

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761255Orig2s000

OTHER REVIEW(S)

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

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

Memorandum

Date: December 18, 2023

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 October 27, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton/container labels for the original-2 BLA submission for Idacio.

PI/Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on December 15, 2023, 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 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 emailed to OPDP on December 15, 2023, and we do not have any comments at this time.

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

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

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/s/

KYLE SNYDER
12/18/2023 03:57:09 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: December 18, 2023

To: Susie Choi
Regulatory 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 B. Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

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

Subject: DMPP Concurrence with Submitted: Medication Guide (MG)

Drug Name (established name): IDACIO (adalimumab-aacf)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761255

Supplement Number: Original 2

Applicant: Fresenius Kabi USA, LLC

1 INTRODUCTION

On 13 December 2021, Fresenius Kabi USA, LLC submitted a 351(k) Biologics License Application (BLA 761255) for MSB11022, as a proposed biosimilar to Humira®. On December 13, 2022, the Agency issued an approval of BLA 761255/Original 1-single-dose prefilled pen and single-dose prefilled glass syringe. Also, on that same date the Agency issue a Complete Response Letter (CRL) for BLA 761255/Original 2 – Single-dose glass vial kit.

On July 7, 2023, Fresenius Kabi USA, LLC submitted responses to the CRL received on 13 December 2022 for the single-dose vial kit, thereby seeking approval for the vial kit presentation. The CRL identified deficiencies at the vial kit manufacturing site, (b) (4) during pre-license inspection (PLI) conducted between (b) (4) and indicated that satisfactory resolution of these deficiencies was required for the application to be approved.

On October 27, 2023, the Division of Rheumatology and Transplant Medicine (DRTM) requested that the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) review the Applicant's proposed MG for IDACIO (adalimumab-aacf). This memorandum documents the DMPP review and concurrence with the Applicant's proposed MG, for IDACIO (adalimumab-aacf) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft IDACIO (adalimumab-aacf) MG received on July 7, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 15, 2023.
- Draft IDACIO (adalimumab-aacf) Prescribing Information (PI) received on July 7, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 15, 2023.

3 CONCLUSIONS

We find the Applicant's proposed MG is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP and OPDP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
12/18/2023 02:12:46 PM

KYLE SNYDER
12/18/2023 03:21:56 PM

MARCIA B WILLIAMS
12/18/2023 03:27:08 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 8, 2023

Requesting Office or Division: Division of Rheumatology and Transplant Medicine (DRTM)

Application Type and Number: BLA 761255

Product Name, Dosage Form, and Strength: Idacio
(adalimumab-aacf)
injection,
40 mg/0.8 mL

Applicant Name: Fresenius Kabi

TTT ID #: 2023-5467-1

DMEPA 1 Safety Evaluator: Sarah K. Vee, PharmD

DMEPA 1 Team Leader (Acting): Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised prescribing information and carton labeling received on December 7, 2023 for Idacio. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised prescribing information and carton labeling for Idacio (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that the Agency made in an information request.^a

2 CONCLUSION

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

^a Choi, S. Information Request for Idacio (BLA 761255). Silver Spring (MD): FDA, CDER, OSE, DRTM (US); 2023 DEC 04.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON DECEMBER 7, 2023

Prescribing information (no image) available at:

<\\CDSESUB1\evsprod\BLA761255\0087\m1\us\114-labeling\114a-draft-label>

Carton labeling



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/s/

SARAH K VEE
12/08/2023 12:56:41 PM

DAMON A BIRKEMEIER
12/08/2023 01:35:33 PM

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:	November 9, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761255
Product Name, Dosage Form, and Strength:	Idacio (adalimumab-aacf) injection, 40 mg/0.8 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fresenius Kabi
FDA Received Date:	July 7, 2023, September 7, 2023, October 19, 2023
TTT ID #:	2023-5467
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

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, container label, and carton labeling for areas of vulnerability that may lead to medication errors.

REGULATORY HISTORY

BLA 761255 was submitted on December 13, 2021 seeking licensure of adalimumab-aacf as a biosimilar to U.S.-licensed Humira (BLA 125057). For administrative purposes, the Division of Rheumatology and Transplant Medicine (DRTM) have designated as follows:

- BLA 761255/Original 1 – single-dose prefilled pen and single-dose prefilled glass syringe
- BLA 761255/Original 2 – single-dose glass vial kit

BLA 761255/Original 1 was approved on December 13, 2022 while BLA 761255/Original 2 received a complete response (CR).

