique.

Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.

(b) (4)

5 LABELS AND LABELING

Table A below includes the identified medication error issues with the submitted product samples, packaging, label and labeling, our rationale for concern, and our proposed recommendations to minimize the risk for medication error.

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU) for the Autoinjector (AI) (b) (4)			
1.	The image in Figure H does not instruct the user to set the autoinjector on a flat clean surface and allow it to acclimate to room temperature for 30 minutes.	The URRA indicates if a user omits or does not perform the task associated with “set autoinjector on a flat clean surface and allows it to acclimate to room temperature” correctly there is risk of chronic underdosing or	Revise Figure H to better portray the autoinjector needs to be set on a clean flat surface to acclimate to room temperature for 30 minutes. For example, revise Figure H to include an image of an AI on a flat surface (e.g., countertop) with the “Wait 30 minutes” image in the background. Additionally, consider making the image more prominent and non-monochromatic.

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
	 Figure H	administration of expired/degraded drug. The AI HF validation study results identified subjective feedback that indicated participants thought the image in Figure H was ambiguous and did not provide clear instructions on what to do for “30 minutes”. Additionally, participants indicated that the monochromatic color scheme of the clock (i.e., black and white) made the clock blend in with the white background.	
Instructions for Use (IFU) for the Autoinjector (AI)			
1.	Step 1 “Prepare for your injection” does not clearly outline all information.	The URRA indicates if a user omits or does not perform the task associated with “collect the necessary supplies to prepare the injection site” correctly there is risk of non-sterile injection technique. The AI HF validation study results identified subjective	Revise the format in the first paragraph, “Each carton comes with 2 alcohol swabs and 2 Idacio pre-filled pens. You will need 1 alcohol swab and 1 Idacio pre-filled pen for each injection.” in step 1 from paragraph format to bulleted statements or numbered statements.

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
		feedback that indicated participants did not see the first paragraph, "Each carton comes with 2 alcohol swabs and 2 Idacio pre-filled pens. You will need 1 alcohol swab and 1 Idacio pre-filled pen for each injection."	
2.	The image of the carton in Figures D, E, and G do not clearly depict that the carton contains MSB11022 Als.	The images of a blank, white carton could lead to confusion.	Consider revising the image of the carton in Figures D, E, and G to more accurately represent the Idacio carton.
3.	We note you proposed the following mitigation strategy for step 1.5: "Change the last sentence of Step 1.5 to 'Put the pen on a clean flat surface and do not remove the cap.'"	The instruction, " do not remove the cap," may be missed because it is at the end of the sentence.	To put more prominence on not removing the cap during step 1.5, consider revising your proposed sentence to read, "Place the capped pen on a clean flat surface."
4.	The instructions in step 4.1 do not inform users to only inject in the front of the thighs or stomach area.	The URRAs indicate if a user omits or does not perform the task associated with "select an injection site (must be different from the previous	Revise the instructions in step 4.1 to more clearly inform users to only inject in the front of the thighs or stomach area. For example, revise the phrase in step 4.1 "Choose an injection site (Figure L). You can use: ..." to

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
		injection site)” correctly there is risk of injection site reaction, too shallow injection might be performed, or the injection site might be contaminated. The AI HF validation study results identified subjective feedback that indicated participants did not clearly understand to only inject in the front of the thighs or stomach area.	“Choose an injection site (Figure L). Only use: ...”
5.	The image in Figure M does not clearly depict the injection site.	The URRRA indicates if a user omits or does not perform the task associated with “clean the skin at the selected injection site” correctly there is risk of injection site contamination. The AI HF validation study results identified subjective feedback from two participants who indicated Figure M did not clearly depict the injection site.	Revise Figure M to more clearly depict the injection site. For example, consider depicting an image that represents the intended areas of injection (i.e., the stomach area or the front of the thigh).

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
6.	The images in Figures Q, R, and S do not intuitively depict the process of pressing the button, hearing a click, holding and watching the plunger move to the base, and holding an additional 5 seconds.	The URRA indicates if a user omits or does not perform the task associated with “maintain pressure on injection site until plunger has moved all the way down” correctly there is risk of chronic underdosing or limited overdosing. The AI HF validation study results identified subjective feedback that indicated participants interpreted the “click” sound to mean the injection was complete. Additionally, some participants misunderstood the instructions “Continue holding the pen for 5 seconds after the syringe plunger has reached the bottom of the transparent syringe housing” to mean “hold the prefilled pen down for 5 seconds after pressing the injection button” or “hold the prefilled pen	Revise the images in Figures Q, R, and S to more clearly depict all of the processes that occur during dose administration. For example, in the image in Figure R, revise the text to state “during injection” and add an indication that the plunger is moving towards the base. Consider adding an additional Figure after current Figure R that depicts the plunger has reached the base and that the user still needs to hold for 5 more seconds.

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
		down for 5 seconds after hearing the click”.	
7.	Step 6.1 “Remove the needle cap” could be improved to instruct users “Do not insert your fingers into the opening of the safety guard”.	The URRRA indicates if a user omits or does not perform the task associated with the KBA “what should you not do when using the pre-filled pen?” correctly there is risk of needle stick injury or expired/degraded drug product. The AI HF validation study results identified subjective feedback that indicated the participants did not notice the relevant information in the IFU.	Revise Section 6.1 to include the instructions “Do not insert your fingers into the opening of the safety guard”.
8.	The header of Step 7 “Throw away your pre-filled pens” does not sufficiently indicate the proper disposal method.	The URRRA indicates if a user omits or does not perform the task associated with “discard the autoinjector into a sharps container” correctly there is risk of third parties being injured or contaminated.	Revise the header of Step 7 to read “Dispose of your pre-filled pens”. Additionally, revise the phrase “throw away” to “dispose of” in instances where proper disposal consists of using a sharps container (e.g., sub-steps 1.2, 3.1, and 3.2).

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
		The AI HF validation study results identified subjective feedback that indicated participants misinterpreted the phrase “throw away” which led them to discard their prefilled pens in the regular trash instead of the sharps container.	
9.	Step 8 “Record your injection” does not clearly indicate what users need to record. (b) (4)	The URRA indicates if a user omits or does not perform the task associated with “record injection” correctly there is risk of limited overdosing or inadequate injection technique (lack of injection site rotation). The AI HF validation study results identified subjective feedback that indicated participants misinterpreted the step 8 heading and overlooked/misinterpreted the text in step 8.1.	Revise step 8 to more clearly indicate what users need to record. For example, revise the heading of Step 8 to read “Document your injection site and date administered”; Revise step 8.1 from “To help you remember when and where to give your next injection, keep a record of the dates and injection sites used for your injections.” to “To help you remember when and where on your body to give your next injection, keep a record of the dates and injection sites used for your injections.”; Revise the image in Figure V to include the language “Date of Administration:” and “Injection Site:” and consider including

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
			example date(s) and site(s) for users to reference.
10.	The layout of the IFU does not sufficiently group similar sub-steps.	The URRA indicates if a user omits or does not perform the task associated with “set autoinjector on a flat clean surface and allows it to acclimate to room temperature” correctly there is risk of chronic underdosing or administration of expired/degraded drug. The AI HF validation study results identified subjective feedback that indicated some participants did not see steps 1.5-1.7 because they were on a different pane not associated with the header “Step 1 Prepare for your injection”.	Revise your IFU to ensure all sub-steps are visibly associable with their step heading.
Inner Part of the Outer Packaging of the AI Starter Packs			
1.	As currently presented, the four AI starter pack contains two trays each containing two AIs.	Subjective feedback from the validation study indicated that one participant associated a tray of two AIs as one dose.	Consider revising the four AI starter pack so that the AI for doses two and three are in separate trays underneath the first dose (i.e.,

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
			consider packaging the bottom two AIs in their own separate trays).
2.	The inner packaging layout of the four-AI starter pack carton labeling is ambiguous about when the third treatment day occurs.	The URRRA indicates if a user omits or does not perform the task associated with “states the correct date of third treatment day” correctly there is risk of users taking the next dose too soon, too late, or not at all. The AI Starter Pack HF validation study results identified subjective feedback that indicated participants thought the third treatment day would occur 2 weeks after the first treatment day instead of 2 weeks after the second treatment day.	Revise the inner packaging layout of the four-AI starter pack carton labeling so that it more clearly defines that the third treatment day occurs two weeks after the second treatment day. For example, revise the statement “2 weeks later” to read “2 weeks after the second treatment day”. To maintain consistency, revise the statement “1 week later” to read “1 week after the first treatment day”.

(b) (4)

6 CONCLUSIONS AND RECOMMENDATIONS

The results of the HF validation studies demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm to the patient. However, Fresenius Kabi proposed revisions to the product user interface to further mitigate the risk for use errors. We found Fresenius Kabi's proposed changes to the user interface to be reasonable and identified additional risk mitigations. Additionally, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table A for Fresenius Kabi. We ask that the Division of Rheumatology and Transplant Medicine (DRTM) convey Table A in its entirety to Fresenius Kabi so that recommendations are implemented. We have determined that in this particular case, we do not need to review additional HF validation study data to support these changes.

6.1 RECOMMENDATIONS FOR THE DIVISION OF RHEUMATOLOGY AND TRANSPLANT MEDICINE

(b) (4)

6.2 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC.

Our evaluation of your human factors (HF) validation studies indicates that there are additional mitigations that can be implemented to address use errors that occurred with critical tasks. We provide recommendations in Table A, and we recommend that you implement these recommendations and submit the revised label and labeling for our review.

(b) (4)

^k Guidance for Industry (April 2016). *Safety Considerations for Product Design to Minimize Medication Errors*. Available from: <https://www.fda.gov/media/84903/download>.



APPENDICIES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 8 presents relevant product information for MSB11022 that Fresenius Kabi USA, LLC submitted on December 13, 2021.

Table 8. Relevant Product Information							
Initial Approval Date	N/A						
Therapeutic Drug Class or New Drug Class	Tumor necrosis factor (TNF) blocker						
Nonproprietary Name	adalimumab-xxxx						
Indication	Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) in patients ≥2 years of age, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn’s Disease (CD) in adults and pediatric patients ≥6 years of age, Adult Ulcerative Colitis (UC), Plaque Psoriasis (Ps), and Hidradenitis Suppurativa (HS)						
Route of Administration	Subcutaneous						
Dosage Form	Injection						
Strength	40 mg/0.8 mL						
Dose and Frequency	Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis: 40 mg every other week. - Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week or 80 mg every other week. Juvenile Idiopathic Arthritis: <table border="1"> <thead> <tr> <th>Pediatric Weight (2 Years of Age and Older)</th> <th>Recommended Dosage</th> </tr> </thead> <tbody> <tr> <td></td> <td>(b) (4)</td> </tr> <tr> <td>30 kg (66 lbs) and greater</td> <td>40 mg every other week</td> </tr> </tbody> </table> Adult Crohn's Disease and Ulcerative Colitis: - Initial dose (Day 1): 160 mg (b) (4)	Pediatric Weight (2 Years of Age and Older)	Recommended Dosage		(b) (4)	30 kg (66 lbs) and greater	40 mg every other week
Pediatric Weight (2 Years of Age and Older)	Recommended Dosage						
	(b) (4)						
30 kg (66 lbs) and greater	40 mg every other week						

(b) (4)

Pediatric Patients 6 Years of Age and Older Crohn's Disease:

Pediatric Weight	Recommended Dosage	
	Days 1 through 15	Starting on Day 29
40 kg (88 lbs) and greater	Day 1: 160 mg Day 15: 80 mg	40 mg every other week

(b) (4)

Plaque Psoriasis:

- 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.

(b) (4)

How Supplied

40 mg/0.8 mL in a single-dose prefilled AI (MSB 11022)

(b) (4)

- AI Carton - 40 mg/0.8 mL 2 pack

(b) (4)

- AI Carton - 40 mg/0.8 mL Starter Pack for Plaque Psoriasis 4 pack
- AI Carton - 40 mg/0.8 mL Starter Pack for Crohn's Disease, Ulcerative Colitis (b) (4) 6 pack

40 mg/0.8 mL in a single-dose PFS

(b) (4)

- PFS Carton - 40 mg/0.8 mL 2 pack

(b) (4)

Storage	MSB11022 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. May be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 28 days.
Container Closure/Device Constituent	• single-dose PFS • single-dose AI (b) (4)
Intended Users	Patients (adults and children), caregivers, and healthcare providers
Intended Use Environment	Home, other non-clinical or clinical setting

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On April 9, 2021, we searched the L: drive and AIMS using the terms, MSB11022, Idacio, BLA 761255 and IND 124098 to identify reviews previously performed by DMEPA.

B.1.2 Results

Our search identified three previous reviews^{c,d,l}, and we considered our previous recommendations to see if they are applicable for this current review. We determined several of our previous recommendations were relevant to this review and we discussed these recommendations above.

B.2 PREVIOUS FDA/SPONSOR INTERACTIONS PERTAINING TO HF

The Agency provided human factors guidance to Fresenius Kabi in three meetings:

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af803c6103&_afRedirect=2211836551469253

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804aeeaf&_afRedirect=2216071878987793

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8062591f&_afRedirect=2214943312292717

^l Mena-Grillasca C. Human Factors and Labeling Review for MSB11022 (IND 124098). Silver Spring (MD): FDA, CDER, OSE, DMEPA; 2016 MAR 17. RCM No.: 2016-715.

APPENDIX C. BACKGROUND INFORMATION OF HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in the HF results report. See Appendix D.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

D.1 PFS

The HF Risk Management Report for MSB11022 PFS can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761255\0001\m3\32-body-data\32r-reg-info\medicaldevice\annexesformedicaldevice\annex-r-2-27.pdf>

The HF Summary and Assessment Report for MSB11022 PFS can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761255\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronicplaquepsoriasis\5354-other-stud-rep\msb11022\pfs\summative-hfs-pfs.pdf>

The HF Threshold Analysis for MSB11022 PFS can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761255\0001\m3\32-body-data\32r-reg-info\medicaldevice\annexesformedicaldevice\annex-r-2-28.pdf>

D.2 AI

The HF Risk Management Report for MSB11022 AI can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761255\0001\m3\32-body-data\32r-reg-info\medicaldevice\annexesformedicaldevice\annex-r-2-36.pdf>

The HF Summary and Assessment Report for MSB11022 AI can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761255\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronicplaquepsoriasis\5354-other-stud-rep\msb11022\autoinjector\summative-hfs-autoinjector.pdf>

The HF Usability Engineering Report for MSB11022 AI can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761255\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronicplaquepsoriasis\5354-other-stud-rep\msb11022\autoinjector\fsb-r-md-073-v01-human-factors-engineering-report-msb11022.pdf>

The HF URRR for MSB11022 AI starter pack can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761255\0022\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronicplaquepsoriasis\5354-other-stud-rep\msb11022\starterpack\fsb-r-md-017-02-starter-pack-use-related-risk-analysis.pdf>

The HF Threshold Analysis for MSB11022 AI starter pack can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761255\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronicplaquepsoriasis\5354-other-stud-rep\msb11022\starterpack\threshold-analysis-msb11022-starter-pack.pdf>

The HF Usability Engineering Report for MSB11022 AI starter pack can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761255\0022\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronicplaquepsoriasis\5354-other-stud-rep\msb11022\starterpack\fsb-r-md-039-01-hf-ue-report-for-starter-pack.pdf>



APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

E.1 On December 23, 2021, we issued an Information Request (IR) to clarify if Fresenius Kabi would be able to:

- update the user interfaces for their AI and PFS configurations as described in the HF validation studies
- conduct an additional human factors validation study for their AI presentation
- conduct a comparative analysis and justification for not submitting HF validation study data for their PFS configuration

Fresenius Kabi provided an acceptable response on January 3, 2022, that can be accessible in EDR via: <\\CDSESUB1\evsprod\bla761255\0002\m1\us\111-info-amend\response-to-hf-information-request.pdf>

E.2 On February 17, 2022, we issued an IR to:

- request Fresenius Kabi resubmit their MSB11022 Starter Pack HF Validation Test Protocol under IND 124098
- clarify if Fresenius Kabi had already conducted their MSB11022 Starter Pack HF Validation study or to obtain their planned timeline for completion of the study

(b) (4)

Fresenius Kabi provided an acceptable response on February 22, 2022, that can be accessible in EDR via: <\\CDSESUB1\evsprod\bla761255\0008\m1\us\111-info-amend\response-to-questions-ir7-device-hfs.pdf> and on May 23, 2022, that can be accessible in EDR via: <\\CDSESUB1\evsprod\bla761255\0022\m1\us\12-cover-letter\cover-letter.pdf>

E.3 On March 7, 2022, we issued an IR to request Fresenius Kabi provide clarifications to:

- how long it takes for the medication to be injected for the AI (e.g., from the moment the injection button is pressed until all medication passes from the prefilled pen into the patient)
- the average injection completion time for the lot of autoinjectors tested in the HF validation study (time required for the autoinjector to complete the delivery of the drug)
- the purpose of watching the syringe plunger reach the bottom of the transparent syringe housing for the AI (i.e., when the plunger reaches the bottom of the transparent syringe housing, is the injection considered complete?)
- justification for the instructions “Continue holding the pen for 5 seconds after the syringe plunger has reached the bottom of the transparent housing” in sub-step 6.3 of your Instructions for Use for MSB11022 40 mg/0.8 mL AI.
- Provide data on how long these [participants with use errors in the AI HF validation study] held the device in place at the injection site during the injection

(b) (4)

Fresenius Kabi provided an acceptable response on March 11, 2022, that can be accessible in EDR via: <\\CDSESUB1\evsprod\bla761255\0010\m1\us\111-info-amend\response-to-questions-ir8-device-hfs.pdf>

E.4 On March 23, 2022, we issued an IR requesting Fresenius Kabi submit:

- The version of the Autoinjector pack used during the HF Validation Study (if available)
- The current version of the Autoinjector pack
-  (b) (4)
- The version of the 4-count autoinjector starter kit used in the HF validation study (at the time of the HF validation study report submission)
- The version of the 6-count autoinjector starter kit used in the HF validation study (at the time of the HF validation study report submission)
- The updated version of the 4-count autoinjector starter kit (at the time of the HF validation study report submission)
- The updated version of the 6-count autoinjector starter kit (at the time of the HF validation study report submission)

On March 25, we requested (via email) Fresenius Kabi submit pdfs for the AI  (b) (4) IFU that display the unfolded layout (front and back, if applicable) of the IFU as it would be used by the end user.

