

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761133Orig1s000

OTHER REVIEW(S)

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:	September 21, 2023
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761133
Product Name, Dosage Form, and Strength:	Entyvio (vedolizumab) injection, 108 mg/0.68 mL Entyvio Pen (vedolizumab) injection, 108 mg/0.68 mL
Applicant/Sponsor Name:	Takeda Development Center Americas, Inc. (Takeda)
TTT ID #:	2023-4194-2
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Idalia Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on September 20, 2023 for Entyvio and Entyvio Pen. The Division of Gastroenterology (DG) requested that we review the revised container labels and carton labeling for Entyvio and Entyvio Pen (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.^a

2 CONCLUSION

We note that Takeda requested a barcode exemption for the prefilled syringe container label on September 1, 2023. Office of Compliance (OC)/Office of Drug Security, Integrity, and Response (ODSIR) granted a barcode exemption under 21 CFR 201.25 (d) (1)(i) for the prefilled syringe container label on September 18, 2023.^b The revised carton labeling and container labels are acceptable from a medication error perspective and we have no further comments at this time.

^a Abraham, S. Label and Labeling Review for Entyvio and Entyvio Pen (BLA 761133). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 SEP 1. TTT ID No.: 2023-4194-1.

^b Chatterjee, S. Barcode Exemption Letter Granted for Entyvio Prefilled Syringe Container Label (BLA 761133). Silver Spring (MD): FDA, CDER, OC, ODSIR, (US); 2023 SEP 18.

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/s/

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09/21/2023 01:39:41 PM

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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:	September 1, 2023
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761133
Product Name, Dosage Form, and Strength:	Entyvio (vedolizumab) injection, 108 mg/0.68 mL Entyvio Pen (vedolizumab) injection, 108 mg/0.68 mL
Applicant/Sponsor Name:	Takeda Development Center Americas, Inc. (Takeda)
TTT ID #:	2023-4194-1
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Idalia Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on August 22, 2023 for Entyvio and Entyvio Pen. The Division of Gastroenterology (DG) requested that we review the revised container labels and carton labeling for Entyvio and Entyvio Pen (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.^a

2 CONCLUSION

The revised carton labeling and container labels may be improved to promote the safe use of the product from a medication error perspective. We provide our recommendations below in Section 3.1 for Takeda.

3 RECOMMENDATIONS FOR TAKEDA DEVELOPMENT CENTER AMERICAS, INC. (TAKEDA)

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

^a Abraham, S. Label and Labeling Review for Entyvio and Entyvio Pen (BLA 761133). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 AUG 7. TTT ID No.: 2023-4194.

3.1 RECOMMENDATIONS FOR TAKEDA DEVELOPMENT CENTER AMERICAS, INC. (TAKEDA)

Table 1. Identified Issues and Recommendations for TAKEDA (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
All Container Labels and Carton Labeling			
1.	As currently presented, route of administration (ROA) statement lacks prominence.	Lack of prominence of route of administration may lead to wrong ROA medication errors.	Increase the prominence of the ROA statement by increasing the font size or using a red font.
Carton Labeling			
1.	The statement, (b) (4) is found on the PDP.	PDP is reserved for the most critical information. Additionally, the package container type term clearly explains the product is a single-dose product and (b) (4) is understood from the package type term.	Delete the statement, (b) (4) to focus on other critical information.
Tray Lid Labels			
1.	The MG statement and the statements, "Store refrigerated.....Do not freeze. Do not shake" are bolded.	Overuse of bold font may diminish its effect on prominence for other important product information on the PDP.	We recommend to remove the bolding from the MG statement.
Prefilled Syringe Label, Prefilled Pen Label, and Tray Lid Labels			
1.	It is unclear what the lines on the right-side of prefilled syringe, the left side bottom of the tray lid labels, and the right-side bottom of the prefilled pen are.	An undefined barcode may lead to identification of medication errors.	Define the undefined lines of the container labels and tray lid labels or remove them.

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

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/s/

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HUMAN FACTORS STUDY REPORT REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	August 31, 2023
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761133
Product Type:	Combination Product (Biologic-Device)
Product Name, Dosage Form, and Strength:	Entyvio and Entyvio Pen ¹ (Vedolizumab) injection, 108 mg/0.68 mL
Device Constituent:	Prefilled syringe with needle safety device and autoinjector
Rx or OTC:	Rx
Applicant/Sponsor Name:	Takeda Pharmaceuticals U.S.A., Inc. (Takeda)
Submission Date:	March 27, 2023
TTT ID #:	2023-4329
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

¹ The proposed proprietary name for this BLA, Entyvio and Entyvio Pen were found conditionally acceptable on June 21, 2023.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study results reports submitted under Biologics License Application (BLA) 761133 for Entyvio (Vedolizumab) prefilled syringe (PFS) and autoinjector (AI).

1.1 PRODUCT DESCRIPTION

Table 1. Relevant Product Information	
Initial Approval Date	May 20, 2014
Therapeutic Drug Class or New Drug Class	integrin receptor antagonist
Active Ingredient (Drug or Biologic)	vedolizumab
Indication	indicated in adults for the treatment of: • moderately to severely active ulcerative colitis (UC). • moderately to severely active Crohn's disease (CD).
Route of Administration	Approved: Intravenous Proposed: Subcutaneous
Dosage Form	Approved: for injection Proposed: Injection
Strength	Approved: 300 mg Proposed: 108 mg/0.68 mL
Dose and Frequency	Approved: Recommended intravenous dosage in UC and CD: 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter. Proposed: Recommended subcutaneous maintenance dosage in UC: 108 mg administered every 2 weeks after at least 2 intravenous infusions.
How Supplied	Approved: <i>Intravenous Infusion</i>

	Entyvio (vedolizumab) for injection for intravenous infusion is supplied in sterile single-dose glass vials, containing 300 mg of vedolizumab as a white to off-white lyophilized cake. 300 mg single-dose vial in individual carton Proposed: (b) (4)
Storage	• Refrigerate Entyvio unopened vials, prefilled syringes, and prefilled pens at 2°C to 8°C (36° to 46°F). • If needed, the Entyvio prefilled syringe or Entyvio Pen can be left out of the refrigerator in original package at room temperature up to 25°C (77°F) for up to 7 days (for example, when traveling). Do not use Entyvio prefilled syringe or Entyvio Pen if left out of the refrigerator for more than 7 days. • Do not freeze Entyvio vial, prefilled syringe, or prefilled pen. Do not use Entyvio vial, prefilled syringe, or prefilled pen if it has been frozen. • Retain in original package to protect from light until the time of use.
Container Closure/Device Constituent	Approved: Vial Proposed: Prefilled syringe with needle safety device

	Autoinjector
Intended Users	Patients, Caregivers, Healthcare professionals (HCPs)
Intended Use Environment	home environment by lay users (patients and caregivers) and in a clinical environment by HCPs

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

Prefilled Syringe:

- On December 19, 2017, Takeda submitted a use-related risk analysis (URRA), comparative analyses, draft labels and labeling, and a justification for not submitting results of a HF validation study for the proposed prefilled syringe (PFS) presentation under IND 118980.
- On February 15, 2018, we completed the review of the submitted comparative analyses, URRA, and the Applicant's justification for the proposed PFS presentation and accepted the Applicant's conclusion that HF validation study results did not need to be submitted to support their marketing application².
- On October 2, 2020, the Applicant submitted their HF validation study protocol under IND 118980 for Entyvio Pen (Vedolizumab) injection, 108 mg/0.68 mL autoinjector (AI) in which they indicated that PFS user interface has changed (e.g., IFU revisions). As such, we recommended the Applicant conduct comparative analysis and determine whether they need to submit the results of a HF validation study. If they determine that an HF validation study does not need to be submitted for their product, we recommended they submit their use-related risk analysis, comparative analyses, and justification for not submitting the HF validation study to the Agency for review.
- On April 30, 2021, the Applicant submitted their HF validation study protocol under IND 118980 for Entyvio (vedolizumab) injection, 108 mg/0.68 mL PFS. We reviewed the protocol and provided recommendations.³
- On March 27, 2023, the Applicant submitted a BLA for Entyvio (Vedolizumab) injection under BLA 761133. This submission included an HF validation study results report for Entyvio (vedolizumab) injection, 108 mg/0.68 mL PFS, which is the subject of this review.

² Abraham, S. URRA and Comparative Analysis Review for Entyvio (IND 118980). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 15. RCM No.: 2018-11.

³ Lee, S. HF Protocol Review for Entyvio (IND 118980). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 SEP 01. RCM No.: 2021-921.

Autoinjector:

- On February 1, 2018, the Applicant submitted a HF study protocol for the proposed AI presentation under IND 118980. We reviewed the protocol and provided recommendations⁴.
- On March 7, 2019, the Applicant submitted a BLA for Entyvio Pen (Vedolizumab) injection under BLA 761133. This submission included an HF validation study results report. We reviewed the study results and recommended that the Applicant implement the provided revisions along with additional mitigations that they determine to be necessary to address the use-related issues and conduct and submit results of another HF validation study to demonstrate that the mitigations are effective and do not introduce new risks.⁵
- On December 17, 2019, a complete response (CR) letter was issued due to deficiencies, including human factors⁶.
- On August 3, 2020, a Type A meeting teleconference was held, where we provided a response to their HF related question and recommended the Applicant submit a HF validation study protocol for our review prior to conducting the HF validation study⁷.
- On October 2, 2020, the Applicant submitted their HF validation study protocol under IND 118980 for Entyvio Pen (Vedolizumab) injection, 108 mg/0.68 mL AI. We reviewed the protocol and provided recommendations.⁸
- On March 27, 2023, the Applicant submitted a BLA for Entyvio Pen (Vedolizumab) injection under BLA 761133. This submission included an HF validation study results report for Entyvio Pen (Vedolizumab) injection, 108 mg/0.68 mL AI, which is also the subject of this review.

1.3 MATERIALS REVIEWED

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

⁴ Abraham, S. HF Protocol Review for Entyvio (IND 118980). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 25. RCM No.: 2018-325.

⁵ Barlow, M. HF Results and Label and Labeling Review for Entyvio (BLA 761133). FDA, CDER, OSE, DMEPA (US); 2019 DEC 13. RCM No.: 2019-550 & 2019-541.

⁶ Richards, K. Complete Response Letter for Entyvio. Silver Spring (MD): FDA, CDER, OND, DGIEP (US); 2019 DEC 17. BLA 761133.

⁷ Richards, K. Type A Guidance Meeting for Entyvio. Silver Spring (MD): FDA, CDER, OND, DG (US); 2020 AUG 03. BLA 761133

⁸ Barlow, M. HF Protocol Review for Entyvio (IND 118980). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 DEC 03. RCM No.: 2020-2105.

Table 2. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	Section 1.1
Background Information Previous DMEPA HF Reviews	A
Background Information on Human Factors Engineering (HFE) Process	B
Human Factors Validation Study Report	C
Information Requests Issued During the Review	D – N/A
Labels and Labeling	E

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

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

Table 3. Study Methodology for Human Factors (HF) Validation Study		
Study Design Elements	Details (PFS)	Details (AI)
Participants	76 participants • 16 Injection-experienced patients • 15 Injection-naïve patients • 15 Injection-experienced caregivers • 15 Injection-naïve caregivers • 15 Healthcare professionals	75 participants • 15 Injection-experienced patients • 15 Injection-naïve patients • 15 Injection-experienced caregivers • 15 Injection-naïve caregivers • 15 Healthcare professionals
Training	No formal training was provided to the participants.	No formal training was provided to the participants.
Test Environment and Materials	The testing environment was manipulated to simulate the user's real-world environment in terms of seating, work surface, and props, and included the following: • Comfortable seating • Adequate lighting • Clean workspaces representative of a home/clinical setting • Background noises typical of a home/clinical environment • Supplies as described below. - o Production-equivalent PFS+NSD in commercially-representative packaging (including IFU) - o Injection pad with expandable strap and	The testing environment was manipulated to simulate the user's real-world environment in terms of seating, work surface, and props, and included the following: • Comfortable seating • Adequate lighting • Clean workspaces representative of a home/clinical setting • Background noises typical of a home/clinical environment • Supplies as described below - o Production-equivalent AI in commercially-representative packaging (including IFU) - o Injection pad with expandable strap and backing (to prevent accidental needle sticks)

	backing (to prevent accidental needle sticks) - o Mannequin (for caregiver and HCP participants only) - o Alcohol prep pads - o Simulated sink - o Hand soap - o Paper towels - o Sharps container - o Trash can - o Gloves (HCPs only) - o Face masks including ClearMask™ transparent surgical masks	- o Mannequin (for caregiver and HCP participants only) - o Alcohol prep pads - o Simulated sink - o Hand soap - o Paper towels - o Sharps container - o Trash can and recycling bin - o Gloves (HCPs only) - o Face masks, including ClearMask™ transparent surgical masks
Sequence of Study	• Simulated use scenario • Root cause probe • Knowledge tasks • Root cause probe • Subjective feedback (Moderator interviewed participant regarding their overall perception of the interface and if the interface is safe and effective for use)	• Simulated use scenario • Root cause probe • Knowledge tasks • Root cause probe • Subjective feedback (Moderator interviewed participant regarding their overall perception of the interface and if the interface is safe and effective for use)

2.2 DISCUSSION OF STUDY METHODOLOGY

PFS-

During the course of our review of the PFS HF validation study, we noted that the Applicant recruited seven proxy injection naïve caregivers. The Applicant indicated that they made extensive efforts to recruit ulcerative colitis (UC) or Crohn's disease (CD) caregivers for the study. Specifically, the Applicant indicated that they

- conducted recruitment and testing in seven different study sites over the course of 11 weeks
- actively prescreened participants in additional cities (50+) to identify any additional study locations
- had personnel engaged with 6+ nationwide recruiting avenues, which included national surveys, social media, patient advocacy groups, and recruitment via friends and family

Additionally, the Applicant indicated that two months after initial recruitment kickoff, the enrollment of UC/CD caregivers was plateauing at 70%. Due to all recruitment avenues being exhausted, the Applicant made a determination to open recruitment to proxy participants in

parallel to continued UC/CD caregiver recruitment efforts. The Applicant identified caregivers of patients living with plaque psoriasis, psoriatic arthritis, or rheumatoid arthritis as a proxy caregiver population for caregivers of patients with UC or CD. The Applicant stated that, *“Caregivers of mentioned patients exhibit similar age distributions, physical and cognitive capabilities, and mental and emotional states as caregivers of patients with UC/CD.”*, *“The treatments for these patients are also similar to the treatments for UC/CD (eg, biologics, steroids, immunosuppressants) and therefore the caregivers of these patients will have a similar familiarity and experience with treatments as UC/CD caregivers (eg, they may or may not have experience with subcutaneous injections as part of a patient’s therapy).”* and *“Caregivers and patients of the proxy disease population would not interact with the device differently than caregivers of patients with UC or CD and patients with UC or CD. Therefore, this proxy population was determined to be acceptable.”* In this particular instance, based on the Applicant’s abovementioned recruiting efforts, we find the inclusion of proxy caregivers of patients living with plaque psoriasis, psoriatic arthritis, or rheumatoid arthritis for caregivers of patients with UC or CD is reasonable.

AI-

During the course of our review of the AI HF validation study, we noted that the Applicant recruited one proxy injection experienced caregiver and seven proxy injection-naïve caregivers. The Applicant indicated that they made extensive efforts to recruit UC or CD caregivers for the study. Specifically, the Applicant indicated that they

- conducted recruitment and testing in five different study sites over the course of 11 weeks
- actively prescreened participants in additional cities (50+) to identify any additional study locations
- had personnel engaged with 6+ nationwide recruiting avenues, which included national surveys, social media, patient advocacy groups, and recruitment via friends and family

Additionally, the Applicant indicated that two months after initial recruitment kickoff, the enrollment of UC/CD caregivers was plateauing at 70%. Due to all recruitment avenues being exhausted, the Applicant made a determination to open recruitment to proxy participants in parallel to continued UC/CD caregiver recruitment efforts. The Applicant identified caregivers of patients living with plaque psoriasis, psoriatic arthritis, or rheumatoid arthritis as a proxy caregiver population for caregivers of patients with UC or CD. The Applicant stated that, *“Caregivers of mentioned patients exhibit similar age distributions, physical and cognitive capabilities, and mental and emotional states as caregivers of patients with UC/CD.”*, *“The treatments for these patients are also similar to the treatments for UC/CD (eg, biologics, steroids, immunosuppressants) and therefore the caregivers of these patients will have a similar familiarity and experience with treatments as UC/CD caregivers (eg, they may or may not have experience with subcutaneous injections as part of a patient’s therapy).”* and *“Caregivers and patients of the proxy disease population would not interact with the device differently than caregivers of patients with UC or CD and patients with UC or CD. Therefore, this proxy population was determined to be acceptable.”* In this particular instance, based on

the Applicant's abovementioned recruiting efforts, we find the inclusion of proxy caregivers of patients living with plaque psoriasis, psoriatic arthritis, or rheumatoid arthritis for caregivers of patients with UC or CD is reasonable.

3 RESULTS AND ANALYSES

We have carefully reviewed each observed event, the Applicant's URRAs, the participants' subjective feedback, the Applicant's RCA, the Applicant's comments, and proposed mitigations below.

3.1 ANALYSIS OF CRITICAL AND NON-CRITICAL TASK ERRORS

The HF validation study showed use errors, use difficulties, and close calls with the tasks listed below in this section; however, based on our review of the available assessment of these use errors/use difficulties/close calls, the available participants' subjective feedback, the Applicant's root cause analysis and the Applicant's mitigation strategies, we determined the residual risk is acceptable. Based on our assessment, we find that the labeling mitigations in place include information that is prominently placed within the labels and labeling to address the tasks below. Subsequently, we did not identify further need for risk mitigation strategies at this time to address the use errors related to the following tasks and find the residual risks are acceptable:

PFS Analysis

- Store product in refrigerator
- Check integrity of box
- Check expiry date
- Wait 30 minutes to allow to warm to room temperature
- Find a clean, flat surface
- Wash hands with soap and water
- Remove PFS from tray
- Inspect the PFS for damage
- Inspect the drug solution
- Select suitable injection site
- Wipe injection site with alcohol pad and allow to dry
- Remove needle cap straight off
- Dispose of needle cap
- Pinch and hold skin at injection site – there were 16 use errors observed with this task. The root cause analysis indicated that these use errors were due to negative transfer (participants did not pinch the injection site because they do not pinch the site when they do their current injections), mental model (participants did not pinch based on their belief on how the device should work), and slip (participants released their pinch of the injection site because they were more focused on the injection at the time). We sought input from the Division of Gastroenterology clinical team regarding the aforementioned errors from a clinical perspective. For more details on this topic, see

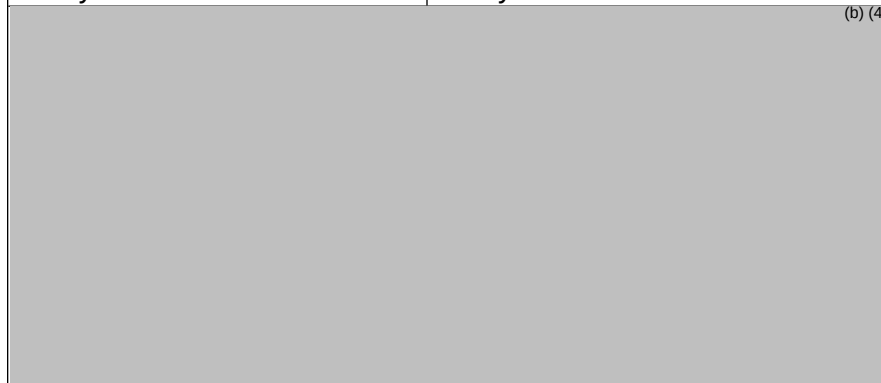
their response in the bullet below. Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.

- Insert the needle into the pinched skin at a 45-degree angle – there were 40 use errors and one close call observed with this task. The root cause analysis indicated that these use errors and close call were due to negative transfer (some participants inserted the needle straight into the skin because that is what they do with their current subcutaneous injections), mental model (some participants inserted the needle straight into the skin based on their belief on how the device should work), and slip (some participants inserted the needle straight into the skin because they did not read the IFU, and some participants accidentally prematurely depressed plunger before injection as they were not aware or did not intentionally push the plunger). The Applicant stated that, *“In addition, injecting at a 45-degree angle, to pinching the skin, users are also instructed to pinch the skin during injection, further reducing the risk of injecting into the IM space. Clinical assessments show IM and SC delivery exhibit similar PK profiles (CSR C13010). Therefore, while injecting at an angle greater than 45-degrees may result in injecting into the IM space, an IM injection is not expected to result in a loss of effect or reoccurrence of disease (flare).”* Our discussions with the Division of Gastroenterology clinical team indicated that they found this explanation acceptable. Based on the use errors and close call, the Applicant added the statement, *“Avoid touching the plunger until the needle is inserted”* to step 11, and updated Figure K to include more whitespace behind the plunger for additional clarity. We acknowledge the Applicant’s mitigation strategy and based on our review of the user interface, we did not identify any additional mitigations to address these user errors and close call and have no recommendations at this time.
- Press down on the PFS plunger until it stops – there was one use error observed with the simulated task. The root cause analysis indicated that this use error was due to resistance at the end of the injection (one participant pushed the plunger to inject all the medication but not enough to activate the needle shield because they felt that they had pushed the plunger all the way and that it would not go any further). Additionally, there were nine incorrect answers for the knowledge task (all nine participants did not report that healthcare provider should be contacted if they are not able to push down the plunger). The root cause analysis indicated that these incorrect answers were due to negative transfer (participants did not report that healthcare provider should be contacted if they are not able to push down the plunger but stated to pull the syringe a little and push it back in because the needle is possibly experiencing a blockage based on their experiences) and mental model (participants did not report that healthcare provider should be contacted if they are not able to push down the plunger but reported to remove the syringe and consider syringe defective based on their thinking).
Based on our review of the user interface, we did not identify any additional mitigations to address these user errors and have no recommendations at this time.
- Remove PFS from injection site following the injection while maintaining pressure on plunger

- Release the plunger to allow the needle-shield to deploy guard to cover the needle
- Dispose of PFS in a sharps container

AI Analysis

- Store product in refrigerator
- Check integrity of the box
- Check expiration date
- Warm AI to room temperature
- Wash hands
- Remove the AI from the box and tray
- Inspect the AI for exterior damage
- Inspect the drug solution for particulates or cloudiness through the window
- Select suitable injection site
- Clean injection site with alcohol pad
- Allow site to dry
- Remove AI Needle Cap
- Dispose of AI cap
- Place AI needle shield on injection site at an approximate 90-degree angle – there were four use errors observed with this task. The root cause analysis indicated that these use errors were due to negative transfer (participant inserted at a 45-degree angle because that is the angle at which she inserts her pre-filled syringe at home), and mental model (participants placed the needle shield at an angle less than 90-degrees based on their belief on how the device should work and one participant understood the illustration in Figure J to be depicting a slightly slanted angle based on her perception of an accurate 90-degree angle). Based on participant subjective feedback, the Applicant made the following IFU changes:
 - o Revised Figure J (b) (4) (b) (4) to provide further clarity regarding the 90-degree angle. See Figures 1 and 2 below:
 - o Adjusted the hand position on the pen (b) (4) to align with the hand position in Figure K through M. See Figures 1 and 2 below:

Figure 1. Image in IFU Step 10 used during the HF validation study	Figure 2. Revised image in IFU Step 10 post the HF validation study
	

We acknowledge the Applicant's mitigation strategy and based on our expert review of the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.