We note that comments for the vial kit instructions for use (IFU) were not relayed to the Applicant during the first review cycle. Thus, on October 5, 2023, we sent an information request (IR)^a containing recommendations for the vial kit IFU. On October 19, 2023, the Applicant submitted a response to the IR (Appendix F).

MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this 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

OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note that the container label and carton labeling for the vial kit was previously reviewed (see Appendix B). Our evaluation of the proposed Idacio Prescribing Information, Medication Guide,

^a BLA 761255 Original-2 MSB11022/Idacio FDA information request- vial kit IFU Dated 2023 OCT 05

and container label did not identify areas of vulnerability that may lead to medication errors. However, our review identified areas for improvement for the carton labeling and instructions for use.

CONCLUSION & RECOMMENDATIONS

The proposed carton labeling and instructions for use are not acceptable from a medication error perspective, and we have provided recommendations for Fresenius Kabi in Section 5.1.

5 RECOMMENDATIONS FOR FRESENIUS KABI

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

A. Instructions for Use

1. Revise step 3.1 to more clearly indicate that the needle is not needed for this step. For example, include an additional bullet stating “Note: the needle is not needed during Step 3. Do not open the needle outer packaging until instructed to do so in Step 4.1”.
1. Step 5.1: The use of the word “Or” could be removed and the bullets cleaned up in step 5.1. In addition, the language regarding injecting in the arm should be updated to include reference to the “back of the arm”. For example: “5.1 Choose an injection site on the:
 - front of the thighs,
 - stomach-area. Do not use the area 2 cm around the belly button (navel)
 - outer area of the back of the upper arm

B. Carton Labeling

1. As currently presented, the background color scheme (b) (4) that is used to highlight the dosage form is more prominent than other important information on the principal display panel (PDP) such as the proprietary name, proper name, and strength. We recommend that you consider to either increase the font size and prominence of the proprietary name, proper name, and strength presentation or decrease the size of the color blocking associated with the dosage form statements to provide greater prominence to more important product information on the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Idacio received on July 7, 2023 from Fresenius Kabi.

Table 2. Relevant Product Information for Idacio	
Initial Approval Date	N/A
Nonproprietary Name	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 adult patients. <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 injection
Dosage Form	injection
Strength	40 mg/0.8 mL

Table 2. Relevant Product Information for Idacio

Dose and Frequency

Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis:

- *Adults:* 40 mg every other week.
- Some patients with RA not receiving methotrexate may benefit from increasing the dosage to 40 mg every week or 80 mg every other week.

Juvenile Idiopathic Arthritis:

Pediatric Weight 2 Years of Age and Older	Recommended Dosage
10 kg (22 lbs) to less than 15 Kg (33 lbs)	10 mg every other week
15 Kg (33 lbs) to less than 30 kg (66 lbs)	20 mg every other week
30 kg (66 lbs) and greater	40 mg every other week

Crohn's Disease:

- *Adults:* 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.
- *Pediatric Patients 6 Years of Age and Older:*

Pediatric Weight	Recommended Dosage	
	Days 1 and 15	Starting on Day 29
17 Kg (37 lbs) to less than 40 Kg	Day 1: 80 mg Day 15: 40 mg	20 mg every other week
40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 15: 80 mg	40 mg every other week

Ulcerative Colitis:

- *Adults:* 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:

Table 2. Relevant Product Information for Idacio	
	<i>Adults:</i> 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.
How Supplied	IDACIO PEN CARTON - 40 MG/0.8 ML (2 COUNT) IDACIO PEN 40 MG/0.8 ML - STARTER PACKAGE FOR PLAQUE PSORIASIS IDACIO PEN 40 MG/0.8 ML - STARTER PACKAGE FOR CROHN'S DISEASE, ULCERATIVE COLITIS IDACIO PREFILLED SYRINGE CARTON - 40 MG/0.8 ML (2 COUNT) IDACIO SINGLE-DOSE VIAL KIT - 40 MG/0.8 ML.
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 (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 September 8, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "Idacio" and "761255". Our search identified three previous reviews^{b,c,d} and we confirmed that our previous recommendations were implemented.

^b McMillan, T. Label and Labeling Review for Idacio (BLA 761255). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 SEP 29. TTT ID No.: 2021-2397.

^c 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.