Fresenius Kabi provided an acceptable response on March 11, 2022, that can be accessible in EDR via: <\\CDSESUB1\evsprod\bla761255\0011\m1\us\12-cover-letter\cover-letter.pdf>, and on May 17, 2022, that can be accessible in EDR via: <\\CDSESUB1\evsprod\bla761255\0017\m1\us\12-cover-letter\cover-letter.pdf>

E.5 On May 3, 2022, we issued an IR requesting Fresenius Kabi submit the referenced document “MRS-AAI_S2_final_report_20191212”

Fresenius Kabi provided an acceptable response on May 5, 2022, that can be accessible in EDR via: <\\CDSESUB1\evsprod\bla761255\0016\m1\us\12-cover-letter\cover-letter.pdf>

E.6 On May 17, 2022, we issued an IR requesting Fresenius Kabi submit:

- The referenced document “MRS-AAI_S2_Description-of-Use-Events_20191205” and any related documents which describe the essential task use events that were observed during each of the simulated autoinjector injections.

Fresenius Kabi provided an acceptable response on May 18, 2022, that can be accessible in EDR via: <\\CDSESUB1\evsprod\bla761255\0019\m1\us\111-info-amend\responses-to-questions-ir17-received-on-17-may-2022.pdf>

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis^m, along with postmarket medication error data, we reviewed the following MSB11022 labels and labeling submitted by Fresenius Kabi USA, LLC. on December 13, 2021.

- Container labels
- Carton labeling
- Instructions for Use (Image not shown) for the PFS available from:
[\\CDSESUB1\evsprod\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-pfs^{\(b\) \(4\)}.pdf](\\CDSESUB1\evsprod\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-pfs^{(b) (4)}.pdf)
- Instructions for Use (Image not shown) for the AI available from:
<\\CDSESUB1\evsprod\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-ai.pdf>
- Instructions for Use (Image not shown) for the AI starter packs available from:
<\\CDSESUB1\evsprod\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-starter-pack.pdf>
-  (b) (4)
- Medication Guide (Image not shown) available from:
<\\CDSESUB1\evsprod\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide.pdf>
- Prescribing Information (Image not shown) available from:
<\\CDSESUB1\evsprod\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide.pdf>

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

^m Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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JASON A FLINT
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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: September 29, 2022
Requesting Office or Division: Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number: BLA 761255
Product Name and Strength: Idacio (adalimumab-aacf)^a
Injection, (b) (4)

Product Type: Combination Product (Biologic-Device)
Rx or OTC: Prescription (Rx)
Applicant/Sponsor Name: Fresenius Kabi USA, LLC
FDA Received Date: December 13, 2021, March 4, 2022, May 23, 2022, and
August 16, 2022
OSE RCM #: 2021-2397
DMEPA 1 Safety Evaluator: Teresa McMillan, PharmD
DMEPA 1 Team Leader: Idalia Rychlik, PharmD

^a The proposed nonproprietary name, "adalimumab-aacf", was found conditionally acceptable on September 19, 2022. We therefore refer to the proposed product as "adalimumab-aacf" throughout this review in place of the nonproprietary name for this product.

1 REASON FOR REVIEW

As part of the approval process for Idacio (adalimumab-aacf) Injection, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed Idacio prescribing information (PI), medication guide (MG), Instructions for Use (IFU), carton labeling, and container label for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D -N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed IFU, carton labeling and container labels may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Fresenius Kabi USA, LLC. Note that DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming."

4 RECOMMENDATIONS FOR DIVISION OF RHEUMATOLOGY AND TRANSPLANT MEDICINE (DRTM)

Table 2. Identified Issues and Recommendations for Division of Rheumatology and Transplant Medicine (DRTM)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Instructions for Use (prefilled syringe)			
1.	Step 6.4 (Insert the needle) and/or Figure S does not have a diagram that depicts the following: Using a quick dart-like motion, insert the needle into the squeezed skin at a 45-degree to 90-degree angle (Figure S).	Lack of a diagram that accurately illustrates Step 6.4 (Insert the needle) and/or Figure S may lead to confusion and the end-user's inability to adequately insert the needle.	Add a figure which accurately depicts Step 6.4 Insert the needle. Using a quick dart-like motion, insert the needle into the squeezed skin at a 45-degree to 90-degree angle

5 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC

Table 3. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date 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

Table 3. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			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.	As currently presented, there is no distinction between the various carton presentations.	A lack of differentiation between the PFS , AI, starter packs (b) (4) cartons may lead to dispensing errors.	Utilize different color font, color blocking and/or boxing to increase the difference between the cartons supplying 1, 2, 4 and 6 of the AI and PFS, starter packs, (b) (4) presentation.
3.	The overuse of (b) (4) font throughout all labels and labeling decreases the readability and prominence of important information, such as strength. and	Difficulty in reading the strength may lead to wrong dose errors.	Utilize a different color font in the strength text and/or color blocking to bring additional prominence to the strength.
Container Label(s)			
(b) (4)			

Table 3. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The Rx Only statement has been omitted.	Missing important information such as the Rx Only statement may lead to confusion.	If space permits, place the Rx Only statement on the container label.
3.	The NDC number is not prominently located.	The NDC number may be overlooked due to lack of prominence.	Place the NDC number in the upper top area of the principal display panel to increase prominence of its location.
4.	The barcode has been omitted.	Missing important information such as the barcode may lead to the inability to accurately verify the intended drug.	Place a scannable barcode on all individual container labels. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual container label as required per 21CFR 201.25(c)(2). The barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).
5.	The route of administration (ROA) has been omitted.	Omitting important information such as the route of administration may lead to wrong route errors.	As space permits, add the route of administration to the principal display panel of all container labels. Consider reformatting the labels to make room for the ROA, for example relocating the NDC to the upper corners of the PDP

Table 3. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			and decreasing the font size of the manufacturer info and License number.
Carton Labeling			
1.	(b) (4)		
2.	The dosage form statement is missing from the principal display panel.	Missing important dosage form information may lead to confusion.	Place the dosage form statement, "Injection" directly beneath the proper name and place the proper name in parenthesis.
3.	The recommended dosage statement is inconsistent with the Prescribing Information.	Inconsistency with the prescribing information may lead to dosing and administration medication errors.	To ensure consistency with the Prescribing Information, Revise "Dosage and Administration: See Package Insert, to read "Recommended Dosage: See Prescribing Information."
4.	(b) (4)		

Note that additional label and labeling comments may be forthcoming when we have completed our evaluation of your human factors validation study results.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Error! Reference source not found. presents relevant product information for Idacio that Fresenius Kabi USA, LLC submitted on March 4, 2022.

Table 4. Relevant Product Information for Idacio	
Initial Approval Date	N/A
Active Ingredient	Adalimumab-aacf
Indication	• 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 2 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. • Crohn’s Disease (CD) : treatment of moderately to severely active Crohn’s disease in adults and pediatric patients 6 years of age and older. • Ulcerative Colitis (UC): treatment of moderately to severely active ulcerative colitis in adults. <u>Limitations of Use:</u> Effectiveness has not been established in patients who have lost response to or were intolerant to TNF blockers. • Plaque Psoriasis (Ps): 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.
Route of Administration	Subcutaneous
Dosage Form	Injection

(b) (4)

Strength	40 mg/0.8 mL
Dose and Frequency	Ulcerative Colitis : • 160 mg on Day 1 (given in one day or split over two consecutive days), 80 mg on Day 15 and 40 mg every other week starting on Day 29. Discontinue in patients without evidence of clinical remission by eight weeks (Day 57). Plaque Psoriasis: • 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose. (b) (4)
How Supplied	preservative-free, sterile, clear, and colorless solution for subcutaneous administration. The following packaging configurations are available (b) (4) • IDACIO Pen Carton - 40 mg/0.8 mL (2 count) IDACIO is supplied in a carton containing 2 alcohol preps and one tray. The tray contains two single-dose pens, each containing a 1 mL prefilled glass syringe with a 29 gauge staked ½ inch needle, providing 40 mg/0.8 mL of IDACIO. The syringe plunger stopper and needle cover are not made with natural rubber latex. The NDC number is xxx (b) (4)

- IDACIO Pen 40 mg/0.8 mL - Starter Package for Plaque Psoriasis

IDACIO is supplied in a carton containing 4 alcohol preps and 2 trays (Starter Package for Plaque Psoriasis). Each tray contains two single-dose pens, each pen containing a 1 mL prefilled glass syringe with a 29 gauge staked ½ inch needle, providing 40 mg/0.8 mL of IDACIO. The syringe plunger stopper and needle cover are not made with natural rubber latex. The NDC number is xxx

- IDACIO Pen 40 mg/0.8 mL - Starter Package for Crohn's Disease, Ulcerative Colitis (b) (4)

IDACIO is supplied in a carton containing 6 alcohol preps and 3 trays (Starter Package for Crohn's Disease, Ulcerative Colitis (b) (4)). Each tray contains two single-dose pens, each pen containing a 1 mL prefilled glass syringe with a 29 gauge staked ½ inch needle, providing 40 mg/0.8 mL of IDACIO. The syringe plunger stopper and needle cover are not made with natural rubber latex. The NDC number is xxx.

	• IDACIO Prefilled Syringe Carton - 40 mg/0.8 mL (2 count) IDACIO is supplied in a carton containing 2 alcohol preps and one tray. The tray contains a single-dose, 1 mL prefilled glass syringe with a 29 gauge staked ½ inch needle, providing 40 mg/0.8 mL of IDACIO. The syringe plunger stopper and needle cover are not made with natural rubber latex. The NDC number is xxx.
Storage	Do not use beyond the expiration date on the container. IDACIO 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, IDACIO may be stored at room temperature up to a maximum of 77°F

(b) (4)

	(25°C) for a period of up to 28 days, with protection from light. IDACIO should be discarded if not used within the 28-day period. Record the date when IDACIO is first removed from the refrigerator in the spaces provided on the carton. Do not store IDACIO in extreme heat or cold.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 27, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Idacio. Our search did not identify any previous reviews.

APPENDIX C. ISMP NEWSLETTERS-N/A

APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)-N/A

APPENDIX E. N/A

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Idacio labels and labeling submitted by Fresenius Kabi USA, LLC.

- Container label(s) received on December 13, 2022 and May 23, 2022
- Carton labeling received on December 13, 2022 and May 23, 2022
- Instructions for Use (prefilled syringe) received on August 16, 2022, available from [\\CDSESUB1\EVSPROD\bla761255\0031\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-pfs-^{\(b\)}_{\(4\)}.docx](#)
- Instructions for Use (prefilled pen or autoinjector) received on December 13, 2022, available from [\\CDSESUB1\EVSPROD\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-ai.docx](#)

(b) (4)

- Instructions for Use (starter pack) received on May 23, 2022, available from [\\CDSESUB1\EVSPROD\bla761255\0022\m1\us\114-labeling\114a-draft-label\draft-starter-pack-ifu-word-version.docx](#)
- [Prescribing Information and Medication Guide \(Image not shown\) received on March 4, 2022, available from \\CDSESUB1\EVSPROD\bla761255\0009\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide.docx](#)

F.2 Label and Labeling Images

Container label(s)

Prefilled Syringe

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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HUMAN FACTORS STUDY REPORT REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	September 13, 2022
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761255
Drug Constituent Name and Strength	Idacio [MSB11022] ^a (adalimumab-xxxx) ^b Injection, 40 mg/0.8 mL
Product Type:	Combination Product (Biologic-Device)
Device Constituents:	Autoinjector (AI); (b) (4)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fresenius Kabi USA, LLC. (Fresenius Kabi)
FDA Received Date:	December 13, 2021; January 3, 2022; February 22, 2022; March 11, 2022; March 25, 2022; May 5, 2022; May 17, 2022; May 18, 2022; May 23, 2022
OSE RCM #:	2021-2398
DMEPA 1 Human Factors Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader (Acting):	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

^a MSB11022 has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). The proprietary name for this BLA, Idacio, was found conditionally acceptable on March 7, 2022. Idacio is referred to as MSB11022 throughout this review.

^b The nonproprietary name suffix for this BLA has not yet been determined, therefore, the placeholder "adalimumab-xxxx" is used throughout this review to refer to the non-proprietary name for this product and is not intended to be included in the final labels and labeling.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study reports submitted under BLA 761255 for MSB11022 (adalimumab-xxxx) 40 mg/0.8 mL Autoinjector (AI), four- and six- AI starter packs, (b) (4)

1.1 PRODUCT DESCRIPTION

MSB11022 is a proposed biosimilar to US-licensed Humira (adalimumab). MSB11022 is a tumor necrosis factor (TNF) blocker that is intended to treat Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) in patients ≥ 2 years of age, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease (CD) in adults and pediatric patients ≥ 6 years of age, adult Ulcerative Colitis (UC), Plaque Psoriasis (Ps), and Hidradenitis Suppurativa (HS). MSB11022 will be supplied (b) (4)

- a single-dose prefilled syringe (PFS)
- a single-dose prefilled autoinjector (AI)

(b) (4)

Each MSB11022 40 mg/0.8 mL PFS and AI will be supplied in one-count, two-count, four-count, and six-count cartons. The MSB11022 40 mg/0.8 mL AI will also be supplied in a four-count starter pack for Psoriasis and in a six-count starter pack for Crohn's Disease, Ulcerative Colitis,

(b) (4)

or additional product information, see Table 8 in [Appendix A](#).