- Inject drug – there were 15 use errors and three use difficulties observed with this task. The root cause analysis indicated that these use errors and use difficulties were due to negative transfer (participants experienced difficulty determining how to initiate the injection because they are used to AIs that have buttons to initiate the injection, participants lifted the pen from site prematurely because they relied on their previous experience with AI and one participant did not realize she had not fully opened the IFU because the edge was folded over), mental model (participants lifted the pen from site prematurely because they associated a click sound with completeness), slip (participants lifted the pen from the site prematurely due to nerves) and study artifact (participant lifted the pen from site prematurely because they relied on being able to feel the medication going into their body to determine when the injection is complete). We note that the Applicant stated that the injection completion time ranges from (b) (4) seconds to (b) (4) seconds with the mean of (b) (4) seconds. We note that three of the 15 participants who experienced use errors or use difficulty with this task had an injection time (i.e., (b) (4) seconds) of more than (b) (4) seconds. Based on this information, these three participants received the full dose. Based on participant subjective feedback, the Applicant made the following IFU changes:
 - o Revised figure K and L to increase the size of the callouts depicting the viewing window before and after injection. Increased the size of the image of the window filled with purple and included the phrase "Injection Complete" with green text box with a check mark. See Figure 3 and 4 below.
 - o Removed the (b) (4) to emphasize the complete injection process carries across Figures K and L.
 - o Repositioned the injection phase labels "Injection Start" and "Injection Ongoing" to be immediately under the "Click" text to further emphasize the meaning of each click. The Applicant increased the font size for these labels from 10 to 11

for legibility and increased the overall figure size as much as possible. See Figures 3 and 4 below:

Figure 3. Image in IFU Step 10 used during the HF validation study

(b) (4)

Figure 4. Revised image in IFU Step 10 post the HF validation study

(b) (4)

- o Added the language “Continue to Step 9” with an associated arrow at the bottom of the first column of use steps (i.e., below step 8) to provide an additional cue to users that the instructions continue.

We acknowledge the Applicant’s mitigation strategies and based on our expert review of the user interface, we did not identify any additional mitigations to address these user errors and use difficulties and have no recommendations at this time.

- Dispose of AI in a sharps container

3.2 LABELS AND LABELING

We note that the DMEPA 1 primary review team evaluated product specific label and labeling under a separate cover.⁹

4 CONCLUSION

The results of the HF validation study demonstrated several use errors, close calls, and use difficulties with critical tasks that may result in harm. However, based on our review of the available participants' subjective feedback, the Applicant's mitigation strategies and root cause analysis from the HF validation study, we did not identify additional risk controls to address the use errors, close calls, and use difficulties. We find that the risks have been mitigated to an acceptable level and no further changes to the user interface are likely to further mitigate these risks. As such, we have no recommendations for this BLA.

⁹ Abraham, S. Label and Labeling Review for Entyvio and Entyvio Pen (BLA 761133). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 AUG 7. TTT ID No.: 2023-4194.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. BACKGROUND INFORMATION

A.1 PREVIOUS HF REVIEWS

A.1.1 Methods

On June 16, 2023, we searched previous DMEPA reviews relevant to this current review using the terms, “IND 118980”, “BLA 761133”, and “vedolizumab”.

A.1.2 Results

Our search identified four previous reviews^{10,11,12,13,14}, and we considered our previous recommendations to see if they are applicable for this current review.

B.2 PREVIOUS FDA/SPONSOR INTERACTIONS PERTAINING TO HF

The Agency provided human factors guidance to the Applicant in one meeting:

- <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805888f2>

APPENDIX B. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

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

APPENDIX C. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

Prefilled syringe- <\\CDSESUB1\EVSPROD\bla761133\0051\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ulcerative-colitis\5354-other-stud-rep\hf-sum-reports\hf-val-report-nsd-dn-000416978.pdf>

Autoinjector- <\\CDSESUB1\EVSPROD\bla761133\0051\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ulcerative-colitis\5354-other-stud-rep\hf-sum-reports\hf-val-report-ai-dn-000416977.pdf>

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

N/A

¹⁰ Abraham, S. URRA and Comparative Analysis Review for Entyvio (IND 118980). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 15. RCM No.: 2018-11.

¹¹ Abraham, S. HF Protocol Review for Entyvio (IND 118980). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 25. RCM No.: 2018-325.

¹² Barlow, M. Human Factors Results and Label and Labeling Review for Entyvio (BLA 761133). FDA, CDER, OSE, DMEPA (US); 2019 DEC 13. RCM No.: 2019-550 & 2019-541.

¹³ Barlow, M. Human Factors Validation Study Protocol Review for Entyvio (IND 118980). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 DEC 03. RCM No.: 2020-2105.

¹⁴ Lee, S. Human Factors Validation Study Protocol Review for Entyvio (IND 118980). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 SEP 01. RCM No.: 2021-921.

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹⁵ along with postmarket medication error data, we reviewed the following Entyvio labels and labeling submitted by Takeda Pharmaceuticals U.S.A., Inc. on March 27, 2023.

- Container label
- Carton labeling
- Instructions for Use (image not shown). Available from:
 - o Prefilled syringe- <\\CDSESUB1\EVSPROD\bla761133\0051\m1\us\entyvio-syringe-us-ifu-clean-26oct2022.pdf>
 - o Autoinjector- <\\CDSESUB1\EVSPROD\bla761133\0051\m1\us\entyvio-pen-us-ifu-clean-28oct2022.pdf>

E.2 Label and Labeling Images

Container label – PFS



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¹⁵ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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

PATIENT LABELING REVIEW

Date: August 21, 2023

To: Kelly Richards, RN, MSN
Senior Regulatory Health Project Manager
Division of Gastroenterology (DG)

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

From: Nyedra W. Booker, PharmD, MPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Quynh-Nhu Capasso, 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 (established name): ENTYVIO (vedolizumab)
ENTYVIO PEN (vedolizumab)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761133

Applicant: Takeda Development Center Americas, Inc.

1 INTRODUCTION

On March 27, 2023, Takeda Development Center Americas, Inc. submitted for the Agency's review a Resubmission of original Biologics License Application (BLA 761133) for ENTYVIO (vedolizumab) injection, for subcutaneous use and ENTYVIO PEN (vedolizumab) injection, for subcutaneous use. The proposed indication is for the maintenance treatment of adults with moderately to severely active Ulcerative Colitis (UC). ENTYVIO (vedolizumab) for injection, for intravenous use is commercially available and was approved on May 20, 2014.

This 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 Gastroenterology (DG) on August 2, 2022, and April 20, 2023, respectively, for DMPP and OPDP to review the Applicant's Medication Guide (MG) and Instructions for Use (IFU) for ENTYVIO (vedolizumab) injection, for subcutaneous use and ENTYVIO PEN (vedolizumab) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft ENTYVIO (vedolizumab) injection, for subcutaneous use and ENTYVIO PEN (vedolizumab) injection, for subcutaneous use MG and IFU received on March 27, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on August 11, 2023.
- Draft ENTYVIO (vedolizumab) injection, for subcutaneous use and ENTYVIO PEN (vedolizumab) injection, for subcutaneous use MG and IFUs received on March 27, 2023, revised by the Review Division throughout the review cycle, and received by OPDP on August 11, 2023.
- Draft ENTYVIO (vedolizumab) injection, for subcutaneous and ENTYVIO PEN (vedolizumab) injection, for subcutaneous use Prescribing Information (PI) received on March 27, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on August 11, 2023.
- Draft ENTYVIO (vedolizumab) injection, for subcutaneous and ENTYVIO PEN (vedolizumab) injection, for subcutaneous use Prescribing Information (PI) received on March 27, 2023, revised by the Review Division throughout the review cycle, and received by OPDP on August 11, 2023.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU 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 IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our review of the MG and IFU is 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 IFU.

Please let us know if you have any questions.

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08/21/2023 11:46:13 AM

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

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

Memorandum

Date: August 21, 2023

To: Kelly Richards, Senior Regulatory Health Project Manager
DROII/Division of Gastroenterology

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for ENTYVIO (vedolizumab) injection, for subcutaneous use; and ENTYVIO PEN (vedolizumab) injection, for subcutaneous use

BLA: 761133

Background:

In response to DG's consult request dated April 20, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), and carton and container labeling for the original BLA submission for ENTYVIO (vedolizumab) injection, for subcutaneous use; and ENTYVIO PEN (vedolizumab) injection, for subcutaneous use.

PI/MG/IFUs:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 11, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed MG and IFUs, and comments were sent under separate cover on August 21, 2023.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the applicant to the electronic document room on March 27, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	August 7, 2023
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761133
Product Name and Strength:	Entyvio (vedolizumab) ^a injection, 108 mg/0.68 mL Entyvio Pen (vedolizumab) ^a injection, 108 mg/0.68 mL
Total Product Strength:	108 mg/0.68 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Takeda Development Center Americas, Inc. (Takeda)
FDA Received Date:	March 27, 2023
TTT ID #:	2023-4194
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Idalia Rychlik, Pharm.D.

^aThe proper name 'vedolizumab' has an exception from the Biologics suffix requirement. Merchant, L. Memo for Evaluation of the Nonproprietary Name Through CDER Director (BLA761133). Silver Spring(MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 13.

1 REASON FOR REVIEW

As part of the approval process for Entyvio (vedolizumab) prefilled syringe and Entyvio Pen (vedolizumab) prefilled pen, the Division of Gastroenterology (DG) requested that we review the proposed Entyvio prefilled syringe and Entyvio Pen prefilled pen prescribing information (PI), medication guide (MG), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Entyvio intravenous formulation (BLA 125476) was approved on May 20, 2014 for the indications of adult ulcerative colitis (UC) and adult Crohn's disease (CD).^b On March 7, 2019, Takeda Pharmaceuticals submitted Entyvio prefilled syringe and Entyvio Pen prefilled pen (BLA 761133) to support maintenance treatment of adult patients with moderately to severely active Ulcerative Colitis (UC). We completed a human factors and label and labeling review on December 13, 2019 (OSE RCM#s 2019-550 & 2019-541).^c On December 17, 2019, BLA 761133 received a complete response (CR) due to product quality/manufacturing, device, and human factors deficiencies.

Thus, Takeda resubmitted BLA 761133 on March 27, 2023 for Entyvio prefilled syringe and Entyvio Pen prefilled pen.

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-N/A
Information Request	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D -N/A
Other	E-N/A
Labels and Labeling	F

^bKhosla, L. Label and Labeling Review for Entyvio (BLA 125476). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 NOV 26. OSE RCM No.: 2013-1621

^cBarlow, M. Human Factors and Label and Labeling Review for Entyvio and Entyvio Pen (BLA 761133). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 13. OSE RCM No.: 2019-550 and 2019-541

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

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

Takeda Pharmaceuticals submitted BLA 761133 to support subcutaneous administration of vedolizumab once every two weeks for maintenance treatment of adult patients with moderately to severely active Ulcerative Colitis (UC).^d The two proposed presentations are prefilled pen (PP) and prefilled syringe (PFS). Entyvio is currently approved in a single-dose vial presentation for UC and CD treatment via intravenous administration only under a separate BLA (BLA 125476).

In review of BLA 761133, we considered the potential medication error implications associated with the introduction of a new dosage form (injection vs. for injection) and new ROA (subcutaneous vs. intravenous) to the marketplace.

Prefilled Syringe:^e

We note there is a possibility of wrong dose errors and wrong route of administration if the intravenous infusion and subcutaneous formulations were confused for one another. However, we note that the strength/dose of the subcutaneous formulation is different from that of the currently marketed vial presentation for intravenous infusion (108 mg/0.68 mL versus 300 mg per vial). In an instance where the intended product is the prefilled syringe presentation, it is unlikely that the intravenous infusion formulation would be inadvertently prepared and administered subcutaneously. The container label and carton labeling of the currently approved intravenous infusion formulation of Entyvio states that the product is “For intravenous use only” and “Must be reconstituted and diluted prior to use”. Given the large volume of the

^dIn BLA 761133, the Applicant proposes the Entyvio (prefilled syringe) and Entyvio Pen presentations for maintenance treatment of adult patients with moderately to severely active Ulcerative Colitis (UC). Resubmission Cover letter. BLA 761133. 2023 March 27. [\CDSESUB1\EVSPROD\bla761133\0051\m1\us\cover-letter.pdf](#)

^eAbraham, S. Proprietary Name Review for Entyvio and Entyvio Pen (IND 118980 and BLA 761133). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 8. OSE Panorama #s: 2019-29312270 and 2019-29348539

intravenous formulation needed to administer a dose of 108 mg subcutaneously, it is unlikely that this error would occur.

Prefilled Pen:^e

Postmarketing experience shows that the introduction of product line extensions result in medication errors if the modifier is omitted and the product characteristics are similar or overlap.^f We also note there is a possibility of wrong dose errors and wrong route of administration if the modifier is omitted or overlooked. If the modifier 'Pen' were to be omitted, we note that the strength/dose of the subcutaneous formulation is different from that of the currently marketed vial presentation for intravenous infusion (108 mg *versus* 300 mg) and it is unlikely that the intravenous formulation would be inadvertently prepared and administered subcutaneously, given the large volume of the intravenous formulation needed to administer a dose of 108 mg subcutaneously.

We reviewed the proposed label and labeling for Entyvio prefilled syringe and Entyvio Pen to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. The proposed PI, MG, IFU, container labels, and carton labeling may be improved to promote the safe use of the product from a medication error perspective. We provide our recommendations below in Section 4.1 for the Division and Section 4.2 for Takeda.

4.1 RECOMMENDATIONS FOR DIVISION OF GASTROENTEROLOGY (DG)

A. Prescribing Information

1. Highlights (HL) of Prescribing Information

- a. Recommendations to increase the readability of important product information for Highlights are noted in track changes below:

(b) (4)



^f Lesar TS. Prescribing Errors Involving Medication Dosage Forms. J Gen Intern Med. 2002; 17(8): 579-587.

2. Full Prescribing Information: Section 2 Dosage and Administration
 - a. Recommendations to increase the readability and prominence of important dosage and administration within Section 2 are noted in track changes below:

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3. Full Prescribing Information: Section 16 How supplied/Storage and Handling
 - a. Recommendations for Section 16 are noted in track changes below:

4. Instructions for Use for Prefilled Syringe

- a. We note that package type terminology terms, “syringe” and “prefilled syringe”, are both used instead of “prefilled syringe” throughout the IFU. Revise the package type terminology to read “prefilled syringe” to be consistent with carton labeling and tray lid label.

5. Instructions for Use for Prefilled Pen

- a. We note that the package type terminology, “pen”, is used in the IFU, (b) (4) is used in the cover letter, prefilled pen is used on the carton labeling and container labels. Clarify the correct package type terminology and use it consistently across all label and labeling including IFU, MG, PI, container labels, and carton labeling.

- b. Entyvio Pen is referred to as “Entyvio” all throughout the IFU. Revise the proprietary name to “Entyvio Pen” to be consistent with the conditionally approved name and label and labeling.

4.2 RECOMMENDATIONS FOR TAKEDA DEVELOPMENT CENTER AMERICAS, INC. (TAKEDA)

Table 2. Identified Issues and Recommendations for Takeda Development Center Americas, Inc. (Takeda) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
All Container Labels and Carton Labeling			
1.	There is inadequate differentiation between the approved 300 mg vial strength presentation (purple color) and the proposed prefilled syringe and prefilled pen strength presentations (b) (4)	Lack of adequate differentiation in strength statement may contribute to product selection errors which may result in the wrong strength being dispensed and hence leading to wrong route of administration errors.	We recommend using different colors to ensure adequate differentiation between the strength statement of approved labeling compared to the container labels and carton labeling. Increase the prominence of the strength statement taking into account the prominence of other important product information on the labels and labeling (e.g. Proprietary name and proper name). See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
Tray Lid Label and Carton Labeling			
1.	The statement, (b) (4) is bolded and inconsistent with the PI.	Inconsistencies between PI and label and labeling may lead to misinterpretation and medication errors.	Revise the statement to read, “Keep in original package to protect from light until the time of use.” and remove the bolded font.
2.	The net quantity statement does not appear on the principal display panel.	21 CFR 201.51 Failure to include the net quantity statement on the principal display panel may	We recommend including a net quantity statement, “1 Single-Dose Prefilled Syringe or Prefilled Pen”, on the tray and

Table 2. Identified Issues and Recommendations for Takeda Development Center Americas, Inc. (Takeda) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		result in confusion regarding the contents of the container.	carton principal display panel and ensure it is located away from and less prominent than the product strength. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
Carton Labeling			
1.	Medication Guide (MG) statement is not on the PDP.	21 CFR 208.24(d). Overuse of bold font may diminish its effect on prominence for other important product information on the PDP.	Relocate the MG statement to the PDP and ensure that it is prominently displayed. Ensure the bolding is removed from the statement.
2.	The terminology within the Recommended Dosage statement [i.e., (b) (4) is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the recommended dosage statement to read, "Dosage: see Prescribing Information."
3.	The statement, "ATTENTION: Read Instructions for Use before use" , is on the PDP.	PDP is reserved for the most important information. Other less important statements should be on the side/back panel.	Relocate the statement, "ATTENTION: Read Instructions for Use before use", to the side/back panel.
4.	The statements, "Do not Use if Seals are broken and Keep Out of Reach of Children" are found on the PDP.	PDP is reserved for the most important information. Other less important statements should be on the side panel.	Relocate the statement, "Do not Use if Seals are broken" to the side/back panel. Delete the duplicated statement (b) (4) from the PDP as it is already on the side panel.

Table 2. Identified Issues and Recommendations for Takeda Development Center Americas, Inc. (Takeda) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
5.	There is inadequate differentiation between the [pre-filled syringe, and pre-filled pen] labeling.	Lack of adequate differentiation may contribute to dispensing wrong device medication errors.	We recommend using different colors, boxing, or some other means to ensure adequate differentiation between the presentations for the carton labeling.
Tray Lid Label			
1.	The strength presentation is not on the PDP.	Prominence and readability of the strength presentation is required per 21 CFR 201.15(a)(6).	Relocate the strength statement from the side panel to PDP. Consider placing the strength statement directly below the dosage form.
2.	The statements, “Single-Dose Prefilled Syringe” (b) (4) are bolded.	Overuse of bold font may diminish its effect on prominence for other important product information on the PDP.	We recommend to decrease the font size and remove the bolding from the statement, “Single-Dose Prefilled Syringe” . Delete the statement, (b) (4) to focus on other critical information.
3.	As currently displayed, the “Rx only” statement appears on the side panel.	Rx only statement is required on the PDP of the drug label by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.	Relocate “Rx only” statement to PDP.
Prefilled Syringe Container Label			
1.	The statement, “Single-Dose Prefilled Syringe” is bolded.	Overuse of bold font may diminish its effect on prominence for other important product information on the PDP.	We recommend to decrease the font size and remove the bolding from the statements, Single-Dose Prefilled Syringe” . Alternatively, consider deleting the statements, (b) (4) (b) (4)

Table 2. Identified Issues and Recommendations for Takeda Development Center Americas, Inc. (Takeda) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			(b) (4) as it is not required on a small container label and to prominently display other critical information such as the ROA statement.
Prefilled Pen Container Label			
1.	The statements, “Single-Dose Prefilled Pen”, ^{(b) (4)} [REDACTED] [REDACTED] are bolded.	Overuse of bold font may diminish its effect on prominence for other important product information on the PDP.	We recommend to decrease the font size and remove the bolding from the statements, “Single-Dose Prefilled Pen” ^{(b) (4)} [REDACTED] Alternatively, consider deleting the statements, ^{(b) (4)} [REDACTED] ^{(b) (4)} [REDACTED] ^{(b) (4)} as they are not required on a small container label and to prominently display other critical information such as the ROA statement.
Prefilled Syringe Container Label and Prefilled Pen Container Label			
1.	It is unclear if the linear barcode on the container label is scannable.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature.	Verify that the linear barcode is oriented in such a fashion as to be fully visible on one plane of reference and not obstructed by the curvature of the container which may render the barcode unscannable. This typically would be in the horizontal position for PFS devices. Confirm that the barcode is scannable.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Entyvio prefilled syringe and Entyvio Pen that Takeda Development Center Americas, Inc submitted on March 27, 2023.

Table 3. Relevant Product Information for Entyvio (prefilled syringe) and Entyvio Pen and Entyvio (intravenous infusion)		
Product Name	Entyvio and Entyvio Pen	Entyvio ^g
Initial Approval Date	N/A	May 20, 2014
Active Ingredient	vedolizumab	
Indication	Entyvio (prefilled syringe) and Entyvio Pen is for the maintenance treatment of adult patients with moderately to severely active Ulcerative Colitis (UC). ^h	Entyvio (vial) is indicated in adults for the treatment of a)moderately to severely active ulcerative colitis b)moderately to severely active Crohn's disease.
Route of Administration	Subcutaneous	Intravenous
Dosage Form	Injection	For Injection
Strength	108 mg/0.68 mL	300 mg/Vial
Dose and Frequency	SC Injection: 108 mg every two weeks (Q2W) for maintenance treatment following at least two intravenous infusions of Entyvio (vedolizumab) injection for intravenous use.	Recommended dosage in UC and CD: 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter.
How Supplied	Prefilled Syringe- 108 mg/0.68 single-dose prefilled syringe in an individual carton The single-dose, disposable ENTYVIO prefilled syringe is	Entyvio (vedolizumab) for injection is supplied as a sterile, white to off-white, preservative-free, lyophilized cake for intravenous infusion:

^gEntyvio Prescribing Information. DailyMed. Accessed April 20, 2023.

<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6e94621c-1a95-4af9-98d1-52b9e6f1949>

^hIn BLA 761133, the Applicant proposes the Entyvio (prefilled syringe) and Entyvio Pen presentations for maintenance treatment of adult patients with moderately to severely active Ulcerative Colitis (UC). Resubmission Cover letter. BLA 761133. 2023 March 27. [\CDSESUB1\EVSPROD\bla761133\0051\m1\us\cover-letter.pdf](#)

	comprised of a 1 mL long glass syringe with a fixed 27 gauge thin wall, ½ inch needle. The syringe has a rubber needle cover encased in a plastic shell and rubber stopper. (b) (4) (b) (4) not made with natural rubber latex. Prefilled Pen - 108 mg/0.68 single-dose prefilled pen in an individual carton The single-dose, disposable ENTYVIO prefilled pen (ENTYVIO Pen) is comprised of a 1 mL long glass syringe with a fixed 27 gauge thin wall, ½ inch needle. The syringe has a rubber needle cover encased in a plastic shell and rubber stopper. (b) (4) not made with natural rubber latex.	300 mg single-dose vial in individual carton.
Storage	Refrigerate ENTYVIO unopened vials, prefilled syringes, and prefilled pens at 2°C to 8°C (36° to 46°F). If needed, the ENTYVIO prefilled syringe or ENTYVIO Pen can be left out of the refrigerator in original package at room temperature up to 25°C (77°F) for up to 7 days (for example, when traveling). Do not use ENTYVIO prefilled syringe or ENTYVIO Pen if left out of the refrigerator for more than 7 days.	

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,ⁱ along with postmarket medication error data, we reviewed the following Entyvio and Entyvio Pen and labeling submitted by Takeda Development Center Americas, Inc. (Takeda).