^d Birkemeier, D. Human Factors Results Review for Idacio (BLA 761255). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 OCT 27. TTT ID No.: 202

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,^e along with postmarket medication error data, we reviewed the following Idacio labels and labeling submitted by Fresenius Kabi.

- Container label received on November 04, 2022
- Carton labeling received on September 7, 2023
- Prescribing Information (Image not shown) received on July 7, 2023, available from <\\Cdsub1\evsprod\BLA761255\0069\m1\us\114-labeling\114a-draft-label>
- Medication Guide received on July 7, 2023, available from <\\Cdsub1\evsprod\BLA761255\0069\m1\us\114-labeling\114a-draft-label>
- Instructions for Use received on October 19, 2023, available from <\\CDSESUB1\evsprod\BLA761255\0079\m1\us\114-labeling\114a-draft-label>

F.2 Label and Labeling Images

Container label



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

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/s/

SARAH K VEE
11/09/2023 12:01:07 PM

IDALIA E RYCHLIK
11/13/2023 09:36:59 AM

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)

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), vial kit

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
Vial Kit	Delivery of the Drug Product

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)

Vial adapter kit. In a May 5, 2022 meeting, the prospect of CDRH reviewing the vial adapter was raised. The vial kit consists of the following:

- One vial containing MSB11022 drug product (40 mg in 0.8 mL)
- One 1 mL syringe (b) (4)
- One injection needle (b) (4)
- two alcohol swabs (b) (4)
- One vial adapter (b) (4)
- One Instructions For Use (IFU), Medication Guide (MG) and Prescribing Information (PI) bundle

The vial adapter, syringe, and needle are pictured below. These components of the kit are 510(k) cleared, (b) (4)

Table 2 Vial kit Vial kit Device Assembly Components

Component	Description / Material	Drawing	(b) (4)
Vial Adapter	(b) (4)		
Syringe			
Needle			

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
Reviewer Comments 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 and Vial)</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:	(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:	3003708554
Responsibilities:	<u>Device Assembly</u> <u>Labeling and Secondary Packaging (PFS (b) (4) and AI)</u>
<u>Inspectional History</u> 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	
<u>Inspection Recommendation:</u> ☐ A choose an item inspection <u>is required</u> 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 <u>is not required</u> 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
Reviewer Comments 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

Design Inputs (Essential Performance Requirement)	Design Outputs (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 a (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						
	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 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						
	Major Injury	8	(b) (6)					
	Serious Injury	6		(b) (6)	(b) (6)			
	Minor Injury	4						
	Delay	2				(b) (6)		
	Inconvenience	1						
			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	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	(b) (6)	(b) (6)	High Risk Level	High Risk Level	High Risk Level	High Risk Level
	Minor Injury	4	(b) (6)	(b) (6)	Medium Risk Level	High Risk Level	High Risk Level	High Risk Level
	Delay	2	(b) (6)	(b) (6)	Medium Risk Level	Medium Risk Level	Medium Risk Level	Medium Risk Level
	Inconvenience	1	(b) (6)	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			

**Autoinjector
 Pre-mitigation**

SEVERITY	Death	10	High Level Risk	High Level Risk	High Level Risk	High Level Risk	High Level Risk	High Level Risk
	Major Injury	8	(b) (6)	High Level Risk	High Level Risk	High Level Risk	High Level Risk	High Level Risk
	Serious Injury	6	Medium Level Risk	(b) (6)	High Level Risk	High Level Risk	High Level Risk	High Level Risk
	Minor Injury	4	(b) (6)	(b) (6)	Medium Level Risk	High Level Risk	High Level Risk	High Level Risk
	Delay	2	Low Level Risk	(b) (6)	(b) (6)	Medium Level Risk	Medium Level Risk	Medium Level Risk
	Inconvenience	1	Low Level Risk	Low Level Risk	Low Level Risk	Low Level Risk	Low Level Risk	Medium Level Risk
			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)	(b) (6)	(b) (6)	(b) (6)	(b) (6)	(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 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

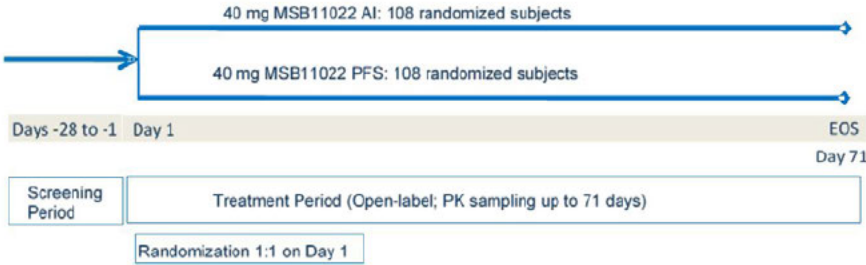
10.1. Review of Clinical Studies Clinical Studies

- 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.								