(b) (4)

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

- On January 23, 2019, Fresenius Kabi submitted human factors (HF) validation study protocols for their proposed MSB11022 40 mg/0.8 mL PFS (b) (4) under IND 124098.
- On January 24, 2019, Fresenius Kabi submitted a human factors (HF) validation study protocol for their proposed MSB11022 40 mg/0.8 mL AI under IND 124098.
- On March 22, 2019, we provided HF validation study protocol recommendations for (b) (4) proposed configurations. Additionally, we recommended the Sponsor submit a

use-related risk analysis (URRA) and threshold analysis for the MSB11022 40 mg/0.8 mL PFS as HF validation study results for the PFS configuration may not need to be submitted for review.^c

- On May 28, 2019, Fresenius Kabi submitted a threshold analysis and URRA for the PFS configuration.
- On September 5, 2019, we determined that results of a HF validation study for the PFS configuration were not required to be submitted for Agency review as part of the marketing application.^d
- On December 13, 2021, Fresenius Kabi submitted MSB11022 AI Starter Pack HF Validation Test Protocol and AI and PFS HF summary reports, assessment reports, and risk management reports to support the 351(k) BLA for MSB11022 40 mg/0.8 mL as a biosimilar to US-licensed Humira 40 mg/0.8 mL (BLA 125057).
- On December 23, 2021, we issued an information request (IR) to clarify if Fresenius Kabi would be able to conduct an additional HF validation study for their AI configuration.^e
- On January 3, 2022, Fresenius Kabi responded to our IR dated December 23, 2021, stating they wrongly submitted the report of a HF validation study that was conducted for the European Marketing Authorization Application, and they resubmitted the correct AI HF validation study results report intended to support the US BLA submission which is the subject of this review.^f
- On February 17, 2022, we issued another IR requesting Fresenius Kabi resubmit their MSB11022 Starter Pack HF Validation Test Protocol under IND 124098 and clarify if they had already conducted the study or provide their planned timeline for completion of the study. (b) (4)
- On February 22, 2022, Fresenius Kabi responded to our IR dated February 17, 2022, stating their human factors validation study has been initiated and is ongoing to demonstrate safe and effective use of the starter packs. Fresenius Kabi conveyed their plan to submit the study results report in May 2022. (b) (4)

^c Barlow M. Human Factors Validation Study Protocol Review for MSB11022 (IND 124098). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 22. RCM No.: 2019-177, 2019-178, and 2019-179.

^d Barlow M. Threshold Analysis and Use-Related Risk Analysis Review for MSB11022 (IND 124098). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 5. RCM No.: 2019-1209.

^e Rashid N. FDA Communication: Human Factors Information Request – BLA 761255 – MSB11022. Silver Spring (MD): FDA, CDER, OSE. 2021 DEC 23. BLA 761255.

^f Response to HF Information Request for MSB11022 (BLA 761255). Lake Zurich (IL): Fresenius Kabi, USA, LLC. 2022 JAN 3. Available from: <\\CDSESUB1\evsprod\bla761255\0002\m1\us\111-info-amend\response-to-hf-information-request.pdf>

(b) (4)

- On May 23, 2022, Fresenius Kabi submitted their four- and six-count AI starter packs HF validation study results report, which is also the subject of this review.¹

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

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
Labels and Labeling	F

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design; use errors, close calls, and use difficulties observed; and our analysis to determine if the results indicate that the user interface has been optimized to support the safe and effective use of the proposed product as a biosimilar to US-licensed Humira 40 mg/0.8 mL AI, AI starter pack, (b) (4)

3 SUMMARY OF HUMAN FACTORS VALIDATION STUDY METHODOLOGY

3.1 SUMMARY OF AUTOINJECTOR HUMAN FACTORS VALIDATION STUDY METHODOLOGY

Table 2 presents a summary of the HF validation study design.

¹ Submission of Starter Pack Human Factors Validation Report for MSB11022 (BLA 761255). Lake Zurich (IL): Fresenius Kabi, USA, LLC. 2022 May 23. Available from: <\\CDSESUB1\evsprod\bla761255\0022\m1\us\12-cover-letter\cover-letter.pdf>

Table 2. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details			
Participants	User Groups	Number of Users		
		Injection Experienced	Injection Naïve	Total
	Trained Adult Patients	10	5	15
	Trained Caregivers	10	5	15
	Untrained Adult Patients	6	9	15
	Untrained Caregivers	10	5	15
	Untrained Adolescent Patients	13	2	15
	Untrained Healthcare Professionals (HCPs)	15	n/a	15
	Total	64	26	90
Training	<u>Trained Participants:</u> The trained participants received a 45-minute training session a week prior to the 1-hour testing session. The training included a brief description of the function of the device and a hands-on demonstration of use, including review of the instructions for use (IFU) and answering user questions about the device. <u>Untrained Participants:</u> The untrained participants did not receive any training prior to completing the 1-hour testing session.			
Test Environment	Simulated the intended use environment for each user group.			

Table 2. Study Methodology for Human Factors (HF) Validation Study	
	
Sequence of Study	1. Session Introduction – review and signage of the informed consent document 2. Background Questions and Administration of RAPID3 Questionnaire 3. Explanation of Overall Testing Procedure 4. For those <u>undergoing training</u>, 45-minute training session followed by a week decay period prior to study participation <u>Three Test Phases</u> 5. Test Phase 1 – Simulated Injection with IFU optional 6. Root Cause Analysis and Debrief for Test Phase 1 7. Test Phase 2 – Simulated Injection with IFU required 8. Root Cause Analysis and Debrief for Test Phase 2 9. Test Phase 3 – IFU Comprehension 10. Root Cause Analysis and Debrief for Test Phase 3

3.2 SUMMARY OF AUTOINJECTOR STARTER PACK HUMAN FACTORS VALIDATION STUDY METHODOLOGY

Table 3 presents a summary of the HF validation study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details

Table 3. Study Methodology for Human Factors (HF) Validation Study

Participants	User Groups	Number of Users*
	Adult patients with one of the indicated conditions	15
	Caregivers who provide care for patients with one of the indicated conditions	15
	HCPs (licensed pharmacists who dispense medication for patients with one of the indicated conditions or nurses who have experience training patients with one of the indicated conditions on how to administer injections)	15
	Adolescents with either hidradenitis suppurativa or Crohn’s disease	15
	Total	60
	* Participants were randomly assigned to the four AI starter pack or the six AI starter pack, such that at the end of the study about half of all users within each intended user group will have used the four AI starter pack or the six AI starter pack during the evaluation activities.	
Training	No training	
Test Environment	Room represented basic characteristics of the intended use environment (clinical offices, home environment). The room was equipped with all materials required to facilitate the hands-on use scenarios. The average lighting level at table level was in the range of 400-750 Lux. The test room was representative of the intended use environments. The room was relatively quiet, comparable to a library reading room. The average sound at desktop level was about 45 dB (the sound pressure level in a quiet room). Test personnel introduced one distraction (sound of a phone ringing for a couple of seconds) when the participant performed use scenario 2.	
Sequence of Study	Scenario 1: Retrieve starter pack and prepare for first day of treatment Scenario 2: Prepare for second day of treatment Scenario 3: Prepare for third day of treatment (four pack only)	

(b) (4)

4 RESULTS AND ANALYSES

4.1 SUMMARY OF AUTOINJECTOR HUMAN FACTORS VALIDATION STUDY RESULTS

Table 5 describes the AI study results, Fresenius Kabi’s analyses of the results, and DMEPA 1’s analyses and recommendations. Section 4.2 describes use errors, close calls and use difficulties with non-critical tasks associated with the use of the AI in the HF validation study.

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

Please note the following:

Test Phases:

- Test Phase 1 – Simulated Injection with IFU optional
- Test Phase 2 – Simulated Injection with IFU required
- Test Phase 3 – IFU Comprehension

Participant ID Acronyms:

- A##T – trained adult patient
- C##T – trained caregiver
- A##UT – untrained adult patient
- C##UT – untrained caregiver
- T##UT – untrained adolescent patient
- H##UT – untrained HCP

	Identified Issue and Rationale for Concern	DMEPA’s Analysis and Findings						
1.	For the “collect necessary supplies to prepare the injection site (alcohol pads included in the box)” task, see the table and list below for a summary of participant performance. <table border="1"> <thead> <tr> <th>Total number of use errors (UE), close calls (CC), and use difficulties (UD)</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UD (n=1)</td> <td>AUT = 1</td> <td>1</td> </tr> </tbody> </table>	Total number of use errors (UE), close calls (CC), and use difficulties (UD)	Type of Participants	Test Phase	UD (n=1)	AUT = 1	1	Our review of the study results identified subjective feedback that indicated a participant misunderstood the IFU instructions and images and thought the instructions were telling him to get cotton balls from the refrigerator.
Total number of use errors (UE), close calls (CC), and use difficulties (UD)	Type of Participants	Test Phase						
UD (n=1)	AUT = 1	1						

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: - Unclear IFU image grouping (1) – one participant stated he was using the instructions and thought the instructions were telling him to get cotton balls from the refrigerator. Based on the URRRA, if this task is omitted or not performed correctly there is risk of non-sterile injection technique. Fresenius Kabi proposed the following mitigation strategy in response to participant performance for this task: - Increase the IFU font size to 10 pt. bold of all sub-step numbers (e.g., 1.1, 1.2 ... 8.1)	(b) (4) We acknowledge Fresenius Kabi’s proposed mitigation strategy, and our review of the revised labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.						
2.	For the “set autoinjector on a flat clean surface and allows it to acclimate to room temperature” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 1101 1329 1338"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=22)</td> <td>AUT = 5 CT = 1 CUT = 2 HUT = 7 TUT = 7</td> <td>1</td> </tr> </tbody> </table>	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=22)	AUT = 5 CT = 1 CUT = 2 HUT = 7 TUT = 7	1	Our review of the study results identified subjective feedback that indicated participants thought the first part of IFU step 1.7 lacked salience compared with the information around it (i.e., the bolding in step 1.6 and the next two points under step 1.7). Additionally, participants overlooked these steps since they were separate from the header “Step 1 Prepare for your injection.”
Total number of UE, CC, and UD	Type of Participants	Test Phase						
UE (n=22)	AUT = 5 CT = 1 CUT = 2 HUT = 7 TUT = 7	1						

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

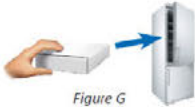
UE (n=4)	AUT = 1 CUT = 2 HUT = 1	2	Subjective feedback also indicated that other participants incorrectly thought the IFU step 1.6 Figure G and step 1.7 Figure H collectively indicated to store their AI in the refrigerator for 30 minutes prior to use. Additionally, other participants stated that the monochromatic appearance of Figure H caused it to be overlooked and that Figure H did not clearly indicate what they were supposed to do for “30 minutes”. We acknowledge Fresenius Kabi’s proposed mitigation strategy, however, the image in Figure H is monochromatic, difficult to read, and does not clearly explain why users need to “wait for 30 minutes”. Based on our overall assessment we find that the user interface can be improved to further mitigate risk of failure to set the autoinjector on a flat clean surface and allow it to acclimate to room temperature. We provide recommendations in the Identified Issues and Recommendations Table to address these concerns. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.
Participant performance includes: - Not allowing the medication to reach room temperature before use Fresenius Kabi provided the following RCA and supportive evidence: - Unclear IFU (Figure G and Figure H) (10) – some participants interpreted Figures G and H as saying that the prefilled pens needed to be put into the refrigerator for 30 minutes because of the pictures’ proximity to each other. Additionally, some participants missed Figure H due to the monochromatic color scheme (i.e., black and white) on the white background and the words “30 minutes” did not indicate participants were supposed to allow the AI to warm to room temperature for 30 minutes prior to use. One participant stated the image in Figure H was too small and she missed it. 1.6 Return the remaining pen in its original carton to the refrigerator (Figure G). See “Storing Idacio pre-filled pens” for information on how to store your unused pen  1.7 Let the Idacio pre-filled pen sit at room temperature for (b) (4) 30 minutes before use to allow the medicine to reach room temperature (Figure H). Do not warm the pen in any other way, such as in a microwave, hot water, or direct sunlight. Do not remove the needle cap until you are ready to inject. - Negative transfer (12) – relied on previous injection experience and did not read the IFU when performing this task. - Insufficient salience of IFU text for step 1.7 (9) – participants did not read the instruction because it did not contain bolded information. 			

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	- IFU design (steps 1.5-1.7) (2) – participants did not see these step(s) because they were on a different pane not associated with the header “Step 1 Prepare for your injection”. Based on the URRRA, if this task is omitted or not performed correctly there is risk of chronic underdosing or administration of expired/degraded drug. Fresenius Kabi proposed the following mitigation strategy in response to participant performance for this task: - Change the directive information in Figure H from “30 minutes” to “wait 30 minutes”.										
3.	For the “clean hands” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 748 1329 948"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=3)</td> <td>AUT = 1 CUT = 1 TUT = 1</td> <td>1</td> </tr> <tr> <td>UE (n=1)</td> <td>TUT = 1</td> <td>2</td> </tr> </tbody> </table> Participant performance includes: - Not washing their hands prior to handling the autoinjector - Wearing gloves instead of washing hands prior to handling the autoinjector Fresenius Kabi provided the following RCA and supportive evidence: - Negative transfer (3) – relied on previous AI use experience when performing this task; wore gloves instead of washing hands.	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=3)	AUT = 1 CUT = 1 TUT = 1	1	UE (n=1)	TUT = 1	2	Our review of the study results identified subjective feedback that indicated the majority of these use errors were due to negative transfer and test artifact. We acknowledge Fresenius Kabi’s proposed mitigation strategy, and our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
Total number of UE, CC, and UD	Type of Participants	Test Phase									
UE (n=3)	AUT = 1 CUT = 1 TUT = 1	1									
UE (n=1)	TUT = 1	2									

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	• Test artifact (2) – one participant was nervous about giving the injection since he had never given an injection; one participant stated since she was not actually letting the AI sit for 30 minutes (verbally stating she would let it sit) she washed her hands before instead of after. • Insufficient salience of IFU text for step 2.1 (1) – one participant stated he did not see the instructions in step 2.1. Based on the URRRA, if this task is omitted or not performed correctly there is risk of bacterial contamination and local infection. Fresenius Kabi proposed the following mitigation strategy in response to participant performance for this task: • Increase the font size to 10 pt. bold of all sub-steps numbers (e.g., 1.1, 1.2 ... 8.1)	(b) (4)						
4.	For the “check product name on the autoinjector” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 1024 1329 1260"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=11)</td> <td>AT = 1 AUT = 3 CUT = 3 HUT = 1 TUT = 3</td> <td>1</td> </tr> </tbody> </table> Participant performance includes: • Not checking product name on pen label before use	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=11)	AT = 1 AUT = 3 CUT = 3 HUT = 1 TUT = 3	1	Our review of the study results identified subjective feedback that indicated the majority of these use errors were due to negative transfer and test artifact. Our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task.
Total number of UE, CC, and UD	Type of Participants	Test Phase						
UE (n=11)	AT = 1 AUT = 3 CUT = 3 HUT = 1 TUT = 3	1						

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Fresenius Kabi provided the following RCA and supportive evidence: • Negative transfer (8) – relied on previous medication experience when performing this task; participants stated they often check the name of the carton when receiving it and not the actual product inside. • Test artifact (2) – in a testing environment; one participant stated she focused on how to administer the medication rather than how to prepare it because that is how she interpreted the study prompt. • Inconspicuous IFU figure (1) – one participant stated she was focused on the step headings and did not notice step 3.2 or Figure K because it was further from the step 3 heading than Figure J. • First time use (1) – one participant stated they were injection naïve, did not know they needed to check the label for the product name and did not read the IFU. Based on the URRRA, if this task is omitted or not performed correctly there is risk of erroneous drug administration. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.	We did not identify areas of improvement and have no recommendations at this time.						
5.	For the “check the autoinjector integrity” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 1260 1329 1377"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=3)</td> <td>AUT = 1 TUT = 2</td> <td>1</td> </tr> </tbody> </table>	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=3)	AUT = 1 TUT = 2	1	Our review of the study results identified subjective feedback that indicated the majority of these use errors were due to negative transfer.
Total number of UE, CC, and UD	Type of Participants	Test Phase						
UE (n=3)	AUT = 1 TUT = 2	1						

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

UE (n=1)	TUT = 1	2	
Participant performance includes: • Not checking the pen for damage before use Fresenius Kabi provided the following RCA and supportive evidence: • Negative transfer (2) – relied on previous medication experience when performing this task. • Insufficient IFU image (Figure J) (1) – one patient stated that the image in Figure J does not say what to check for. (b) (4) • Insufficient IFU step (step 3.1) (1) – one participant stated she expected to check the needle for damage, but she could not check the needle because it was not visible, and she did not check the device for damage because she did not know what a damaged device would look like. • First time use (1) – one participant stated they were injection naïve, did not know they needed to check the prefilled pen for damage and did not read the IFU. Based on the URRRA, if this task is omitted or not performed correctly there is risk of drug product coming in contact with skin or delayed treatment. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.			Our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
6.	For the “check the drug product integrity” task, see the table and list below for a summary of participant performance.		Our review of the study results identified subjective feedback that indicated the

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

Total number of use errors, close calls, and use difficulties	Type of Participants	Test Phase	
Use errors (n=7)	AUT = 1 CT = 1 CUT = 1 HUT = 1 TUT = 3	1	majority of these use errors were due to negative transfer. We acknowledge Fresenius Kabi’s proposed mitigation strategy, and our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
Participant performance includes: • Not checking the integrity of the liquid before use Fresenius Kabi provided the following RCA and supportive evidence: • Negative transfer (5) – relied on previous medication experience when performing this task. • Test artifact (1) – one participant stated she did not check because she was in a testing environment and typically relies on the hospital pharmacy to check the medication. • Insufficient IFU image (Figure J) (1) – one participant stated that the image in Figure J does not say what to check for. • IFU design/ambiguous step text/lack of visual salience of sub-steps (3.1 and 3.2) (1) – one participant stated she interpreted the word “check” in the step header to mean check the expiration date and she only read the header for step 3, not the sub-steps, because the header was colored and stood out more.			