- Container label(s) received on March 27, 2023
- Tray Lid Labels received on March 27, 2023
- Carton labeling received on March 27, 2023
- Sample Container label(s) received on March 27, 2023
- Sample Carton labeling received on March 27, 2023
- Medication Guide (Image not shown) received on March 27, 2023 available from <\\CDSESUB1\EVSPROD\bla761133\0051\m1\us\entyvio-vmb245-rx-medguide-clean-26dec2022.doc>
- Prescribing Information (Image not shown) received on March 27, 2023 available from <\\CDSESUB1\EVSPROD\bla761133\0051\m1\us\entyvio-vmb245-rx-uspi-clean-26dec2022.doc>
- Instructions for Use (Image not shown) received on March 27, 2023 available from [\\CDSESUB1\EVSPROD\bla761133\0051\m1\us\entyvio-\(b\)\(4\)-us-ifu-clean-26oct2022.doc](\\CDSESUB1\EVSPROD\bla761133\0051\m1\us\entyvio-(b)(4)-us-ifu-clean-26oct2022.doc)
<\\CDSESUB1\EVSPROD\bla761133\0051\m1\us\entyvio-pen-us-ifu-clean-28oct2022.doc>

F.2 Label and Labeling Images

Carton Labeling and Container Labels

Prefilled Syringe Label



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

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
08/07/2023 03:24:20 PM

IDALIA E RYCHLIK
08/07/2023 03:44:02 PM



DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	8/2/2023		
To:	Andrew Shiber		
Requesting Center/Office	CDER/OPQ	Clinical Review Division	N/A-OPQ/OSE led
From	Paige Spence OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Direct, Injection Team OPEQ/OHT3/DHT3C GHDB		
Subject	BLA 761133, Vedolizumab ICC2300285 00908322		
Recommendation	Filing Recommendation Date: 04/19/2023 ☐ CDRH did not provide a Filing Recommendation ☒ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5 for Deficiencies Mid-Cycle Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: Click or tap to enter a date. ☐ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761133
Sponsor	TAKEDA DEVELOPMENT CENTER AMERICAS INC
Drug/Biologic	Vedolizumab
Indications for Use	Ulcerative colitis
Device Constituent	Pre-Filled Syringe and Autoinjector
Related Files	ICC1900197, ICC2100671, ICC2000571

Important Dates	
Filing	4/18/2023
74-Day Letter	N/A
Final Lead Device Review Memo Due	7/12/2023
PDUFA Date	09/27/2023

Memo Legend:

Text quoted from the sponsor is provided in black italic text.

Text that represents the reviewer thoughts/comments is provided in blue.

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](#).

The sponsor made changes to the device needle tip cap (b) (4) This change adequately resolves CR1 related to needle clogging. The sponsor updated CAPA procedures and purchasing controls. These changes adequately address CR2 and CR3. The sponsor updated the AI cap removal force specification and provided verification data to support conformance. This adequately addressed CR4.

All CR deficiencies have been resolved. Changes made to the device post-CR are acceptable. There are no gaps or remaining deficiencies.

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:

PER CR Deficiency #1:

CDRH defers to CDER for the acceptability of the leachability study, assessment of the drug product protein concentration and addressing any biocompatibility concerns that may arise if a partial clog is injected into the body.

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 <u>Commitments or Requirements</u>	☐
CDRH does not have Post-Market Commitments or Requirements	☒

3. PURPOSE/BACKGROUND

3.1. Scope

TAKEDA DEVELOPMENT CENTER AMERICAS INC is requesting approval of Vedolizumab. The device constituent of the combination product is a Pre-Filled Syringe and Autoinjector.

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

We request a consult to review this BLA Resubmission. This application received a CRL on 12/17/2019.

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

- ☒ Device performance
- ☒ Biocompatibility of the patient contacting components
- ☐ Sterility
- ☒ Stability – device performance on stability
- ☒ Essential Performance Requirements (EPR) Control strategy
- ☒ Quality Systems Assessment

This review will not cover the following review areas:

- Compatibility of the drug with the device materials (deferred to CDER)
- Biocompatibility of the primary container closure, including needle (deferred to CDER)
- Sterility (primary container closure sterility deferred to CDER)
- Human Factors (deferred to DMEPA)

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

3.1.1. Related Files

See section 1 above.

3.2. Prior Interactions

The original BLA 761133 was submitted on March 7, 2019. The Complete Response Letter was issued on December 17, 2019. The CR Deficiencies under the purview of CDRH included: needle clogging, quality systems, and cap removal. Additional interactions post CR address approaches to address our concern. This review is reviewing the response to CR deficiencies from prior review

3.3. Indications for Use

Combination Product	Indications for Use
Vedolizumab	Ulcerative colitis
Pre-Filled Syringe and Autoinjector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0052	3, 2, 1
0054	3, 1
0058	1

4. DEVICE DESCRIPTION

4.1. Device [Description](#)

The following description was captured from the review memo for original review and is italicized to reflect this.

The following information was obtained from:

- 3.2.R Detailed Device Description PFS+NSD (DN000192017)
- 3.2.R Device PFS+AI Detailed Device Description (DN-000192131)

The prefilled syringe with needle safety device (PFS-NSD) (510(k) (b) (4)) is a single use combination product that delivers 0.68ml/108mg subcutaneously and includes a passive needle safety mechanism that is activated by the user at the end of the injection.

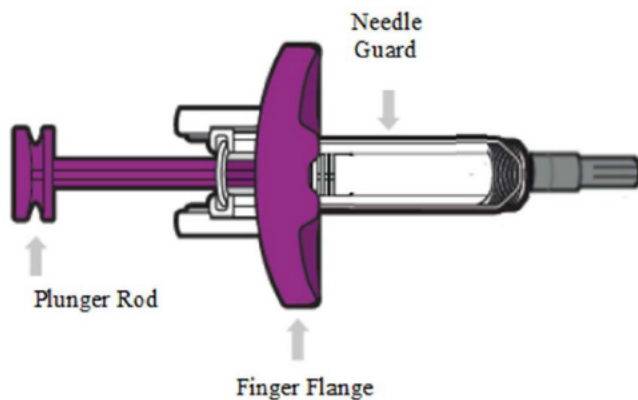


Table 1.a Details of PFS+NSD Components

Component	Description	Specification	Drawing Number	Supplier
Needle Guard				(b) (4)
Finger Flange				
Plunger Rod				
Prefilled Syringe				
Stopper				

The autoinjector (AI) is a single use combination product that delivers 0.68ml/108mg subcutaneously. The device is activated by removing the cap (purple) and pushing the needle cover onto the injection site. During the injection the user can see the injection progress.

Figure 1.b Illustration of Vedolizumab SC PFS+AI after Cap Removal



Figure 1.c Illustration of Vedolizumab SC PFS+AI Device Constituent Cross-section View of AI after Cap Removal



Table 1.a Technical Specification and Drawing for Each Component of Vedolizumab SC PFS+AI Combination Product

Component	Description	Specification	Drawing Number	Supplier
Cap & Body Subassembly	(b) (4)			
Prefilled Syringe	(b) (4)			
Stopper				

The PFS and AI are intended for home and clinic use environments and by lay-user and HCP users.

CR COMMENT 1:

You encountered multiple instances of full and partial needle clogging during stability and design verification testing

(b) (4)

The cap (b) (4) change is acceptable. This supported by reverification of performance discussed in Device Performance Review Section 7 below. CDRH agrees the 18-month shelf-life for all 3 configurations is acceptable.

4.2. Design Requirements
Basic Syringe Description/Requirements

Requirement	Reviewer Comment
-------------	------------------

Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Self-Administering/Caregiver/HCP																																																																																																																
Injection Site	Back of the Arms, Stomach Area, Thigh																																																																																																																
Injection tissue and depth of injection	Subcutaneous																																																																																																																
Type of Use (e.g. single use, disposable, reusable, other)	Single-Use, Disposable																																																																																																																
Environments of use (e.g. home, clinic)	Home/Clinic																																																																																																																
Storage conditions and expiry	Refrigerated 2°C to 8°C (36°F to 46°F) 25°C (77°F) for up to 7 days																																																																																																																
Needle connection (e.g. luer, slip tip, staked)	Staked																																																																																																																
Syringe/Autoinjector Volume	0.68 mL																																																																																																																
Device materials (b) (4)	<table><tr><td colspan="5">Table 1.a List of Components and Materials of Construction for Vedolizumab SC PFS+NSD</td></tr><tr><td>Item No.</td><td>Description</td><td>Quantity</td><td>Color</td><td>Material</td></tr><tr><td>1</td><td>Needle Guard</td><td>1</td><td>(b) (4)</td><td rowspan="6">(b) (4)</td></tr><tr><td>2</td><td>Spring</td><td>1</td><td></td></tr><tr><td>3</td><td>Body</td><td>1</td><td></td></tr><tr><td>4</td><td>Prefilled Syringe (PFS)</td><td>1</td><td>N/A*</td></tr><tr><td>5</td><td>Plunger Rod</td><td>1</td><td>Purple</td></tr><tr><td>6</td><td>Add-on Finger Flange (AFF)</td><td>1</td><td>Purple</td></tr><tr><td colspan="5">* See Module 3.2.P.1 Description and Composition of the Drug Product, PFS.</td></tr><tr><td colspan="5">Table 1.a List of Components and Materials of Construction for Vedolizumab SC PFS+AI</td></tr><tr><td>Item No.</td><td>Description</td><td>Quantity</td><td>Color</td><td>Material</td></tr><tr><td>1</td><td>Cap</td><td>1</td><td>Purple</td><td rowspan="14">(b) (4)</td></tr><tr><td>2</td><td></td><td></td><td>(b) (4)</td></tr><tr><td>3</td><td></td><td></td><td></td></tr><tr><td>4</td><td>Needle Cover</td><td>1</td><td>Yellow</td></tr><tr><td>5</td><td></td><td></td><td>(b) (4)</td></tr><tr><td>6</td><td>Body</td><td>1</td><td>White</td></tr><tr><td>7</td><td></td><td></td><td>(b) (4)</td></tr><tr><td>8</td><td>Pre-filled Syringe (PFS)</td><td>1</td><td>N/A*</td></tr><tr><td>9</td><td>Plunger Rod</td><td>1</td><td>Purple</td></tr><tr><td>10</td><td></td><td></td><td>(b) (4)</td></tr><tr><td>11</td><td></td><td></td><td></td></tr><tr><td>12</td><td></td><td></td><td></td></tr><tr><td>13</td><td></td><td></td><td></td></tr><tr><td>14</td><td></td><td></td><td></td></tr><tr><td colspan="5">* See Module 3.2.P.1 Description and Composition of the Drug Product, PFS.</td></tr></table>	Table 1.a List of Components and Materials of Construction for Vedolizumab SC PFS+NSD					Item No.	Description	Quantity	Color	Material	1	Needle Guard	1	(b) (4)	(b) (4)	2	Spring	1		3	Body	1		4	Prefilled Syringe (PFS)	1	N/A*	5	Plunger Rod	1	Purple	6	Add-on Finger Flange (AFF)	1	Purple	* See Module 3.2.P.1 Description and Composition of the Drug Product, PFS.					Table 1.a List of Components and Materials of Construction for Vedolizumab SC PFS+AI					Item No.	Description	Quantity	Color	Material	1	Cap	1	Purple	(b) (4)	2			(b) (4)	3				4	Needle Cover	1	Yellow	5			(b) (4)	6	Body	1	White	7			(b) (4)	8	Pre-filled Syringe (PFS)	1	N/A*	9	Plunger Rod	1	Purple	10			(b) (4)	11				12				13				14				* See Module 3.2.P.1 Description and Composition of the Drug Product, PFS.				
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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 As a part of the original review, the (b) (4) tip cap (b) (4) was identified as a cause of unacceptable needle clogging. The sponsor has changed the tip cap (b) (4). They described the updates acceptably and have provided a root cause analysis demonstrating the needle clogging issue has been mitigated. This is acceptable		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

5. FILING REVIEW

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

5.1. Filing Review Checklist

Filing Review Checklist				
Description		Present		
		Yes	No	N/A
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Reliability	X		
	Biocompatibility	X		
	Sterility	X		
	Shelf Life, Aging and Transportation of EPRs	X		
Quality Systems/ Manufacturing Controls Check	Description of Quality Systems	X		
	Control Strategy provided for EPRs	X		

5.2. Facilities & Quality Systems Triage Inspection Recommendation Information

CDRH completed a review of the Facilities	☒ Yes ☐ No ☐ N/A
Inspection Recommendation	☐ Pre-Approval Inspection (PAI) ☒ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection Needed ☐ N/A
CDRH completed a review of the Quality Systems	☒ Yes ☐ No ☐ N/A

*If a Facilities and/or Quality Systems Review is completed, the review is located in [Appendix B](#)

ADD COMMENT BOX TO DISCUSS THE DEFICIENCY

5.3. Filing Recommendation

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: See Appendix B for full Facilities Memo
Refuse to File Deficiencies: ☐ Yes ☒ No ☐ N/A
74-Day Letter Deficiencies: ☐ Yes ☒ No ☐ N/A

☒ **No Additional Information Requests to add**

6. RISK ANALYSIS

1. Risk Management Plan

Reviewer Comments: The sponsor's approach to risk management has not changed. The sponsor has provided an adequate description of the risk assessments and summary of risk reduction, evaluation, mitigation, and acceptance in the original submission. There were no outstanding deficiencies. The risk management plan is acceptable.

2. Hazard Analysis and Risk Summary Report

Reviewer Comments: The hazards and harms identified in the Hazard Analysis on the original submission were determined to be complete. The device cap (b) (4) has been changed to address an issue with needle clogged due to (b) (4) the needle cap (CR1). The hazard analysis has been appropriately revised to reflect hazards associated with needle clogging. The hazard analysis is acceptable.

3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION	
Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments There are no additional risk management concerns. This section is resolved.	
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No	

7. DEVICE PERFORMANCE REVIEW

7.1. Design Verification/Validation

7.1.1. Device Specification Standards and Guidance Documents

Syringe		Data Adequate		
		Yes	No	N/A
Pre-filled Syringe	ISO 11040-8, Prefilled syringes – Part 8: Requirements and test methods for prefilled syringes	☒	☐	☐
Co-packaged Syringe	ISO 7886-1, Sterile Hypodermic Syringes for Single Use—Part 1: Syringes for Manual Use	☐	☐	☒
Insulin Syringe	ISO 8537, Sterile single-use syringes, with or without needle, for insulin	☐	☐	☒
Needle/Sharps		Data Adequate		
		Yes	No	N/A
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use	☒	☐	☐

Needle	ISO 6009, Hypodermic needles for single use – Color coding for identification	☐	☐	☒
Sharps Injury Prevention Feature	ISO 23908 - Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	☒	☐	☐
Luer Lock		Data Adequate		
		Yes	No	N/A
<u>Connection</u>	ISO 80369-7, Small-bore connectors for liquids and gases in healthcare applications -- Part 7: Connectors for intravascular or hypodermic applications ** (replaces ISO 594-1 and 594-2 as of 2020) ISO 594-1, Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment -- Part 1: General requirements ISO 594-2, Conical fittings with 6 % (Luer) taper for syringes, needles and certain other medical equipment -- Part 2: Lock fittings	☐	☐	☒
Other - Autoinjector		Data Adequate		
		Yes	No	N/A
[Other]	11608-1,	☐	☐	☐
Automated Functions	11608-5,			

7.1.2. Device Performance Evaluation

Prefilled Syringe

<u>Design Input</u>	<u>Design Output</u>	<u>Verification Method</u>	<u>Results/Deviations</u>	Stability (Y/N)	Validated (Y/N)	Shipping (Y/N)
Safety Activation Force		(b) (4)	PASS	Y		
Dose Accuracy			PASS	Y		
Break loose Force			PASS	Y		
Gliding Force			PASS	Y		
Safety Shield Override Force			PASS	Y		
Pull off of Needle Shield			PASS	Y		
Finger Flange/Body Separation Force			PASS	N/A		
Body/Body Separation Force			PASS	N/A		
Needle Length			PASS	N/A		

Autoinjector

Essential Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy		(b) (4)	Y	Y – (b) (4) see comment	Y
Activation Force			Y	Y – (b) (4)	Y
Activation Stroke			Y	Y – (b) (4)	Y

Injection Time	(b) (4)	Y	Y	(b) (4)	Y
Needle Extension Length		Y	Y		Y
Cap Removal Force		~~N~~ CR#4 Y	Y		Y
Needle Cover Override Force		Y	Y		Y
Separation Force		Y	Y		Y

Title:	Cap Removal Force
Scope/Objective & Acceptance Criteria:	Scope is to evaluate the device cap removal force under standard conditions. Acceptance criteria - (b) (4) - -
Methods	ISO 11608-5
Results:	All samples met the acceptance criteria, sampling is appropriate, no deviations
Conclusions/ Reviewer Comments:	Method validated and designed as recommended by the standard, no deviations, tested new/updated specification. CR#4adequately resolved. See appdx. A for original CR deficiency.
Acceptable:	☐ Yes ☒ No

CR Comment 4: While you reduced your prefilled syringe tip cap removal specification to from (b) (4) based on your simulated use strength data (b) (4), you made no changes to the autoinjector cap removal force specification and it remains at (b) (4). Therefore, the proposed autoinjector cap removal force specification remains too high based on the simulated use testing provided, and you did not provide adequate evidence to validate the (b) (4) specification. Update your autoinjector cap removal force specification to (b) (4) and provide updated design verification reports demonstrating your autoinjector meets the updated specification.

CR Response: The AI cap removal force specification was updated in both the design input requirement document and the product specification to require a force greater than or equal to (b) (4) and less than or equal to (b) (4). Design Verification data demonstrated conformance with this specification at the (b) (4) confidence, (b) (4) reliability level. Data are provided in Module 3.2.P.2.4 Pharmaceutical Development – Container Closure System. PFS+AI stability data also demonstrating conformance with the specification are provided in Module 3.2.P.8.3 Stability Data – (b) (4) Primary Studies, PFS+AI.

Reviewer Comment: The AI cap removal force specification has been changed (b) (4). The sponsor has provided verification data to demonstrate conformance with this specification. This is acceptable.

7.1.3. Stability Review Summary

Shelf-life:	18-months
Storage conditions:	stored at 2-8°C with up to 7 days at 30°C
Time period and storage conditions provided for accelerated aging:	6-mo, 25°C±2°C/60%±5% RH
Time period and storage conditions provided for stressed aging:	1-mo, 40°C±2°C /75%±5% RH
Time period and storage conditions provided for real-time aging:	18-mo (PFS, 15-mo (PFS+NSD), 12-mo (PFS+AI), 5°C±3°C

*Endpoint evaluation is provided in [section 7.1.2](#).

Accelerated Conditions:

PFS:

MPI Lot #: 12100129 Manufactured At: (b) (4) Protocol Number: PRTC-0005216
 Batch Size: (b) (4) units Container / Closure: Glass 1mL, 27G 1/2 TW (b) (4) RNS (b) (4) with (b) (4) rubber stopper
 Conditions: 25°C / 60% RH Manufacture Date: 10 Jun 2021 Stab. Init. Date: 26 Jul 2021

Test Attribute	Initial	1 Month	3 Months	6 Months
Break Loose Force max value (N)	6	6	6	6
Glide Force max value (N)	7	7	7	10
Injectable Volume min value (mL)	0.70	0.72	0.70	0.73
Tip Cap Removal Force min value (N)	8	9	10	10
max value (N)	14	12	15	13

PFS+NSD:

MPI Lot #: 12143065 Assembled At: Takeda Austria Linz Protocol Number: PRTC-0004931
 Batch Size: (b) (4) units Assembly Date: 02 Nov 2021 Container / Closure: Glass 1mL, 27G 1/2 TW (b) (4) RNS (b) (4) with (b) (4) rubber stopper and NSD
 Conditions: 25°C / 60% RH PFS Fill Date: 10 Jun 2021 Stab. Init. Date: 24 Nov 2021

Test Attribute	Initial	1 Month	3 Months	6 Months
Break Loose Force max value (N)	6	6	6	6
Glide Force max value (N)	7	7	8	8
Safety Activation Force max value (N)	9	9	10	10
Dose Accuracy min value (mL)	0.71	0.71	0.71	0.71
Tip Cap Removal Force min value (N)	9	7	7	9
max value (N)	17	18	18	15

ICC2300285
 BLA 761133, Vedolizumab
 TAKEDA DEVELOPMENT CENTER AMERICAS INC

PFS+AI:

MPI Lot #: 12218263 Assembled At: Takeda Austria Linz Protocol Number: PRTC-0005810
 Batch Size: (b) (4) units Assembly Date: 11 Mar 2022 Container / Closure: Glass 1mL, 27G 1/2 TW (b) (4) RNS (b) (4) with (b) (4) rubber stopper and autoinjector
 Conditions: 25°C / 60% RH PFS Fill Date: 25 Aug 2021 Stab. Init. Date: 24 Mar 2022

Test Attribute	Initial	1 Month	3 Months	6 Months
Needle Extension				
min value (mm)	5.7	6.0	5.8	5.8
max value (mm)	6.7	6.7	6.6	7.6
Dose Accuracy				
min value (mL)	0.71	0.71	0.71	0.56 ^a
Activation Force				
min value (N)	8	7	7	7
max value (N)	8	9	8	75 ^b
Activation Stroke				
min value (mm)	12	12	12	12
max value (mm)	12	12	12	12
Injection Time				
min value (s)	4	4	4	4
max value (s)	5	5	5	6
Cap Removal Force				
min value (N)	6	8	8	7
max value (N)	12	12	13	11
Needle Cover Override Force				
min value (N)	170	164	167	173 ^c

a = For one unit (#24) out of the 60 tested not all the liquid was captured in the beaker. All other units are within specification limits.

b = Due to a side stream of one unit (#41) of the 60 tested, the laser detection of injection start was delayed. All other units are within the specification limits.

c = Min value is determined using 59 replicates as no data for unit 41 could be captured.