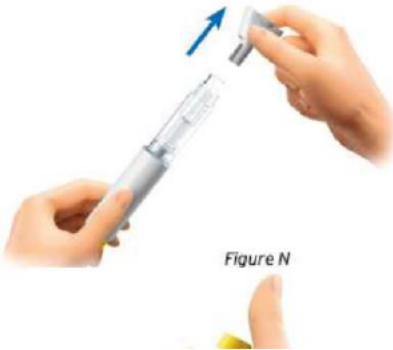
	There was one observed device failure. For subject (b) (6), a lower abdomen injection “UPON STARTING OF INJECTION, DEVICE STARTED MAKING A FIZZING/GURGLING SOUND AND TH [sic] IP STARTED TO BUBBLE OUT AROUND THE TOP OF THE NEEDLE.” Furthermore, “UNABLE TO ESTIMATE AMOUNT SUBJECT RECEIVED. WHEN THE DEVICE 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.  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	X ☒
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: a. 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. b. 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. c. 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. d. 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></td> <td></td> <td></td> <td>(b) (4)</td> </tr> <tr> <td>Break-Loose</td> <td></td> <td></td> <td></td> <td>(b) (4)</td> </tr> <tr> <td>Glide Force</td> <td></td> <td></td> <td></td> <td>(b) (4)</td> </tr> <tr> <td>Extra Activation Force</td> <td></td> <td></td> <td></td> <td>(b) (4)</td> </tr> <tr> <td>Override Force</td> <td></td> <td></td> <td></td> <td>(b) (4)</td> </tr> <tr> <td>Activation/locking of the safety system</td> <td></td> <td></td> <td></td> <td>(b) (4)</td> </tr> <tr> <td>Deliverable Volume</td> <td></td> <td></td> <td></td> <td>(b) (4)</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				(b) (4)	Glide Force				(b) (4)	Extra Activation Force				(b) (4)	Override Force				(b) (4)	Activation/locking of the safety system				(b) (4)	Deliverable Volume				(b) (4)
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Override Force				(b) (4)																																								
Activation/locking of the safety system				(b) (4)																																								
Deliverable Volume				(b) (4)																																								
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>>

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/s/

SUSIE B CHOI

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

**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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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 and vial cartons 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:

{ See appended electronic signature page }

Jenn Sellers, M.D., Ph.D.,
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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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/s/

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JENN W SELLERS
11/02/2022 09:12:27 AM

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

DATE: October 27, 2022

TO: Nikolay P. Nikolov, MD
Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Office of New Drugs

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

THROUGH: Kimberly A. Benson, Ph.D.
Deputy Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of MTZ Clinical Research,
sp. z o.o., Warsaw, Poland

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study FKS022-002 (BLA 761255, adalimumab biosimilar) conducted at MTZ Clinical Research, sp. z o.o., Warsaw, Poland.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out.

After reviewing the inspectional findings, I conclude that data from the audited study FKS022-002 are reliable.

2. Inspected Study:

Study Number: FKS022-002 (BLA 761255)
Study Title: "A randomized, double-blind, parallel-group, single-dose study to compare the pharmacokinetics, safety, tolerability, and immunogenicity of MSB11022 (acetate formulation) versus us-licensed reference product Humira® and Idacio® in healthy subjects"
Dates of conduct: 11/20/2019 - 12/30/2020

3. Inspectional Findings

ORA investigator Lakecha N. Lewis inspected MTZ Clinical Research, sp. z o.o., Warsaw, Poland from June 27 to July 8, 2022.

This was the first OSIS inspection of MTZ Clinical Research under the BA/BE program.

The current inspection included review of the subject screening and enrollment processes, source documents, informed consent, ethics committee approvals, delegation logs, subject site visits, monitoring site visits, concomitant medications, randomization, investigational product dispensing and retention, adverse events, test article accountability, laboratory results, and study protocol and amendments.

