

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761059Orig1s000**

**OTHER REVIEW(S)**

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

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

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<b>Date of This Review:</b>	July 19, 2019
<b>Requesting Office or Division:</b>	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
<b>Application Type and Number:</b>	BLA 761059
<b>Product Name, Dosage Form, and Strength:</b>	Hadlima and Hadlima PushTouch <sup>a</sup> (adalimumab-bwwd) Injection 40 mg/0.8 mL
<b>Product Type:</b>	Combination Product (Biologic-Device)
<b>Rx or OTC:</b>	Prescription (Rx)
<b>Applicant/Sponsor Name:</b>	Samsung Bioepis
<b>FDA Received Date:</b>	July 23, 2018; February 27, 2019; March 14, 2019
<b>OSE RCM #:</b>	2016-1978
<b>DMEPA Safety Evaluator:</b>	Matthew Barlow, RN, BSN
<b>DMEPA Team Leader (Acting):</b>	Millie Shah, PharmD, BCPS
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<sup>a</sup> The proposed proprietary name (Hadlima) and proposed nonproprietary name (adalimumab-bwwd) are only conditionally accepted for this product until the application is approved.

## 1 REASON FOR REVIEW

On July 23, 2018 Samsung Bioepis resubmitted BLA 761059 under section 351(k) after a refusal to file for a proposed biosimilar to US-licensed Humira. This is a proposed combination product, available as a pre-filled syringe (PFS) and autoinjector (AI) (PushTouch). We reviewed the human factors (HF) validation study report submitted under BLA 761059 for Hadlima and Hadlima PushTouch (adalimumab-bwwd).

## 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.

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

N/A=not applicable for this review

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

\*Container Labels and Carton Labeling Reviewed under RCM #2016-1974

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our assessment of the HF validation study results and IFU for Hadlima and Hadlima PushTouch is described below.

### 3.1 3.1 ANALYSIS OF THE HF STUDY RESULTS

Tables 2 and 3 describes the errors/close calls/use difficulties observed in the HF study for the AI, the Applicant's reporting of the results and proposed mitigations, and DMEPA's analyses and recommendations. Tables 4 and 5 describes the errors/close calls/use difficulties observed in the HF study for the PFS, the Applicant's reporting of the results and proposed mitigations, and DMEPA's analyses and recommendations.

Table 2: Analysis of HF Study Results for the Autoinjector					
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	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Check Expiration Date [c]	Use Errors (n=13 [3 excluded due to study artifact]) -3 AI Inexperienced Patients -6 AI Experienced Patients -3 Caregivers -1 HCP	-12 participants did not check the expiration date on the device label during the simulation study.  -1 participant misread the expiration date on the provided device.	-3 participants did not perform this step as they would rely on the pharmacist to check expiration.  -2 participants did not notice this step in the IFU and would not expect pharmacist to dispense an expired product.  -1 HCP would rely on assistant who manages the stocking  -2 participants normally check when they first receive their drug package and not again.	There are quality and contracting controls to ensure only appropriately dated product is given to patients.  Also, the expiration date is featured on the outer carton, inner carton, and device label. Additionally, the IFU instructs users to "always" check the date, and explains what to do if the product is expired -- do not use, get a new AI and call the help line for more information.  All the participants who did not check during injection were still able to locate and understand the	We note the potential harm associated with failure to check the expiration date is a loss of drug efficacy and an administration of an expired product. We acknowledge that all the participants were able to locate and understand the expiration date, along with comprehending the instruction to check the expiration date. We acknowledge the Applicant's discussion of mitigation factors, specifically having the expiration date on the outer carton and inner carton which allows for larger font. However, per the provided subjective feedback three participants missed this step during the simulated injection. Therefore, we recommend revising the figure in Step 3 to point to where the expiration date is located and state "check

			<p>-1 participant did not fully read the IFU step</p> <p>-2 participants knew to check the expiration date, but stated they forgot to (1 not noticing the step in the IFU either).</p> <p>- 1 participant skipped this step in the IFU as she assumed it would be like her Humira AI, which she never checks.</p> <p>-1 participant incorrectly reported the medication expired 2 years later: October 2018 instead of October 2016. This was due to small font on the device label per the subjective feedback.</p>	<p>expiration date when asked to do so. In addition, all participants in the study demonstrated comprehension of the instruction to check expiration as well as what to do if the product is expired. The root causes listed here are not driven by product design, and changes to the user interface will not reduce these root causes as seen in testing. Results show the risk is low and controlled as far as possible.</p> <p>- There are quality and contracting controls to ensure only appropriately dated product is given to patients. Also, the participant was able to read all but one digit</p>	<p>expiration date” to provide emphasis on this important piece of information and clarify on where to find it. We have determined that these changes can be implemented without additional validation testing</p>
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				<p>correctly on the device label. She did not repeat the error during the follow-up, trained trial, and there is no pattern of this root cause (all other participants could read and comprehend the date). This use error is additionally mitigated by the presence of the expiration date on the outer carton and inner carton. The dates shown on the cartons are in larger font size than the device label allows. Results show the risk is low and controlled as far as possible.</p>	
Check the drug integrity [c]	<p>Use Errors (n=10 [2 others excluded for study artifact])  -3 AI Inexperienced Participants  - 1 AI Experienced Participant  - 5 Caregivers  - 1 HCP</p>	<p>10 participants did not check the drug integrity via the viewing window.</p>	<p>-4 participants saw the instruction to check the drug in the IFU, but they forgot to do so during the simulation.</p>	<p>There are quality and contracting controls to ensure only appropriate product is given to patients. The majority of instances of this use</p>	<p>We note the potential harm of associated with failure to check the drug integrity is administration of a degraded or contaminated drug product. We reviewed the subjective feedback and root cause analysis provided by the applicant, and we</p>