Real-Time Conditions:

PFS:

Lot #: 12100129 Manufactured At: (b) (4) Protocol Number: PRTC-0005216
 Batch Size: (b) (4) units Container / Closure: Glass 1mL, 27G 1/2 TW (b) (4) RNS (b) (4) with (b) (4) rubber stopper
 Conditions: 5°C Manufacture Date: 10 Jun 2021 Stab. Init. Date: 26 Jul 2021

Test Attribute	Initial	1 Month	3 Months	6 Months	9 Months	12 Months	15 Months	18 Months
Break Loose Force								
max value (N)	6	6	6	6	6	6	5	6
Glide Force								
max value (N)	7	7	7	7	7	6	7	7
Injectable Volume								
min value (mL)	0.70	0.71	0.72	0.72	0.71	0.72	0.72	0.72
Tip Cap Removal Force								
min value (N)	8	9	10	10	7	6	8	5
max value (N)	14	15	14	13	21	13	18	15

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PFS+NSD:

Lot #: 12143065 Assembled At: Takeda Austria Linz Protocol Number: PRTC-0004931
 Batch Size: (b) (4) units Assembly Date: 02 Nov 2021 Container / Closure: Glass 1mL, 27G 1/2 TW (b) (4) RNS (b) (4) with (b) (4) rubber stopper and NSD
 Conditions: 5°C PFS Fill Date: 10 Jun 2021 Stab. Init. Date: 24 Nov 2021

Test Attribute	Initial	1 Month	3 Months	6 Months	9 Months	12 Months	15 Months
Break Loose Force							
max value (N)	6	6	6	7	7	7	6
Glide Force							
max value (N)	7	7	7	9	8	8	7
Safety Activation Force							
max value (N)	9	10	10	11	10	11	10
Dose Accuracy							
min value (mL)	0.71	0.70	0.70	0.70	0.72	0.70	0.71
Tip Cap Removal Force							
min value (N)	9	9	9	10	8	10	7
max value (N)	17	18	15	20	17	18	17

PFS+AI:

Lot #: 12218073 Assembled At: Takeda Austria Linz Protocol Number: PRTC-0005810
 Batch Size: (b) (4) units Assembly Date: 09 Mar 2022 Container / Closure: Glass 1mL, 27G 1/2 TW (b) (4) RNS (b) (4) with (b) (4) rubber stopper and autoinjector
 Conditions: 5°C PFS Fill Date: 09 Aug 2021 Stab. Init. Date: 18 Mar 2022

Test Attribute	Initial	1 Month	3 Months	6 Months	9 Months	12 Months
Needle Extension Length						
min value (N)	5.9	5.9	5.9	5.8	6.0	6.1
max value (N)	6.5	6.6	6.5	6.5	6.5	6.7
Dose Accuracy						
min value (mL)	0.70	0.70	0.70	0.70	0.69	0.70
Activation Force						
min value (N)	8	8	7	7	8	7
max value (N)	9	9	8	8	8	8
Activation Stroke						
min value (mm)	12	12	12	12	12	12
max value (mm)	12	12	12	12	12	12
Injection Time						
min value (s)	4	4	4	4	4	4
max value (s)	7	5	6	5	5	5
Cap Removal Force						
min value (N)	8	7	7	7	8	8
max value (N)	12	12	11	12	11	11
Needle Cover Override Force						
min value (N)	161	167	165	165	173	164

Dual Temperature Data:

ICC2300285
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 TAKEDA DEVELOPMENT CENTER AMERICAS INC

PFS:

Lot #: 12100129 **Manufactured At:** (b) (4) **Protocol Number:** PRTC-0005216
Batch Size: (b) (4) units **Container / Closure:** Glass 1mL, 27G 1/2 TW (b) (4) RNS
Conditions: 25°C / 60% **Manufacture Date:** 10 Jun 2021 **Stab. Init. Date:** 26 Jul 2021
Dual Temp. Init. Date: 28 Oct 2022

<u>Test</u>			
Attribute	Initial (15M 5°C)	1 Week	2 Weeks
Break Loose Force			
max value (N)	5	6	6
Glide Force			
max value (N)	7	7	6
Injectable Volume			
min value (mL)	0.72	0.71	0.72
Tip Cap Removal Force			
min value (N)	8	6	8
max value (N)	18	13	13

PFS+NSD:

Lot #: 12143065 **Assembled At:** Takeda Austria Linz **Protocol Number:** PRTC-0004931
Batch Size: (b) (4) units **Assembly Date:** 02 Nov 2021 **Container / Closure:** Glass 1mL, 27G 1/2 TW (b) (4) RNS (b) (4)
Conditions: 25°C / 60% RH **PFS Fill Date:** 10 Jun 2021 **Stab. Init. Date:** 24 Nov 2021
Dual Temp. Init. Date: 25 Nov 2022

<u>Test</u>			
Attribute	Initial (12M 5°C)	1 Week	2 Weeks
Break Loose Force			
max value (N)	7	6	7
Glide Force			
max value (N)	8	7	9
Safety Activation Force			
max value (N)	11	11	11
Dose Accuracy			
min value (mL)	0.70	0.71	0.71
Tip Cap Removal Force			
min value (N)	10	8	7
max value (N)	18	17	16

PFS+AI:

Lot #: 12218073	Assembled At: Takeda Austria Linz	Protocol Number: PRTC-0005810
Batch Size: (b) (4) units	Assembly Date: 09 Mar 2022	Container / Closure: Glass 1mL, 27G 1/2 TW (b) (4) RNS (b) (4) with (b) (4) rubber stopper and autoinjector
Conditions: 25°C / 60% RH	PFS Fill Date: 09 Aug 2021	Stab. Init. Date: 18 Mar 2022
		Dual Temp. Init. Date: 20 Mar 2023

Test Attribute	Initial (12M 5°C)	1 Week	2 Weeks
Needle Extension Length			
min value (N)	6.1	6.1	6.1
max value (N)	6.7	6.6	6.6
Dose Accuracy			
min value (mL)	0.70	0.70	0.70
Activation Force			
min value (N)	7	8	8
max value (N)	8	8	9
Activation Stroke			
min value (mm)	12	12	12
max value (mm)	12	12	12
Injection Time			
min value (s)	4	4	4
max value (s)	5	6	5
Cap Removal Force			
min value (N)	8	8	8
max value (N)	11	12	12
Needle Cover Override Force			
min value (N)	164	169	168

Stressed is not called out in graphical format in this memo. See Sequence 0051 Module 3.2.P.8.1 for full stressed data.

Reviewer Comments

The sponsor has provided updated stability data. An in-depth discuss of needle clogging concerns (CR#1), the tip cap (b) (4) change, and resulting stability testing is discussed in Section 4 Device Description. The proposed shelf-life is acceptable.

The device has been labeled for an 18-month shelf-life with up to 7 days Call out dual temp and acceptability of the data.

7.1.4. Biocompatibility Evaluation

- ☐ Biocompatibility was **evaluated** [e.g. co-packaged syringes, co-packaged components outside of primary container closure]
- ☒ Biocompatibility was not evaluated **because**: no changes to patient contacting device components changed. Changes to the material to address the needle clogging change is deferred to CDER.

7.1.5. Sterility Evaluation

- ☐ Sterility **Evaluated** (e.g. co-packaged syringes, co-packaged components outside of primary container closure)

- ☒ Sterility not evaluated (syringe, including needle are part of primary container closure, sterility evaluation is under the purview of CDER)

7.2. Device Performance Review Conclusion

DEVICE PERFORMANCE REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments Device performance is acceptable.		
CDRH sent Device Performance Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

8. CLINICAL VALIDATION REVIEW

1. Review of Clinical Studies Clinical Studies

- ☐ There is no device related clinical studies for review
☒ There are clinical studies for review

Reviewer Comment: Clinical studies were reviewed in ICC1900197. For both the PFS+NSD and PFS+AI, full studies included 51 health males with injection sites in the thigh abdomen and arm. The studies were conducted with the final finished, to be marketed product. There were no deficiencies with the clinical studies. New clinical data was submitted non-related to CDHR deficiencies. **Assessment of the clinical data is deferred to CDER.**

2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION	
Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments	
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No	

- ☒ **No Additional Information Requests – Finalize Clinical Validation Review Section**

9. CONTROL STRATEGY REVIEW

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

Essential Performance Requirements Control Strategy Table – PFS

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

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or <u>release testing activities</u> :	Acceptable (Y/N/NA)
Safety Activation Force	Release testing of PFS+NSD	Y
Dose Accuracy	Release testing of PFS only	Y
Breakloose Force	Release testing of PFS only	Y
Gliding force	Release testing of PFS only	Y
Tip Cap Removal	Release testing of PFS only	Y

Essential Performance Requirements Control Strategy Table – AI

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

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or <u>release testing activities</u> :	Acceptable (Y/N/NA)
Dose Accuracy	Release testing	Y
Activation Force	Release testing	Y
Activation Stroke	Release testing	Y
Injection Time	Release testing	Y
Needle Extension Length	Release testing	Y

Reviewer Comments

Essential performance requirements control strategy was evaluated in the prior review (ICC1900197) and determined to be adequate.

Control Strategy Conclusion

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

9.1. Control Strategy Review Conclusion

CONTROL STRATEGY REVIEW CONCLUSION

ICC2300285
BLA 761133, Vedolizumab
TAKEDA DEVELOPMENT CENTER AMERICAS INC

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

<<END OF REVIEW>>

10.APPENDIX A (INFORMATION REQUESTS)

10.1. Complete Response Deficiencies

CR Deficiency #1 – Needle Clogging, see Section 4 of memo

CR Deficiency #2 – CAPA, see Section 11 (11.3.2)

CR Deficiency #3 – Purchasing Controls, see Section 11 (11.3.2)

CR Deficiency #4 – Cap Removal Force, see Section 7 (7.1.2)

All CR Deficiencies have been addressed.

(b) (4)



11.APPENDIX B: FACILITIES & QUALITY SYSTEMS REVIEW

11.1. Facilities Review Memo

ICCR FACILITIES REVIEW MEMO

Date: April 17, 2023

To: Andrew Shiber, OC/CDER/OPQ/OPRO/DRBPMI/RBPMB1

Courtney Evans, Injection Team (THT3C1), OHT3, OPEQ, CDRH
Office of Combination Products at combination@fda.gov

RPM: Andrew Shiber

Through: Alan Stevens, Assistant Director, Injection Team (THT3C1),
OHT3, OPEQ, CDRH

From: Paige Spence, Injection Devices, OHT3, OPEQ, CDRH

Applicant: Takeda Austria GmbH (TAU)
St. Peter-Straße 25
4020 Linz, Austria
FEI# 3001157285

Application # BLA 761133

Consult # ICC# 2300287

Product Name: Vedolizumab Injection

Combination Product Intended Use: Intended for use as a single-entity, single-use combination product for fixed-dosing of 108 mg vedolizumab to deliver a subcutaneous (SC) injection. The intended users are patients with Ulcerative Colitis (CD) or Crohn's Disease (CD), Health Care Provides (HCPs), or caregivers.

Pre-Approval Inspection: No

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BLA 761133, Vedolizumab
TAKEDA DEVELOPMENT CENTER AMERICAS INC

The Office of Gastrorenal, ObGyn, General Hospital, Urology Devices at CDRH received a consult from CDER requesting the identification of the device manufacturing sites for Application #761133 which will require a device inspection.

PRODUCT DESCRIPTION

The following information was obtained from:
3.2.R Detailed Device Description PFS+NSD (DN-000192017)
3.2.R DEVICE PSF+AI Detailed Device Description (DN-000192131)

The prefilled syringe (PFS) with needle safety device (NSD) is a single-entity, single use, fixed-dose combination product that delivers 0.68 mL vedolizumab subcutaneous (SC) drug product. The PFS+NSD is intended for use by patients with Ulcerative Colitis (CD) or Crohn’s Disease (CD), Health Care Provides (HCPs), or caregivers.

Figure 1.a Representative Illustration of Vedolizumab SC PFS+NSD

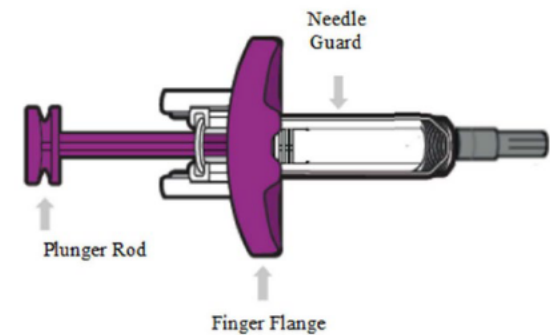


Table 1.a Details of PFS+NSD Components				
Component	Description	Specification	Drawing Number	Supplier
Needle Guard	(b) (4)			(b) (4)
Finger Flange				
Plunger Rod				
Prefilled Syringe	1 mL (b) (4) glass, 27G Thin Wall (b) (4) needle			
Stopper	(b) (4) rubber, (b) (4)			

The autoinjector (AI) is a single-entity, single-use, fixed-dose combination product with a pre-filled syringe (PFS) and Autoinjector (AI) device. The device contains 108 mg/0.68 mL vedolizumab SC drug product. The device is intended to be used in a home use environment, medical office, or hospital environment by patients with Ulcerative Colitis (CD) or Crohn’s Disease (CD), Health Care Providers (HCPs), or caregivers. To use, the AI cap (purple) is removed and the needle cover is pushed into the injection site. This action activates the automatic plunger and the used can see the plunger rod in the device viewing window.

Figure 1.b Illustration of Vedolizumab SC PFS+AI after Cap Removal



Table 1.a Technical Specification and Drawing for Each Component of Vedolizumab SC PFS+AI Combination Product				
Component	Description	Specification	Drawing Number	Supplier
Cap & Body Subassembly	(b) (4)			(b) (4)
	(b) (4)			
Prefilled Syringe	1mL (b) (4) glass, 27G Thin Wall 1/2" (b) (4) needle			
Stopper	(b) (4) rubber, (b) (4)			

Figure 1.c Illustration of Vedolizumab SC PFS+AI Device Constituent Cross-section View of AI after Cap Removal



REGULATORY HISTORY

The following facilities were identified as being involved in the manufacturing and/or development of the Vedolizumab SC PFS+NSD and Vedolizumab SC PFS+AI in Application #761133

1. Takeda Austria GmbH (TAU)
St. Peter-Straße 25
4020 Linz, Austria
FEI# 3001157285

Responsibility –

DP Function (PFS+NSD): Labeling & Assembly, Visual Inspection, Release and Stability Testing, Secondary Packaging, Secondary Labeling, and Batch Release.

DP Testing Performed (PFS+NSD): In-Process Testing, Functional Testing, and Post-Packaging Identity Testing.

DP Function (PFS+AI): Assembly & Labeling, Visual Inspection, Stability Testing, Release Testing, Secondary Packaging, Secondary Labeling, and Batch Release.

DP Testing Performed (PFS+AI): In-Process Testing, Functional Testing, Container Closure Integrity and Post-Packaging Identity Testing.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted 6/27/2022 to 07/01/2022. The inspection covered drug GMP and Coronavirus Activities and was classified NAI.

An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected for medical device QS.

Inspection Recommendation:

An inspection is required because:

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

2.



(b) (4)

Responsibility –

(b) (4)

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted [REDACTED] (b) (4). The inspection covered Drug Process Inspections (DPI) and was classified NAI.

Inspection Recommendation:

An inspection is not required because:

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

3.

[REDACTED] (b) (4)

Responsibility –

[REDACTED] (b) (4)

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted [REDACTED] (b) (4). The inspection covered mutual reliance human drug GMP and was classified VAI.

Inspection Recommendation:

An inspection is not required because:

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

Paige Spence

Inspectional Assignment

Firm to be inspected:

1. Takeda Austria GmbH (TAU)
St. Peter-Straße 25
4020 Linz, Austria
FEI# 3001157285

CDRH recommends a post-approval inspection under the applicable Medical Device Regulations.

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the Vedolizumab Injection (761133).

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY

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

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

Primary Contact

Paige Spence
TPLC Reviewer
Infusion Team
DHT3C
OHT3: Office of Gastrorenal, ObGyn, General Hospital, Urology Devices

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Courtney Evans
Team Lead
Injection Team
DHT3C
OHT3: Office of Gastrorenal, ObGyn, General Hospital, Urology Devices

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

11.2. Facility Inspection Report Review

Reviewer Comments

See Section 11.3.2 cGMP Review below for a discussion of the CAPA Deficiency (CR2) and Purchasing Controls Deficiency (CR3) and how they have been mitigated. These deficiencies have been adequately addressed.

Add Facility

☐ **No Additional Facilities**

Facilities Review Conclusion

The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.

☐ Yes

☐ No

11.3. Quality Systems Documentation Review

11.3.1. 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:

See ICC1900197

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:

See ICC1900197

Reviewer Comments

The Quality Systems Documentation Review was evaluated in ICC1900197 and determined to be adequate.

Device Manufacturing Process Conclusion

The Sponsor provided adequate information for the summary of the manufacturing process / production flow.

☒ Yes

☐ No

11.3.2. 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

☒ Drug cGMP-Based Streamline – [Review Instructions](#)

☐ Stream-line Both ([no streamlined approach](#))

21 CFR 820.20 Summary of Management Responsibility	Firm(s): Takeda	Reviewer Discussion – acceptable
21 CFR 820.30 Summary of Design Controls	Firm(s): Takeda	Reviewer Discussion – Reviewed in detail in Section 6
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): Takeda	Reviewer Discussion – CR3
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s): Takeda	Reviewer Discussion – Reviewed in Section 9.2.3 . CR2
21 CFR 820.170 Summary of Installation	Firm(s): N/A	Reviewer Discussion –

21 CFR 820.200 Summary Servicing	Firm(s): N/A	Reviewer Discussion –
Subpart F – Identification and Traceability	Firm(s):	Reviewer Discussion –
Subpart G – Production and Process Controls	Firm(s):	Reviewer Discussion – Reviewed in Section 7
Subpart H – Acceptance Activities	Firm(s):	Reviewer Discussion –
Subpart I – Nonconforming Product	Firm(s):	Reviewer Discussion –
Subpart K – Labeling and Packaging Controls	Firm(s):	Reviewer Discussion –
Subpart L – Handling, Storage, Distribution	Firm(s): Takeda	Reviewer Discussion –
Subpart M – Records	Firm(s): N/A	Reviewer Discussion –
Subpart O – Statistical Techniques	Firm(s): N/A	Reviewer Discussion –

Complete Response 2: You provided several SOPs which you state collectively address requirements for CAPAs.

(b) (4)

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

11.3.3. Corrective and Preventive Action Review

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

(b) (4)

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

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

Reviewer Comments

The Sponsor has addressed all CAPA related concerns called out in CR#2. The CAPA procedures are acceptable.

CAPA Conclusion

The Sponsor provided adequate information for corrective and preventive actions.

☒ Yes

☐ No

11.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION

Filing Deficiencies: ☐ Yes ☒ No
☐ N/A

Mid-Cycle Deficiencies: ☐ Yes
☒ No ☐ N/A

Final Deficiencies: ☐ Yes ☒ No
☐ N/A

Reviewer Comments: All Facilities and Quality Systems Review concerns have been addressed. See cGMP section above.

CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☒ No



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs, Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date of Consult Request: March 8, 2019
From: Division of Pediatric and Maternal Health (DPMH)
To: Division of Gastroenterology and Inborn Error Products (DGIEP)
BLA Number: 761133
Drug: Vedolizumab
Applicant: Takeda Development Center Americas, Inc
Indication: Ulcerative colitis and Crohn's disease

DGIEP submitted a consult request to DPMH on March 8, 2019 requesting assistance with preparation to discuss post-marketing requirements (PMR) under the Pediatric Research Equity Act (PREA) with the Pediatric Review Committee for this original BLA.

DPMH participated in internal team meetings with DGIEP from April to November 2019 to discuss the application. Due to the plan to issue a Complete Response, the team did not proceed with PREA PMR development.

The BLA contains an Agreed initial Pediatric Study Plan, and there are no changes in the planned deferrals for pediatric studies in patients 2 to 17 years of age with ulcerative colitis and Crohn's disease.

The DPMH Pediatrics Team has no further comments at this time. Therefore, this memorandum will close out the consult request. If labeling discussions resume, DPMH may be re-consulted.

DPMH Pediatric Team Leader- Mona Khurana, MD
DPMH Regulatory Project Manager- Denise Pica-Branco

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MONA K KHURANA
12/23/2019 02:50:55 PM

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

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Date of This Review:	December 13, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	BLA 761133
Product Name and Strength:	Entyvio (b) (4) and Entyvio Pen (vedolizumab) Injection, 108 mg/0.68 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	TAKEDA PHARMACEUTICALS
FDA Received Date:	March 7, 2019; March 26, 2019; August 13, 2019
OSE RCM #:	2019-550 & 2019-541
DMEPA Safety Evaluator:	Matthew Barlow, RN, BSN
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
DMEPA Associate Director of Human Factors:	QuynhNhu Nguyen, M.S.
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

Takeda Pharmaceuticals submitted BLA 761133 to support subcutaneous administration of vedolizumab once every two weeks for maintenance treatment of adult patients with moderately to severely active Ulcerative Colitis (UC) (b) (4)

(b) (4) The two proposed presentations under BLA 761133 are a prefilled pen and prefilled syringe (PFS). Entyvio is currently approved in a single -dose vial presentation for UC and Crohn's Disease (CD) treatment via intravenous administration only (BLA 125476).

We reviewed the human factors (HF) study report and proposed Entyvio prefilled pen (Entyvio Pen) and pre-filled syringe (Entyvio (b) (4) labels and labeling submitted on March 7, 2019 and March 26, 2019 for areas of vulnerability that may lead to medication errors.

1.2 REGULATORY HISTORY

Prefilled Syringe:

On December 19, 2017, Takeda submitted a use-related risk analysis (URRA), comparative analyses, draft labels and labeling, and a justification for not submitting results of a HF validation study for the proposed prefilled syringe (PFS) presentation under IND 118980.

On February 15, 2018, we completed the review of the submitted comparative analyses, URRA, and the Applicant's justification for the proposed PFS presentation and accepted the Applicant's conclusion that HF validation study results did not need to be submitted to support the marketing application^a.

Prefilled Pen:

On February 1, 2018, the Applicant submitted a HF protocol for the proposed prefilled pen presentation under IND 118980. On April 25, 2018, we completed the review of the submitted HF protocol and provided our recommendations^b for the HF protocol and proposed instructions for use (IFU) along with DMPP's IFU recommendations. We confirmed the Applicant implemented our recommendations.

2 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 Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A

^a Abraham, S. URRA and Comparative Analysis Review for Entyvio (IND 118980). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 15. RCM No.: 2018-11.

^b Abraham, S. HF Protocol Review for Entyvio (IND 118980). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 25. RCM No.: 2018-325.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters*	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Information Request Response from Applicant	F
Labels and Labeling	G

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 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our assessment of the HF validation study results and labels and labeling for the proposed vedolizumab injection is described below.

3.1 ANALYSIS OF THE HUMAN FACTORS VALIDATION STUDY RESULTS FOR ENTYVIO PREFILLED PEN

Tables 2 and 3 describes the errors/close calls/use difficulties observed in the HF validation study, the Applicant's reporting of the results and proposed mitigations, and DMEPA's analyses and recommendations.