At the conclusion of the inspection, investigator Lakecha N. Lewis did not observe objectionable conditions and did not issue Form FDA 483 to the clinical site. There were no discussion items presented to the firm at the close-out meeting.

Note: Study subjects were also seen at an alternate address [MTZ Clinical Research Sp.z o.o.; Samodzielny Publiczny Zespół Zakładów Opieki Zdrowotnej (SPZ ZOZ); Independent Public Complex of Healthcare Institutions; Henryka Sienkiewicza 7, 09-100 Plonsk, Poland]. This alternate site was used to house the overflow of subjects during the overnight stays before and after dosing, mainly for sleeping. The Plonsk site was not used for other purposes. This temporary study site was closed during the COVID-19 pandemic.

4.1 Conclusion

After reviewing the inspectional findings, I recommend that clinical data from study FKS022-002 are reliable.

4.2. Specific concerns from OND (if applicable)

Not applicable.

cc: OTS/OSIS/Kassim/Folian/Pham/Yu/Mitchell/Fenty-Stewart/
Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Benson/Skelly/Au/Irier/Chen
ORA/OMPTO/OBIMO/FDAInternational BIMO@fda.hhs.gov
ORA/OMPTO/OBIMO/Lewis

ECMS Link:

<http://ecmsweb.fda.gov/webtop/drl/objectId/0b0026f883cb5578>

OSIS File #: BE9326 (BLA 761255)

eNSpect Operation ID #: 220526

Draft: XC 09/27/2022

Edits: MFS 09/27/2022; KAB 10/27/2022

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/s/

XIKUI CHEN
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MICHAEL F SKELLY
10/27/2022 01:29:44 PM

KIMBERLY A BENSON
10/27/2022 02:37:57 PM

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 and vial 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, and vial 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)			
1.	The statement (b) (4) " on the vial kit container label can be improved for readability and consistency with the carton labeling.	Improved readability and consistency with this statement will minimize confusion.	Revise the " (b) (4) " statement to the following: " Single dose vial- discard unused portion" "

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.	The statement (b) (4) on the principal display panel of the vial kit carton labeling is inconsistent.	Inconsistency amongst these statements may lead to confusion.	Revise the " (b) (4) to 'For subcutaneous use only' to align with the other carton labeling.
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.	There is no statement on the principal display panel of the vial kit carton labeling that states "Discard Unused Portion" after the 'single-dose vial' statement.	Omission of this statement may cause users to believe that the vial can be used for multiple doses.	Consider the following: 1 Single Dose Vial– Discard Unused Portion" to minimize risk of the entire contents of the vial being given as a single dose.

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. • Hidradenitis Suppurativa (HS): treatment of moderate to severe hidradenitis suppurativa in adult patients.
Route of Administration	Subcutaneous
Dosage Form	Injection

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. Hidradenitis Suppurativa: • Day 1: 160 mg (given in one day or split over two consecutive days) • Day 15: 80 mg • Day 29 and subsequent doses: 40 mg every week or 80 mg every other week
How Supplied	IDACIO (adalimumab-xxxx) injection is supplied as a preservative-free, sterile, clear, and colorless solution for subcutaneous administration. The following packaging configurations are available. • IDACIO Pen Carton - 40 mg/0.8 mL (1 count) IDACIO is supplied in a carton containing 2 alcohol preps and one tray. The tray contains a single-dose 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 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 • IDACIO Pen Carton - 40 mg/0.8 mL (4 count) IDACIO is supplied in a carton containing 4 alcohol preps and 2 trays. 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 Carton - 40 mg/0.8 mL (6 count)
IDACIO is supplied in a carton containing 6 alcohol preps and 3 trays. 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 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 or Hidradenitis Suppurativa
IDACIO is supplied in a carton containing 6 alcohol preps and 3 trays (Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa). 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 (1 count)
IDACIO is supplied in a carton containing 2 alcohol preps and one tray. The tray consists of 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.