			<p>-1 participant does not check her husband's Lantus and purposefully skipped reading this step in the IFU.</p> <p>-2 participants chose not to read the IFU.</p> <p>-1 participant did not see the step because page 5 and 6 of the IFU stuck together and said it was hard to flip through</p> <p>-1 participant stated they trusted the pharmacist not to give out bad medication</p> <p>-1 participant stated they saw the instruction in the IFU, but the package didn't</p>	<p>error were driven by habit/choice, or by trust in the manufacturer, sealed package or pharmacist. Among these participants, all saw the instructions in the IFU. The root causes would not be mitigated by product design changes. Also, all participants in the study demonstrated comprehension of the instruction to check integrity as well as what to do if the product is not clear, colorless or free of particles. A few participants chose not to read the IFU; however, all of those were able to find the IFU in the package. Two unique instances of the error relate to product design but show no pattern and</p>	<p>acknowledge that all participants were able to demonstrate comprehension of the task instruction and what to do if the product is not clear, colorless, or free of particles. Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations at this time.</p>
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			<p>look tampered with and since she opened it up herself, she trusted it'd be okay</p>	<p>would not be mitigated by design change: One participant misunderstood where the drug was in the autoinjector, owing to the clarity of the solution inside. In this case, clear solution represents product that is acceptable for injection. The participant chose not to read the IFU, however it describes the window as the "medication window", and uses illustration and text to guide the user to look at the window to check for clarity and lack of particles. Another participant had a unique issue with IFU pages sticking together, and no other participant experienced this issue.</p>	
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				Results show the risk is low and controlled as far as possible.	
Check Drug Integrity [c]	Close Call (n=1) -1 AI Experienced Participant	-1 participant incorrectly checked drug integrity by looking for air bubbles	The participant reported that if there was an air bubble she would not use the AI and would call the pharmacist. She said she always thought an air bubble was a problem. She found and read the IFU but overlooked the statement that an air bubble is okay.	This close call was driven by previous understanding of air bubbles in medication, and would result in no clinical harm in this case (participant would call the pharmacist and during the simulation delivered a complete dose). Also, the IFU explains to users that an air bubble is okay, it is normal to see them, and there is no reason to remove them. This single close call shows no pattern in root cause and would not be mitigated further by design changes. Results show the risk is low and controlled as far as possible.	We note the potential harm associated with incorrectly checking drug integrity is a missed or delay in dose. In the provided subjective feedback, the participant relied on previous knowledge with her approach to this task. Additionally, we note that under step 3, the IFU informs users that air bubbles may be seen, and this is okay. Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations at this time.

Clean the Injection Site	Use Errors (n=3 [1 participant excluded due to study artifact]) -2 AI Inexperienced Patients -1 AI Experienced Patient	3 participants did not clean the injection site	<p>-1 participant saw the full instruction in the IFU, but forgot to clean during the simulation. She said her Humira comes with swabs in the box and that reminds her to clean.</p> <p>-1 participant said he was “wrapped up in the [AI] technology” and may have read only the first part of IFU Step 4 (read about choosing site, but not cleaning site).</p> <p>-1 participant knew she was supposed to clean the injection site and saw the instruction in the IFU, but chose not to because she thinks she is a</p>	<p>These use errors show no pattern in root cause, and the participants comprehended the step in the IFU. From a clinical perspective, the injection site can be clean without using an alcohol swab. Results show the risk is low and controlled as far as possible.</p>	<p>We note the potential harm associated with not cleaning the injection site is an increased chance for infection. We acknowledge the mitigation strategies currently in place, which includes “Step 4: choose site and clean skin” in the IFU, and this step directs users to clean the skin at the injection site. Additionally, the IFU includes images of alcohol swabs under step 1 and step 4 of the IFU. Therefore, we find the applicant’s conclusion and residual risk acceptable and have no further recommendations at this time.</p>
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			generally clean person.		
Take off the Cap [c]	<p>Use Errors (n=4) -1 AI Inexperienced Patient -3 Caregivers</p> <p>Close Calls (n=2) -2 Caregivers</p>	<p>Use Errors: 4 participants removed the cap early</p> <p>Close Calls: -1 participant tugged on the red base -1 participant did not remove the cap initially</p>	<p><u>Use Errors:</u> -2 participants removed the cap early to see where the needle was (1 doing so twice) and then recapped it. Both participants overlooked the warnings against early cap removal on the package and IFU.</p> <p>-1 participant forgot to clean the injection site until after she removed the cap. Then, when she remembered she was supposed to clean the site, she recapped the needle before doing so. Said she saw the IFU warning not to recap, but forgot about it.</p>	<p><u>Use Errors:</u> The outer carton includes a warning against early cap removal. The IFU includes 3 warnings against early cap removal, all emphasized with formatting. Additionally, the injector is never illustrated with the needle cap off until the appropriate step in the IFU. The IFU also explains the consequences of early cap removal and recapping, and tells users what to do if they've removed the cap early. All participants demonstrated comprehension of the instructions to only remove the cap when ready to inject, and not before then.</p>	<p>We note the potential harm associated with failure to remove the cap or removing the cap incorrectly includes accidental injection into hand or finger, missing a dose, or a delay in therapy. We acknowledge that all participants demonstrated comprehension of the instructions to only remove the cap when ready to inject and not before then. Additionally, we note the IFU warnings related to taking off the cap too early. Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations at this time.</p>

			<p>-1 participant removed the cap and set the AI down on table so everything was “ready to go” before injecting. She saw the IFU warnings not to take off cap until ready to inject. The needle did not touch anything before the injection.</p> <p><u>Close Calls:</u> -1 participant thought the needle would be visible before injection and tried to remove the red base to expose the needle. The base did not come off, and the participant read the IFU and self-corrected</p>	<p>For the participants who removed the cap early and recapped, the needles were not touched or clogged by the recapping, and the participants were able to initiate injection.</p> <p>For the participant who chose to remove the cap early in the preparation process, despite seeing and comprehending the instructions in the IFU, the needle was not touched and the participant was able to initiate the injection.</p> <p>Results show the risk is low and controlled as far as possible.</p> <p><u>Close Calls:</u> The base is designed to cover the needle before and after injection, to ease fears of injection to protect against accidental needle</p>	
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			<p>-1 participant initially forgot to remove the needle cap, then realized the injection did not start when the injector pressed against the skin and they self-corrected.</p>	<p>sticks and reduce the risk of dirtying the needle. The IFU describes that the “needle is hidden below the red base”, and does not show an exposed needle in illustration at any point. This participant recovered based on the effective mitigations incorporated into the IFU. Additionally, there is no pattern in this single close call. Results show the risk is low and controlled as far as possible.</p> <p>Results show no pattern in this issue, and the participant recovered based on the design of the device itself (no click or other haptic feedback if the injection is not properly initiated). The participant was</p>	
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				able to recognize and remove the cap. Further changes to the product design would not reduce the close call seen in testing. Results show the risk is low and controlled as far as possible.	
Press Injector Perpendicularly against the Injection Site [c]	<p>Use Error (n=1) -1 Caregiver</p> <p>Close Calls (=4) -1 AI Inexperienced Patient -1 AI Experienced Patient -1 Caregiver -1 HCP</p>	<p>Use Error: -1 participant dropped the AI and participant still used the AI to deliver a dose</p> <p>Close Calls: -4 participants had some confusion with how to trigger the injection</p>	<p><u>Use Error:</u> -1 participant positioned AI for injection, pressed down to initiate the injection, and then dropped the AI. He reflexively picked up the AI (which had begun to expel medicine) and inserted the needle into the injection site to deliver the rest of the dose. After the partial dose was delivered, the participant remembered from the IFU that</p>	<p><u>Use Error:</u> The participant understood how to initiate the injection, that the first attempt was a partial injection, and that patients should not use an autoinjector that has been dropped with the cap off. The IFU also instructs users to call the help line, but this participant instead delivered a full dose to compensate for the initial use error. He did not repeat the use error in his</p>	<p>We note the potential harm associated with failure to start the injection or starting the injection incorrectly includes a partial dose, a double dose, broken syringe/damage/contaminated device. We acknowledge the warnings and information provided in the IFU regarding this error. Additionally, we note in the provided root cause analysis the participant remembered from the IFU not to use an AI that was dropped with the cap off.</p> <p>Additionally, we acknowledge that all four participants were able to self-correct. Additionally, we note the mitigation strategies</p>