Table 2: Analysis of HF Validation Study Results for Entyvio Prefilled Pen

Tasks (include C for critical and E for essential)	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis and Subjective Feedback	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Select a Correct Injection Site [C*] *The Applicant categorized this as an essential task, but we consider this task to be critical because a use error may result in harm.	Use Error (n=3; 3 injection-naïve patients)	-All 3 participants stated they would inject in their forearm.	The use errors observed for this task had a common root cause, negative transfer, in injection naïve patients who chose their forearms due to previous experience receiving medication in that area of their body. Many patients with UC/CD receive infusions, which are injected intravenously into the arm, as stated by two (2) of the users. This use error is not device specific.	None discussed.	Based on the Applicant's use-related risk analysis (URRA), the potential harm associated with failure to select a correct injection site includes an underdose, discomfort, and vascular damage if injected into a vessel. Our review of the labels and labeling finds that the IFU instructs users to "choose an injection site" (b) (4) under ste (b) (4) and includes a related figure to identify correct sites. (b) (4) Although we acknowledge that these participants relied on previous experience, we note that two participants (b) (4) (b) (4) overlooked this information. Therefore, we recommend revising (b) (4) to inform the user of the appropriate injection sites. Additionally, the current figure in (b) (4) the IFU (b) (4) that is intended to depict the injection

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					sites is unclear as to whether the shaded areas depict the front or the back of the arm (b) (4). As such, we recommend revising the figure depicting the back of the arm injection sites in the (b) (4) IFU to better anatomically capture the appropriate injection sites.
Remove the Device Cap [C*] *The Applicant categorized this as an essential task, but we consider this task to be critical because a use error may result in harm	Close Call (n=5; 2 caregivers; 3 HCPs)	-5 participants initially attempted to inject with cap on.	All end-users removed the cap from the AI, but five (5) participants almost did not remove the cap initially. After referencing the instructions after attempting an injection with the cap on, these users self-corrected. Users that did not initially remove the device cap mentioned that they did not think they would need to remove a cap or thought the medication would be dispensed from the white end.	None discussed	Based on the Applicant's URRAs, the potential harm associated with failure to remove the device cap is no dose and a recurrence of disease. We acknowledge that although the participants attempted to inject with the cap on, they were able to self-correct and remove the cap. However, (b) (4) we recommend revising (b) (4) to add a figure to the related instruction of removing the cap. Additionally, as some participants thought the medication would be dispensed from the incorrect ("white") end, we recommend

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			One (1) end-user removed the device cap and placed it down on the table prior to performing the injection and stated "I had to switch positions. It was just a surface. I used the alcohol swab on the skin."		labeling the body of the device to indicate which end contains the needle.
Keep Device Uncapped Prior to Injection [C*]	Use Errors (n=11; 2 injection-naïve participants, 1 injection experienced participant, 3 caregivers, 5 HCPs)	-11 participants took the cap off initially to explore the device, or due to confusion as they were expecting a button to be there, or due to wanting to know where the needle was specifically. Additionally, one of these participants activated the prefilled pen when recapping.	Eleven (11) end-users recapped the AI prior to administering the medication. One (1) of these users activated the AI when recapping. Some users appeared to be initially confused after removing the cap due to seeing the (b) (4) of the cap covering the needle coming off with the purple cap and thought they broke it. Some users were confused after removing the cap because they did not see the needle after removal.	Mitigations to prevent needle stick include instructions in the IFU not to recap the device and the yellow needle guard serves as a barrier to the needle. In addition, the needle guard must be depressed significantly in order to	Based on the Applicant's URRAs, the potential harm associated with recapping the device prior to injection is a missed dose and needlestick. We acknowledge that several participants initially removed the cap to examine the device, and then recapped the device once finished. Additionally, we acknowledge the current mitigation strategies in place to prevent a needle stick or premature activation including: the (b) (4) statement under step (b) (4) of the IFU, and the device design to include the yellow needle guard and activation force required to activate the pen. However, several

*The Applicant categorized this as an essential task, but we

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consider this task to be critical because a use error may result in harm.			This use error carries a low risk to the patient and/or user. Mitigations to prevent needle stick include instructions in the IFU not to recap the device and the yellow needle guard serves as a barrier to the needle. In addition, the needle guard must be depressed significantly in order to activate the AI.	activate the AI.	participants referenced (b) (4) the (b) (4) IFU and still recapped the pen. Therefore, we recommend adding a bold statement (b) (4) (b) (4). Additionally, we recommend improving the emphasis of the "Do not" statements under "Pull the purple cap straight off and throw it away" in the IFU.
Place Needle End Against Skin [C*]	Use Errors (n=2; 1 injection-naïve patient, 1 injection experienced caregiver) Close Calls (n=2; 2 HCPs)	-1 caregiver and 1 patient incorrectly oriented the AI and were stopped by the moderator and asked to check the orientation of the AI. -2 HCPs attempted the injection with the cap on, while pressing the cap end. They stated the cap looked like a spring/something you would push.	Users specified that they thought that the cap looked like a button or spring due to the ridges and suggested on-device labeling to indicate needle end of the device.	None discussed	Based on the Applicant's URRAs, the potential harm associated with incorrect orientation is injection into user's hand, pain, injury, and underdose. We acknowledge the current mitigation strategies in the IFU (b) (4) including: the figures showing where the needle is within the pen, the figure on the IFU (b) (4) (b) (4) showing the correct orientation to place the pen on the skin and the related instructions. However, 2 participants required moderator intervention as they had

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*The Applicant categorized this as an essential task, but we consider this task to be critical because a use error may result in harm					the needle end toward their finger, and 2 HCPs both attempted the injection with the cap on stating the cap looked like a spring or a button you should push. Therefore, we recommend modifying the device design to address the subjective feedback. For example, we recommend that the Applicant consider removing the ridges from the purple needle cap to minimize the risk of users misinterpreting the needle cap as a button to push. Additionally, because there is a risk of user not orienting the autoinjector properly which can result in needle stick injuries, we recommend labeling the device body to indicate which end contains the needle.
Hold at a 90-degree angle [C*]	Use Errors (n=1; 1 injection-naïve patient)	-1 participant stated they didn't know what a 90-degree angle is. They stated they should've looked at the picture, as they would've known they were wrong.	One (1) user injected at a 45-degree angle due to confusion about what the (b) (4) meant by a 90-degree angle. This user did not deliver a	None discussed	Based on the Applicant's URRAs, the potential harm associated with failing to hold the prefilled pen at a 90-degree angle is an underdose, injection into the incorrect tissue and pain. We acknowledge the current mitigation strategies in

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*The Applicant categorized this as an essential task, but we consider this task to be critical because a use error may result in harm			full dose due to leakage from the AI during the injection		place including: the IFU (b) (4) figures showing the prefilled pen at a 90-degree angle to the injection site along with the related instructions to place the prefilled pen at 90 degrees to the injection site. Therefore, we find the residual risk acceptable, and have no recommendations at this time for the observed error.
Administer a Full Dose [C*]	Use Errors (n=7*; 3 injection naïve patients, 3 caregivers, 1 HCP)	-1 participant activated with his fingers pressed on the yellow needle shield and dispensed the entire contents of the AI into the air prior to holding against the skin. -1 participant had inserted it at a 45-degree angle, resulting in medication leaking onto the injection pad. -5 participants lifted early	Full dose is indicated by the viewing window becoming completely blocked, but the user is instructed to count to ten to ensure the contents have been dispensed. Additional device feedback in the form of two audible clicks was also used by some users to indicate full dose. One (1) user squeezed the injection site prior to injecting. Five (5) end-users lifted early, one (1) user	None discussed	Based on the Applicant's URRAs, the potential harm associated with failure to administer a full dose is an under dose and disease flare up. 39 participants did not hold the prefilled pen at the injection site for 10 seconds, as indicated in the IFU; however, the Applicant did not categorize all these instances as use errors. Additionally, 5 participants lifted early enough for a stream of liquid medication to be observed (i.e., wet injection). Per the subjective feedback, participants were relying on different cues to signal that the injection was complete, such as, the second click,

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*The Applicant categorized this as an essential task, but we consider this task to be critical because a use error may result in harm	*Based on the provided data in the 8/13/19 IR response from the Applicant, we consider 8 participants to have had administered an incomplete dose (See Appendix F for IR response).		activated with his fingers, and one (1) user administered at a 45-degree angle, resulting in medication leaking onto the injection pad. The user that activated the device with his fingers pressed on the yellow needle shield and dispensed the entire contents of the AI into the air prior to holding it against the skin.		the viewing window being full, and/or counting to 10 seconds. However, per the report and IFU, the user is to confirm a full dose has been given by checking if the viewing window has been filled. Thus, we sent an information request (IR) to clarify why the Applicant did not categorize the 39 participants who held the prefilled pen at the injection site for less than 10 seconds as use errors and to better understand the average injection time (time required for the prefilled pen to complete delivery of the drug). The Applicant's IR response indicates the IFU provides guidance to count to 10, allowing for expected variation between users and is, on average, approximately (b) (4) the required time to deliver a complete injection based on their design verification data, which shows "the average injection completion time (b) (4)

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					(b) (4) (b) (4). However, the Applicant chose to only categorize a use error/incomplete dose for any participant that held the prefilled pen down on the injection site for less than (b) (4). Based on the data provided, we do not agree with the categorization and identified 8 participants that did not hold the prefilled pen at the injection site for at least (b) (4). Therefore, we recommend revising the IFU (b) (4) to further clarify the end of injection cues. Additionally, we recommend the Applicant consider revising the figures related to the injection sequence to add "clicks" placed near the needle end of the device and clarify to the user what each click signifies.
Check the Window is Filled with Purple [C*]	Use Errors (n=7; 3 injection experienced patients, 2 injection-naïve patients, 2 HCPs)	-1 patient participant stated they usually count to 10 or hear a click. They heard a click, wasn't sure if	Many of these users specified that they relied on the device clicks or counting to 10 to	None discussed	Based on the Applicant's URRAs, the potential harm associated with the failure to check the window is filled with purple is an incomplete or

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*The Applicant categorized this as an essential task, but we consider this task to be critical because a use error may result in harm		10 seconds but felt it was long enough. -2 patient participants heard the clicks and that was enough for them. -2 patient participants stated they didn't know to check the window. They were focused on just counting to 10 and hearing a second click. -1 HCP participant thought the second click was enough of a cue. -1 HCP participant stated they missed that highlighted piece.	determine if the injection was complete. Users that did not administer a full dose were not evaluated for this task, as the device operates differently when dispensed into air compared to during an injection. The IFU recommends that the user watch the window during the injection, but the user can also check if the window is filled with purple following the injection, for additional confirmation.		underdose and disease flare up. We acknowledge the current mitigation strategies in the IFU (b) (4) to address the risk of failing to check the window; however, several participants still overlooked this information and did not use the window as confirmation. Therefore, we recommend revising the IFU (b) (4) to improve emphasis and clarity around this task. Additionally, we recommend the Applicant consider including a fourth figure under " (b) (4) after the confirmation figure that depicts lifting the prefilled pen from the injection site to complete the sequence.

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Dispose of the AI in the Sharps Container [C]	Use Errors (n=10; 5 injection-naïve patients, 2 injection experienced patients, 3 injection-naïve caregivers)	-4 patients stated they didn't have a sharps container at home. -1 caregiver and 1 patient didn't see the sharps container. -1 patients stated they would throw it in the trash. -2 patients stated they would place it in a can/plastic bottle and then throw in the trash. -1 patient stated they would place them in a separate bag and take to the doctor's office.	This use error is common to all injection devices. Ten (10) users did not dispose of the AI in a sharps container due to information oversight on proper disposal or disposal in a sharps container not occurring to them.	Risks associated with this task are mitigated by the device locking out the needle, preventing access by most fingers, and the IFU (b) (4) instruct the user to dispose properly in a sharps container.	Based on the Applicant's URRAs, the potential harm associated with failure to dispose of the autoinjector in the sharps container is a needlestick and infection with a blood-borne pathogen. We acknowledge the current mitigation strategies in the IFU (b) (4) to address the risk of a needlestick and infection includes: step (b) (4) in the IFU which states the proper disposal method and contains a related image (b) (4). Therefore, we find the residual risk acceptable and have no further recommendations at this time.

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What indicated to you that the injection was complete? [C*] *The Applicant categorized this as an essential task, but we consider this task to be critical because a use error may result in harm.	Use Errors (n=1*) Close Calls (n=9) *Several participants provided multiple answers, one of which being the correct answer. However due to how the question was framed we did not consider these use errors, but rather study artifact.	-1 participant did not provide the correct response after reviewing the IFU. -9 participants provided the correct answer after reviewing the IFU	None discussed.	None discussed.	See analysis and recommendations for the tasks "Administer a full dose" and "Check the Window is Filled with Purple," as this knowledge question is related to the above tasks' evaluation.
Where would you store this product? [C*]	Use errors (n=1) Close Calls (n=12)	-13 participants initially stated they would store it at room temperature in another	None discussed.	None discussed.	Based on the Applicant's URRAs, the potential harm associated with failure to store the product in the refrigerator is a degraded product,

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*The Applicant categorized this as an essential task, but we consider this task to be critical because a use error may result in harm.		location; however, after review of the IFU, 1 injection-naïve participant stated they would store it at room temperature in a medicine closet.			missed dose, underdose, or contamination. We acknowledge that 12 users were able to correctly locate and identify the information on the IFU. Additionally, we note the current mitigation strategies in place in the labeling to address the risk of failing to store in the refrigerator includes: storage statement on the (b) (4) tray, and carton labeling, the bold storage statement in the IFU, and a remove from refrigerator statement in the IFU (b) (4). Based on our expert and heuristic review of the labels and

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					labeling we recommend revising the storage statement on the carton labeling, tray lid labeling ^{(b) (4)} to further emphasize this important information.
Do you have any concerns having this product in the home if you have young children? [C]	Use errors (n=2) Close Calls (n=5)	-7 participants initially did not locate or specify they would keep it out of reach of children; however, after review of the IFU, only 2 participants did not provide the correct response.	Suggestions for improvement included not putting the instruction in a light gray box, highlighting the instruction more, addition of a visual icon, or other methods to cause the instruction to stand out in the IFU.	None discussed	Based on the Applicant's URRAs, the potential harm associated with failing to store the product out of the reach of children is a choking incident. We acknowledge the current mitigation strategy in the IFU to address the risk of failing to store the product out of the reach of children is the statement ^{(b) (4)}

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					along with the statement on the back of the carton labeling. However, two participants were unable to locate this information. Therefore, we recommend revising the IFU to provide more emphasis (b) (4) and add the statement under the storage section.
You left the medication out of the refrigerator overnight. It is now time to give an injection. How do you proceed? [E]	Use errors (n=13) Close Calls (n=13)	-26 participants were initially unable to provide the correct response and stated they wouldn't use the product; however, after reviewing the	None discussed.	The IFU specifies that the product can be left in the box at room temperature for up to 7 days.	See analysis and recommendations under the question, <i>Where would you store this product?</i> above as this question is related.

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		IFU, 13 participants were unable to provide the correct answer			
You are preparing to give an injection. You just took the medicine out of the refrigerator. What do you do next? [E]	Use errors (n=7) Close Calls (n=18)	-25 participants initially said they would either immediately prepare the site and administer an injection, warm the device at RT less than 30 minutes, or would warm it in their hands. 18 found the instruction in the materials, but seven did not find the correct answer.	None discussed.	The IFU (b) (4) mention that the device should be removed from the refrigerator for 30 minutes to come to RT prior to use; however, the IFU also includes instructions not to warm the AI any other way.	Based on the Applicant's URRAs, the potential harm associated with failing to warm the syringe to room temperature is pain, high injection force required, and a partial dose. We acknowledge the current mitigation strategies in the IFU (b) (4) to address the risk of failing to warm the syringe to room temp includes: a sub-task statement (b) (4) that instructs users to wait 30 minutes to let the pen come to room

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					temperature along with a related figure, (b) (4) However, several people were unable to find this information and provide the correct response. Therefore, we recommend the applicant consider revising the IFU (b) (4) to increase prominence and improve clarity to this preparation task.
You are in the process of giving an injection and removed the cap, when you get a phone call. How do	Use errors (n=4) Close Calls (n=5)	-9 participants initially said they would re-cap the device and attend to the interruption,	None discussed.	The IFU instructs users not to remove the device from the tray until ready to inject and instructs them not to recap the device.	Based on the Applicant's URRAs, the potential harm associated with placing the prefilled pen uncapped down is contamination or

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you proceed? OR Your patient is at home and is in the process of giving an injection. He has removed the device cap and is about to inject when he's interrupted. It's nothing urgent – his phone rings or he got a text. How would you tell him to proceed? [C]		set the device down uncapped, or take it with them out of the room. 5 participants found answers in the instructions related to this topic, including (b) (4) and 'Do not remove the cap until ready to inject,' but 4 users did not locate the correct answer after consulting the instructions.			damage to the needle. We acknowledge 5 participants were able to locate the information in the IFU. We note the current mitigation strategies to address the risk of leaving the device uncapped include statements in the IFU under step (b) (4) (do not take the prefilled pen out of the tray until you are ready to inject) and (b) (4). Therefore, we find the residual risk acceptable, and we have no recommendations at this time.
You are preparing to give an injection and have just opened the box. How would you	Use errors (n=7)	-7 participants were unable to find this information in	None discussed	None discussed	Based on the Applicant's URRRA, the potential harm associated with

Table 3: Analysis of HF Study Results Knowledge Comprehension Questions for Entyvio Prefilled Pen					
Tasks (include C for critical and E for essential)	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis and Subjective Feedback	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
know the autoinjector is safe to use? [C*] *The Applicant categorized this as an essential task, but we consider this task to be critical because a use error may result in harm.		the IFU (b) (4)			failure to inspect the prefilled pen for exterior damage, drug product quality (clear, colorless, not cloudy or containing particles), or expiration is use of a degraded product, contaminated product, or inability to deliver the dose (particles or change in viscosity), which could cause an immune reaction, infection or reoccurrence of disease. We acknowledge that most participants were able to locate this information; however, several participants were unable to find this information in the (b) (4) IFU. Therefore,

Table 3: Analysis of HF Study Results Knowledge Comprehension Questions for Entyvio Prefilled Pen					
Tasks (include C for critical and E for essential)	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis and Subjective Feedback	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
					we recommend the applicant consider revising the (b) (4) IFU to emphasize this information.
You are about to give an injection. You uncover the right thigh and notice it is bruised and tender. How would you proceed? [E]	Use error (n=1)	-1 participant only referenced (b) (4) and was unable to find the correct response.	None discussed.	None discussed	Based on the Applicant's URRAs, the potential harm associated with injection into a bruised and tender area is pain. We acknowledge that 1 participant was able to self-correct after reviewing the IFU. Additionally, we note the current mitigation strategies in place in the IFU to address the risk of choosing an injection site that is bruised/tender includes a statement under Step (b) (4). However, 1

Table 3: Analysis of HF Study Results Knowledge Comprehension Questions for Entyvio Prefilled Pen					
Tasks (include C for critical and E for essential)	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis and Subjective Feedback	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
					participant only referenced (b) (4) and was unable to find this information. Therefore, we recommend the applicant consider revising (b) (4) to include this important information.
One week has passed since the last injection, which was administered into the right thigh. Where would you administer the next injection?* *We are unable to determine whether this knowledge question is critical or essential because the Applicant did not evaluate it in the URRA.	Use error (n=3)	-3 participants were unable to find the correct response.	Common suggestions for improvement of the instructions were to include it in (b) (4) call attention to the instruction using bolding, and changing the location of the instruction to separate it out from the (b) (4) instruction. Another point of confusion was that the phrase (b) (4) was not clear to users. Some found that it might refer to never using the same "spot" again, while others were not sure if it is	None discussed	This information is not evaluated in the Applicant's use-related risk analysis. We note the current mitigation strategies in place in the IFU to address this use issue including a statement under Ste (b) (4). However, this information is not included in (b) (4). Therefore, we recommend revising (b) (4) to include this information.

Table 3: Analysis of HF Study Results Knowledge Comprehension Questions for Entyvio Prefilled Pen					
Tasks (include C for critical and E for essential)	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis and Subjective Feedback	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
			only for a second injection or if the same site can never be used again.		

3.2 ANALYSIS OF ESSENTIAL/NON-CRITICAL TASKS

We acknowledge that there were use errors with the following non-critical/essential tasks:

- Remove device from packaging
- Wash hands
- Clean site with alcohol pad
- Allow site to dry

However, upon evaluation, we found the Applicant's conclusion and residual risk acceptable. We have no further recommendations at this time.

3.3 ANALYSIS OF THE LABELS AND LABELING

Our evaluation of the proposed Entyvio (b) (4) and Entyvio Pen prescribing information (PI) did not identify any areas of vulnerability that may lead to medication errors. We note areas of the Entyvio carton labeling and container labels that can be improved to minimize the risk for medication errors. These changes do not require additional human factors validation data for review.

4 CONCLUSION & RECOMMENDATIONS

The HF validation study results submitted on March 7, 2019 for the Entyvio Pen identified several use errors, close calls, and use difficulties with critical and non-critical tasks. However, the applicant did not implement revisions to the product user interface to address these use-related issues. Upon review of the subjective feedback from study participants and the applicant's root cause analyses, we identified several recommendations to revise the user interface, including: device design, revisions to the device label/labeling, and the IFU to improve prominence, clarity, and understanding of important information. Because these revisions are based on our review of the subjective feedback and root cause analysis of the use-related issues, we recommend that the Applicant implement these revisions along with any additional mitigations that the Applicant determines necessary to address these use-related issues, and then conduct and submit results of another human factors validation study to demonstrate that the mitigations are effective and do not introduce new risks.

4.1 RECOMMENDATIONS FOR TAKEDA PHARMACEUTICALS

The human factors (HF) validation study results submitted on March 7, 2019 identified several use errors, close calls, and use difficulties with critical and non-critical tasks. However, you did not implement revisions to the product user interface to address these use-related issues. Upon review of the subjective feedback from study participants and your root cause analyses, we identified several recommendations to revise the user interface, including revisions to: device design, device label/labeling, (b) (4) and the Instructions for Use (IFU) to improve prominence, clarity, and understanding of important information.

The below recommendations (see Section Product Design, Labels, and Labeling) are based on our review of the subjective feedback and root cause analysis of the use-related issues. We recommend that you implement these revisions along with additional mitigations that you determine to be necessary to address these use-related issues and conduct and submit results of another human factors validation study to demonstrate that the mitigations are effective and do not introduce new risks.

Product Design, Labels, and Labeling:

A. General Comments for Prefilled Pen and Prefilled Syringe (Container labels, Tray Lid labeling, & Carton Labeling)

1. Based on the incorrect responses related to the knowledge task comprehension question “Where would you store this product?” we recommend bolding the storage statement: “Store refrigerated at 2°C to 8°C (36°F to 46°F).” to increase prominence and minimize the risk of the storage information being overlooked.
2. As currently presented, the format for the expiration date is defined as MM/YYYY. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. We recommend revising the proposed expiration date format to improve clarity^c.

B.



^c Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>

C. Prefilled Pen Instructions for Use (IFU)

1. Based on the HF study results and our heuristic analysis and expert review, we recommend labeling each figure (e.g., Figure A, B, C, etc.) and identifying which figure is related to the respective task/step, to improve the understanding and clarity of each task. For example:

(b) (4)

2. Based on the errors observed related to selecting the correct injection site, we recommend revising the figure depicting the back of the arm injection sites to better anatomically capture the appropriate injection sites. It is unclear from the current figure whether the shaded areas depict the front or the back of the arm
(b) (4)
3. Based on the errors observed with participants recapping the pen, we recommend improving the emphasis of the “Do not” statements under “Pull the purple cap straight off and throw it away” in the IFU to minimize the risk of dose omission and disease reoccurrence.
4. Based on the errors observed related to administering a full dose, we recommend revising the IFU to further clarify the end of injection cues and better present this information to minimize the risk(s) of an underdose and disease reoccurrence. Additionally, consider revising the figures under (b) (4) related to the injection sequence to add “clicks” placed near the needle end of the device and clarify to the user what each click signifies.
5. Based on the errors observed related to checking that the window is filled with purple, we recommend revising the IFU to improve emphasis and clarity around this task to minimize the risk of an underdose and disease reoccurrence. Additionally, consider including a fourth figure under (b) (4) after the confirmation figure that depicts lifting the prefilled pen from the injection site to complete the sequence. Based on the errors observed related to the knowledge task of having concerns with this product around children, we recommend revising the IFU to increase prominence (b) (4) You may also consider adding the statement under the storage section as well to minimize the risk of inadvertent pediatric exposure.
6. Based on the errors observed related to the knowledge task of what to do after removing the product from the refrigerator, consider revising the IFU to increase prominence and improve clarity to this preparation task to minimize the risk of pain at the injection site.
7. Based on the errors observed related to the knowledge task of knowing the device is safe to use, we recommend revising the IFU to emphasize this

information to minimize the risk of an immune reaction, infection or reoccurrence of disease.

D. Prefilled Pen Device Labeling

1. Based on the errors observed and subjective feedback related to removing the cap and placing the needle against the skin, we recommend labeling the needle end on the device body to minimize the risk of a needle stick injury and an underdose.