	• 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. • IDACIO Prefilled Syringe Carton - 40 mg/0.8 mL (4 count) IDACIO is supplied in a carton containing 4 alcohol preps and 2 trays. Each tray contains two 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. • IDACIO Prefilled Syringe Carton - 40 mg/0.8 mL (6 count) IDACIO is supplied in a carton containing 6 alcohol preps and 3 trays. Each tray contains two 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. • IDACIO Single-Dose Vial kit - 40 mg/0.8 mL IDACIO is supplied in a carton containing 1 sterile single-use syringe, an adapter, 2 alcohol preps and 1 glass vial providing 40 mg/0.8 mL of IDACIO. The vial stopper is 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

	(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](\\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>
- Instructions for Use (vial) received on December 13, 2022, available from <\\CDSESUB1\EVSPROD\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-vial-kit.docx>
- 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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/s/

TERESA S MCMILLAN
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IDALIA E RYCHLIK
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MEMORANDUM

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

DATE: June 15, 2022

TO: Steven J. Lemery, MD, MHS
Director
Division of Oncology III
Office of Oncologic Diseases

Nikolay P. Nikolov, MD
Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation

FROM: Kara A. Scheibner, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Xingfang Li, MD, RAC
DGDSI
OSIS

THROUGH: Kimberly A. Benson, Ph.D.
Deputy Director
DGDSI
OSIS

SUBJECT: Remote record review (RRR) of [REDACTED] (b) (4)
[REDACTED]

1. RRR Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) of the analytical portion of Studies [REDACTED] (b) (4) and FSK022-002 (BLA 761255, Adalimumab), conducted at [REDACTED] (b) (4)

We observed the following objectionable conditions affecting study [REDACTED] (b) (4) did not report all acceptable data, and 2) [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

Based on our review of the objectionable conditions observed during the RRR and the firm's response to the RRR observations, we conclude that objectionable condition 2 may impact the reliability of data from the audited studies. Based on the data, and acknowledged in (b) (4) response (**Attachment 1**), the NAb assay from study (b) (4) may yield false negative results and/or low titer values in NAb-positive samples (see Section 4.1.2 for additional details). Thus, data from the NAb assay (b) (4)

(b) (4) may not be reliable to support a regulatory decision. However, the objectionable conditions were isolated in nature and did not impact the reliability of pharmacokinetic and anti-drug antibody assays (b) (4)

Furthermore, the data from studies (b) (4) FSK022-002 are reliable.

2. Reviewed Studies

(b) (4)

Study FSK022-002 (BLA 761255)

"A randomized, double-blind, parallel group, single dose study to compare the pharmacokinetics, safety, tolerability and immunogenicity of MSB11022 (acetate formulation) versus US-licensed reference product Humira® and Idacio® in healthy subjects"

Please note: Only project RMMX (anti-drug antibodies) was audited for this study.

Sample Analysis Period: 04/01/2020 - 03/03/2021

3. Scope of RRR

OSIS scientists Kara A. Scheibner, Ph.D. and Xingfang Li, MD, RAC, reviewed the analytical portion of the above studies

[REDACTED]
[REDACTED]

conducted at [REDACTED] from

[REDACTED]

The RRR included an examination of study records, method validations, and sample analyses. The RRR also included interviews with the firm's management and staff.

4. RRR Observations

At the conclusion of the RRR, we observed objectionable conditions, specifically for study [REDACTED]. We discussed the following items (see Section 4.1) with the firm's management during the RRR close-out meeting.

Our evaluation of the observations that were discussed, and the firm's response dated [REDACTED] (**Attachment 1**) are presented below.

[REDACTED]

(b) (4)

(b) (4)

(b) (4)

5. Conclusion

After review of the findings, and (b) (4) response (**Attachment 1**) to the RRR observations, data from the NAb assay (b) (4) may not be reliable to support a regulatory decision. However, the objectionable conditions were isolated in nature and did not impact reliability of pharmacokinetic and anti-drug antibody assays (b) (4). (b) (4) Furthermore, the data from studies (b) (4) and FSK022-002 are reliable.

cc: OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGSI/Cho/Benson/Skelly/Au/Lewin/Scheibner/Li

Draft: KAS 06/13/2022
Edit: XFL 06/13/2022
Edit: MFS 06/14/2022
Edit: KAB 06/15/2022

[REDACTED] (b) (4)

ECMS: Cabinets/CDER OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/ANALYTICAL/ [REDACTED]

(b) (4)

[REDACTED] (b) (4)

OSIS File #:

[REDACTED] (b) (4)

[REDACTED] (b) (4) (BLA 761255)

[REDACTED] (b) (4)

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XINGFANG LI
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KARA A SCHEIBNER
06/15/2022 01:25:05 PM

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06/15/2022 01:31:14 PM

KIMBERLY A BENSON
06/15/2022 02:45:26 PM