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	• First time use (1) – one participant stated they were injection naïve, did not know they needed to check the medication and did not read the IFU. Based on the URRRA, if this task is omitted or not performed correctly there is risk of degraded drug being administered. Fresenius Kabi proposed one mitigation strategy in response to participant performance for this task: • Increase the font size to 10 pt. bold of all sub-step numbers (e.g., 1.1, 1.2 ... 8.1)													
7.	For the “select an injection site (must be different from the previous injection site)” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 789 1329 1183"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE(n=6)</td> <td>AUT = 4 CT = 1 CUT = 1</td> <td>1</td> </tr> <tr> <td>UE (n=12)</td> <td>AT= 1 AUT = 2 CUT = 2 HUT = 1 TUT = 6</td> <td>2</td> </tr> <tr> <td>CC (n=1)</td> <td>TUT = 1</td> <td>1</td> </tr> </tbody> </table> Participant performance includes: • No rotation of injection site • Selection of inappropriate injection site Fresenius Kabi provided the following RCA and supportive evidence:	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE(n=6)	AUT = 4 CT = 1 CUT = 1	1	UE (n=12)	AT= 1 AUT = 2 CUT = 2 HUT = 1 TUT = 6	2	CC (n=1)	TUT = 1	1	Our review of the study results identified subjective feedback that indicated the majority of these use errors were due to insufficient salience of the instructions for the first line of step 4.2 and the inconspicuous location of step 4.2 as it was located on a separate page away from the rest of step 4. Additionally, a few participants did not clearly understand the instructions to only inject into the front of the thigh or stomach area. We acknowledge Fresenius Kabi’s proposed mitigation strategy, however, our review of the labels and labeling (user interface, etc.) indicates that the wording of step 4.1 could be improved to better portray to only inject in the front of the thighs or stomach area. We provide recommendations in the
Total number of UE, CC, and UD	Type of Participants	Test Phase												
UE(n=6)	AUT = 4 CT = 1 CUT = 1	1												
UE (n=12)	AT= 1 AUT = 2 CUT = 2 HUT = 1 TUT = 6	2												
CC (n=1)	TUT = 1	1												

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

- Negative transfer (6) – relied on previous injection experience when performing this task. Participants often injected into the arm or forearm.
- Insufficient salience of instructions (5) – participants stated that the first line of step 4.2 is the only line in that step that does not include a bolded, “do not,” statement.
- IFU design (inconspicuous location for step 4.2) (5) – participants did not see step 4.2 because it was located at the top of the second page without a header.
- Ambiguous IFU (3) – one participant stated he interpreted the word “choose” in the header of step four meant he could choose his injection site; another participant stated she interpreted the text “the front of your thigh or stomach-area” to mean inject into a fatty area.
- Test artifact (2) – one participant stated he changed the injection site from his knee because the injection pad would not fit there.
- Insufficient training (1) – one participant stated she did not know she needed to change injection sites because she only used one autoinjector during training.
- Mental model (1) – one participant stated he expected to administer the medication where he was experiencing pain.

Step 4 Choose the injection site

- 4.1 Choose an injection site (Figure L). You can use:
- the front of your thighs or
 - your stomach-area. If you choose your stomach - area, do not use the area 2 inches around your belly button (navel). (See Figure L)



Only inject into injection sites shown (Figure L)

- 4.2 Choose a different site (at least one inch away from your last injection site) for each injection to reduce redness, irritation or other skin problems.
Do not inject into an area that is sore (tender), bruised, red, hard, scarred or where you have stretch marks or tattoos.
 If you have psoriasis, do not inject into any lesions or red, thick, raised or scaly patches.
Do not inject through your clothes.

Identified Issues and Recommendations Table to address this concern.

We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Based on the URRRA, if this task is omitted or not performed correctly there is risk of injection site reaction, too shallow injection might be performed, or the injection site might be contaminated. Fresenius Kabi proposed one mitigation strategy in response to participant performance for this task: The two sub-steps 4.1 and 4.2 are joined in the same page and the same column													
8.	For the “clean the skin at the selected injection site” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 630 1329 1024"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=9)</td> <td>AT = 2 AUT = 3 CT = 1 CUT = 1 HUT = 2</td> <td>1</td> </tr> <tr> <td>UE (n=5)</td> <td>AT= 2 AUT = 3</td> <td>2</td> </tr> <tr> <td>CC (n=2)</td> <td>AUT = 1 CT = 1</td> <td>2</td> </tr> </tbody> </table> Participant performance includes: - Not cleaning site before administering medication - Blowing on injection site after cleaning the site - Cleaning with a cotton ball instead of alcohol pad - Drying the injection site with a cotton ball after cleaning with an alcohol pad - Initially forgetting to clean the injection site but self-correcting Fresenius Kabi provided the following RCA and supportive evidence:	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=9)	AT = 2 AUT = 3 CT = 1 CUT = 1 HUT = 2	1	UE (n=5)	AT= 2 AUT = 3	2	CC (n=2)	AUT = 1 CT = 1	2	Our review of the study results identified subjective feedback that indicated many participants had difficulty locating the alcohol swabs within the package. Participants stated that they did not see the alcohol swabs in the packaging because the IFU was covering them. Some participants stated the image in Figure M did not clearly depict the injection site. We acknowledge Fresenius Kabi’s proposed mitigation strategy, however, our review of the labels and labeling (user interface, etc.) indicates that Figure M could be improved to better depict the injection site. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.
Total number of UE, CC, and UD	Type of Participants	Test Phase												
UE (n=9)	AT = 2 AUT = 3 CT = 1 CUT = 1 HUT = 2	1												
UE (n=5)	AT= 2 AUT = 3	2												
CC (n=2)	AUT = 1 CT = 1	2												

Table 5: Identified Issues and DMEPA's Findings – AI Configuration

- Inconspicuous alcohol swab location (4) – participants stated they did not see the alcohol swabs in the packaging because the IFU was covering them.
- Ambiguous figure in step 5.1 (Figure M) (2) – two participants stated the image in Figure M did not clearly depict the injection site.

(b) (4)

- IFU design (step 5 header placement) (1) – one participant stated he overlooked step 5 since the step 5 header was not at the top of page 3 and was placed between step 4.2 and 5.1.
- IFU design (1) – one participant stated it was his first time giving an injection and that he did not know there was a back to the instructions because he did not notice the line at the bottom of the instructions saying to Continue on the other side.

(b) (4)

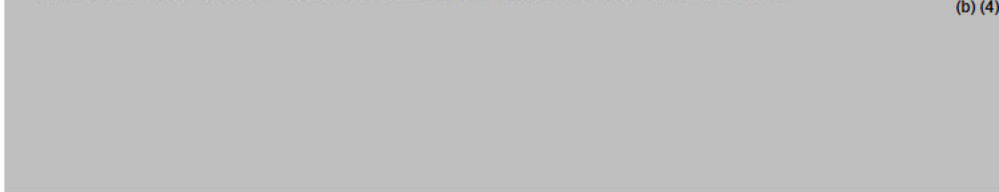
- IFU design (lack of step 1 instr
1.1 through 1.7 did not indicate to remove the alcohol swabs; one patient expected to find information about where the alcohol swabs were stored in step 5 and did not see the information during step 1.

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	• Test artifact (1) – one participant stated she expected to find the alcohol swabs on the table because the moderator provided the other study supplies. Based on the URRRA, if this task is omitted or not performed correctly there is risk of injection site contamination. Fresenius Kabi proposed one mitigation strategy in response to participant performance for this task: • Increase the font size to 10 pt. bold of all sub-step numbers (e.g., 1.1, 1.2 ... 8.1)										
9.	For the “remove cap of the device” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 748 1329 911"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=2)</td> <td>AUT = 1 HUT = 1</td> <td>1</td> </tr> <tr> <td>CC (n=1)</td> <td>HUT = 1</td> <td>1</td> </tr> </tbody> </table> Participant performance includes: • Removing the cap [too early] before cleaning the injection site • Twisting the cap off instead of pulling • Discarding cap into the trashcan instead of the sharps container Fresenius Kabi provided the following RCA and supportive evidence: • Negative transfer (3) – two participants stated they discarded the needle cap in the trash because that is what they normally do with other injections. One participant stated he typically removes the cap of his syringe ^{(b) (4)} immediately.	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=2)	AUT = 1 HUT = 1	1	CC (n=1)	HUT = 1	1	Our review of the study results identified subjective feedback that indicated the majority of these use errors were due to negative transfer. We acknowledge Fresenius Kabi’s proposed mitigation strategies, and our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. However, we note Fresenius Kabi proposes to change the last sentence of Step 1.5 to “Put the pen on a clean flat surface and do not remove the cap.” We consider the phrase “do not remove the cap” may be made more prominent, and therefore we provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern.
Total number of UE, CC, and UD	Type of Participants	Test Phase									
UE (n=2)	AUT = 1 HUT = 1	1									
CC (n=1)	HUT = 1	1									

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

- IFU design (inconspicuous footer, ambiguous arrow icon in footer) (1) – one participant stated he did not see the “Continue on the other side” text or the image of the orange triangle icon.
- IFU design (step 1.5) – one participant interpreted the word “packaging” in the second bullet point in step 1.5 to mean remove the needle cap from the prefilled pen because she thought the prefilled pen was encased in an external package, and she thought the prefilled pen was an external package. She heard the click sound after removing the needle cap and therefore attempted to recap the needle.



- Device design (force required to remove needle cap) (1) – one participant stated he twisted the cap off because the force required to pull it off was too great.
- Device design (arrows on needle cap, needle cap size and shape) (1) – one participant interpreted the arrows on the needle cap to mean “remove” and she removed the needle cap too early, immediately after removing the pen from the carton.

Based on the URRRA, if this task is omitted or not performed correctly there is risk of the autoinjector being unable to be used, the needle might be contaminated, or a drop might appear at the tip of the needle leading to limited underdosing.

Fresenius Kabi proposed the following mitigation strategies in response to participant performance for this task:

We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	• Change the last sentence of step 1.5 to: “Put the pen on a clean flat surface and do not remove the cap” • Increase the font size to 10 pt. bold of all sub-steps numbers (e.g., 1.1, 1.2 ... 8.1) • Improve the structuring of step 6 by reducing the white space between sub-steps • Improve visibility of the third bullet point on step 6.1 by bolding “Throw away” • Increase the visibility of the blue arrows in the figures, and the call for actions, by using a bigger line thickness							
10.	For the “press the autoinjector against the skin at a 90 degree angle. (b) (4) [redacted]” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 756 1329 837"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=1)</td> <td>CUT = 1</td> <td>1</td> </tr> </tbody> </table> Participant performance includes: • Attempt to hold the pen a few inches above the injection site and press the injection button Fresenius Kabi provided the following RCA and supportive evidence: • IFU design (ambiguous step 6.1 text and figure O) – one participant stated she held the pen over the injection site because she interpreted the text in step 6.1 “you may see drops of liquid at the needle tip” and Figure O to mean she needed to prime the prefilled pen. Based on the URRR, if this task is omitted or not performed correctly there is risk of the injection site contamination, the autoinjector not activating, the injection not being triggered, or the injection not starting (delays in treatment).	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=1)	CUT = 1	1	Our review of the study results identified subjective feedback that indicated this error was due to misinterpretation of the text in step 6.1 and Figure O. We acknowledge Fresenius Kabi’s proposed mitigation strategies, and our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
Total number of UE, CC, and UD	Type of Participants	Test Phase						
UE (n=1)	CUT = 1	1						

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Fresenius Kabi proposed the following mitigation strategies in response to participant performance for this task: • Reduce spacing between sub-steps 6.1 and 6.2 and within sub-step 6.2 • Increase visibility of the third bullet point of step 6.1 by using bold appearance of “Throw away” • Increase the visibility of the blue arrows in the figures, and the call for actions, by using a bigger line thickness										
11.	For the “maintain pressure on injection site until plunger has moved all the way down” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 906 1329 1144"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=18)</td> <td>AUT = 6 CUT = 3 HUT = 4 TUT = 5</td> <td>1</td> </tr> <tr> <td>UE (n=2)</td> <td>AUT = 2</td> <td>2</td> </tr> </tbody> </table> Participant performance includes: • Preemptive lifting of pen from injection site often resulting in wet injection Fresenius Kabi provided the following RCA and supportive evidence:	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=18)	AUT = 6 CUT = 3 HUT = 4 TUT = 5	1	UE (n=2)	AUT = 2	2	Our review of the study results identified subjective feedback that indicated many of these use errors were due to negative transfer. Subjective feedback also indicated that the placement of step 6.3 and 6.4 was inconspicuous and may have been overlooked until after the administration was complete or overlooked entirely. Additionally, some participants indicated that they interpreted the “click” sound to mean the injection was complete. Other participants misunderstood the instructions to mean “hold the prefilled pen down for 5 seconds after pressing the injection button”
Total number of UE, CC, and UD	Type of Participants	Test Phase									
UE (n=18)	AUT = 6 CUT = 3 HUT = 4 TUT = 5	1									
UE (n=2)	AUT = 2	2									

Table 5: Identified Issues and DMEPA's Findings – AI Configuration

- Negative transfer (8) – relied on previous injection experience when performing this task.
- Device design (lack of auditory feedback and clear plunger area) (12) – one participant stated it was unclear when the device was empty due to a lack of indicator; one participant stated he did not know when the pre-filled syringe was successfully delivering medication; two participants stated they lifted the prefilled pen after hearing the clicking sound because it scared/startled them; one participant stated the safety guard can be interpreted as a mechanism indicating the injection was completed; two participants stated the spring of the syringe plunger can be interpreted as a quick release; one participant stated she interpreted the design of the safety guard to mean that she had to lift the pre-filled pen from the injection site after pressing the injection button and the medication would be administered as soon as she lifted up the prefilled pen; three participants stated they did not realize the medication was in the clear part of the device; one participant stated she did not expect to have to hold the device down that long while injecting.
- Ambiguous text (step 6.2 and step 6.3) (2) – one participant stated she gave herself the injection during step 6.2 and did not read step 6.3 Administer the Injection until afterwards; three participants stated they held the prefilled pen down for 5 seconds after pressing the injection button; three participants stated they thought the click sound meant the injection was completed; two participants stated they did not notice

or “hold the prefilled pen down for 5 seconds after hearing the click” instead of holding for 5 seconds after the plunger has moved all the way down.