			<p>he should not use an injector dropped with the cap off. In response, he opened a new AI and delivered a complete second injection. The participant said he was not careful and pressing caused the AI to come out of his hand. He also said he was nervous.</p> <p><u>Close Calls:</u> -2 participants at first tried pulling on the distal end of the AI thinking there was a cap there. Among them, 1 said the notches on the sides of the AI signaled a cap, and 1 expected a cap based on experience with Humira.</p>	<p>second trial (following training and a one-week decay period). There is no pattern in this use error or the root cause. Results show the risk is low and controlled as far as possible.</p> <p><u>Close Calls:</u> The package contains a warning on the primary panel that there is “NO button” on the autoinjector. The IFU cover also explains that the injector is buttonless. And the buttonless activation is described as part of the injector diagram in the IFU, as well as in the IFU steps. The hand positions illustrated in the IFU emphasize that there is no button, and the fingers are never positioned as if</p>	<p>within the IFU, including: the description of the AI, the figures, and the instruction of which side to press against the skin. Furthermore, we acknowledge the device was designed to mitigate the risk of confusing which end is the needle end by only having one cap (per the data submitted). Therefore, we find the applicant’s conclusion and residual risk acceptable and have no further recommendations at this time.</p>
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			<p>-1 participant at first tried pulling and pressing on the distal end of the AI thinking either there was a cap or a button there. This was based on experience with injectors with caps and buttons, and compounded by the notches on the AI (notches seemed like a trigger at first).</p> <p>-1 participant at first tried pressing on the distal end of the AI, thinking that the different shade of gray / materials represented a button.</p>	<p>pressing a button to inject. The device itself is designed with one clear cap, to communicate the directionality of the device (we saw in early in testing that two caps increases confusion about which end is the needle end). The injector has been designed without a button to support safer and more comfortable activation, especially for patients with dexterity issues who may not be able to reach or press a button. And to the extent possible within manufacturing constraints, the body and label of the injector are a uniform color and texture (again to signal that there is no button). Still, there is necessarily some</p>	
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			<p>-All 4 participants self-corrected by reading the IFU and successfully initiated injection.</p> <p>-All 4 participants understood the directionality of the device (i.e., which end contains the needle).</p>	<p>difference in plastic molded parts versus a printed label, even when the basic PMS colors are the same. And the two small notches on the injector are required for machine assembly of the components. In testing, all participants recovered based on the effective mitigations built into the product design. Results show the risk is low and controlled as far as possible.</p>	
Confirm/Monitor the Drug Delivery Process [c]	<p>Use Error (n=3 [1 participant excluded due to study artifact])</p> <p>-1 AI Inexperienced Patient</p> <p>-2 Caregivers</p> <p>Close Call (N=1)</p> <p>-1 AI Inexperienced Patient</p>	<p><u>Use Errors:</u></p> <p>-3 participants lifted the AI before full dose was administered</p> <p><u>Close Calls:</u></p> <p>-1 participant had difficulty monitoring the drug delivery process</p>	<p><u>Use Errors:</u></p> <p>-2 participants thought the first click meant the dose was administered. They both saw that the IFU mentioned clicks, but they did not pick up on the IFU distinction between the first</p>	<p><u>Use Errors:</u></p> <p>The IFU emphasizes that users should continue to hold after the first click. It instructs users to hold until the “yellow indicator” (plunger) fills the medication window and stops moving. The IFU also distinguishes between first and</p>	<p>We note the harm associated with <u>failure to administer a full dose and failure to confirm drug delivery</u> includes a partial dose, double dose, and/or an improper injection. We acknowledge the strategies within the IFU to mitigate this error/risk including: distinct statements regarding the first and second clicks, monitoring the yellow bar,</p>

			<p>and second click. Both participants saw liquid squirting out of the AI when they lifted early, and both then reinserted the needle. Among the 2, 1 participant thought a complete dose was administered. Among the 2, 1 participant realized a complete dose was not administered, but thought a second compensatory dose needed to be administered.</p>	<p>second clicks with text and formatting for emphasis. And it gives users a checklist to confirm whether or not a full dose has been delivered – and tells them to call the help line if they are unsure. The clicks and haptic feedback are important indicators that signal that the injection has started. The vast majority of users tested (56) did not lift early, and 2 of the 3 users who lifted early understood that they delivered a partial dose. All 3 participants who lifted early were inexperienced with autoinjectors, and lifted early on their first</p>	<p>and the “checklist<sup>b</sup>.” Additionally, we note the device design that includes the first and second clicks along with the tactile feedback and the yellow plunger filling the medication window to show the full dose has been given. The applicant states that with the current mitigation strategies coupled with the results, there is no further need for additional strategies. We do not find the applicant’s conclusion acceptable and recommend Step 7 be revised to provide clarification as to what the second click means. Additionally, we note PLT has since recommended to include what the first click means in Step 6. We have determined that these changes can be implemented without additional validation testing</p>
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<sup>b</sup> The checklist refers to the “you got your dose if...” and has a check in front of “window is yellow” and “no medicine leaked out (a small drop is okay).” See Step 8: confirm completion & dispose autoinjector of the IFU for the autoinjector.