E. Prefilled Pen Device Design

1. Based on the errors observed related to removing the cap and placing the needle against the skin along with the subjective feedback provided by the participants (e.g., the cap looked like a spring or button), consider revising the design of the cap to remove the ridges to minimize the risk of a needle stick injury and an underdose.

F. (b) (4)

(b) (4)

G. Prefilled Syringe IFU

1. We recommend applying the following recommendations found under the Autoinjector IFU recommendations: C.1-2 and C.7-8 to the PFS IFU.

We acknowledge you submitted a HF study results report on December 9, 2019; however, we recommend you consider our recommendations for the user interface above, which may result in changes to your final intend-to-market user interface.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Entyvio (b) (4) and Entyvio Pen received on March 7, 2019 from TAKEDA PHARMACEUTICALS, and the listed drug (LD).

Table 2. Relevant Product Information for Entyvio (b) (4) and Entyvio Pen and the Listed Drug		
Product Name	Entyvio (b) (4) Pen	Entyvio ^d
Initial Approval Date	N/A	May 20, 2014
Active Ingredient	vedolizumab	vedolizumab
Indication	(b) (4)	Adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids: • inducing and maintaining clinical response • inducing and maintaining clinical remission • improving endoscopic appearance of the mucosa • achieving corticosteroid-free remission Adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids: • achieving clinical response • achieving clinical remission • achieving corticosteroid-free remission
Route of Administration		Intravenous
Dosage Form	Injection	For Injection

^d Entyvio [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 September 3. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125476s024lbl.pdf.

Strength	108 mg/0.68 mL	300 mg/Vial
Dose and Frequency	Recommended subcutaneous (SC) maintenance dosage in UC: 108 mg administered every 2 weeks after 2 or more IV infusions	Recommended dosage in UC and CD: 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter.
How Supplied	(b) (4)	ENTYVIO (vedolizumab) for injection is supplied in sterile 20 mL single-dose glass vials, containing 300 mg of vedolizumab as a white to off-white lyophilized cake. NDC 64764-300-20 300 mg single-dose vial in individual carton
Storage	Refrigerate unopened vials, prefilled syringes, and prefilled pens at 2°C to 8°C (36°F to 46°F). Retain in original package to protect from light.	Refrigerate unopened vials at 2° to 8°C (36° to 46°F). Retain in original package to protect from light.
Intended Users/Use Environments	PFS & Pen: • Patient Self-administration and Caregiver administration in the home setting	Vial For Injection (IV): • HCP administration only

	• HCP administration in the clinical/hospital setting Vial For Injection (IV): • HCP administration only	
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APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 3, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, vedolizumab and 118980. Our search identified two previous reviews^{e,f}, and we confirmed that our previous recommendations were implemented.

^e Abraham, S. URRRA and Comparative Analysis Review for Entyvio (IND 118980). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 15. RCM No.: 2018-11.

^f Abraham, S. HF Protocol Review for Entyvio (IND 118980). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 25. RCM No.: 2018-325.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design & Results

<\\cdsesub1\evsprod\bla761133\0000\m3\32-body-data\32r-reg-info\regional-information-dn-000206289.pdf>

APPENDIX D. ISMP NEWSLETTERS—N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)—N/A

APPENDIX F. INFORMATION REQUEST RESPONSES FROM APPLICANT

- March 26, 2019: <\\cdsesub1\evsprod\bla761133\0002\m1\us\response-to-agency-questions-dated-20190328-human-factors.pdf>
- August 13, 2019: <\\cdsesub1\evsprod\bla761133\0013\m1\us\entyvio-sc-us-rtq-rec-08-aug-2019.pdf>

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁹ along with postmarket medication error data, we reviewed the following Entyvio (b) (4) and Entyvio Pen labels and labeling submitted by TAKEDA PHARMACEUTICALS.

- Container label received on March 7, 2019
- Carton labeling received on March 7, 2019
- Professional Sample Carton Labeling received on March 7, 2019
- Professional Sample Container labeling received on March 7, 2019
- (b) (4)
- Instructions for Use (image not shown) received on March 7, 2019
 - o Prefilled Pen: <\\cdsesub1\evsprod\bla761133\0000\m1\us\entyvio-pen-us-ifu-draft-1-26feb2019.docx>
 - o PFS: [\\cdsesub1\evsprod\bla761133\0000\m1\us\entyvio-\(b\) \(4\)-us-ifu-draft-1-26feb2019.docx](\\cdsesub1\evsprod\bla761133\0000\m1\us\entyvio-(b) (4)-us-ifu-draft-1-26feb2019.docx)
- Prescribing Information (Image not shown) received on March 7, 2019:
<\\cdsesub1\evsprod\bla761133\0000\m1\us\entyvio-vmb245-r5-uspi-clean-01mar2019.docx>

G.2 Label and Labeling Images

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

⁹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MILLIE B SHAH on behalf of MATTHEW J BARLOW
12/13/2019 04:42:52 PM

MILLIE B SHAH
12/13/2019 04:44:24 PM

QUYNHNHU T NGUYEN
12/13/2019 04:52:25 PM

MISHALE P MISTRY
12/13/2019 04:55:26 PM

Clinical Inspection Summary

Date	December 3, 2019
From	Zana Marks, M.D, M.P.H., OSI Reviewer Aisha Johnson, MD, MPH, MBA, Acting TL Kassa Ayalew, M.D., M.P.H., Branch Chief Office of Scientific Investigations/GCPAB
To	Marjorie Dannis, M.D. Tara Altepeter, M.D. Kelley Richards, RPM Division of Gastroenterology and Inborn Errors Products (DGIEP)
BLA #	761133
Applicant	Takeda Pharmaceuticals, U.S.A., Inc.
Drug	Vedolizumab Subcutaneous Injection
NME (Yes/No)	No
Therapeutic Classification	Biologic Therapy
Proposed Indication(s)	Maintenance treatment of adult patients with moderately to severely active Ulcerative Colitis (b) (4) (b) (4)
Consultation Request Date	May 5, 2019
Summary Goal Date	December 12, 2019
Action Goal Date	January 7, 2020
PDUFA Date	January 7, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Coates and Hellstern as well as the sponsor Takeda Pharmaceuticals, U.S.A., Inc. were inspected in support of BLA 761133.

The study data derived from the clinical investigator inspections are considered reliable. During the sponsor (Takeda Pharmaceuticals) inspection, stratification errors from incorrectly entering a variable such as remission status or prior TNF- α antagonist failure into IWRS were identified.

Protocol MLN0002SC-3027 specifies randomization based on 3 factors: concomitant use of oral corticosteroids, clinical remission status at Week 6, and previous TNF- α antagonist failure or concomitant immunomodulator use. Eighty (37%) of 216 randomized subjects who showed clinical response to open-label treatment with intravenous ENTYVIO at Week 6 across 56 sites were mis-stratified based on one or more factors such as remission status or prior TNF- α antagonist failure. In addition, the Protocol also specifies randomization of subjects achieving clinical response at Week 6, defined as reduction in complete Mayo score of ≥ 3 points and

≥30% from Baseline. At least twelve (5.6%) of 216 subjects across 11 sites were randomized based on a partial Mayo score at Week 6 that did not include the patient's endoscopy sub-score (although these scores were available). Of these subjects, 5 were retrospectively determined to be ineligible when their endoscopy subscores were used to compute the complete Mayo score. Please see Section 3, #3 for a more detailed account of this issue.

The sponsor did not ensure the sites followed the proper stratification and randomization criteria. Other than the stratification errors and randomization issues described above, the data generated by the sponsor are considered acceptable and may be used in support of this application. We recommend the review division considers the clinical relevance of the mis-stratification and randomization issues in product labeling.

II. BACKGROUND

The sponsor submitted this original BLA for vedolizumab subcutaneous injection for the indication of maintenance treatment of adult patients with moderately to severely active Ulcerative Colitis (UC) (b) (4)

The product is a human monoclonal antibody directed against the $\alpha 4\beta 7$ integrin antagonist which results in gut selective anti-inflammatory activity. The FDA approved vedolizumab (Entyvio®) for intravenous use in May 2014 for the indication of treatment (maintenance and remission) of patients with Ulcerative Colitis and Crohn's Disease.

Inflammatory bowel disease (IBD) includes UC and Crohn's disease that are characterized by inflammation of the gastrointestinal tract, resulting in abdominal pain, diarrhea, and rectal bleeding. The goal of UC treatment is the induction and maintenance of disease remission in order to provide an improved quality of life, reduction in need for long-term corticosteroids, and minimization of cancer risk. Conventional therapies for the treatment of UC include mesalamine, glucocorticoids, and thiopurines.

Approved systemic therapies for the treatment of UC patients who are no longer responding to corticosteroids, or immunomodulators include the drug tofacitinib (Xeljanz®) and numerous biologic agents including anti-tumor necrosis factor α (TNF α) agents such as golimumab (Simponi®), infliximab (Remicade®), and adalimumab (Humira®), and IV vedolizumab (Entyvio®) as noted above.

The proposed vedolizumab subcutaneous maintenance dosage for UC is 108 mg, administered Q2W after 2 or more vedolizumab IV infusions.

Summary of Protocol MLN0002SC-3027

Study Design: Multicenter, randomized, double-blind, double dummy, placebo-controlled

Primary Endpoint: Proportion of subjects with clinical remission, defined as a complete Mayo score of ≤2 points and no individual sub score >1 point, at Week 52.

Protocol MLN0002SC-3027 entitled “A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study, with a Vedolizumab IV Reference Arm, to Evaluate the Efficacy and Safety of Vedolizumab Subcutaneous as Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy” had a primary objective to assess the effect of vedolizumab subcutaneous (SC) maintenance treatment on clinical remission at Week 52 in subjects with moderately to severely active ulcerative colitis (UC) who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2. The study was conducted from December 2015 to August 2018 and enrolled 383 subjects at 140 sites in 29 countries including the U.S.

The study included a 4-week (28-day) Screening Period, a 6-week open-label vedolizumab IV Induction Phase, and a 46-week randomized, double-blind, double-dummy, placebo-controlled Maintenance Phase with vedolizumab SC or vedolizumab IV with a final visit at Week 52. All endoscopic assessments (i.e., for disease severity at baseline and for clinical endpoints at the end of the Induction and Maintenance Phases) were performed via central reading. Subject assessments for the Mayo score were collected on an eDiary. The instructions to subjects and staff are included in the background package.

In the Induction Phase, subjects received open-label IV vedolizumab treatment. Those who demonstrated a clinical response according to protocol-specified criteria, (assessed by complete Mayo score at Week 6) were randomized in a 2:1:1 ratio to double-blind treatment with vedolizumab SC administered once every 2 weeks, vedolizumab IV administered once every 8 weeks, or placebo. Randomization was stratified by 3 factors: concomitant use of oral corticosteroids, clinical remission at Week 6, and previous exposure to tumor necrosis factor-alpha (TNF- α) antagonists or concomitant immunomodulators.

Primary and secondary efficacy assessments during the Maintenance Period were based on Mayo scores. A complete Mayo score was obtained within 10 days prior to enrollment, using subject diary entries within the 10 days prior to enrollment and flexible sigmoidoscopy results obtained during the Screening Period; this assessment was the baseline complete Mayo score for disease activity assessment. Sigmoidoscopy was done at Week 6 and Week 52 (or ET Visit), and a complete Mayo score was calculated for these visits for endpoints assessment. All endoscopies (Week 0, 6, and 52) were centrally read. Additional information regarding the sigmoidoscopy requirements and central reader assessments are in the Study Manual.

The baseline complete Mayo score was used for the comparison with the Week 6 complete Mayo score to determine response and remission at Week 6 and with the Week 52 complete Mayo score to determine response and remission at Week 52. The Week 0, 6, and 52 complete Mayo score was calculated by the investigator or designee and recorded in the subject's source documents, with the endoscopic component subscore being provided by the central reader. The Week 6 assessment was determined whether the subject achieved clinical response at Week 6, and therefore, determine eligibility for randomization in to the Maintenance Period. A partial Mayo score was derived at the visits at which endoscopy was not performed.

III. RESULTS (by site):

**1. Paul Hellstern, M.D.,
Site # 58002
411 West Highland Boulevard
Inverness, FL, 34452**

Inspection dates: July 16-17, 2019.

At this site, 6 subjects were screened and enrolled into this study. None of the 6 subjects met the response criteria for randomization at week 6 so no subjects were randomized for treatment.

For this inspection, a complete review of regulatory documentation at the study site was performed. Source records for the 6 subjects enrolled at the site were reviewed. The protocol, signed investigator agreements, financial disclosure statements, IRB approvals and site submissions to the IRB and the sponsor were reviewed. The correspondence, monitoring reports, subject case history files, informed consent forms, subject visits and assessments, case report forms, subject diary data, test article accountability and subject adverse events were also reviewed.

Source documents for all enrolled subjects were verified against case report forms and NDA subject line listings for eligibility, adverse events, and serious adverse event reporting.

Given that the subjects at this site were not randomized, the primary endpoint was not verified.

At the closeout meeting of the inspection, the following discussion items were discussed:

1. Subject (b) (6) received the vedolizumab intravenous infusion at Week 2, Visit 3 although the subject's lymphocyte value was 0.4 and the protocol required treatment to be held if <0.5;
2. Subject (b) (6) had pharmacogenomics (PGx) sampling conducted during the study although the subject did not sign the Optional PGx Study consent form; and
3. Subject (b) (6) had no laboratory sample collected for hematology and chemistry testing at Week 14.

Reviewer's Comment: The aforementioned listed discussion items were listed as protocol deviations in the CSR. [Application 761133 - Protocol Deviations -](#).

A Form FDA 483 (Inspectional Observations) was not issued at the close of the inspection. In general, this clinical site appeared to follow Good Clinical Practice. There was no under-reporting of AEs. No significant inspectional observations were observed.

Reviewer's Comment: Each of the observations of failure to follow the protocol occurred once. These isolated incidents do not appear to represent systemic issues at this site.

2. Allan Coates, D.O.

Site # 58034

2093 Health Drive SW, Suite 201

Wyoming, Michigan, 49519

Inspection dates: August 5-8, 2019.

At this site, 11 subjects were screened, 7 subjects were enrolled, and 1 subject was randomized (Subject (b) (6) into this study. Subject (b) (6) was terminated from the Study at Week 30 (prior to primary endpoint assessment).

For this inspection, a complete review of regulatory documentation at the study site was performed. The study protocol, signed investigator agreements, financial disclosure statements, IRB approvals and site submissions to the IRB and the sponsor were reviewed. The correspondence, monitoring reports, subject case history files, informed consent forms, subject visits and assessments, case report forms, subject diary data, test article accountability and subject adverse events were also reviewed. There was no under reporting of adverse events. Standard Operating Procedures for the clinical site were present, reviewed, and appeared to be followed appropriately.

In general, this clinical site appeared to be following Good Clinical Practice. No significant inspectional observations were observed during this inspection. A Form FDA 483 (Inspectional Observations) was not issued at the close of the inspection

3. Takeda Pharmaceuticals USA, Inspection dates: October 21-25, 2019

This sponsor inspection was conducted with the specific purpose of investigating the issue of randomization stratification errors that occurred during the study.

Due to this widespread issue of mis-stratification, a Form FDA 483 was issued based on failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols. Specifically:

1. Study No. MLN0002SC-3027 Protocol specifies randomization based on 3 factors: concomitant use of oral corticosteroids, clinical remission status at Week 6, and previous TNF- α antagonist failure or concomitant immunomodulator use. Eighty of 216 randomized subjects (37%) across 56 sites were mis-stratified based one or more of these factors.
2. Study No. MLN0002SC-3027 Protocol specifies randomization of subjects achieving clinical response at Week 6, defined as reduction in complete Mayo score of ≥ 3 points

and $\geq 30\%$ from Baseline. At least twelve of 216 subjects across 11 sites were randomized based on a partial Mayo score at Week 6 that did not include an endoscopy sub-score, of whom 5 were retrospectively determined to be ineligible based on their complete Mayo score.

Data for calculation of the total Mayo score for determining clinical response at week 6 and eligibility for randomization into the blinded maintenance phase of the study were collected from different sources: The patient reported data (stool frequency and rectal bleeding) entered in (b) (4); the physician global assessment data entered in (b) (4); the centrally read endoscopy score evaluated by (b) (4) that was provided to the site (via the portal and email) and manually entered by the site into (b) (4).

The (b) (4) data were used for the (b) (4) portal programmatical calculations. The (b) (4) portal provided the following information to the sites at Week 6:

- *Mayo score summary report*: Mayo total scores and sub-scores
- *Eligibility report*: clinical response status for randomization

While eligibility for randomization based on clinical response was provided by (b) (4), the clinical remission status for stratification was not included, and sites had to use the Mayo score summary report to determine whether the subject was in clinical remission according to the definition in the study protocol.

The eligibility for randomization and information about stratification were then entered into the IWRS by the site and, based on the entered information, the subject was randomly assigned to a treatment arm by IWRS following a pre-defined algorithm. The questions for the sites regarding clinical response and clinical remission appeared in the IWRS as:

- Has the subject achieved clinical response? (yes/no)
- Is the subject in clinical remission? (yes/no)
- Have you confirmed whether the subject meets the Mayo score eligibility criteria on the EPX "Eligibility for randomization report" (yes/no)

Takeda provided a written response to the FDA Form 483 outlining the results of their root cause analysis of the mis-stratification issue. Takeda also provided a prevention strategy that includes a new study oversight framework including risk-based monitoring and employee training.

Reviewer's Comment: It appears that Sponsor oversight was insufficient to detect that the clinical investigator sites were incorrectly enrolling and/or randomizing subjects utilizing a partial Mayo score. Additionally, actual site monitoring did not detect those subjects who were randomized using a partial Mayo score but were confirmed to be eligible for randomization. To assess the impact of inclusion of the six Week 6 non-responders on the efficacy results, post hoc sensitivity analyses of the primary and secondary efficacy endpoints were conducted by the Sponsor and the Agency, excluding these six Week 6 non-responders from the FAS. Results of

these post hoc analyses are consistent with the primary and secondary endpoint analyses using the FAS population provided in the CSR.

Takeda responded to the 483 observations on 11/14/2019. Takeda's plans for better oversight appear reasonable. The response was adequate.

{See appended electronic signature page}

Zana H. Marks, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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Review Division /Medical Team Leader/Tara Altepeter

Review Division /Project Manager/Kelly Richards
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OSI/Office Director/David Burrow
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/s/

ZANA H MARKS
12/04/2019 09:12:58 AM

AISHA P JOHNSON
12/04/2019 11:52:50 AM

KASSA AYALEW
12/04/2019 12:01:48 PM



CLINICAL OUTCOME ASSESSMENT (COA) REVIEW MEMORANDUM

RE: BLA 761133

FROM: Onyeka Illoh
COA Reviewer

Sarrit Kovacs
COA Team Lead

SUBJECT: Division of Gastroenterology and Inborn Errors Products (DGIEP) consult to Division of Clinical Outcome Assessment requesting input on the adequacy of the sponsor's proposed patient-reported outcome assessments to support labeling claims (DARRTS Reference ID: 4497984)

DRUG: Vedolizumab (Entyvio; Kynteles)

This memo serves to close out the clinical outcome assessment (COA) consult C2019369 (filed in DARRTS by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on September 26, 2019) for BLA 761133 vedolizumab for the treatment of ulcerative colitis in adults. DGIEP requested COA Staff informal input into the applicant's proposal

(b) (4)

(U) (4)

Please see below for COA Staff internal comments to DGIEP for further discussion:

1.

(b) (4)

2.

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/s/

ONYEKACHUKWU A ILLOH
11/22/2019 12:37:18 PM

SARRIT M KOVACS
11/22/2019 12:38:47 PM

ELEKTRA J PAPADOPOULOS
11/22/2019 12:50:31 PM



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

Date	8/12/2019		
To:	Kelly Richards		
Requesting Center/Office:	CDER/OND	Clinical Review Division:	DGIEP
From	Rumi Young OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	BLA761133 , vedolizumab ICC1900197 ICCR2019-04579		
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: 9/4/2019 ☐ 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: 11/6/2019 ☐ 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	BLA761133
Sponsor	Takeda
Drug/Biologic	vedolizumab
Indications for Use	Ulcerative colitis and Crohn's disease
Device Constituent	Pre-Filled Syringe and Autoinjector
Related Files	None

Review Team		
Lead Device Reviewer		<i>Rumi Young</i>
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #
None		

Interim Due Dates	Meeting/Due Date
Filing	5/6/2019
Mid-Cycle	8/14/2019
Primary Review	11/7/2019

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	X			
Labeling	X			
Design Controls		X		Complete Response 1
Risk Analysis		X		
Design Verification	X			Complete Response 2
Consultant Discipline Reviews			X	
Clinical Validation			X	
Human Factors Validation			X	
Facilities & Quality Systems				Complete Response 2, 3, 4, 5

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:

The following comments were communicated to the CDER midcycle meeting on August 14, 2019

Comment #1: The sponsor's primary container uses (b) (4) History (b) (4) shows needle clogging (b) (4). This is evident in the functional performance of the device (PFS and AI) and may have safety issues with respect to DP quality and injection into patient. Correction would require a new primary container ,which indicates a significant approvability issue.

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:

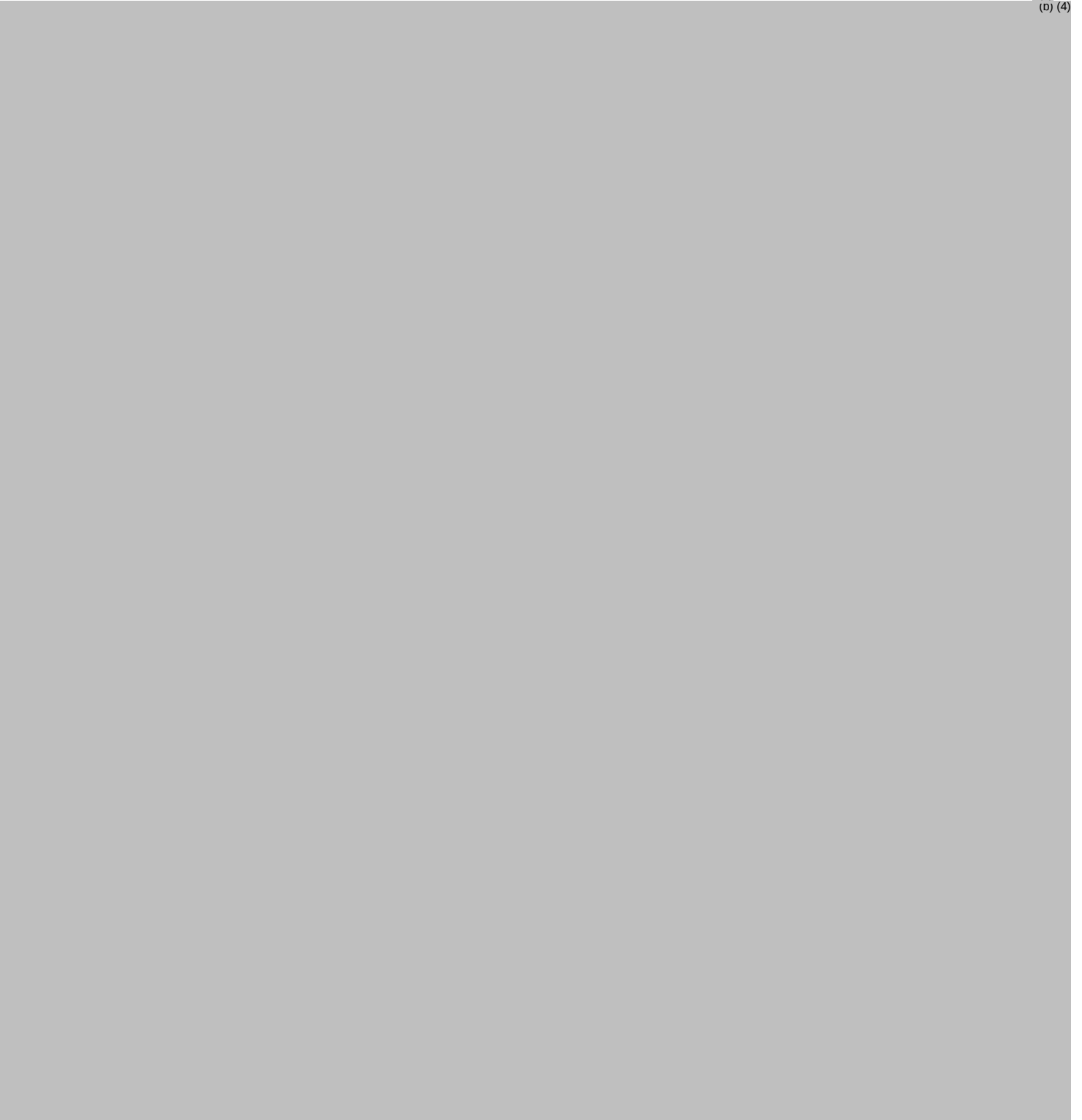
CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

Major Deficiencies:

1. While you reduced your prefilled syringe tip cap removal specification to from (b) (4) based on your simulated use strength data (b) (4), you made no changes to the autoinjector cap removal force specification and it remains at (b) (4). Therefore, the proposed autoinjector cap removal force specification remains too high based on the simulated use testing provided, and you did not provide adequate evidence to validate the (b) (4) specification. Update your autoinjector

cap removal force specification to (b) (4) and provide updated design verification reports demonstrating your autoinjector meets the updated specification.