We acknowledge Fresenius Kabi’s proposed mitigation strategies, however, there is inadequate instruction denoting when the injection is complete. Our review of the labels and labeling (user interface, etc.) indicates that the images in Figures Q and R may be confusing and do not clearly indicate how long users are to hold the injection button/prefilled pen down. Additionally, Figures Q, R, and S do not intuitively depict the process of pressing the button, hearing a click, holding and watching the plunger move to the base, and holding an additional 5 seconds. Based on our overall assessment we find that the user interface can be improved to further mitigate risk of failure to maintain pressure on injection site until plunger has moved all the way down. **We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address these concerns.**

We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.

Table 5: Identified Issues and DMEPA's Findings – AI Configuration

	the phrase “after the plunger has reached the bottom” because it was not in bold font. • IFU design (figures R and S) (2) – one participant stated the blue arrows in the images in Figure R and S could be misinterpreted to mean push the autoinjector down and then lift it back up and did not depict a waiting action; one participant stated the phrase “watch” in the image in Figure R did not clearly indicate to watch the plunger come down to ensure the injection as completed. • IFU design (step 6.3 and 6.4) (1) – one participant stated they did not see step 6.3 or step 6.4 because they were at the top right of the IFU and did not have their own step headers. • Dexterity issue (1) – one participant stated they had difficulty keeping the syringe down due to her arthritis. • IFU design (footer) (1) – one participant stated he did not see the “Continue on other side” text and the orange triangle because the font size was too small and did not look like an arrow. • Slip (1) – one participant unknowingly adjusted the injection angle while she was rereading the IFU and while the injection was being administered. • Test artifact (2) – one participant stated they were nervous in the testing environment; one participant stated they administered the second prefilled pen (limited overdose) because the first attempt resulted in a partial dose, and they were administering a manikin.	(b) (4)

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

Based on the URRR, if this task is omitted or not performed correctly there is risk of chronic underdosing or limited overdosing. Fresenius Kabi stated that acceptance criteria for the injection is between (b) (4) seconds, and that the maximum injection time measured during design verification was 10 seconds. Fresenius Kabi further stated that when the syringe plunger reaches the bottom of the syringe barrel, the injection is considered complete. Therefore, the syringe plunger provides visual feedback of the completion of the injection. Fresenius Kabi stated they included the instruction “Continue holding the pen for 5 seconds after the syringe plunger has reached the bottom of the transparent housing” as a reasonable risk mitigation measure to prevent underdosing. Additionally, Fresenius Kabi stated that the average hold time for all participants was 8.1 seconds (minimum 1 second, maximum 30 seconds) during test phase 1 and 9.5 seconds (minimum 1 second, maximum 48 seconds) during test phase 2. Fresenius Kabi noted that 18 use errors were observed related to not holding the AI to the injection site long enough resulting in the loss of some medication during test phase 1 and two use errors were observed related to not holding the AI to the injection site long enough resulting in the loss of some medication during test phase 2. Fresenius Kabi proposed the following mitigation strategies in response to participant performance for this task. • Increase the font size to 10 pt. bold of all sub-step numbers (e.g., 1.1, 1.2 ... 8.1) • Improve the design of step 6.3 and Figure R and provide further guidance by changing the caption of the call out in Figure R from “watch” to “watch plunger and hold” • Increase the font size and improve the visibility of the “continue on other side” and “continue” note at the bottom of the front page and the top of the back page	

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

12. For the “^{(b) (4)} pressing a cotton ball or gauze on the injection site” task, see the table and list below for a summary of participant performance.

Total number of UE, CC, and UD	Type of Participants	Test Phase
UE (n=3)	AUT = 2 CUT = 1	1

Participant performance includes:

- Not treating the injection site with a cotton ball after injection
- Wiping the site with an alcohol pad after injection

Fresenius Kabi provided the following RCA and supportive evidence:

- IFU design (step 6.4) (2) – one participant stated he did not notice step 6.4 because he interpreted step 6.3 Figure S to mean the injection was complete and read step 7 and discarded the prefilled pen; one participant stated he did not see this step because he did not know the IFU had a back page
- Test artifact (1) – one participant stated he did not treat the injection site with a cotton ball because there was no blood at the injection site.
- Negative transfer (1) – one participant stated she used a cotton ball but then re-cleaned the injection site because she typically does this before putting a bandage on it.

Our review of the study results identified subjective feedback that indicated these use errors were due to negative transfer and IFU design.

We acknowledge Fresenius Kabi’s proposed mitigation strategy, and our review of the labels and labeling (user interface, etc.) indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Based on the URRRA, if this task is omitted or not performed correctly there is risk of drug product coming in contact with the skin or injection site contamination. Fresenius Kabi proposed the following mitigation strategy in response to participants performance for this task: • Increase the font size and improve the visibility of the “continue on other side” and “continue” note at the bottom of the front page and the top of the back page													
13.	For the “Discard the autoinjector into a sharps container” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 670 1329 870"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> <th>Test Phase</th> </tr> </thead> <tbody> <tr> <td>UE (n=4)</td> <td>AUT = 3 TUT = 1</td> <td>1</td> </tr> <tr> <td>CC (n=1)</td> <td>TUT = 1</td> <td>1</td> </tr> <tr> <td>CC (n=1)</td> <td>AUT = 1</td> <td>2</td> </tr> </tbody> </table> Participant performance includes: • Discarding the pen in the trashcan instead of the sharps container • Discarding or almost discarding in the trashcan and then self-correcting Fresenius Kabi provided the following RCA and supportive evidence: • Unclear IFU wording (4) – two participants stated they interpreted the heading of step 7 “throw away” to mean throw away in the trash, but they then read the phrase “do not throw away pre-filled pens in your household trash” and corrected their mistake; one participant stated he interpreted the heading of step 7 “throw away” to mean throw away in the trash; one participant stated he read the bolded text in step 3.2 “throw away used prefilled pens”; two participants did not see the	Total number of UE, CC, and UD	Type of Participants	Test Phase	UE (n=4)	AUT = 3 TUT = 1	1	CC (n=1)	TUT = 1	1	CC (n=1)	AUT = 1	2	Our review of the study results identified subjective feedback that indicated these use errors were due to misinterpretation of the header of step 7 and association of the phrase “throw away” with “trash”. We acknowledge Fresenius Kabi’s proposed mitigation strategy, however, our review of the labels and labeling (user interface, etc.) indicates that the header of step 7 could instruct users more clearly how to discard their used prefilled pens. Based on our overall assessment we find that the user interface can be improved to further mitigate risk of third parties being injured or contaminated. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern.
Total number of UE, CC, and UD	Type of Participants	Test Phase												
UE (n=4)	AUT = 3 TUT = 1	1												
CC (n=1)	TUT = 1	1												
CC (n=1)	AUT = 1	2												

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	instructions in step 7 because they were not aware there was a back to the instructions. • Test artifact (2) – one participant stated he saw the red sharps container in Figure U and did not think he could use the green sharps container provided on the table; one participant stated she did not notice the sharps container because she was nervous. • Negative transfer (2) – two participants stated they typically throw away items in the trash. Based on the URRRA, if this task is omitted or not performed correctly there is risk of third parties being injured or contaminated. Fresenius Kabi proposed the following mitigation strategy in response to participant performance for this task. • Increase the font size and improve the visibility of the “continue on other side” and “continue” note at the bottom of the front page and the top of the back page	(b) (4)	We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.					
14.	For the “Record injection” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 1377 1329 1412"> <thead> <tr> <th data-bbox="317 1377 764 1412">Total number of UE, CC, and UD</th> <th data-bbox="764 1377 1079 1412">Type of Participants</th> <th data-bbox="1079 1377 1329 1412">Test Phase</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Total number of UE, CC, and UD	Type of Participants	Test Phase				Our review of the study results identified subjective feedback that indicated the
Total number of UE, CC, and UD	Type of Participants	Test Phase						

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

UE (n=27)	AT = 3 AUT = 8 CT = 2 CUT = 6 HUT = 2 TUT = 6	1
UE (n=4)	AUT = 1 CT = 1 CUT = 1 TUT = 1	2

Participant performance includes:

- Did not record the injection site location
- Did not record the injection date
- Did not record injection site location or injection date

Fresenius Kabi provided the following RCA and supportive evidence:

- Negative transfer (14) – relied on previous injection experience when performing this task.
- IFU design (ambiguous text in step 8.1) (12) – one participant stated she typically only records the injection date and the phrase “remember when” indicated a timeframe, therefore she recorded the injection date but not the injection location; two participants stated they interpreted the phrase “record your injection” in step 8 header to mean record the injection date and did not record the location; two participants stated they interpreted the word “site” to mean physical location and did not think it was necessary to record the physical location of the study environment; two participants stated they expected to find this information in the Important Information section; four participants

majority of these use errors occurred due to negative transfer.

Subjective feedback also indicated ambiguity in step 8.1. Participants stated they interpreted the wording of the header and step 8.1 to mean to only record the date, and some participants stated they misinterpreted the word “site” to mean physical location of injection (e.g., at home).

We acknowledge Fresenius Kabi’s proposed mitigation strategy, however, our review of the labels and labeling (user interface, etc.) indicates that the step 7 heading, text in step 8.1 and the image in Figure V could instruct users more clearly what to record. Based on our overall assessment we find that the user interface can be improved to further mitigate risk of failure to record the injection. **We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern.**

We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.

Table 5: Identified Issues and DMEPA's Findings – AI Configuration

	stated the instructions blended in with the extra text at the bottom of the page and they would have followed this step if the items that needed to be recorded were separated by bullets like the other steps in the instructions; one participant stated she thought the word record referred to recording the injection with a camera, and she thought that the phrase “next injection” told her to record the date for the next injection. • IFU design (ambiguous step 7) (3) – three participants read step 7 (Throw away your pre-filled pens) but not step 8 (Record your injection) interpreting step 7 as the last step in the administration process. • IFU design (inconspicuous footer) (1) – one participant stated he did not read step 8.1 because he did not know there were instructions on the other side of the IFU. • IFU design (Figure V) (1) – one participant stated she uses the computer to record this information and assumed these instructions were for the home setting. • Test artifact (3) – one participant stated she read and understood the step instruction but disregarded it because she did not know if she could use the pen and paper provided; one participant stated she did not record the injection information because she was nervous since she did not successfully administer the medication; one participant stated she did not record the injection information because she was not in her normal work environment and did not have an electronic health record system.	(b) (4)

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Based on the URRRA, if this task is omitted or not performed correctly there is risk of limited overdosing or inadequate injection technique (lack of injection site rotation). Fresenius Kabi proposed the following mitigation strategy in response to participant performance for this task. Increase the font size to 10 pt. bold of all sub-step numbers (e.g., 1.1, 1.2 ... 8.1)					
15.	For the knowledge-based question “what should you not do when using the pre-filled pen?” see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 631 1335 829"> <thead> <tr> <th>Total number of “incorrect answers”</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>Incorrect answers (n=8)</td> <td>AT = 4 CT = 1 CUT = 2 TUT = 1</td> </tr> </tbody> </table> The subjective data and Fresenius Kabi’s root cause analysis indicated: - Unclear IFU wording (2) – one participant stated she was unsure whether the opening to the safety guard was referring to an opening on the box or something on the device; one participant stated if the pen cannot be frozen it should say do not place the pen in a freezer, as opposed to do not freeze. - Negative transfer (2) – one participant stated she thought that “safety guard” was referring to the tamper seal on her medications at home; one participant stated she only used the instructions to use the device and therefore did not expect to find information in the important information section. - Font size (2) – two participants stated the font size was too small and they were having difficulty reading the instructions.	Total number of “incorrect answers”	Type of Participants	Incorrect answers (n=8)	AT = 4 CT = 1 CUT = 2 TUT = 1	Our review of the study results identified subjective feedback that indicated the participants did not notice the relevant information in the IFU. Our review of the label and labeling (user interface, etc.) finds that the “Important Information” section of the IFU states: “Idacio pre-filled pen is for single-dose (one-time) use only” and “Do not try to reuse the Idacio pre-filled pen” “Do not insert your fingers into the opening of the safety guard” “Do not freeze Idacio” and “Do not use an Idacio pre-filled pen that has been frozen or left in direct sunlight” However, our review of the labels and labeling (user interface, etc.) indicates that Step 6.1 Remove the needle cap could be improved to remind users “Do not insert your fingers into the opening of the safety guard.”
Total number of “incorrect answers”	Type of Participants					
Incorrect answers (n=8)	AT = 4 CT = 1 CUT = 2 TUT = 1					

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	• Inconspicuous step location (2) – one participant stated she did not see the second to last bullet point (“Do not use an Idacio pre-filled pen that has been frozen or left in direct sunlight”) in the Using the Idacio Pre-filled Pen section of the IFU because she expected this information to be grouped or be placed after the third bullet point; one participant stated he expected the bullet stating “do not insert your fingers into the opening of the safety guard” to be located in step 6 because the step 6 text pertains to using the prefilled pen while the safety guard was exposed. • Insufficient salience (“read this instructions for use”) (1) – one participant stated he did not read the “Important Information” section because it did not stand out to him, and other instructions have “important information” that he does not perceive as important therefore he does not read. • Training artifact (1) – one participant stated during training he was told during traveling he could put the pen on ice in a cooler and he interpreted this to mean the pen could be frozen and thawed. Based on the URRRA, if this task is omitted or not performed correctly there is risk of needle stick injury or expired/degraded drug product. Fresenius Kabi did not propose any risk mitigation strategies for these “incorrect responses.”	Based on our overall assessment we find that the user interface can be improved to further mitigate risk of needle stick injury or expired/degraded drug product. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern.				
16.	For the knowledge-based question “what additional supplies are needed beside the pre-filled pen?” see the table and list below for a summary of participant performance. <table border="1" data-bbox="310 1255 1335 1412"> <thead> <tr> <th data-bbox="310 1255 1045 1299">Total number of “incorrect answers”</th> <th data-bbox="1045 1255 1335 1299">Type of Participants</th> </tr> </thead> <tbody> <tr> <td data-bbox="310 1299 1045 1412">Incorrect answers (n=5)</td> <td data-bbox="1045 1299 1335 1412"> AT = 1 CT = 2 CUT = 1 </td> </tr> </tbody> </table>	Total number of “incorrect answers”	Type of Participants	Incorrect answers (n=5)	AT = 1 CT = 2 CUT = 1	Our review of the study results identified subjective feedback that indicated the participants did not see the information immediately under step 1 because it was in paragraph format.
Total number of “incorrect answers”	Type of Participants					
Incorrect answers (n=5)	AT = 1 CT = 2 CUT = 1					

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;"></td> <td style="width: 50%; text-align: center;">TUT = 1</td> </tr> </table> The subjective data and Fresenius Kabi’s root cause analysis indicated: Insufficient salience of instructions (step 1) (5) – four participants stated they did not see the paragraph mentioning the alcohol pads at the top of the step because it was not bulleted or numbered; one participant did not provide subjective feedback. Based on the URRRA, if this task is omitted or not performed correctly there is risk of non-sterile injection technique. Fresenius Kabi did not propose any risk mitigation strategies for these “incorrect responses.”		TUT = 1	Our review of the label and labeling (user interface, etc.) finds that the IFU includes information about the alcohol swabs directly beneath step 1. These instructions are separated from step 1.2 which states users will need additional items that are not included in the carton (cotton ball or gauze and a sharps container). We agree this is the appropriate location for this information, however, based on our overall assessment we find that the user interface can be improved to further mitigate risk of failure to gather the supplies necessary for a sterile injection. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.		
	TUT = 1					
17.	For the knowledge-based question “How can you tell that the pre-filled pen device itself is okay to use?” see the table and list below for a summary of participant performance. <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Total number of “incorrect answers”</td> <td style="width: 50%;">Type of Participants</td> </tr> <tr> <td>Incorrect answers (n=1)</td> <td>AT = 1</td> </tr> </table> The subjective data and Fresenius Kabi’s root cause analysis indicated: Insufficient salience of step 3.1 (1) – the moderator noted she did not use the IFU	Total number of “incorrect answers”	Type of Participants	Incorrect answers (n=1)	AT = 1	Our review of the study results identified moderator feedback that indicated the participant did not use the IFU. Our review of the label and labeling (user interface, etc.) finds that the IFU includes instructions to check the prefilled pen to make sure it is not cracked or damaged in step 3.1. Based on our review of the user
Total number of “incorrect answers”	Type of Participants					
Incorrect answers (n=1)	AT = 1					