			<p>-1 participant said she felt a “little push” when the needle inserted and so she thought the injection was completed. She lifted early, saw the liquid squirting out of the AI and reinserted the needle. She understood that she did not deliver a complete dose, and said she would call the pharmacy if this happened in real life.</p> <p><u>Close Call:</u> The participant reported difficulty looking at the window while injecting into the thigh. He misunderstood the IFU and thought he was</p>	<p>untrained trial. They did not repeat the use error after training (and a 1-week decay period). Results show the risk is low and controlled as far as possible.</p> <p><u>Close Call:</u> The second click occurs when the plunger rod is in the “finished” position in the window. It is an acceptable indicator of the end of drug delivery. Separately, the IFU instructs the user to check the position of the plunger in the window AFTER pulling the device away from the injection site. This instruction is specifically designed to avoid tilting and early lifting during injection.</p>	
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			required to watch the window during the injection. He was worried he would bend the needle while tilting the device to see the window. Rather than tilt the device to see the window, he said he would listen for the second click to know when the injection is complete.	This close call occurred with an inexperienced patient, who recovered, delivered a complete dose, and did not repeat the close call after training (and a one-week decay period). He also demonstrated comprehension of the IFU instructions on checking for complete dose deliver. Results show the risk is low and controlled as far as possible.	
Dispose of Product [c]	<p>Use Errors (n=4) -1 AI Experienced Patient -3 Caregivers</p> <p>Close Call (n=2) -1 AI Inexperienced Patient -1 Caregiver</p>	<p><u>Use Errors:</u> -4 participants disposed of AI in trash can</p> <p><u>Close Call:</u> -1 participant initially disposed in trashcan but self-corrected</p>	<p><u>Use Errors:</u> - 1 participant saw sharps container information in the IFU but forgot.</p> <p>-1 participant disposed of used AI the way she currently</p>	<p><u>Use Errors &amp; Close Call:</u> The base locks after injection to cover the needle and prevent accidental sticks. Additionally, the IFU explains and reinforces sharps disposal in several ways. At the</p>	We note the potential harm of the associated failure to dispose of the product or disposing the product incorrectly includes accidental injection, broken syringe, and/or contamination. We acknowledge that 1 participant forgot after reading the proper disposal,

		<p>-1 participant thought the needle would detach based on experience with reusable injection devices.</p>	<p>disposes of them. She said she skipped the disposal information in the IFU.</p> <p>-1 participant said he knew the AI could not be reused and when something is done (in real-life) he puts it in the trash. He said he saw in the IFU to put the AI in a sharps container, but he had never heard of a sharps container before.</p> <p>-1 participant said she wanted the used AI to be in a safe place, and she thought the inner carton was safe. She said she skipped the disposal step in the IFU.</p>	<p>beginning of the IFU, text and illustration emphasize that the product is single-use and should be disposed in a sharps container. Also, disposal into a sharps container is included as the final step in the injection process in the IFU. The IFU includes two illustrations to show what a sharps container looks like, and invites users to call the manufacturer help line if they do not have a sharps container. Finally, the IFU tells users NOT to dispose of injectors in the household trash and includes a description of safe alternatives to sharps containers, as well as directs users to the FDA's website on safe sharps disposal. These use issues were not driven by product design</p>	<p>2 participants skipped the disposal information, and 1 participant was unfamiliar with a sharps container. Additionally, we note 2 participants were able to self-correct due to the information included in the IFU. Also, we note the mitigation strategies that are currently within the IFU and the device design. Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations at this time.</p>
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			<p><u>Close Call:</u></p> <p>-1 participant initially disposed of used AI in trash can because he forgot, but remembered and self-corrected.</p> <p>-1 participant tried to pull the extended red base (needle shield) off of the AI, but when it would not come off he reread the IFU and self-corrected, disposing of the entire AI. He said with his wife's MS autoinjector, which uses cartridges, he removes the needle.</p>	<p>(participants could find the sharps information in the IFU, or purposefully chose to skip it). The issues were rooted in habit, or mental models of disposal. In one case, the participant was unfamiliar with a sharps container as a term.</p> <p>Results show the risk is low and controlled as far as possible.</p>	
Dispose of Product [c]	Use Error (n=1) -1 Caregiver	1 participant misunderstood the autoinjector is single dose/disposable	-1 participant reported she would put the used AI in the refrigerator because the AI	The base locks after injection to cover the needle, prevent accidental sticks, and prevent	We note the potential harm associated with failure to dispose of the product includes accidental injection and/or contamination. We acknowledge the current

			<p>label said store in the refrigerator. She said she stores her husband's Lantus in the refrigerator between injections. She thought the device may be refillable and did not think one would throw the whole AI away.</p>	<p>any attempts to reuse the injector. The outer carton describes the injectors as "single-dose", as does the cover of the IFU. Inside the IFU booklet, headings emphasize that each injector is single-dose. There is a warning to users to "Use each autoinjector only once. Never reuse an autoinjector." The IFU lists disposal into a sharps container as the last step in the injection process. The use error was driven by experience with insulin pens, not by product design, and there is no pattern in this root cause. Results show the risk is low and controlled as far as possible.</p>	<p>mitigation strategies within the IFU including a statement that the AI is "single-dose" in the beginning and Step 8 explaining the proper way to dispose of the AI. Furthermore, we note the carton and container labeling includes the statement "single-dose" in as another mitigation strategy. Additionally, we note the device design of the needle base locking preventing re-use or an accidental needlestick. Therefore, we find the applicant's conclusion acceptable and have no further recommendations at this time.</p>
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<b>Tasks (include C for critical and E for essential)</b>	<b>Number of Failures/Use Errors, Close Calls and Use Difficulties</b>	<b>Description of Failures/Use Errors, Close Calls and Use Difficulties</b>	<b>Applicant's Root Cause Analysis</b>	<b>Applicant's Discussion of Mitigation Strategies</b>	<b>DMEPA's Analysis and Recommendations</b>
Question: Where should you store your autoinjectors before you're ready to use one? [c]	Incorrect Answers (n=3) -2 HCPs  Close Call (n=1) -1 Caregiver	<u>Incorrect Answers:</u> -2 participants assumed light only meant "sunlight." <u>Close Call:</u> -1 participant initially confused on how to refrigerate.	<u>Incorrect Answers:</u> - Both participants understood to store in the refrigerator, however: -1 participant said if the text applies to room light too, it should say "all light", "any light" or "sunlight and room light".  -1 participant said she did not see the light bulb icon, but only the sun icon, because the red 'X' kind of skewed the light bulb icon.  <u>Close Call:</u> -1 participant at first thought she would put the AI in the refrigerator 24 hours	<u>Incorrect Answers:</u> The room temperature stable time exceeds the time described in the IFU. The outer carton and the IFU both include instructions to store in the refrigerator, within a certain temperature range, out of light and in the box/carton. Additionally, the statements are accompanied by an icon representing both sunlight and light bulb light. For these two use errors, both participants would store in a refrigerator, effectively keeping the products from all direct light. And both participants properly completed	We note the potential harm associated with failure to store the product correctly includes administration of a degraded drug product. We acknowledge the mitigation factors currently in place within the packaging and the IFU. Also, we note 1 participant was able to self-correct after re-reading the related page. Furthermore, we acknowledge that the participants would still store the product in the refrigerator, effectively keeping it away from light. However, per the subjective feedback, there was some confusion amongst the participants as to how to interpret light. Therefore, we recommend providing further explanation on what "light" includes to improve clarity on this important storage information. Given