2. You encountered multiple instances of full and partial needle clogging during stability and design verification testing (b) (4)



5. During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

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

Takeda is requesting approval of vedolizumab. The device constituent of the combination product is a Choose an item..

Choose an item. has requested the following [consult](#) for review of the device constituent of the combination product:

Review of submitted AI/PFS to support approval of the new route of administration

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

Device Performance, Biocompatibility (non-drug contacting), inspection status.
--

This review will not cover the following review areas:

Drug Product Quality, 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

None,

3.2.1. Related Files

N/A

3.3. Indications for Use

Combination Product	Indications for Use
vedolizumab	Ulcerative colitis and Crohn's disease
Pre-Filled Syringe & Autoinjector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0000	3.2.P.3.1 Manufacturer(s)
0000	3.2.R Regional Information
0003	1.1.2 Form FDA 356h: Application to market a new drug, biologic, or an antibiotic drug for human use
0005	1.14.1.3 Draft Labeling text
0000	1.14.1.1 Draft Carton and Container Labels
0000	5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports [Study ID-Study Title]
0000	3.2.P.3 Manufacturer(s)
0015	1.11.1 Quality Information Amendment
EMAIL	EIR for (b) (4)
EMAIL	483
EMAIL	(b) (4) response October 2019

4. DEVICE DESCRIPTION

4.1. Device Description

The following information was obtained from:

- 3.2.R Detailed Device Description PFS+NSD (DN000192017)
- 3.2.R Device PFS+AI Detailed Device Description (DN-000192131)

The prefilled syringe with needle safety device (PFS-NSD) (510(k) (b) (4)) is a single use combination product that delivers 0.68ml/108mg subcutaneously and includes a passive needle safety mechanism that is activated by the user at the end of the injection.

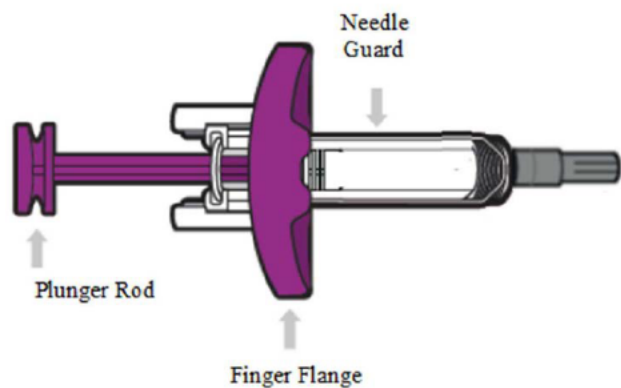


Table 1.a Details of PFS+NSD Components				
Component	Description	Specification	Drawing Number	Supplier
Needle Guard	(b) (4)			(b) (4)
Finger Flange				
Plunger Rod				
Prefilled Syringe	1 mL, 27G Thin Wall 1/2"	(b) (4) Ins., (b) (4) ccille		
Stopper	rubber,	(b) (4) (b) (4)		

The autoinjector (AI) is a single use combination product that delivers 0.68ml/108mg subcutaneously. The device is activated by removing the cap (purple) and pushing the needle cover onto the injection site. During the injection the user can see the injection progress.

Figure 1.b Illustration of Vedolizumab SC PFS+AI after Cap Removal



Figure 1.c Illustration of Vedolizumab SC PFS+AI Device Constituent Cross-section View of AI after Cap Removal

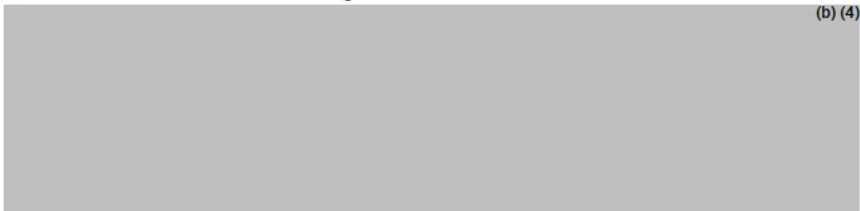


**Table 1.a Technical Specification and Drawing for Each Component of Vedolizumab SC
PFS+AI Combination Product**

Component	Description	Specification	Drawing Number	Supplier
Cap & Body Subassembly	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Prefilled Syringe	1mL, (b) (4) glass, 27G Thin Wall 1/2", (b) (4) needle	(b) (4)	(b) (4)	(b) (4)
Stopper	(b) (4) rubber, (b) (4)	(b) (4)	(b) (4)	(b) (4)

The PFS and AI are intended for home and clinic use environments and by lay-user and HCP users.

Reviewer Comment:

- The device constituent parts of the devices are developed/designed by (b) (4) for the PFS-NSD and AI, respectively. The prefilled syringe is the same for both designs.
- It is noted that the sponsor used (b) (4) needle shield (b) (4). This may significantly impact the functional performance of the devices. See [Comment to CDER #1](#). Comment was communicated at CDER midcycle meeting on 8/14

4.2. Steps for Using the Device

PFS – Remove cap, insert needle, depress plunger

AI – Remove cap, apply to skin, push down and hold for 10 seconds

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments The device description is adequate		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

5. FILING REVIEW

CDRH performed Filing Review ☐ Finalize Filing Review Section	☒
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description		Present		
		Yes	No	N/A
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability	X		
	Biocompatibility	X		
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors	X		
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment: The sponsor provided sufficient information to begin review.

5.2. Facilities Information

No inspection or quality system review will be performed for the PFS device constituent because it is non-emergency use. Below is the review regarding the autoinjector device.

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	
Inspectional History An analysis of the firm's inspection history over the past 2 years:	

- ☒ Inspection was conducted (b) (4) . The inspection covered medical device QS and was classified VAI.
- ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.
- ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:

- ☒ A pre-approval inspection is required because:
Their last inspection was over two year ago, the inspection did not review labeling controls, equipment qualification, and design controls. In addition, a 483 was issued that cited issues with management review per 21 CFR 820.20(c) specifically, management with executive responsibility has not reviewed the suitability and effectiveness of the quality system at defined intervals.
- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm revealed major deficiencies.
- ☐ An inspection is not required because Choose an item.

Firm Name:

Address:

FEI:

Responsibilities:

Inspectional History

An analysis of the firm's inspection history over the past 2 years:

- ☒ Inspection was conducted (b) (4) . The inspection covered medical device QS and was classified VAI.
- ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.
- ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:

- ☐ A choose an item inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm Choose an item.
- ☒ An inspection is not required because the manufacturing site does not require an inspection at this time given the risk of the combination product(PFS).

5.3. Quality System Documentation Triage Checklist

Device Type Table

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: PFS configuration If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☒ High Risk of cGMP issues: AI configuration 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

A quality systems review will be conducted on the AI configuration only since there is a low cGMP risk for the prefilled syringe configuration. See section 12 of this memo for additional QS review for the AI.

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION	
Acceptable for Filing: ☒ Yes ☐ No (Convert to a RTF Memo) ☐ N/A	
Facilities Inspection Recommendation: ☒ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☐ N/A	
Site(s) needing inspection: (b) (4)	
<u>Reviewer Comments</u> We are recommending PAI inspection for (b) (4)	
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

- The Medication guide, instructions for use and carton/product labeling for the prefilled syringe and autoinjector were complete.

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 The labeling was complete.		
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		

7.2. Design Inputs and Outputs

PFS

<u>Design Inputs</u> (Essential Performance Requirement)	Design Outputs (Specification)
Safety Activation Force	(b) (4)
Dose Accuracy	
Breakloose Force	
Gliding Force	
Safety Shield Override Force	
Pull off of Needle Shield	
Finger Flange/Body Separation Force	
Body/Body Separation Force	
Needle Length	

* Bold are EPRs

<u>Reviewer Comments</u>
- The sponsor's design inputs and EPRs appear complete. - The specifications for each design input appear adequate except for Pull off of Needle shield (Cap removal) upper limit of (b) (4). Forces closer to (b) (4) are adequate based on similar marketed products. Therefore, will request rationale/validation of the upper specification limit. See Midcycle Deficiency 1. Unresolved –their simulated use and literature did not support (b) (4). IR#1 – Resolved updated PFS specification to (b) (4) for pull of Needle Shield

Autoinjector

<u>Design Inputs</u> (Essential Performance Requirement)	Design Outputs (Specification)
Dose Accuracy	(b) (4)
Activation Force	
Activation Stroke	
Injection Time	

Needle Extension Length	(b) (4)
Cap Removal Force	
Needle Cover Override Force	
Separation force	

*Bold are EPRs

Reviewer <u>Comments</u> - The identified EPRs for the autoinjector are adequate. - The needle guard override force appears too low when comparing it against the prefilled syringe override force (b) (4). This might be because they are implementing the ISO 11608 recommendation of 2x the activation force. However, it should be supported by a risk assessment to ensure the forces are not too low, thus causing an accidental needle sticks of a used needle. See Midcycle Deficiency 2. Unresolved – their device performance and complaint monitoring only support a higher specification. IR #2. – Resolved they updated the specification to (b) (4). - Similar to the prefilled syringe configuration, the cap removal force specification also appears high compared to other similar marketed products (b) (4). If forces are too high the user cannot remove the cap. See Midcycle Deficiency 1. Unresolved –their simulated use and literature did not support (b) (4). IR#1.- Unresolved They did not change their specification – Complete Response 1

7.3. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☒ Yes ☐ No ☐ N/A
Reviewer Comments See Complete Response 1		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		



Response Adequate:	☒ Yes, PENDING DV REPORTS	☐ No, See IR 1#
--------------------	--	--

8. RISK ANALYSIS

The scope of the risk analysis section was limited to the autoinjector since the risks associated with a prefilled syringe configuration are known/well-established.

The following document was reviewed:

- 3.2.R Regional Information Risk Management, PFS+AI (DN-000194321)
- 3.2.R Med Harms (DN-000073729)
- 3.2.R PHA-AI (DN-000114868)
- 3.2.R DEVICE PFS+AI Design Failure Modes and Effects Analysis (dFMEA) (DN-000214462)
- 3.2.R DEVICE PFS+AI Process Failure Modes and Effects Analysis (pFMEA) (DN-000214460)
- 3.2.R DEVICE PFS+AI Use Failure Modes and Effects Analysis (uFMEA) (DN-000214473)

8.1. Risk Management Plan

The sponsor provides an adequate description of their scoring system for the risk assessments and summary of risk reduction, evaluation, mitigation and acceptance.

Table 1: Severity of Harm Scoring System (from PROC-0003250)

(b) (4)



Reviewer Comments

- The (b) (4) document provides general harms and hazards while the (b) (4) provided harms specific to the indication/device.
- The severity scoring for harms was clear, and adequately assigned.
- The sponsor does not define the occurrence or detection scoring values in the Risk management plan or individual risk assessments. In addition, they do not define the overall risk categories (Acceptable/green, As

Far as possible/yellow, intolerable/red). Therefore we cannot make a determination if we agree with their risk assessments. Midcycle Deficiency 3 – **RESOLVED** the sponsor provided the definitions.

- The sponsors RMP does not provide a clear risk/benefit analysis for risk risks in the yellow region. They just refer to it. This is important as it is recommended in ISO 14971 and the sponsor states that any residual risks are communicated in the labeling. Without the R/B analysis we cannot determine if labeling is an adequate method of managing the residual risk or if the R/B is adequate. Midcycle Deficiency 4. – **RESOLVED** the sponsor provided a R/B analysis and rationale for accepting the risks based on clinical data and benefit to the patient.

8.2. Hazard Analysis and Risk Summary Report

Reviewer Comments

The hazards and harms identified in the HAs appear complete. Additional IRs may be issued after the sponsor addresses Midcycle deficiencies #3 & #4. **RESOLVED**- the sponsor provided definitions and a R/B analysis

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 None		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Midcycle Deficiency #3	You do not define the occurrence or detection scoring criteria (i.e., values) in your autoinjector Risk Management Summary or individual risk assessments. You do not define the values associated with the overall risk categories (Acceptable/green, As Far as possible/yellow, Intolerable/red). Therefore, we cannot evaluate your risk assessments for adequacy. Update your risk management plan to define the occurrence, detection and overall risk criteria.	
Sponsor Response	Updated risk management plans for the PFs and AI were provided.	

Table 3.a Occurrence Scoring System, Development (Qualitative)

Score	Category	Description
10	Very High	This harm or failure is almost inevitable
8	High	This harm or failure happens routinely and relatively frequently
6	Moderate	This harm or failure happens occasionally
4	Low	This harm or failure has not happened (or has happened relatively rarely)
2	Remote	This harm or failure is extremely unlikely

Table 3.b Occurrence Scoring System, Post-Market (Quantitative)

Score	Probability of Occurrence	Description
2	Improbable	1×10^{-6} (less than or equal to 1 per 1,000,000)
4	Remote	$1 \times 10^{-5} > 1 \times 10^{-6}$ (less than or equal to 1 per 100,000, more than 1 per 1,000,000)
6	Occasional	$1 \times 10^{-4} > 1 \times 10^{-5}$ (less than or equal to 1 per 10,000, more than 1 per 100,000)
8	Probable	$1 \times 10^{-3} > 1 \times 10^{-4}$ (less than or equal to 1 per 1,000, more than 1 per 10,000)
10	Frequent	1×10^{-2} (more than 1 in 1,000)

Table 3.d Table 3d: RPN Calculation and Acceptability, DFMEA and UFMEA

Takeda Risk Matrix		Probability of Occurrence				
		2	4	6	8	10
Severity	Catastrophic - 10	20	40	60	80	100
	Serious - 8	16	32	48	64	80
	Moderate - 6	12	24	36	48	60
	Minor - 4	8	16	24	32	40
	Negligible -2	4	8	12	16	20
Risk Scores						
		NAC: Not Acceptable/Intolerable (High)				
		AFAP: Reduce Risk As Far As Possible (Medium)				
		AC: Acceptable (Low)				

Table 3.c Severity of Harm Scoring System

Score	Category	Description
10	Catastrophic	Results in patient or user death Catastrophic/irreversible chemical or radiological impact on the environment.
8	Serious	Serious injury (irreversible) to the patient or user. Hazard may cause permanent impairment of a body function or permanent damage to a body structure, or requires medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure. Serious chemical or radiological impact on the environment (may require significant resources to preclude permanent/irreversible damage)
6	Moderate	A significant but reversible injury to the patient or user. May require medication or first aid to facilitate healing or pain management of injury. Moderately negative impact on the environment, reversible but requires resources to mitigate/correct the damage. .
4	Minor	Hazard may cause minor or temporary impairment of a body function or temporary damage to a body structure but does not require medical intervention to resolve. Minor negative impact on the environment, reversible impact, self resolving.
2	Negligible	No injury to the patient or user. No negative impact on the environment

	Table 3.e Combination Product Assembly PFMEA Risk Score Matrix			
	Score	Severity (S)	Occurrence (O)	Detection (D)
	1 (Low)	No effect Slope (dCQA/dPP) is small and UCL/LCL is far from the EoF (or EoK). Statistically significant impact but Z-score = not practically significant	Unlikely	High Probability to detect, validated system, technical control
	3 (Medium)	Moderate Slope (dCQA/dPP) is small; however, UCL/LCL is close to EoF (EoK). Statistically significant impact and Z-score = practically significant	Occasionally	Middle Probability to detect, defect occasionally not identified, eg. visual check
	5 (High)	High (CPP) Slope (dCQA/dPP) is large BUT the UCL/LCL is far from the EoF/EoK. Statistically significant impact and Z-score = practically significant	Frequently or lack of knowledge	Low probability to detect, defect frequently not identified, no technical, manual or visual check,
Reviewer Comments	The sponsor addressed this deficiency by providing definitions and scoring criteria for occurrence, detection and overall risk			
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.			

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Midcycle Deficiency #4	Your autoinjector Risk Management Summary does not provide a clear risk/benefit analysis for risks in the As Far as Possible/yellow region. You state that any residual risks are communicated in the labeling. However, without the risk/benefit analysis we cannot determine if labeling is an adequate method of managing the residual risks or if the risk/benefit analysis itself is adequate.	
Sponsor Response	The sponsor updated their risk management summary to include a more thorough risk - benefit assessment. They provided additional detail regarding the drug and device risks.	
Reviewer Comments	The risk/benefit analysis is adequate and relies on the clinical study for accepting the risks.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

9. DESIGN VERIFICATION REVIEW

9.1. Prefilled Syringe Performance/Engineering Verification

9.1.1. Verification of Design Inputs Evaluation

<u>Design Input</u>	<u>Design Output</u>	<u>Verification Method</u>	<u>Results/Deviations</u>	<u>Stability (Y/N)</u>	<u>Validated (Y/N)</u>	<u>Shipping (Y/N)</u>
Safety Activation Force		(b) (4)	PASS, clogging identified (b) (4) . Midcycle Def 7. CR#2	Y – see comment	N – see comment	
Dose Accuracy			PASS	Y – see comment	N – see comment	
Breakloose Force			PASS, clogging identified (b) (4) . Midcycle Def 7. CR#2	Y – see comment	N – see comment	
Gliding Force			PASS, clogging identified (b) (4) . Midcycle Def 7. CR#2	Y- see comment	N – see comment	
Safety Shield Override Force			PASS	Y	N – see comment	
Pull off of Needle Shield			PASS	Y	Y	
Finger Flange/Body Separation Force			PASS	N/A	N – see comment	
Body/Body Separation Force			PASS	N/A	N – see comment	
Needle Length			PASS	N/A	N – see comment	

* EPRS in BOLD

Reviewer Comment The sponsor does not provide the design verification reports. While they provide a summary of the test method validation approach which has the test methods this information is insufficient in determining if the testing was carried out adequately. Midcycle Deficiency 5 – RESOLVED the sponsor provided reports.

- A (b) (4) confidence and reliability is not adequate for safety activation force or safety shield override force since they are associated with risks of needles sticks/bloodborne pathogens. The FDA guidance recommends a (b) (4) confidence and reliability for this risk. However, the sponsor can leverage the testing performed under the 510k for needle safety activation (b) (4). This study does not address the override force functionality. Midcycle Deficiency 6. **RESOLVED** – the sponsor provided testing demonstrating the device meets the reliability using the (b) (4) specification.
- You note that samples clogged in your accelerated stability testing at 30 month and 36 months accelerated aging testing for breakloose force, glide force and safety activation force and that these samples were invalidated. Clogged samples may increase the injection forces and render the device unusable. Provide the root cause for this clogging and why it would not be observed during real time aging when testing breakloose force, glide force and safety activation force. This clogging and practice of invalidating samples was also observed at the facility visit. **Midcycle Deficiency 7 – UNRESOVLED- IR #3 issued – UNRESOLVED – Evaluation of root cause inadequate and proposed mitigation not proven effective. Complete Response 2**
- The sponsor referred to simulated use testing and clinical study as validation of their specifications. This information is not adequate to validate their specifications aside from dose accuracy and needle length since the devices used in simulated use and clinical studies would not perform at the specification limits only the nominal. However, a review of the proposed specifications for breakloose force and glide force, even considering the test speed are adequate compared to other marketed products.

9.1.2. Stability Review Summary

Shelf-life:	(b) (4) months
Storage conditions:	2-8C and excursions to 25C up to 7 days
Time period and storage conditions provided for accelerated aging:	Design Verification: 30/36 months (7.5 & 9 months accelerated) Stability: (3-6 months accelerated)
Time period and storage conditions provided for real-time aging:	Design Verification: 18 months Stability: 12 months

Reviewer Comment

- The sponsor is claiming a (b) (4) month shelf life based on the prefilled syringe container alone (not device constituents). Separate stability and design verification shelf life testing demonstrate a longer shelf life for the device constituents. We agree with this approach.
- The sponsor identified that the design verification data was not normalized and switched to n=60/attribute testing. To achieve the appropriate sample size they pooled timepoints. Their manner of pooling uses newer/younger samples to claim a longer shelf life. Therefore, they only have 6 months worth of real time testing . For establishing the (b) (4) month shelf life they need to use n=60 with samples that are at least 24 months or older for the proposed PFS EPRs (breakloose force, glide force, safety activation force & dose accuracy). At a minimum they should provide 12 months real time (n=60) testing for approval. However, given the observation/risk of clogging the sponsor should provide (b) (4) months real time. A review of their stability data did not address this issue since they only reported the max value observed with no indication of sample size. Therefore we do not know if the prefilled syringe can maintain the claimed reliability over its shelf life. See Midcycle Deficiency 8. – **RESOLVED** Sponsor provided real-time data at 18 months at an adequate

confidence and reliability. However, the risk of clogging is still present, uncontrolled and may occur at real-time aging . Therefore their design is not verified. See **Complete Response #2**.

- The sponsor did not test needle safety override force over real time or accelerated stability testing. The performance of this attribute can change over time since it is comprised of plastic components that degrade and change surface friction over time. See Midcycle Deficiency 6, **RESOLVED** - The sponsor provided testing demonstrating the device meets the reliability using the (b) (4) specification aged ((b) (4)).
- The sponsors labeling wants to claim excursions to 25C up to 7 days. They included a dual temperature study that used T=12 month samples and subjected them to 1 week, 2 weeks and 4 weeks at 25C. They evaluated breakloose force and glide force. The summary provided for this study is inadequate because with the risk of clogging the sponsor should provide the injection force curves so that we can determine if clogging is developing. In addition, it is unclear how this extrapolates to a (b) (4) month expiry for PFS-NSD and AI. No such study is conducted using the autoinjector. See Midcycle Deficiency 9 – Provided data for the Ai. However, failed to provide the injection force curves. **IR#4 – RESOLVED** – sponsor provided the curves.