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	Based on the URRRA, if this task is omitted or not performed correctly there is risk of drug product coming in contact with skin or delayed treatment. Fresenius Kabi did not propose any risk mitigation strategies for this “incorrect response.”	interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.				
18.	For the knowledge-based question “What are the circumstances under which you should not use the pre-filled pen anymore?” see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 591 1335 672"> <tr> <td>Total number of “incorrect answers”</td> <td>Type of Participants</td> </tr> <tr> <td>Incorrect answers (n=1)</td> <td>AT = 1</td> </tr> </table> The subjective data and Fresenius Kabi’s root cause analysis indicated: • Insufficient salience of step 3.1 (1) – the moderator noted she did not use the IFU Based on the URRRA, if this task is omitted or not performed correctly there is risk of non-sterile injection technique. Fresenius Kabi did not propose any risk mitigation strategies for these “incorrect responses.”	Total number of “incorrect answers”	Type of Participants	Incorrect answers (n=1)	AT = 1	Our review of the study results identified moderator feedback that indicated the participant did not use the IFU. Our review of the label and labeling (user interface, etc.) finds that the IFU includes instructions “Do not use the pen if the liquid is cloudy or colored, if it has particles or flakes in it or shows any sign of damage” in step 3.1. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
Total number of “incorrect answers”	Type of Participants					
Incorrect answers (n=1)	AT = 1					
19.	For the knowledge-based question “Which sites are okay to inject into?” see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 1143 1335 1224"> <tr> <td>Total number of “incorrect answers”</td> <td>Type of Participants</td> </tr> <tr> <td>Incorrect answers (n=1)</td> <td>AT = 1</td> </tr> </table> The subjective data and Fresenius Kabi’s root cause analysis indicated:	Total number of “incorrect answers”	Type of Participants	Incorrect answers (n=1)	AT = 1	Our review of the study results identified subjective feedback that indicated the participant misinterpreted the image in Figure L. Our review of the label and labeling (user interface, etc.) finds that the IFU includes images and the instructions “You can use: the front of your thighs or your stomach-area. If
Total number of “incorrect answers”	Type of Participants					
Incorrect answers (n=1)	AT = 1					

Table 5: Identified Issues and DMEPA’s Findings – AI Configuration

	• Unclear IFU image (1) – one participant stated the injection could be given in the middle of the stomach while pointing to her belly button and referencing the picture in the IFU. Based on the URRRA, if this task is omitted or not performed correctly there is risk of inadequate injection technique (injection site reaction), too shall injection, or non-sterile technique. Fresenius Kabi did not propose any risk mitigation strategies for these “incorrect responses.”	 Figure L	you choose your stomach-area, do not use the area 2 inches around your belly button (navel)” in step 4.1. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.

4.1.1 ANALYSES OF AUTOINJECTOR HUMAN FACTORS VALIDATION STUDY NON-CRITICAL TASK ERRORS

The AI HF validation study showed use errors and use difficulties with the following non-critical tasks; however, based on our review of the available participants’ subjective feedback, Fresenius Kabi’s root cause analysis, and Fresenius Kabi’s proposed risk mitigation strategies, we determined the residual risk is acceptable. Specifically, we find that the labeling mitigations in place include information that is prominently placed within the labels and labeling to address the non-critical tasks below. We also find the labels and labeling are in alignment with labeling best practices. In addition, we considered the use tasks of the proposed product as compared with the use tasks in similar marketed products with the same user groups to determine if there are any known concerns of vulnerability to use error and did not identify any concerns. Subsequently, we did not identify further need to implement additional risk mitigation strategies at this time to address the use errors and use difficulties related to the following non-critical tasks:

- Open the carton
- Place the remaining prefilled pen in its original carton back in the refrigerator
- Check the prefilled pen to make sure that the glass syringe or other parts are not cracked or damaged
- Push and hold the prefilled pen firmly against your skin until the safety guard is fully depressed

4.2 SUMMARY OF AUTOINJECTOR STARTER PACK HUMAN FACTORS VALIDATION STUDY RESULTS

Table 6 describes the AI starter pack study results, Fresenius Kabi’s analyses of the results, and DMEPA 1’s analyses and recommendations.

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs						
<u>Please note the following:</u> <u>Scenarios:</u> Scenario 1: Retrieve starter pack and prepare for first day of treatment Scenario 2: Prepare for second day of treatment Scenario 3: Prepare for third day of treatment (4-pack only) <u>Participant ID Acronyms:</u> A##: Adult patients T##: Adolescent patients C##: Caregivers P##: Pharmacists						
	Identified Issue and Rationale for Concern	DMEPA’s Analysis and Findings				
Scenario 1: Retrieve starter pack and prepare for first day of treatment						
1.	For the “Open the box” task, see the table and list below for a summary of participant performance. <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 50%;">Total number of UE, CC, and UD</th> <th style="width: 50%;">Type of Participants</th> </tr> </thead> <tbody> <tr> <td>UE (n=1)</td> <td>C = 1</td> </tr> </tbody> </table> Participant performance includes: • Tearing the cardboard flap slightly while opening the box Fresenius Kabi provided the following RCA and supportive evidence: • Unintended action (1): one participant pulled the cardboard flap at an angle in the process of lifting it up, causing it to tear, but this did not obscure Important Information or Starter Schedule sections	Total number of UE, CC, and UD	Type of Participants	UE (n=1)	C = 1	We note that Fresenius Kabi’s RCA was incomplete because it did not identify why the participant pulled the cardboard flap at an angle in the process of lifting it up, causing it to tear. Our review of the labels and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule contains instructions and/or images to support this task. Based on our review of the user interface, we find the residual risk acceptable for this task. We did
Total number of UE, CC, and UD	Type of Participants					
UE (n=1)	C = 1					

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	Based on the URRRA, if this task is omitted or not performed correctly there is risk of non-sterile injection technique. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.	not identify areas of improvement and have no recommendations at this time.						
2.	For the “Determine the correct number of injections” and “Remove correct number of autoinjectors from the blister” tasks, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 553 1325 792"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>UE (n=8)</td> <td>T = 5 A = 3</td> </tr> <tr> <td>UD (n=4)</td> <td>T = 2 A = 1 C = 1</td> </tr> </tbody> </table> Participant performance includes: • Two participants selected 2 AIs instead of 4 AIs (six-pack) because the blue second treatment day box attracted their attention more than the yellow first treatment day box and they did not find the number in the IFU • One participant selected 1 AI instead of 4 AIs (six-pack) because it was not clear the small and large colored boxes for each treatment day on the carton lid were related to one another • Two participants selected of 1 AI instead of 2 AIs (four-pack) because the IFU only showed one AI • One participant selected 4 AIs instead of 2 AIs (four-pack) • Two participants selected the wrong number of AI because they made assumptions about the number of AI rather than referencing the on-carton directions	Total number of UE, CC, and UD	Type of Participants	UE (n=8)	T = 5 A = 3	UD (n=4)	T = 2 A = 1 C = 1	Our review of the study results identified subjective feedback that indicated some participants expected to find the number of AIs needed in the IFU and some participants stated they would have had help from their parents at home. We acknowledge Fresenius Kabi’s proposed mitigation strategies, and our review of the labels and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
Total number of UE, CC, and UD	Type of Participants							
UE (n=8)	T = 5 A = 3							
UD (n=4)	T = 2 A = 1 C = 1							

Table 6: Identified Issues and DMEPA's Findings – AI Configuration Starter Packs

- One participant selected 1 AI instead of 2 AIs (four-pack) before reviewing on-carton instructions, noting the on-carton phrase “ (b) (4) ” led her to think the correct number of AI could vary
- One participant read the instructions and selected 1 AI instead of 4 AIs (six-pack) before reviewing the on-carton labeling and selecting 3 more because the IFU only showed 1 AI
- One participant initially referred to the IFU and selected 1 AI instead of 4 (six-pack) before correctly selecting 4 AI, based on previous experience
- One participant initially removed all 6 AIs before correctly putting 2 AIs back (six-pack) noting they misheard the moderator prompt

Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence:

- Inconspicuous packaging illustration (1) – inconspicuous yellow color of box with AI needed for first treatment day relative to blue color of second treatment day
- Insufficient IFU (2) – two participants expected to find required number of AI needed in the IFU
- Test artifact (2) – two participants would have adult assistance reading directions at home

Based on the URRRA, if these tasks are omitted or not performed correctly there is risk of underdose or overdose.

Fresenius Kabi proposed the following mitigation strategies in response to participants performance for this task:

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

- The sentence in the starter schedule “ (b) (4) ” may be misunderstood as a necessary preliminary request to the physician to ask about each injection. This information is redundant and not necessary in this box (removal of statement depicted below)
- The boxes depicting number of pens and injection date are merged to better associate those information

Before Change:



3. For the “Remove correct number of alcohol swabs” task, see the table and list below for a summary of participant performance.

Total number of UE, CC, and UD	Type of Participants
UE (n=9)	T = 7 A = 2

Our review of the study results identified subjective feedback that indicated some participants did not see the alcohol swabs folded on top of each tray because they were folded together between trays.

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

Participant performance includes: • One participant selected one alcohol swab instead of two because she missed seeing the swabs that were folded together between trays • One participant did not remove any alcohol swabs instead of two because she missed seeing the other swabs that were folded together between the trays, and she explained she would not use them anyways because she washes her hands and injects her current medication into her palm • One participant selected four alcohol swabs instead of two because the IFU did not state how many to use • Six participants removed the incorrect number of alcohol swabs because of a use event on the prior task Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: • Inconspicuous packaging design (2) – folded over alcohol swabs led participants to think the box only provided the 2 alcohol swabs on the top tray • Incorrect mental model (1) – participant assumed injection site would be the same as her current site (palm) and thought washing hands was sufficient • Insufficient IFU (1) – IFU does not state number of alcohol swabs are required for the first day of treatment Based on the URRRA, if these tasks are omitted or not performed correctly there is risk non-sterile injection technique. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.	Our review of the label and labeling (user interface, etc.) finds that the IFU includes information about the alcohol swabs directly beneath step 1, instructing users “You will need 1 alcohol swab and 1 Idacio pre-filled pen for each injection.” Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

Scenario 2: Prepare for second day of treatment

1. For the “Determine the correct number of injections” task, see the table and list below for a summary of participant performance.

Total number of UE, CC, and UD	Type of Participants
UE (n=3)	T = 2 A = 1
UD (n=1)	C = 1

Participant performance includes:

- One participant removed two AIs instead of one (four-pack). He explained seeing two AIs in the tray together led him to think they were for a single day
- One participant removed two AIs instead of one (four-pack). She explained the phrase “(b) (4)” made her think her physician would repeat the same instructions for the second treatment day
- One participant removed one AI instead of two (six-pack) because they assumed the number of AIs needed was one instead of referencing the on-carton instructions
- One participant had difficulty determining the correct number of AIs because of the unclear visual hierarchy and low visual importance of the phrase “2 weeks later”

Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence:

- Misleading package design (1) – layout of 2 AIs grouped together in each layer signaled they should be administered together
- Insufficient labeling (1) – ambiguous instruction “(b) (4)” leading participant to think the dose was dependent on the individual patient’s dosage

Our review of the study results identified subjective feedback that indicated one participant associated a tray of two AI as one dose and one participant assumed the dose was the same as the first treatment dose.

Our review of the labels and labeling (user interface, etc.) indicates that the packaging of the AIs could be improved to more clearly indicate that users only need to administer one AI for the second and third doses. **We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern.**

We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	• Test artifact (1) – protocol deviation in which “treatment day” was replaced by “dose” in moderator prompts might have led participant to think the number of AI would be the same as first treatment • Incorrect mental model (1) – participant made assumptions rather than referring to on-carton instructions • Inconspicuous packaging design (1) – unclear visual hierarchy and low visual salience of the phrase “2 weeks later” Based on the URRRA, if these tasks are omitted or not performed correctly there is risk of underdose or overdose. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.									
2.	For the “States correct date of second treatment day” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 829 1325 1146"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>UE (n=5)</td> <td>T = 1 A = 2 C = 2</td> </tr> <tr> <td>CC (n=2)</td> <td>C = 1 P = 1</td> </tr> <tr> <td>UD (n=3)</td> <td>A = 2 C = 1</td> </tr> </tbody> </table> Participant performance includes: • One participant stated the second treatment day would take place 24 hours instead of 2 weeks after (six-pack) because of the low visual salience of the phrase “2 weeks later” relative to the surrounding information	Total number of UE, CC, and UD	Type of Participants	UE (n=5)	T = 1 A = 2 C = 2	CC (n=2)	C = 1 P = 1	UD (n=3)	A = 2 C = 1	Our review of the study results identified subjective feedback that indicated there was low salience around the “2 weeks later” statement (six-pack) and more emphasis between the blue and purple boxes as compared to the yellow and blue boxes. We acknowledge that Fresenius Kabi removed the statement “(b) (4)” from the on-carton starter schedule. Our review of the labels and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this
Total number of UE, CC, and UD	Type of Participants									
UE (n=5)	T = 1 A = 2 C = 2									
CC (n=2)	C = 1 P = 1									
UD (n=3)	A = 2 C = 1									

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	● One participant stated the second treatment day would take place 2 weeks instead of 1 week after (four-pack) because the information for a single treatment day was not contained in its own square on the on-carton label ● One participant stated the second treatment day would happen 2 weeks instead of 1 week (four-pack) after the first treatment day because she assumed it was the same as her current medication ● One participant stated the second treatment day would take place 2 weeks instead of 1 week after (four-pack) because she skipped ahead when reading on the carton labeling ● One participant stated the second treatment day would happen the day after instead of 1 week after (four-pack) because he could not read, and his mom would help him at home ● Two participants stated the second treatment day would occur two weeks after and correctly changed to 1 week after. ○ One participant stated the layout divides the yellow box from the blue and purple boxes, which emphasizes “2 weeks later” ○ One participant stated the blue and purple boxes stood out more, which emphasizes “2 weeks later” ● Three participants had difficulty determining the correct date ○ One participant stated the “tue” in “Tuesday” and “2 weeks” caused her to initially misspeak ○ Two participants stated an incorrect date before reflecting and responding with the correct date because the simulated environment caused them to behave differently Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence:	task. We did not identify areas of improvement and have no recommendations at this time.

Table 6: Identified Issues and DMEPA's Findings – AI Configuration Starter Packs

- Inconspicuous packaging illustration – low visual importance of “2 weeks later”
- Insufficient labeling – information for a single treatment day is divided across different boxes within the on-carton label
- Incorrect mental model – participant’s experience caring for daughter with diabetes led her to pay more attention to amount of medication than to the treatment day
- Incorrect mental model – assumed the timing of treatment days would be the same as her current medication
- User state – participant might have experienced brain fog due to multiple sclerosis
- User state – participant did not know how to read
- Test artifact – participant would have adult assistance in reading directions at home
- Inconspicuous packaging illustration – blue and purple colors of the second and third treatment day boxes stand out more than the yellow starting day box and caused “2 weeks later” to stand out more than “1 week later”
- Slip – stated the correct time between doses but misspoke the date after saying the day of the week
- Test artifact – simulated environment caused participant to behave differently than at home

Based on the URRR, if these tasks are omitted or not performed correctly there is risk of user taking the next dose too soon, too late, or not at all.

Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

3.	For the “Remove correct number of autoinjectors form the blister” task, see the table and list below for a summary of participant performance.		Our review of the study results identified subjective feedback that indicated one participant misunderstood the moderator instructions. Our review of the labels and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
	Total number of UE, CC, and UD	Type of Participants	
	UE (n=1)	T = 1	
	N/A ^j (n=4)	T = 2 A = 2	

Participant performance includes:

- One participant removed two AIs instead of 1 because they removed the supplies for both the second and third treatment days in response to the moderator prompt
- Three participants removed the incorrect number of AIs from the blister because of a use event on a previous task
- One participant’s performance could not be assessed because she selected all 4 AIs instead of 2 on the first treatment day and therefore did not have any available AIs for the second treatment day

Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence:

- Test artifact (1) – simulated environment caused the participant to behave differently form how they would at home

Based on the URRRA, if these tasks are omitted or not performed correctly there is risk of underdose or overdose.