			<p>before injection to chill it. She then re-read the page in the IFU and answered correctly.</p>	<p>the drug integrity check during their injection simulations. Results show the risk is low and controlled as far as possible.</p> <p><u>Close Call:</u> The product is stable at room temperature for longer than is listed in the IFU. The outer carton and the IFU both include instructions to store in the refrigerator, within a certain temperature range, out of light and in the box/carton. The injection process described in the IFU also includes a step to visually check drug integrity before injection. In this case, the participant recovered (close call only, no use error) based on the content in the IFU.</p>	<p>that the modifications are intended to add clarity to the instruction, we do not require additional human factors validation data.</p>
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				Results show the risk is low and controlled as far as possible.	
Question: What is the recommended temperature condition that the device should be at when you give the injection? [c]	Close Call (n=1) -1 AI Inexperienced Patient	<u>Close Call:</u> -1 participant expressed as to the acceptable range of degrees for “room temperature”	<u>Close Call:</u> -1 participant wondered if it changes the medication if it is winter or summer. She said with her condition she does not use air conditioning in the summer and her apartment can be very hot. She said would call the pharmacist and ask.	<u>Incorrect Answer and Close Call:</u> The IFU tells users to remove the autoinjector from the refrigerator and “wait 15-30 minutes” for it to reach room temperature. It explains that waiting until the product is room temperature can help to reduce pain.  The product is stable at room temperature for longer than is listed in the IFU. The close-call participant correctly comprehended the IFU but was looking for more specificity in degrees. The medication guide and IFU included in each autoinjector package will describe specific storage instructions, including time the product can be left at room temperature and the associated specific degree limit.	We note the potential harm associated failure to store the product correctly includes administration of a degraded product. We acknowledge the mitigation factors currently in place within the IFU (specifically, the statements to “wait 15-30 minutes” and “For a more comfortable injection, you should wait 15 to 30 minutes”) and packaging. Additionally, we note the participant was able to answer with an acceptable course of action regarding the respective question. Therefore, we find the applicant’s conclusion and residual risk acceptable and have no further recommendations at this time.

				<p>The IFU also includes a step to visually check drug integrity before injection (and after the drug is brought to room temperature). Results show the risk is low and controlled as far as possible.</p>	
<p>Question: What should you do to bring your autoinjector to room temperature? [c]</p>	<p>Incorrect Answer (n=1): -1 Caregiver</p>	<p><u>Incorrect Answer:</u> -1 participant did not understand how to bring to room temperature.</p>	<p><u>Incorrect Answer:</u> -1 participant said he would put the AI in the refrigerator for 30 minutes to bring it to room temperature. He said that is what he thought the IFU said at Step 2.</p>	<p>The IFU tells users to remove the autoinjector from the refrigerator and “wait 15-30 minutes” for it to reach room temperature. It explains that waiting until the product is room temperature can help to reduce pain. Also, the product is stable at room temperature for longer than is described in the IFU. Both the outer carton and IFU describe how to store the product, and the medication guide included in every autoinjector package will include additional specific storage information.</p>	<p>We note the potential harm associated with the failure to bring the product to room temperatures correctly includes administration of a degraded product. We acknowledge the mitigation factors currently in place within the IFU (specifically, the statements to “wait 15-30 minutes” and “For a more comfortable injection, you should wait 15 to 30 minutes”) and packaging. However, the participant expressed confusion as to the steps and refrigeration vs. room temperature. According to the provided subjective feedback the participant appeared confused as to step 1 and step 2 order of operations. Therefore, we recommend revising Step 1 to include the</p>

				The IFU also includes a step to visually check drug integrity before injection (but after the drug reaches room temperature). Results show the risk is low and controlled as far as possible.	following statement in the beginning: “Remove your autoinjector from the refrigerator” to provide clarity as to the correct sequence of events for preparation. We have determined that these changes can be implemented without additional validation testing
Question: What is the maximum amount of time you can leave your autoinjector at room temperature? [c]	Incorrect Answers (n=2) -1 AI Inexperienced Patient -1 Caregiver	-1 participant (caregiver) appeared confused as to refrigeration time and room temperature time  -1 participant (patient) thought direct light in the FAQ only referred to sunlight.	-1 participant said he would call the manufacturer help line (1-800 number) if the AI was in the refrigerator for more than 24 hours before injecting.  -1 participant said that sun would change the temperature of the medication (relating time at room temperature to exposure to sunlight). He saw the light icon on the storage page in the IFU, but overlooked the light bulb component of the icon.	<u>Incorrect (caregiver) Answer:</u> The IFU tells users to remove the autoinjector from the refrigerator and “wait 15-30 minutes” for it to reach room temperature, and asks them to call if the autoinjector is out of refrigeration for more than 24 hours. It also includes a step to visually check drug integrity before injection. Also, the product is stable at room temperature for longer than is described in the IFU. Both the outer carton and IFU describe how to store the product, and the medication guide included in every	We note the potential harm associated with exceeding the correct amount of time the product can remain at room temperature includes infection and discomfort. We acknowledge the mitigation strategies currently in place in the IFU including: the warnings, step 2, and step 3. Therefore, we find the applicant’s conclusion and residual risk acceptable and have no further recommendations at this time.

				<p>autoinjector package will include additional specific storage information. Results show the risk is low and controlled as far as possible.</p> <p><u>Incorrect (patient)</u> <u>Answer:</u> The room temperature stable time exceeds the time described in the IFU. The outer carton and the IFU both include instructions to store in the refrigerator, within a certain temperature range, out of light and in the box/carton. Additionally, the statements are accompanied by an icon representing both sunlight and light bulb light. This participant demonstrated comprehension of other related IFU elements – how to store (refrigerator, in box, away from light) and how</p>	
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				to bring to room temperature (15-30 minutes at room temperature). He also properly completed the visual drug integrity check before his simulated injections (both his untrained trial and trained trial). Results show the risk is low and controlled as far as possible.	
Question: How many times should you use your autoinjector? [c]	Close Call (n=1) -1 Caregiver	-Participant correctly interpreted the IFU and answered the question, but seemed to misunderstand in simulation.	- The participant comprehended the IFU (correctly answered question during IFU comprehension portion of the study), but during injection simulation said that there was more than 1 dose in the AI. She thought the AI was big and the outer carton text said that there were 2 single-dose pre-filled autoinjectors. She did not fully read the statement.	The statement of contents on the outer carton "2 single-dose pre-filled autoinjectors" is consistent with FDA-recommended labeling as described in guidance documents. This use event was a close call only, and the initial confusion was mitigated with the additional clarifying information presented in the IFU. There is no pattern in the event and the device itself is designed to prevent reuse (base locks after injection, covering	We note the potential harm associated with reusing the AI includes accidental injection and/or contamination. We acknowledge the participant was able to clarify initial confusion with information provided in the IFU. Additionally, we note the device is designed to prevent re-use as the base locks after injection and covers the needle. Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations at this time.

				the needle and preventing reuse). Results show the risk is low and controlled as far as possible.	
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**Table 4: Analysis of the HF Study Results for the PFS**