9.2. Autoinjector Performance/Engineering Verification

9.2.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification	Verification Method <u>Acceptable</u> (Y/N)	<u>Validation</u> (Y/N)	Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy		(b) (4)	Y	Y – (b) (4) see comment	Y
Activation Force			Y	Y – (b) (4)	Y
Activation Stroke			Y	Y –	Y
Injection Time			Y	Y –	Y
Needle Extension Length			Y	Y –	Y
Cap Removal Force			N – CR #1	Y –	Y
Needle Cover Override Force			Y	Y –	Y
Separation force			Y	Y	Y

*EPRS in BOLD

Reviewer Comment

- The sponsor does not provide the design verification reports. While they provide a summary of the test method validation approach which has the test methods this information is insufficient in determining if the testing was carried out adequately. Midcycle Deficiency 5 – **RESOLVED** the sponsor provided reports for review.
- The sponsor's design verification shelf life testing was conducted at a lower reliability limit than $t=0$ ((b) (4)) for dose accuracy as recommended in ISO 11608-1. Therefore, they did not demonstrate they can meet the performance reliability requirements at the end of shelf life. Midcycle Deficiency 10 – **RESOLVED** - The sponsor provided testing demonstrating they can meet reliability requirements at the end of shelf life assuming product does not clog. **See Complete Response #2**
- Simulated shipping was performed per ASTM 4169 conditioning on three lots for all EPRs and design inputs except for separation force.
- The sponsor did not test separation force after stability or shipping. They should provide rationale why. **Midcycle deficiency 12. RESOLVED** - The sponsor provided rationale demonstrating that the impact is negligible

9.2.2. Stability Review Summary

Shelf-life:	(b) (4) months
Storage conditions:	2-8C and excursions to 25C up to 7 days
Time period and storage conditions provided for accelerated aging:	Design Verification: 24 months (3-6 months accelerated 25C). Clogged samples Midcycle Def 11. CR#2 Stability: Supportive/Development 24 months (6 months accelerated 25C), Validation lots (2 weeks 25C)
Time period and storage conditions provided for real-time aging:	Design Verification: 12 months 5C Stability: Supportive/Development 12 months 5C, Validation T=0 only

Reviewer Comment

- The sponsor observed clogging at 3 and 6 months accelerated aging (correlates to 12 and 24 months real time) and chose to invalidate test samples. Clogged AIs can lead to incomplete doses and higher injection times. In addition, it may indicate incompatibilities with the primary container components (see comment 1). The sponsor should provide the root cause and provide rationale why it would not occur during real time stability. **Midcycle Deficiency 11. UNRESOLVED - IR #3 issued UNRESOLVED – Evaluation of root cause inadequate and proposed mitigation not proven effective. Complete Response 2**
- The stability data provided by the sponsor is not adequate because it does not test the device and drug up to the proposed shelf life ((b) (4) months 5C) or demonstrate that it can be left at ambient for up to 7 days. It only tested the PFS_NSD up to 12 months 5C and 4 weeks 25C. They should provide rationale why it can apply to the AI as well. **See Midcycle Deficiency 9 – Provided data for the AI. However, failed to provide the injection force curves. IR#4 - RESOLVED** – sponsor provided the curves.

- Neither the primary or supportive stability demonstrated that the AI functions up to (b) (4) months shelf life. However, they do provide justification why 6 months accelerated aging extrapolates to 24 months real time. (b) (4)

9.3. 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 Complete Response #2		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Midcycle Deficiency #5	While you provided a design verification summary for your prefilled syringe and autoinjector, you did not provide the actual design verification reports. The design verification reports are needed to assess how the verification testing was conducted and determine if it was conducted adequately. Provide the prefilled syringe and autoinjector design verification reports including the real time and accelerated aging testing. Ensure that the test reports contain the data collected, including force traces (e.g., injection force), and statistical summary (mean, min, max, standard deviation, graph) for variable data.	
Sponsor Response	The sponsor provided reports for review.	
Reviewer Comments	The sponsor addressed our requested. Adequacy of the content will be further reviewed.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Midcycle Deficiency #6	You tested the prefilled syringe design inputs using a (b) (4) confidence and reliability. This confidence and reliability is not adequate for needle safety override force testing since failure of this device features can lead to contaminated needle sticks. FDA guidance Medical Devices with Sharps Injury Prevention Features - Guidance for Industry and FDA Staff (https://www.fda.gov/media/71142/download) recommends a (b) (4) confidence in order to detect defective devices at a 1% level. In addition, you did not verify needle safety override force over stability or provide evidence that the performance and reliability does not change over time. Therefore, provide data demonstrating that your prefilled syringe needle safety override force meets a (b) (4) confidence and reliability up to the proposed shelf life (real-time or accelerated).	

Sponsor Response	Takeda acknowledges that the confidence and reliability applied to the PFS+NSD needle safety shield override force was specified in error during Design Verification at (b) (4). The PFS+NSD utilizes the commercial (b) (4) design without modification and we therefore obtained and verified that (b) (4) has real time and accelerated aging data to support product performance over the shelf at the (b) (4) level. (b) (4) report (Design Control Evidence with data (b) (4), provide passing results for 5 yrs accelerated aging and real time data (t=0, 1yr and 2yr), respectively. We have also re-analyzed the raw data from two Design Verification/Validation studies, t=0 and post simulated shipping, and determined that the Safety Shield override force passes the 95%/99% confidence and reliability criteria. Both reports will be updated within the design history file to include the revised acceptance criteria, additional analyses, and conclusions. A summary of these analyses are provided below. • Safety Shield override force data from (b) (4) report R1707010-01-02, passes the (b) (4) confidence and reliability criteria. A brief description of the analysis is provided below: • Data were normalized with Minitab using the Johnson Transformation. See histograms – Figure 1 (raw data), Figure 2 (normalized) and the transformation results. • The acceptance criterion of (b) (4) was transformed using the Johnson function to provide the Lower Specification Limit (LSL= (b) (4). • The one-sided (b) (4) statistical tolerance interval was calculated using the transformed mean minus the standard deviation, multiplied by the corresponding k value (b) (4). • Results yielded Mean -(k*sd) = (b) (4) which is greater than the LSL (b) (4).
Reviewer Comments	The sponsor's response is adequate. It is noted that they used the (b) (4) specification during their analysis. The data also addresses the shelf life of (b) (4) months.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Midcycle Deficiency #7	You state that prefilled syringe samples clogged (b) (4) verification testing for breakloose force, glide force and safety activation force and that these samples were invalidated. You also observed clogging at (b) (4) stability testing for the prefilled syringe. Clogged prefilled syringes may increase the injection forces and render the device unusable. (b) (4) Provide the root cause for this clogging and explain why it would not be observed after real time aging up to the proposed shelf life for the prefilled syringe.	
Sponsor Response	The sponsor states the root cause of the clogging is (b) (4) (b) (4)	
Reviewer Comments	We disagree that root cause is related to the (b) (4) interaction and that it is not indicative of the quality of the batch. Results indicate that their DP (drug and closure) is susceptible to partial clogging and full clogging which has a negative impact on their device performance (dose accuracy and injection forces) and can lead to negative consequences to the user (incomplete injections, injection of (b) (4) material). The sponsor should provide a full root cause investigation report demonstrating	

	that they correctly identified the root cause, ruled out other potential root cause and eliminated (not reduced) the appearance of full clogs and potential clogs. Based on their assertion that accelerated aging is not indicative of real time, the sponsor can only use real time aging to support expiry verify the device for breakloose force, glide force, dose accuracy and safety activation force for PFS and dose accuracy, injection time for AI. All other attributes can rely on the accelerated aging since they do not depend on the drug. The accelerated aging PFS DV data shows that (b) (4) (b) (4) A review of the following real-time reports show the following 6 months RT 12 months RT 18 months RT A major issue is that they do not consider this to be indicative of DP quality which lead them to resampling. If the same procedure is followed they would be releasing material that clogs. Another issue is that they did not address how they are mitigating the risk by design.
Response Adequate:	☐ Yes ☒ No, See IR #3 Sent on Click or tap to enter a date.

(b) (4)

(b) (4)

Response Adequate:	☐ Yes, ☒ No, See Compete Response 2#
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	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Midcycle Deficiency #8	You state that you pooled PFS samples to achieve an n=60 sample size (b) (4) for real time and accelerated design verification testing for breakloose force, gliding force, safety activation force, and pull of force of needle shield. However, with this approach you have only verified the performance of your device up to 6 months real time aging and 30 months accelerated aging since you cannot use test articles from an earlier timepoint to evaluate a later timepoint. In addition, your stability testing only evaluated up to 12 months real-time aging. Provide functional testing for EPRs (breakloose force, glide force, safety activation force, tip cap removal force and dose accuracy) up to your proposed shelf life (b) (4) months) using samples aged at least (b) (4) months real time or older.	
Sponsor Response	Sponsor provided real-time data at 18 months.	
Reviewer Comments	The analysis is adequate. Breakloose, glide force and activation force met (b) (4) which dose accuracy met (b) (4)	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Midcycle Deficiency #9	In your labeling you state that your prefilled syringe (PFS) and autoinjector (AI) can withstand excursions up to 25C up to 7 days and you propose a (b) (4) months 2-8C shelf-life. Please address the following concerns regarding your claim: - Your Dual Temperature study only evaluated the PFS, not the AI, up to 12 months 5C storage and 14 days 25C. Provide stability data demonstrating the PFS and AI meets its EPRs after (b) (4) months 2-8C and 7 days 25C. - Your stability data summaries (i.e., min, max) are not sufficient to determine if your PFS and AI constituent performance is adequate. Provide stability testing reports for your PFS and AI stability testing. The reports should include the sample size, statistical summary (mean, min, max, standard deviation, graph), data values recorded (tabular summary), injection force curves (PFS only, and deviations).	

Sponsor Response	a) To support the proposed shelf life of (b) (4) months at 2-8 C with allowable excursions up to 7 days at 25 C, Takeda assessed both the product quality attributes of the drug product in the primary container and functionality of the autoinjector. As referenced, the Dual Temperature study is leveraged to demonstrate that product quality is not impacted through 7 days at 25 C. To support the functionality of the combination product, the PFS+AI is being assessed through ongoing stability studies. Based on the available stability data, vedolizumab SC PFS + AI continued to meet the acceptance criteria for the monitored functional attributes after storage at 5°±3°C for one PFS+AI lot up through 18 months at the long-term condition. There were no out of specification results observed on studies conducted at 5°±3°C storage condition on any of the ongoing stability studies. The available stability data at 25°C ± 2°C, 60% ± 5% RH condition on six lots, show that vedolizumab SC PFS + AI can be stored for up to one month at 25°C with no impact to the functional attributes. The ongoing long-term, and accelerated on vedolizumab SC PFS+AI are provided in Module 3.2.P.8.1 Stability Summary and Conclusion Pre-Filled Syringe + Autoinjector (PFS+AI) and the stability studies data tables and reports are provided in 3.2.P.8.3 Stability Data, Prefilled Syringe + Autoinjector (PFS+AI). b) Stability test reports are provided for the PFS+AI. The below stability testing reports for the autoinjector performance functional attributes testing are provided in Module 3.2.P.8.1 Stability Summary and Conclusions, Prefilled Syringe + Autoinjector (PFS+AI): For evaluating the overall functional performance of Prefilled Syringe (PFS) and Prefilled Syringe plus Needle Safety Device (PFS+NSD) over time, a discussion of a Bivariate statistical analysis performed on cumulative stability data is provided in Module 3.2.P.8.1 Stability Summary and Conclusions, PFS+NSD. A representative PFS stability time point break loose glide force and PFS+NSD stability time point safety activation force test report is provided in Module 3.2.P.8.1 Stability Summary and Conclusions, PFS+NSD. The minimum and maximum
Reviewer Comments	The response is adequate for the AI. The earliest evidence of clogging was at (b) (4) for the PFS. The response to B) is not adequate for the PFS+NSD. We reiterate our request for stability injection for curves as it would visual any clogging peaks (secondary peaks). This again shows that the sponsor is not capable of evaluating and detecting for clogging.
Response Adequate:	☐ Yes ☒ No, See IR #4 (below) Sent on Click or tap to enter a date.



(b) (4)

Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.
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	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Midcycle Deficiency #10	You verified the functional performance (dose accuracy, injection time, activation stroke, activation force, needle extension, needle cover override force and cap removal force) of your autoinjector using a (b) (4) confidence and reliability limit. However, your real-time (12 months) and accelerated (24 months) shelf life testing only tested the functional performance up to a (b) (4) reliability. Therefore, you did not provide data demonstrating that the your autoinjector can maintain its performance up to the proposed shelf-life for the combination product ((b) (4) months, 2-8°C). Provide data demonstrating that your autoinjector can maintain the initial reliability limits (b) (4) up to the proposed shelf-life of the combination product (b) (4) months).	
Sponsor Response	They provide an analysis of the attributes via variable analysis demonstrating (b) (4) for dose accuracy and (b) (4) for needle cover override force. They refer to 12 months real-time and 24 months accelerated.	
Reviewer Comments	Adequate for real time testing.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Midcycle Deficiency #11	You state that autoinjector samples clogged (b) (4) Clogged autoinjectors may lead to incomplete injections (dose accuracy, injection time) and render the device unusable. Invalidating test samples from analysis is not acceptable. Provide the root cause for this clogging in the autoinjector and explain why it would not be observed after real time aging up to the proposed shelf life for the autoinjector.	
Sponsor Response	Same as response to question 7	
Reviewer Comments	See question 7 analysis and below for analysis of data For the AI DV testing the sponsor only has up to 12 months real time testing. The testing was done per ISO 11608-1 n=60 k value analysis. The sample size in this testing is adequate. Regardless the shelf-life of the AI can only be granted to (b) (4) months since the sponsor claimed that accelerated aging is not representative. Update shelf-life to (b) (4) months only	
Response Adequate:	☐ Yes ☒ No, See IR #3→ Complete Response #2 Sent on Click or tap to enter a date.	

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Midcycle Deficiency #12	You did not verify the separation force of your AI in your design verification real time/accelerated aging or shipping testing. You should verify your design inputs after conditioning that is representative of intended use. Provide data verifying the separation force of your AI after aging (real-time or accelerated) and simulated shipping. Alternatively, provide rationale why separation force would not be impacted by aging or shipping.	
Sponsor Response	The sponsor says the following, The aging and shipping conditions of the autoinjector are considered to have minimal effect on the strength of the final assembly interface (b) (4) (b) (4)	

Reviewer Comments	The sponsor provided rationale demonstrating that the impact is negligible.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

9.4. 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:

- Device Design and development PFS+NSD (DN-000192962)
- Device Design and development PFS+AI (DN-000172240)
- Vedolizumab SC-1017 – Report Body
- Vedolizumab SC -1018 – Report Body
- Vedolizumab SC-1021 - Report Body
- Vedolizumab SC-1022 - Report Body

PFS-NSD

Table 1.q Summary of Clinical Experience for PFS+NSD

Study	Description of Study	Reference
Study Vedolizumab SC-1017	Pilot: PK comparison of single SC injections of vedolizumab administered in PFS versus PFS+NSD	Module 2.7.1 Summary of Biopharmaceutical Studies
Study Vedolizumab SC-1018	PK comparison of single SC injections of vedolizumab administered in PFS versus PFS+NSD	

Reviewer Comments:

- The pilot study included 12 healthy male subjects and the full study included 51 healthy male subjects. Injection sites were equally distributed among arm, thigh and abdomen (21 subjects per injection site).
- The sponsor states the clinical studies were performed using the final finished combination product. While the report does not provide a clear description, this device constituent (needle safety) is well known and would not impact the clinical study endpoints. Therefore, no additional information is required.

AI

Table 1.o Summary of Clinical Experience for PFS+AI

Study	Description of Study	Reference
Study Vedolizumab SC-1021	Pilot: PK comparison of single SC injections of vedolizumab administered in PFS versus PFS+AI	Module 2.7.1 Summary of Biopharmaceutical Studies
Study Vedolizumab SC-1022	PK comparison of single SC injections of vedolizumab administered in PFS versus PFS+AI	

Reviewer Comment:

- The pilot study included 12 adult healthy males and the full used 51 health males. Injection sites were distributed (thigh, abdomen, and arm).
- The clinical studies were conducted using the final finished device. However, the device description is not detailed enough to determine if the design of the clinical AI is the same as the commercial (to be marketed). The sponsor should confirm the design iteration and provide a justification why any differences would not impact the clinical study endpoints or validation of their design. See **Midcycle Deficiency 13. – RESOLVED** design and manufacturing was identical

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

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Midcycle Deficiency #13	In Vedolizumab SC-1021 and Vedolizumab SC-1022 clinical studies you state that a prefilled syringe assembled into an autoinjector was used. However, your clinical study reports do not provide an adequate description of the AI design iteration used in the clinical studies. Please provide a comparison of the autoinjector device design and manufacturing used in the clinical studies against the final commercial design and manufacturing. For any differences identified, provide justification why it would not impact the clinical study endpoints or design validation.	
Sponsor Response	The sponsor clarified the design and manufacturing is identical.	
Reviewer Comments	The response is adequate.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

11. HUMAN FACTORS VALIDATION REVIEW

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

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

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

A preapproval inspection was completed on (b) (4) at (b) (4) (b) (4).

A 483 was issued for the following:

Out-of-specification (OOS) investigations #18014, #18015, #18017, #18018, and #18019 were opened (b) (4) through (b) (4) to investigate failures to eject drug product upon activation during injection tests performed for accelerated stability testing. The root cause was identified (b) (4) however the firm failed to document and take corrective and preventative actions once the root cause was identified leading to continued failures for accelerated testing up through 11/28/18

(b) (4) issued a response (below) on July 24 (Attachments 1 – Response to 483 and 2 – Supporting documents) adding that they will provide a followup response to FDA on or before October 6, 2019 upon completion of Preventive actions.



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Facilities Review Conclusion

The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.

☐ Yes

☒ No

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted for AI only	☒
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

The following information was obtained from *Manufacturing Process and controls – PFS+AI* (b) (4) (DN-000194334)
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)

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

12.2.2. cGMP Review

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

What Quality System did the Sponsor choose:

v05.02.2019

- ☐ Device QSR-based
☒ Drug cGMP-Based Streamline –
☐ Stream-line Both (no streamlined approach)

21 CFR 820.20 Summary of Management Responsibility	Firm(s): Takeda	Reviewer Discussion – The sponsor completes this through design reviews which is comprised of a cross functional team. The team includes “leadership”.
21 CFR 820.30 Summary of Design Controls	Firm(s): Takeda	Reviewer Discussion – Reviewed in detail in Section 7
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): Takeda	Reviewer Discussion – (b) (4) (b) (4) (b) (4) IR 6- UNRESOLVED Complete Response #4
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s): Takeda	Reviewer Discussion – Reviewed in Section 12.2.3 . IR #5 Unresolved – Complete Response #3
21 CFR 820.170 Summary of Installation	Firm(s): N/A	Reviewer Discussion – Sponsor states that this is not applicable since the PFS and AI are single use and disposable
21 CFR 820.200 Summary Servicing	Firm(s): N/A	Reviewer Discussion – Sponsor states that this is not applicable since the PFS and AI are single use and disposable

Reviewer Comments

The sponsor did not specify the QS system or address how they meet any of the regulations. See **Midcycle Deficiency 14**. Serious question regarding CAPA and purchasing controls. See **IR#5** regarding CAPA procedures and **IR#6** regarding purchasing controls. **UNRESOLVED-** (b) (4)
Complete Response #3 and #4

GMP Compliance Summary Conclusion

The Sponsor provided adequate summary information about the GMP compliance activities	☐ Yes	☒ No
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12.2.3. Corrective and Preventive Action Review

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

(b) (4)

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

CAPA Procedure Required Elements	Present
Procedures include requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.	Yes
Procedures include review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.	No
Procedures include appropriate statistical analysis of these quality data to detect recurring quality problems	No
Investigations into the cause of nonconformities relating to product, processes, and the quality system	No
Includes requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems	Yes
Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device	Yes
Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications	No
Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems	Yes – IR#5 response
Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems	No
Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review	No
Requires documentation of all CAPA activities	Yes

<u>Reviewer Comments</u>

The sponsor is missing the elements identified. Their CAPA sop will be requested. IR #5 – UNRESOLVED their CAPA SOP is missing the elements in red above. Complete Response #3

CAPA Conclusion

The Sponsor provided adequate information for corrective and preventive actions.

☐ Yes

☒ No

12.3. Control Strategy Review

12.3.1. PFS Review

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

Essential Performance Requirements Control Strategy Table - PFS

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

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or <u>release testing activities</u> :	Acceptable (Y/N/NA)
Safety Activation Force	Release testing of PFS+NSD	Y
Dose Accuracy	Release testing of PFS only	Y
Breakloose Force	Release testing of PFS only	Y
Gliding force	Release testing of PFS only	Y
Tip Cap Removal	Release testing of PFS only	Y

Reviewer Comments

The sponsor adequately identified the EPRs. While they only test breakloose force, glide force and dose accuracy on the prefilled syringe (no device constituent). This is adequate because they test the safety activation force on the final assembled device (PFS +NSD). Safety activation force is the only attribute that would not be captured in the prefilled syringe alone testing (dose accuracy, breakloose force and glide force).

Control Strategy Conclusion

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

☐ Yes

☐ No

12.3.2. Autoinjector Review

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

Essential Performance Requirements Control Strategy Table - AI

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

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are	Acceptable (Y/N/NA)
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	controlled through incoming acceptance, in-process control, and/or release testing activities:	
Dose Accuracy	Release testing	Y
Activation Force	Release testing	Y
Activation Stroke	Release testing	Y
Injection Time	Release testing	Y
Needle Extension Length	Release testing	Y

Reviewer Comments

The sponsor adequately identified the EPRs and is controlling all of them on release.

Control Strategy Conclusion

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

☒ Yes

☐ No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION

Filing Deficiencies:

☐ Yes ☐ No ☐ N/A

Mid-Cycle Deficiencies:

☒ Yes ☐ No ☐ N/A

Final Deficiencies:

☒ Yes ☐ No ☐ N/A

Reviewer Comments

Complete Response #3-5

CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Midcycle Deficiency #14	Your prefilled syringe and autoinjector are drug-device combination product. Therefore, provide a complete summary of your base operating system as described in the FDA guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products issued in January 2017 (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf) and eCTD Technical Conformance Guide (https://www.fda.gov/media/93818/download) . Also ensure that you describe how you are meeting the applicable regulations based on your base operating system.	
Sponsor Response	The sponsor provided the requested information	
Reviewer Comments	The sponsor addressed the request. It will be reviewed in Section 12.2.2 and 12.2.3 of this memo. Additional requests will be sent as IRs.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
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	• •	(b) (4)
Response Adequate:	☐ Yes ☒ No, See Complete Response #4 Sent on Click or tap to enter a date.	

<<END OF REVIEW>>

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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: 6/21/2019

TO: Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation IV

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

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

RE: BLA 761133

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rational

OSIS inspected the site in (b) (4) which falls within the surveillance interval. The inspection was conducted under the following submissions: Non-responsive

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

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

Ting

Wang -S

Digitally signed by Ting Wang -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Ting Wang -S,
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TING WANG
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