^j Fresenius Kabi noted that the coding “N/A” used throughout Table 6 indicates that the participant did not complete the step because of a previous error on a previous task.

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.							
4.	For the “Remove correct number of alcohol swabs” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 396 1325 672"> <thead> <tr> <th data-bbox="317 396 905 435">Total number of UE, CC, and UD</th> <th data-bbox="905 396 1325 435">Type of Participants</th> </tr> </thead> <tbody> <tr> <td data-bbox="317 435 905 594">UE (n=6)</td> <td data-bbox="905 435 1325 594"> T = 3 A = 1 C = 1 P = 1 </td> </tr> <tr> <td data-bbox="317 594 905 672">N/A (n=4)</td> <td data-bbox="905 594 1325 672"> T = 3 A = 1 </td> </tr> </tbody> </table> Participant performance includes: • One participant removed two alcohol swabs instead of one alcohol swab (four pack) explaining he saw the tray with two AIs and two alcohol swabs and assumed they were for one day • One participant removed two alcohol swabs instead of one alcohol swab (four-pack) explaining she did not think to unfold the swabs and did not realize they were connected • One participant selected two alcohol swabs instead of 1 alcohol swab (four-pack) explaining she did not notice the two alcohol swabs were connected because they were folded together to look like there was one • Three participants did not select any alcohol swabs because they were not performing an injection • Three participants removed the incorrect number of AIs from the blister because of a use event on a previous task • One participant’s performance could not be assessed because she selected all 4 AIs instead of 2 on the first treatment day and therefore did not have any available AIs for the second treatment day	Total number of UE, CC, and UD	Type of Participants	UE (n=6)	T = 3 A = 1 C = 1 P = 1	N/A (n=4)	T = 3 A = 1	Our review of the study results identified subjective feedback that indicated the majority of these use errors occurred due to test artifact. Our review of the label and labeling (user interface, etc.) finds that the IFU includes information about the alcohol swabs directly beneath step 1, instructing users “You will need 1 alcohol swab and 1 Idacio pre-filled pen for each injection.” However, based on our overall assessment we find that the user interface can be improved to further mitigate risk of failure to remove correct number of alcohol swabs. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.
Total number of UE, CC, and UD	Type of Participants							
UE (n=6)	T = 3 A = 1 C = 1 P = 1							
N/A (n=4)	T = 3 A = 1							

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: • Misleading package design – layout of 2 alcohol swabs and 2 AIs grouped together in each layer signaled they should be administered together • Test artifact (2) – participant removed two alcohol swabs instead of one because they were folded together • Test artifact (3) – simulated environment caused the participant to behave differently from how they would at home					
Scenario 3: Prepare for third day of treatment (4-pack only)						
1.	For the “Determine correct number of injections” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 764 1325 883"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>N/A (n=2)</td> <td>T = 1 A = 1</td> </tr> </tbody> </table> Participant performance includes: • Two participants determined the incorrect number of injections because of a use event on the prior task Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: • These use events were attributed to previous use events when participants determined the number of injections required. The participants being N/A for the following use scenarios is due to them determining the incorrect number of injections from the pack from the beginning and start of the use scenario	Total number of UE, CC, and UD	Type of Participants	N/A (n=2)	T = 1 A = 1	Our review of the labels and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule contains instructions and/or images to support this task. Based on our review of the user interface, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
Total number of UE, CC, and UD	Type of Participants					
N/A (n=2)	T = 1 A = 1					

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	Based on the URRRA, if these tasks are omitted or not performed correctly there is risk of underdose or overdose. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.									
2.	For the “States correct date of third treatment day” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 513 1325 711"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>UE (n=4)</td> <td>T = 1 A = 3</td> </tr> <tr> <td>CC (n=1)</td> <td>T = 1</td> </tr> <tr> <td>UD (n=2)</td> <td>C = 2</td> </tr> </tbody> </table> Participant performance includes: • Two participants stated the third treatment day would take place 2 weeks after the first treatment day instead of 2 weeks after the second treatment day because the phrase “2 weeks later same weekday” was ambiguous about which treatment day to count from • One participant stated the third treatment day would take place 28 days instead of 2 weeks after the second treatment day because she expected to find the dosage instructions in the IFU • One participant did not check the starter pack and stated the third treatment day would happen on Saturday (the day after the first treatment day) because he could not read • One participant stated the treatment day would occur 1 week after the first treatment day before self-correcting because the phrase “2 weeks later same weekday” was ambiguous • Two participants had difficulty determining the correct date of the third treatment day. They expressed uncertainty about which day the third	Total number of UE, CC, and UD	Type of Participants	UE (n=4)	T = 1 A = 3	CC (n=1)	T = 1	UD (n=2)	C = 2	Our review of the study results identified subjective feedback that indicated some participants thought the third treatment day would occur 2 weeks after the first treatment day instead of 2 weeks after the second treatment day. Our review of the label and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule does not clearly indicate when the third treatment day occurs. Based on our overall assessment we find that the user interface can be improved to further mitigate risk of users taking the next dose too soon, too late, or not at all. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.
Total number of UE, CC, and UD	Type of Participants									
UE (n=4)	T = 1 A = 3									
CC (n=1)	T = 1									
UD (n=2)	C = 2									

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	treatment day was 2 weeks from (i.e., 2 weeks after the first treatment day or after the second treatment day) Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: • Insufficient labeling (2) – ambiguous instruction “2 weeks later same weekday” led participant to think the third treatment day should occur 2 weeks after the first treatment day instead of two weeks after the second treatment day • Insufficient IFU (1) – the participant expected to find the dosage instructions in the IFU • User state (1) – the participant did not know how to read Based on the URRRA, if these tasks are omitted or not performed correctly there is risk of users taking the next dose too soon, too late, or not at all. Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.							
3.	For the “Remove correct number of autoinjectors from the blister” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 1024 1325 1182"> <thead> <tr> <th>Total number of UE, CC, and UD</th> <th>Type of Participants</th> </tr> </thead> <tbody> <tr> <td>UD (n=1)</td> <td>T = 1</td> </tr> <tr> <td>N/A (n=3)</td> <td>T = 1 A = 2</td> </tr> </tbody> </table> Participant performance includes: • One participant removed one of the AIs from the plastic tray and the cap detached from the AI body. He explained he had no idea what happened, but he removed the AI in the same way he removed the	Total number of UE, CC, and UD	Type of Participants	UD (n=1)	T = 1	N/A (n=3)	T = 1 A = 2	Our review of the study results identified subjective feedback that indicated one participant had the cap pop off while removing the AI from the tray, this might have occurred because the AIs were dropped prior to the session, which might have caused the AI cap to become loose. Our review of the labels and labeling (user interface, etc.) indicates that the IFU and on-carton starter schedule contains instructions and/or images to support this task. Based on
Total number of UE, CC, and UD	Type of Participants							
UD (n=1)	T = 1							
N/A (n=3)	T = 1 A = 2							

Table 6: Identified Issues and DMEPA's Findings – AI Configuration Starter Packs

	others, by holding the AI in the middle. He explained he was removing the AI normally when he heard a popping noise • Three participants performance could not be assessed because of previous use events Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: • Test artifact – the AIs were dropped prior to the session, which might have caused the AI cap to become loose • Previous use event – determined incorrect number of AIs for the second treatment day • Misleading packaging design – layout of 2 AIs grouped together in each layer implied they should be administered together • Previous use event – determined incorrect number of AIs for the first treatment day or the second treatment day • Previous user state – the participant might have experienced brain fog due to multiple sclerosis • Labeling – ambiguous instruction “ (b) (4) ” led participant to think the number of AIs needed for the first dose depended upon the individual patient’s dosage • Test artifact – protocol deviation in which “treatment day” was replaced by “dose” in moderator prompts might have led participant to think the number of AIs for subsequent treatments would be the same as the first treatment Based on the URRRA, if these tasks are omitted or not performed correctly there is risk of underdose or overdose.	our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.

Table 6: Identified Issues and DMEPA’s Findings – AI Configuration Starter Packs

	Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.							
4.	For the “Remove correct number of alcohol swabs” task, see the table and list below for a summary of participant performance. <table border="1" data-bbox="317 396 1325 594"> <thead> <tr> <th data-bbox="317 396 905 435">Total number of UE, CC, and UD</th> <th data-bbox="905 396 1325 435">Type of Participants</th> </tr> </thead> <tbody> <tr> <td data-bbox="317 435 905 516">UE (n=2)</td> <td data-bbox="905 435 1325 516">T = 1 A = 1</td> </tr> <tr> <td data-bbox="317 516 905 594">N/A (n=4)</td> <td data-bbox="905 516 1325 594">T = 3 A = 1</td> </tr> </tbody> </table> Participant performance includes: • One participant removed the correct supplies for both the second and third treatment days on the second treatment day but indicated she would not use the swabs because she washes her hands and injects her current medication into her palm • One participant did not select any alcohol swabs for the third treatment day because she was not performing an injection • Four participants removed the incorrect number of alcohol swabs because of a use event on the prior task Fresenius Kabi provided the following root cause analysis (RCA) and supportive evidence: • Incorrect mental model – would not use alcohol swabs because she assumed the injection site would be the same as her current medication • Test artifact – simulated environment caused participant to behave differently from how they would at home • Previous use event – remove incorrect number of alcohol swabs for the second treatment day • Inconspicuous packaging design – participant removed 2 alcohol swabs instead of 1 because they were folded together to appear as one	Total number of UE, CC, and UD	Type of Participants	UE (n=2)	T = 1 A = 1	N/A (n=4)	T = 3 A = 1	Our review of the study results identified subjective feedback that indicated the majority of these use errors occurred due to test artifact. Our review of the label and labeling (user interface, etc.) finds that the IFU includes information about the alcohol swabs directly beneath step 1, instructing users “You will need 1 alcohol swab and 1 Idacio pre-filled pen for each injection.” However, based on our overall assessment we find that the user interface can be improved to further mitigate risk of failure to remove correct number of alcohol swabs. We provide recommendations in the Identified Issues and Recommendations Table for Fresenius Kabi to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.
Total number of UE, CC, and UD	Type of Participants							
UE (n=2)	T = 1 A = 1							
N/A (n=4)	T = 3 A = 1							

Table 6: Identified Issues and DMEPA's Findings – AI Configuration Starter Packs

- Previous use event – removed incorrect number of alcohol swabs for the first treatment day
- Insufficient IFU – paper instructions do not state how many alcohol swabs are required for the first day of treatment
- Misleading packaging design – layout of 2 alcohol swabs and 2 AIs grouped together in each layer signaled they should be administered together

Based on the URRRA, if these tasks are omitted or not performed correctly there is risk non-sterile injection technique.

Fresenius Kabi did not propose mitigation strategies in response to participant performance for this task.

(b) (4)



5 LABELS AND LABELING

Table A below includes the identified medication error issues with the submitted product samples, packaging, label and labeling, our rationale for concern, and our proposed recommendations to minimize the risk for medication error.

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU) for the Autoinjector (AI) (b) (4)			
1.	The image in Figure H does not instruct the user to set the autoinjector on a flat clean surface and allow it to acclimate to room temperature for 30 minutes.	The URRRA indicates if a user omits or does not perform the task associated with “set autoinjector on a flat clean surface and allows it to acclimate to room temperature” correctly there is risk of chronic underdosing or	Revise Figure H to better portray the autoinjector needs to be set on a clean flat surface to acclimate to room temperature for 30 minutes. For example, revise Figure H to include an image of an AI on a flat surface (e.g., countertop) with the “Wait 30 minutes” image in the background. Additionally, consider making the image more prominent and non-monochromatic.

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
	 Figure H	administration of expired/degraded drug. The AI HF validation study results identified subjective feedback that indicated participants thought the image in Figure H was ambiguous and did not provide clear instructions on what to do for “30 minutes”. Additionally, participants indicated that the monochromatic color scheme of the clock (i.e., black and white) made the clock blend in with the white background.	
Instructions for Use (IFU) for the Autoinjector (AI)			
1.	Step 1 “Prepare for your injection” does not clearly outline all information.	The URRA indicates if a user omits or does not perform the task associated with “collect the necessary supplies to prepare the injection site” correctly there is risk of non-sterile injection technique. The AI HF validation study results identified subjective	Revise the format in the first paragraph, “Each carton comes with 2 alcohol swabs and 2 Idacio pre-filled pens. You will need 1 alcohol swab and 1 Idacio pre-filled pen for each injection.” in step 1 from paragraph format to bulleted statements or numbered statements.

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
		feedback that indicated participants did not see the first paragraph, "Each carton comes with 2 alcohol swabs and 2 Idacio pre-filled pens. You will need 1 alcohol swab and 1 Idacio pre-filled pen for each injection."	
2.	The image of the carton in Figures D, E, and G do not clearly depict that the carton contains MSB11022 Als.	The images of a blank, white carton could lead to confusion.	Consider revising the image of the carton in Figures D, E, and G to more accurately represent the Idacio carton.
3.	We note you proposed the following mitigation strategy for step 1.5: "Change the last sentence of Step 1.5 to 'Put the pen on a clean flat surface and do not remove the cap.'"	The instruction, " do not remove the cap," may be missed because it is at the end of the sentence.	To put more prominence on not removing the cap during step 1.5, consider revising your proposed sentence to read, "Place the capped pen on a clean flat surface."
4.	The instructions in step 4.1 do not inform users to only inject in the front of the thighs or stomach area.	The URRAs indicate if a user omits or does not perform the task associated with "select an injection site (must be different from the previous	Revise the instructions in step 4.1 to more clearly inform users to only inject in the front of the thighs or stomach area. For example, revise the phrase in step 4.1 "Choose an injection site (Figure L). You can use: ..." to

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
		injection site)” correctly there is risk of injection site reaction, too shallow injection might be performed, or the injection site might be contaminated. The AI HF validation study results identified subjective feedback that indicated participants did not clearly understand to only inject in the front of the thighs or stomach area.	“Choose an injection site (Figure L). Only use: ...”
5.	The image in Figure M does not clearly depict the injection site.	The URRRA indicates if a user omits or does not perform the task associated with “clean the skin at the selected injection site” correctly there is risk of injection site contamination. The AI HF validation study results identified subjective feedback from two participants who indicated Figure M did not clearly depict the injection site.	Revise Figure M to more clearly depict the injection site. For example, consider depicting an image that represents the intended areas of injection (i.e., the stomach area or the front of the thigh).

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
6.	The images in Figures Q, R, and S do not intuitively depict the process of pressing the button, hearing a click, holding and watching the plunger move to the base, and holding an additional 5 seconds. (b) (4)	The URRA indicates if a user omits or does not perform the task associated with “maintain pressure on injection site until plunger has moved all the way down” correctly there is risk of chronic underdosing or limited overdosing. The AI HF validation study results identified subjective feedback that indicated participants interpreted the “click” sound to mean the injection was complete. Additionally, some participants misunderstood the instructions “Continue holding the pen for 5 seconds after the syringe plunger has reached the bottom of the transparent syringe housing” to mean “hold the prefilled pen down for 5 seconds after pressing the injection button” or “hold the prefilled pen	Revise the images in Figures Q, R, and S to more clearly depict all of the processes that occur during dose administration. For example, in the image in Figure R, revise the text to state “during injection” and add an indication that the plunger is moving towards the base. Consider adding an additional Figure after current Figure R that depicts the plunger has reached the base and that the user still needs to hold for 5 more seconds.