<b>Tasks (include C for critical and E for essential)</b>	<b>Number of Failures/Use Errors, Close Calls and Use Difficulties</b>	<b>Description of Failures/Use Errors, Close Calls and Use Difficulties</b>	<b>Applicant's Root Cause Analysis</b>	<b>Applicant's Discussion of Mitigation Strategies</b>	<b>DMEPA's Analysis and Recommendations</b>
Open Package [c]	Close Calls (n=3) -1 PFS Inexperienced Patient -1 PFS Experienced Patient -1 Caregiver	-3 participants said the PFS felt stuck in the tray.	Among the 3 participants who struggled to remove the PFS from the tray: -1 participant was concerned that the force to get the PFS out of the tray could make the cap come off (it did not come off). -1 participant said the PFS felt stuck and she was concerned she could puncture herself struggling to	All 63 participants in the study were able to remove the syringe from the tray without damaging the product or delaying therapy, including the participants with disease-related dexterity issues. The tray is designed with openings to encourage holding the syringe at the appropriate location to remove from the tray. The openings are designed to be large enough	We note the potential harm associated with failure to open the package includes delayed therapy, broken/damaged syringe, and/or broken glass. We acknowledge that all participants were able to safely and effectively remove the PFS from the packaging. Therefore, we find the applicant's conclusion and residual risk acceptable and have no recommendations at this time.

			<p>get it out (no needle stick occurred).</p> <p>-Additionally, 1 participant commented that the lack of instructions for how to remove a device from a tray may have contributed to the struggle.</p>	<p>for users with dexterity issues. The fit of the tray on the device is designed to keep the syringe stable during distribution, but to allow users with dexterity issues to remove it safely.</p> <p>Results show the risk is low and controlled as far as possible.</p>	
Check Expiration [c]	<p>Use Errors (n=17 [6 excluded due to study artifact])</p> <ul style="list-style-type: none"> <li>-5 PFS Inexperienced Patients</li> <li>-6 PFS Experienced Patients</li> <li>-5 Caregivers</li> <li>-1 HCP</li> </ul>	-17 participants did not check expiration date.	<p>- 9 participants believed a pharmacist would not distribute expired medication, or that a new, sealed package would not contain expired medication: Among them, 3 participants saw the instruction in the IFU, 4 did not see the instruction in the IFU, and 2 chose not to read the IFU at all.</p>	<p>There are quality and contracting controls to ensure only appropriately dated product is given to patients.</p> <p>Also, the expiration date is featured on the outer carton, inner carton, and device label. Additionally, the IFU instructs users to “always” check the date, and explains what to do if the product is expired -- do not use, get a new syringe, and call the help line for more information.</p>	<p>We note the potential harm associated with failure to check the expiration date includes administration of a degraded drug. We acknowledge that all participants were able to locate and understand the expiration date when asked. Additionally, we acknowledge the mitigation factors currently in place within the IFU and packaging. However, per the root cause and subjective feedback, several participants missed this task in the IFU. Therefore, we recommend revising the figure in Step 3 to point to</p>

			<p>-3 participants knew to check, but forgot to do so. Among them, 2 saw the specific instruction in the IFU.</p> <p>-2 participants saw the instruction in the IFU but said in real life they do not check the expiration date immediately prior to injecting (instead check only when they first receive the package).</p> <p>-1 participant did not see the instruction in the IFU and was inexperienced so did not know to check expiration.</p> <p>-1 participant said since the drug integrity looked good she chose to not check the</p>	<p>All of the participants who did not check during injection were still able to locate and understand the expiration date when asked to do so. In addition, all 63 participants in the study demonstrated comprehension of the instruction to check expiration as well as what to do if the product is expired.</p> <p>The root causes listed here show no pattern driven by product design. The 1 participant who did not know to check expiration did not repeat the use error after training (and 1-week training decay period). Results show the risk is low and controlled as far as possible</p>	<p>the where the expiration date is located and state “check expiration date” to provide emphasis on this important piece of information and clarify on where to find it. We have determined that these changes can be implemented without additional validation testing</p>
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			<p>expiration (assuming acceptable integrity implied acceptable dating). She saw the instruction to check expiration in the IFU.</p> <p>-1 Participant saw the instruction in the IFU, but assumed the product had not expired.</p>		
Check Expiration Date [c]	<p>Close Calls:</p> <p>-1 PFS Inexperienced Patient</p> <p>-1 Caregiver</p>	<p>-2 participants struggled to read expiration date on PFS label</p>	<p>During the study all participants correctly read the expiration date.</p> <p>-2 participants said they struggled to read the expiration date because the font size was small.</p> <p>-Among the 2, 1 participant said she would check the cartons and assume the carton and syringe label dates match.</p> <p>-Among the 2, 1 participant said she</p>	<p>There are quality and contracting controls to ensure only appropriately dated product is given to patients.</p> <p>All 63 study participants were able to read and comprehend the expiration date shown the syringe label (these close calls were in the form of comments).</p> <p>These close calls are additionally mitigated by the presence of the expiration date on the</p>	<p>We note the potential harm associated with failure to check the expiration date includes administration of a degraded drug. We note that all participants were able to read and comprehend the expiration date on the PFS label. We acknowledge the subjective feedback provided. We find the responses acceptable. Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations at this time.</p>

			would use her magnifying card to read the label.	outer carton and inner carton. The dates printed on the cartons are in larger font size than the syringe label allows. Because the syringe itself is small and there are regulatory requirements governing the amount of information that must be displayed as and the relative size of that information, expiration display options are limited. We also need to keep sufficient clear area in the label so that users can check drug integrity before injection. Results show the risk is low and controlled as far as possible	
Check Drug Integrity [c]	Use Errors (n=10 [1 excluded due to study artifact]) -4 PFS Inexperienced Patients -3 PFS Experienced Patients -1 Caregiver -2 HCPs	-10 participants did not check the drug integrity.	- 4 participants would rely on the pharmacist, manufacturer, and tamper seal. Among these 4: 2 saw the instructions in the IFU, 1 chose not to read the IFU, and 1 did not see the	There are quality and contracting controls to ensure only appropriate product is given to patients. The majority of instances of this use error were driven by habit/choice, by trust in the manufacturer, sealed package or pharmacist,	We note the potential harm associated with failure to check the drug integrity includes administration of a degraded product or contaminated product. We acknowledge all participants were able to comprehend the instruction to check the integrity as well as what to do if the product is not

			<p>instruction in the IFU.</p> <p>-1 participant said she only checks to see if there is medication in the PFS, not for particles. She did not see the instruction in the IFU before injecting.</p> <p>-1 participant said he has become complacent and in real life does not check his Humira drug integrity. He saw the IFU instruction.</p> <p>-1 participant said in real life she did not check her drug integrity and she thought she knew what she was doing, so she chose to skip Step 3.</p> <p>-1 participant did not specifically look at the liquid, but thought she would</p>	<p>or assumption that damaged product would be obvious.</p> <p>Also, all participants in the study demonstrated comprehension of the instruction to check integrity as well as what to do if the product is not clear, colorless or free of particles. No participants repeated this use error after training (and a one-week decay period). A few participants who skipped the integrity check also chose not to read the IFU. However all of those were able to find the IFU in the package.</p> <p>In all cases of this use error, the root causes would not be mitigated by product design changes.</p> <p>Results show the risk is low and controlled as far as possible.</p>	<p>clear, colorless, or particle free. However, we note per the root cause analysis and subjective feedback, two of the ten use errors did not see the instruction to check the drug integrity.</p> <p>Therefore, we recommend revising the figure in Step 3 to point directly to the viewing window and include the statement “check to make sure drug is clear and free of particles” to improve clarity as to where and what the user should be looking for. We note the Patient Labeling Team (PLT) has made a similar recommendation and we agree; therefore we decided not to include this recommendation in section 4.1. We have determined that these changes can be implemented without additional validation testing</p>
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			<p>notice if something was out of order before injection. She saw the instruction in the IFU.</p> <p>-1 participant said she checked the name on the PFS label and thought she would have noticed then (while looking at the syringe barrel) if something was visibly wrong with the drug. She saw the instruction in the IFU. Also, she does not check her Enbrel.</p> <p>-1 participant looked at the liquid to see what color and density it was, but he did not know what he was looking for. He did not read the IFU.</p>		
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Clean Injection Site [c]	Use Errors (n=6 [2 excluded due to study artifact]) -1 PFS Inexperienced Patient -4 PFS Experienced Patients -1 Caregiver	-6 participants did not clean injection site.	<p>-1 participant was excited about administering the medication and knew to clean but forgot. She saw the instruction in the IFU.</p> <p>-1 participant remembered after he inserted the needle.</p> <p>-1 participant said when he opens his package at home he sees alcohol swabs in it and they remind him to clean.</p> <p>-2 participants knew they were supposed to clean and chose not to. Both participants felt they were already "clean."</p> <p>-1 participant chose not to read IFU and said he was not familiar with</p>	<p>From a clinical perspective, the injection site can be clean without using an alcohol swab. Also, these root causes would not be mitigated by further design changes. Though some chose not to read the IFU, all participants with this use error were able to find it. And among those who chose to read the IFU all saw and comprehended the instruction. Results show the risk is low and controlled as far as possible.</p>	<p>We note the potential harm associated with not cleaning the injection site is an increased chance for infection. We acknowledge the mitigation strategies currently in place, which includes "step 4: choose site and clean skin" in the IFU, and this step directs users to clean the skin at the injection site. Additionally, the IFU includes images of alcohol swabs under step 1 and step 4 of the IFU. Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations at this time.</p>
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			cleaning an injection site.		
Take off Needle Cap [c]	<p>Use Errors (n=1) -1 Caregiver</p> <p>Close Calls (n=5) -3 PFS Inexperienced Patients -1 PFS Experienced Patient -1 HCP</p>	<p><u>Use Error:</u> -1 participant did not take off needle cap</p> <p><u>Close Calls:</u> -3 participants thought needle and/or medication would pass through the needle cap -2 participants struggled to remove due to force -1 participant removed cap early but didn't recap -2 participants pulled on plunger while removing cap.</p>	<p><u>Use Error:</u> -1 participant thought she had removed the needle cap. She recognized she had not delivered a complete dose, but did not know why, and said she would call the 1-800 number. She reported it was harder to push the plunger than she expected.</p> <p><u>Close Call:</u> -1 participant attempted to inject twice with the needle cap on. He felt the plunger was hard to press and saw the liquid leak out, so he called the doctor and self-corrected. He did not see the IFU in the box. He did see the needle cap, but</p>	<p><u>Use Error:</u> All but 1 instance of this use issue were close calls. Among the close calls, 3 participants recovered based on the design of the syringe (force to plunge with cap on, expelled liquid, general similarity to syringes, and presence of the spring). The design of the syringe also led the 1 participant with an error to detect the missed dose / expelled medicine. In real life she would call the help line, and in testing did not repeat the error after training (and a decay period). 2 participants commented on the difficulty to remove the cap, but were both able to do so, despite existing dexterity issues in one case. The remaining 61 participants did not comment on the force to remove the cap.</p>	<p>We note the potential harm associated with failure to remove the needle cap includes a delay in therapy, missing a dose, and/or accidental injection in hand/finger. We acknowledge that all but one participant was able to self-correct. Additionally, the one participant that did not self-correct, was able to recognize a dose was not given and utilized the 1-800 number for assistance. Furthermore, we note the IFU provides the information for pulling off the needle cap with an image depicting the user action. Therefore, we find the Applicant's conclusion and residual risk acceptable and have no further recommendations.</p>

			<p>thought it was an extra safety feature and the needle would poke through it.</p> <p>-2 participants thought the hole at the end of the needle cap indicated the needle or medication would come through it. Both participants self-corrected – among them, 1 participant remembered needle caps come off of PFSs, and the other thought the needle cap was holding the spring back and therefore it needed to come off.</p> <p>-2 participants struggled to remove the needle cap but were able to. Among them, 1</p>	Results show the risk is low and controlled as far as possible.	
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			participant said this was normal for her, but this was somewhat more difficulty. The other participant thought she had to pinch and pull the cap off.		
Take off Needle Cap [c]	Use Errors (n=1) -1 PFS Experienced Patient	-1 participant partially pressed the plunger while taking off the needle cap as this is habit.	-1 participant expelled some medication as she was removing the cap. She saw the liquid, and understood it meant a partial dose – but she would inject the remaining medication (partial dose) because her insurance only allows a certain number of PFSs per month. She said she was focused on the left side of the Step 5 image (hand removing the cap), not the right side where the hand is holding the PFS. But	There is no pattern in this use issue or root cause, and product design changes would not mitigate this error. The user understood the correct way to use the product and the consequences of her choice to use it differently. Results show the risk is low and controlled as far as possible.	We note the potential harm associated with incorrectly removing the needle cap includes a partial dose. We acknowledge, per the subjective feedback, the participant utilized this method due to habit, and the participant was able to recognize that her grip was different than the grip shown in the IFU. Therefore, we find the applicant's conclusion and residual risk acceptable and have no recommendations at this time.