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
		down for 5 seconds after hearing the click”.	
7.	Step 6.1 “Remove the needle cap” could be improved to instruct users “Do not insert your fingers into the opening of the safety guard”.	The URRRA indicates if a user omits or does not perform the task associated with the KBA “what should you not do when using the pre-filled pen?” correctly there is risk of needle stick injury or expired/degraded drug product. The AI HF validation study results identified subjective feedback that indicated the participants did not notice the relevant information in the IFU.	Revise Section 6.1 to include the instructions “Do not insert your fingers into the opening of the safety guard”.
8.	The header of Step 7 “Throw away your pre-filled pens” does not sufficiently indicate the proper disposal method.	The URRRA indicates if a user omits or does not perform the task associated with “discard the autoinjector into a sharps container” correctly there is risk of third parties being injured or contaminated.	Revise the header of Step 7 to read “Dispose of your pre-filled pens”. Additionally, revise the phrase “throw away” to “dispose of” in instances where proper disposal consists of using a sharps container (e.g., sub-steps 1.2, 3.1, and 3.2).

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
		The AI HF validation study results identified subjective feedback that indicated participants misinterpreted the phrase “throw away” which led them to discard their prefilled pens in the regular trash instead of the sharps container.	
9.	Step 8 “Record your injection” does not clearly indicate what users need to record. (b) (4)	The URRA indicates if a user omits or does not perform the task associated with “record injection” correctly there is risk of limited overdosing or inadequate injection technique (lack of injection site rotation). The AI HF validation study results identified subjective feedback that indicated participants misinterpreted the step 8 heading and overlooked/misinterpreted the text in step 8.1.	Revise step 8 to more clearly indicate what users need to record. For example, revise the heading of Step 8 to read “Document your injection site and date administered”; Revise step 8.1 from “To help you remember when and where to give your next injection, keep a record of the dates and injection sites used for your injections.” to “To help you remember when and where on your body to give your next injection, keep a record of the dates and injection sites used for your injections.”; Revise the image in Figure V to include the language “Date of Administration:” and “Injection Site:” and consider including

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
			example date(s) and site(s) for users to reference.
10.	The layout of the IFU does not sufficiently group similar sub-steps.	The URRA indicates if a user omits or does not perform the task associated with “set autoinjector on a flat clean surface and allows it to acclimate to room temperature” correctly there is risk of chronic underdosing or administration of expired/degraded drug. The AI HF validation study results identified subjective feedback that indicated some participants did not see steps 1.5-1.7 because they were on a different pane not associated with the header “Step 1 Prepare for your injection”.	Revise your IFU to ensure all sub-steps are visibly associable with their step heading.
Inner Part of the Outer Packaging of the AI Starter Packs			
1.	As currently presented, the four AI starter pack contains two trays each containing two AIs.	Subjective feedback from the validation study indicated that one participant associated a tray of two AIs as one dose.	Consider revising the four AI starter pack so that the AI for doses two and three are in separate trays underneath the first dose (i.e.,

Table A: Identified Issues and Recommendations for Fresenius Kabi, USA, LLC. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
			consider packaging the bottom two AIs in their own separate trays).
2.	The inner packaging layout of the four-AI starter pack carton labeling is ambiguous about when the third treatment day occurs.	The URRA indicates if a user omits or does not perform the task associated with “states the correct date of third treatment day” correctly there is risk of users taking the next dose too soon, too late, or not at all. The AI Starter Pack HF validation study results identified subjective feedback that indicated participants thought the third treatment day would occur 2 weeks after the first treatment day instead of 2 weeks after the second treatment day.	Revise the inner packaging layout of the four-AI starter pack carton labeling so that it more clearly defines that the third treatment day occurs two weeks after the second treatment day. For example, revise the statement “2 weeks later” to read “2 weeks after the second treatment day”. To maintain consistency, revise the statement “1 week later” to read “1 week after the first treatment day”.

(b) (4)

6 CONCLUSIONS AND RECOMMENDATIONS

The results of the HF validation studies demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm to the patient. However, Fresenius Kabi proposed revisions to the product user interface to further mitigate the risk for use errors. We found Fresenius Kabi's proposed changes to the user interface to be reasonable and identified additional risk mitigations. Additionally, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table A for Fresenius Kabi. We ask that the Division of Rheumatology and Transplant Medicine (DRTM) convey Table A in its entirety to Fresenius Kabi so that recommendations are implemented. We have determined that in this particular case, we do not need to review additional HF validation study data to support these changes.

6.1 RECOMMENDATIONS FOR FRESENIUM KABI USA, LLC.

Our evaluation results of your human factors (HF) validation studies indicates that there are additional mitigations that can be implemented to address use errors that occurred with critical tasks. We provide recommendations in Table A, and we recommend that you implement these recommendations and submit the revised label and labeling for our review.

APPENDICIES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 8 presents relevant product information for MSB11022 that Fresenius Kabi USA, LLC submitted on December 13, 2022.

Table 8. Relevant Product Information							
Initial Approval Date	N/A						
Therapeutic Drug Class or New Drug Class	Tumor necrosis factor (TNF) blocker						
Nonproprietary Name	adalimumab-xxxx						
Indication	Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) in patients ≥2 years of age, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn’s Disease (CD) in adults and pediatric patients ≥6 years of age, Adult Ulcerative Colitis (UC), Plaque Psoriasis (Ps), and Hidradenitis Suppurativa (HS)						
Route of Administration	Subcutaneous						
Dosage Form	Injection						
Strength	40 mg/0.8 mL						
Dose and Frequency	Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis: 40 mg every other week. - Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week or 80 mg every other week. Juvenile Idiopathic Arthritis: <table border="1"> <thead> <tr> <th>Pediatric Weight (2 Years of Age and Older)</th> <th>Recommended Dosage</th> </tr> </thead> <tbody> <tr> <td></td> <td>(b) (4)</td> </tr> <tr> <td>30 kg (66 lbs) and greater</td> <td>40 mg every other week</td> </tr> </tbody> </table> Adult Crohn's Disease and Ulcerative Colitis: - Initial dose (Day 1): 160 mg (b) (4)	Pediatric Weight (2 Years of Age and Older)	Recommended Dosage		(b) (4)	30 kg (66 lbs) and greater	40 mg every other week
Pediatric Weight (2 Years of Age and Older)	Recommended Dosage						
	(b) (4)						
30 kg (66 lbs) and greater	40 mg every other week						

(b) (4)

Pediatric Patients 6 Years of Age and Older Crohn's Disease:

Pediatric Weight	Recommended Dosage	
	Days 1 through 15	Starting on Day 29
40 kg (88 lbs) and greater	Day 1: 160 mg Day 15: 80 mg	40 mg every other week

(b) (4)

Plaque Psoriasis:

- 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.

(b) (4)

How Supplied

40 mg/0.8 mL in a single-dose prefilled AI (MSB 11022)

(b) (4)

- AI Carton - 40 mg/0.8 mL 2 pack

(b) (4)

- AI Carton - 40 mg/0.8 mL Starter Pack for Plaque Psoriasis 4 pack
- AI Carton - 40 mg/0.8 mL Starter Pack for Crohn's Disease, Ulcerative Colitis

(b) (4)

40 mg/0.8 mL in a single-dose PFS

(b) (4)

- PFS Carton - 40 mg/0.8 mL 2 pack

(b) (4)

Storage	MSB11022 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. May be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 28 days.
Container Closure/Device Constituent	• single-dose PFS • single-dose AI (b) (4)
Intended Users	Patients (adults and children), caregivers, and healthcare providers
Intended Use Environment	Home, other non-clinical or clinical setting

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On April 9, 2021, we searched the L: drive and AIMS using the terms, MSB11022, Idacio, BLA 761255 and IND 124098 to identify reviews previously performed by DMEPA.

B.1.2 Results

Our search identified three previous reviews^{c,d,k}, and we considered our previous recommendations to see if they are applicable for this current review. We determined several of our previous recommendations were relevant to this review and we discussed these recommendations above.

B.2 PREVIOUS FDA/SPONSOR INTERACTIONS PERTAINING TO HF

The Agency provided human factors guidance to Fresenius Kabi in three meetings:

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af803c6103&_afRedirect=2211836551469253

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804aeeaf&_afRedirect=2216071878987793

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8062591f&_afRedirect=2214943312292717

^k Mena-Grillasca C. Human Factors and Labeling Review for MSB11022 (IND 124098). Silver Spring (MD): FDA, CDER, OSE, DMEPA; 2016 MAR 17. RCM No.: 2016-715.

APPENDIX C. BACKGROUND INFORMATION OF HUMAN FACTORS ENGINEERING PROCESS The background information can be accessed in the HF results report. See Appendix D.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

D.1 PFS

The HF Risk Management Report for MSB11022 PFS that can be accessed in EDR via:

<\\CDSESUB1\evsprod\bla761255\0001\m3\32-body-data\32r-reg-info\medicaldevice\annexesformedicaldevice\annex-r-2-27.pdf>

The HF Summary and Assessment Report for MSB11022 PFS that can be accessed in EDR

via: <\\CDSESUB1\evsprod\bla761255\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronicplaquepsoriasis\5354-other-stud-rep\msb11022\pfs\summative-hfs-pfs.pdf>

The HF Threshold Analysis for MSB11022 PFS that can be accessed in EDR via:

<\\CDSESUB1\evsprod\bla761255\0001\m3\32-body-data\32r-reg-info\medicaldevice\annexesformedicaldevice\annex-r-2-28.pdf>

D.2 AI

The HF Risk Management Report for MSB11022 AI that can be accessed in EDR via:

<\\CDSESUB1\evsprod\bla761255\0001\m3\32-body-data\32r-reg-info\medicaldevice\annexesformedicaldevice\annex-r-2-36.pdf>

The HF Summary and Assessment Report for MSB11022 AI that can be accessed in EDR via:

<\\CDSESUB1\evsprod\bla761255\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronicplaquepsoriasis\5354-other-stud-rep\msb11022\autoinjector\summative-hfs-autoinjector.pdf>

The HF Usability Engineering Report for MSB11022 AI that can be accessed in EDR via:

<\\CDSESUB1\evsprod\bla761255\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronicplaquepsoriasis\5354-other-stud-rep\msb11022\autoinjector\fksb-r-md-073-v01-human-factors-engineering-report-msb11022.pdf>

The HF URRR for MSB11022 AI starter pack that can be accessed in EDR via:

<\\CDSESUB1\evsprod\bla761255\0022\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronicplaquepsoriasis\5354-other-stud-rep\msb11022\starterpack\fksb-r-md-017-02-starter-pack-use-related-risk-analysis.pdf>

The HF Threshold Analysis for MSB11022 AI starter pack that can be accessed in EDR via:

<\\CDSESUB1\evsprod\bla761255\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronicplaquepsoriasis\5354-other-stud-rep\msb11022\starterpack\threshold-analysis-msb11022-starter-pack.pdf>

The HF Usability Engineering Report for MSB11022 AI starter pack that can be accessed in EDR

via: <\\CDSESUB1\evsprod\bla761255\0022\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronicplaquepsoriasis\5354-other-stud-rep\msb11022\starterpack\fksb-r-md-039-01-hf-ue-report-for-starter-pack.pdf>



APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

E.1 On December 23, 2021, we issued an Information Request (IR) to clarify if Fresenius Kabi would be able to:

- update the user interfaces for their AI and PFS configurations as described in the HF validation studies
- conduct an additional human factors validation study for their AI presentation
- conduct a comparative analysis and justification for not submitting HF validation study data for their PFS configuration

Fresenius Kabi provided an acceptable response on January 3, 2022, that can be accessed in EDR via: <\\CDSESUB1\evsprod\bla761255\0002\m1\us\111-info-amend\response-to-hf-information-request.pdf>

E.2 On February 17, 2022, we issued an IR to:

- request Fresenius Kabi resubmit their MSB11022 Starter Pack HF Validation Test Protocol under IND 124098
- clarify if Fresenius Kabi had already conducted their MSB11022 Starter Pack HF Validation study or to obtain their planned timeline for completion of the study
-  (b) (4)

Fresenius Kabi provided an acceptable response on February 22, 2022, that can be accessed in EDR via: <\\CDSESUB1\evsprod\bla761255\0008\m1\us\111-info-amend\response-to-questions-ir7-device-hfs.pdf> and on May 23, 2022, that can be accessed in EDR via: <\\CDSESUB1\evsprod\bla761255\0022\m1\us\12-cover-letter\cover-letter.pdf>

E.3 On March 7, 2022, we issued an IR to request Fresenius Kabi provide clarifications to:

- how long it takes for the medication to be injected for the AI (e.g., from the moment the injection button is pressed until all medication passes from the prefilled pen into the patient)
- the average injection completion time for the lot of autoinjectors tested in the HF validation study (time required for the autoinjector to complete the delivery of the drug)
- the purpose of watching the syringe plunger reach the bottom of the transparent syringe housing for the AI (i.e., when the plunger reaches the bottom of the transparent syringe housing, is the injection considered complete?)
- justification for the instructions “Continue holding the pen for 5 seconds after the syringe plunger has reached the bottom of the transparent housing” in sub-step 6.3 of your Instructions for Use for MSB11022 40 mg/0.8 mL AI.
- Provide data on how long these [participants with use errors in the AI HF validation study] held the device in place at the injection site during the injection

(b) (4)

Fresenius Kabi provided an acceptable response on March 11, 2022, that can be accessed in EDR via: <\\CDSESUB1\evsprod\bla761255\0010\m1\us\111-info-amend\response-to-questions-ir8-device-hfs.pdf>

E.4 On March 23, 2022, we issued an IR requesting Fresenius Kabi submit:

- The version of the Autoinjector pack used during the HF Validation Study (if available)
- The current version of the Autoinjector pack
-  (b) (4)
- The version of the 4-count autoinjector starter kit used in the HF validation study (at the time of the HF validation study report submission)
- The version of the 6-count autoinjector starter kit used in the HF validation study (at the time of the HF validation study report submission)
- The updated version of the 4-count autoinjector starter kit (at the time of the HF validation study report submission)
- The updated version of the 6-count autoinjector starter kit (at the time of the HF validation study report submission)

On March 25, we requested (via email) Fresenius Kabi submit pdfs for the AI  (b) (4) IFU that display the unfolded layout (front and back, if applicable) of the IFU as it would be used by the end user.

Fresenius Kabi provided an acceptable response on March 11, 2022, that can be accessed in EDR via: <\\CDSESUB1\evsprod\bla761255\0011\m1\us\12-cover-letter\cover-letter.pdf>, and on May 17, 2022, that can be accessed in EDR via: <\\CDSESUB1\evsprod\bla761255\0017\m1\us\12-cover-letter\cover-letter.pdf>

E.5 On May 3, 2022, we issued an IR requesting Fresenius Kabi submit the referenced document “MRS-AAI_S2_final_report_20191212”

Fresenius Kabi provided an acceptable response on May 5, 2022, that can be accessed in EDR via: <\\CDSESUB1\evsprod\bla761255\0016\m1\us\12-cover-letter\cover-letter.pdf>

E.6 On May 17, 2022, we issued an IR requesting Fresenius Kabi submit:

- The referenced document “MRS-AAI_S2_Description-of-Use-Events_20191205” and any related documents which describe the essential task use events that were observed during each of the simulated autoinjector injections.

Fresenius Kabi provided an acceptable response on May 18, 2022, that can be accessed in EDR via: <\\CDSESUB1\evsprod\bla761255\0019\m1\us\111-info-amend\responses-to-questions-ir17-received-on-17-may-2022.pdf>

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis¹, along with postmarket medication error data, we reviewed the following MSB11022 labels and labeling submitted by Fresenius Kabi USA, LLC. on December 13, 2021.

- Container labels
- Carton labeling
- Instructions for Use (Image not shown) for the PFS available from:
[\\CDSESUB1\evsprod\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-pfs^{\(b\) \(4\)}.pdf](\\CDSESUB1\evsprod\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-pfs^{(b) (4)}.pdf)
- Instructions for Use (Image not shown) for the AI available from:
<\\CDSESUB1\evsprod\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-ai.pdf>
- Instructions for Use (Image not shown) for the AI starter packs available from:
<\\CDSESUB1\evsprod\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-starter-pack.pdf>
-  (b) (4)
- Medication Guide (Image not shown) available from:
<\\CDSESUB1\evsprod\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide.pdf>
- Prescribing Information (Image not shown) available from:
<\\CDSESUB1\evsprod\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide.pdf>

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

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

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