			when she went back to the IFU, she understood that the grip in the illustration was different than her grip.		
Take off Needle Cap [c]	<p>Use Errors (n=1) -1 PFS experienced Patient</p> <p>Close Calls (n=1) -1 Caregiver</p>	<p><u>Use Error:</u> -1 participant removed cap early and recapped</p> <p><u>Close Call:</u> -1 participant removed cap early but didn't recap</p>	<p><u>Use Error:</u> -1 participant removed needle cap to expel the air bubble and then recapped to keep the needle clean. He chose to do this before he read the IFU because he is experienced with PFSs.</p> <p><u>Close Call:</u> -1 participant removed the needle cap early, set the device down, and cleaned his injection site. The needle did not touch anything. He said it would be easier to inject with the cap already off (in other words, ready to go as soon</p>	There is no pattern in the root cause, both participants demonstrated comprehension of the IFU (not to remove cap early or recap, and the consequences of doing so), and both participants went on to deliver a full dose during injection simulation. Changes to the user interface would not further mitigate this use issue. Results show the risk is low and controlled as far as possible.	We note the potential harm associated with removing the cap early includes an accidental injection into the hand/finger, delayed therapy, and/or missing a dose. We acknowledge, per the subjective feedback 1 participant removed the cap due to prior experience, and the other participant removed the cap based on his mental model of making it easier. Also, we note in Steps 1, 2, and 3 there is a clear statement "Don't remove the cap just yet." Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations.

			as site cleaning is finished).		
Take off Needle Cap [c]	Close Calls (n=2) -1 PFS Inexperienced Patient -1 Caregiver	-2 participants initially pulled on plunger when taking off needle cap.	-1 participant pulled the plunger then self-corrected by holding the flange while removing the needle cap. She did not remember from training where to hold the PFS during cap removal, and said she held the plunger partially because it is the same color as the flange. -1 participant performed the task correctly/did not pull on the plunger, but speculated that he may hold the plunger while removing the needle cap because the IFU does not tell the user NOT to hold the plunger (in text).	Both participants recovered, properly held the syringe to remove the cap, and went on to deliver the full dose. The IFU illustration shows the hands positioned away from the plunger at this step. Both participants understood the hand position shown in the illustration. Product design changes would not further mitigate this risk. Results show the risk is low and controlled as far as possible.	We note the harm associated with pulling on the plunger while removing the needle cap includes missing a dose. We acknowledge, per the subjective feedback, that one participant was able to self-correct, and the other did perform the task correctly, though he may at some point have held, but did not pull, onto the plunger while removing the cap because the IFU does not say not to hold the plunger; holding, but not pulling, the plunger is not expected to result in the harm noted above. Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations at this time.

<p>Insert Needle into the Skin [c]</p>	<p>Use Errors (n=5[1 excluded due to study artifact])  -1 PFS Experienced Patient  -1 Caregiver  -3 HCPs</p> <p>Close Calls (n=1)  -1 HCP</p>	<p>-6 participants attempted to expel air bubble from PFS</p>	<p>-Only a drop of medication was expelled in each instance (except the close call, where no air or medication was expelled).  -All participants in this case had a habit or were previously taught to remove air bubbles from other syringes.  -Among them, 2 participants chose not to read the IFU, 1 participant thought the IFU allowed for air bubble removal (though recognized it did not require it), 1 participant skimmed the IFU, and 1 participant initially misread the statement in the IFU as an instruction to check for rather than allow an air bubble.</p>	<p>The IFU tells users to make sure all of the medicine goes into their skin, but that a drop leftover is okay. If a drop is expelled at some point, the user still receives a full dose. All participants in this case (5 who removed the bubble, and 1 who only had a close call) successfully delivered a full dose.  All the use errors in this case were driven by previous knowledge rather than product design. The single participant with a close call misread the IFU and had a habit to remove air.  She later demonstrated comprehension of the IFU instruction on what to check.  Results show the risk is low and controlled as far as possible.</p>	<p>We note the potential harm associated with expelling the air bubble includes a partial dose. We acknowledge, per the provided subjective data, that all participants expelled the air bubble due to previous knowledge. Although a drop of medication was expelled in each error observed, the sponsor states that this would still result in a full dose. Additionally, we note Step 3 includes a statement that the air bubble is okay and there is no reason to remove it. Therefore, we find the applicant's conclusion and residual risk acceptable and we have no recommendations at this time.</p>
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			Also, 1 participant “saw it on TV” (air bubble removal) and said that manufacturers account for the expelled drop in the volume of the PFS.		
Insert the Needle into the Skin [c]	Close Calls (n=5) -1 PFS Inexperienced Patient -2 PFS Experienced Patients -1 Caregiver -1 HCP	-5 participants had difficulty inserting needle correctly.	-2 participants were not sure what angle to insert the needle at, but both participants inserted the needle correctly. Among them 1 participant was worried about pain and absorption depending on the angle, and followed the IFU image showed. The other participant guessed the angle was 45 degrees based on her knowledge of other subcutaneous injections, but she wanted the IFU to specify an exact angle as well.	All participants inserted the needle correctly. For angle of insertion, the illustration in the IFU guides users to inject at an appropriate angle (between approximately 45-90 degrees, defined as acceptable in the use error analysis). Although grip-adjustment was a challenge for one patient, she commented that the study PFS is easier to grip than ones she has experience with. The wobble of the plunger is actually a function of the fit of the syringe within the safety shield (a fixed characteristic that is the	We note the potential harm associated with failure to insert the needle at the correct angle includes a partial dose and/or missing a dose. We acknowledge that all the participants were able to complete a full injection. Additionally, we note the IFU illustration in Step 6 guides users to inject at an appropriate angle; however, it does not give specific guidance. Therefore, we recommend revising step 6 and the related figure to include the proper angle of insertion/injection to improve clarity of this administration task. We have determined that these changes can be implemented without additional validation testing.

			<p>-1 participant reported difficulty adjusting grip from needle insertion position to plunge position. She was concerned she would bend the needle. She said she now knew how to hold the PFS, and this was just a first-time use concern. She said the study PFS was easier to use than her current PFS because of the flange design and size of plunger head.</p> <p>-1 participant had difficulty getting a good grip with her thumb on the plunger during needle insertion and while pressing the plunger down because of the syringe movement</p>	<p>function of the off-the-shelf designs of the safety shield and the syringe). Only 1 participant in 63 commented, and she was able to deliver a full dose during injection simulation. An adjustment of the weight of the syringe would not reduce risk, given the 1 participant who expelled some dose had done the same with her lighter Humira PFS, and she recovered to deliver a complete dose with a different syringe. Results show the risk is low and controlled as far as possible.</p>	
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			<p>within the needle shield. She was able to deliver a complete injection.</p> <p>-1 participant pressed the plunger down while approaching the injection site to insert the needle. She saw liquid squirt out, got a new PFS, and injected correctly. She said she would call the pharmacist and report the close call. She said the study PFS may be a little bit heavier than her Humira PFS, but this happened once with her Humira syringe as well. She also commented that she is not accustomed to injecting in front of</p>		
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			someone (as in the study facilitator).		
Press the Plunger all the way down to Deliver the Drug [c]	Use Error (n=1) -1 PFS Experienced Patient  Close Call (n=1) -1 PFS Inexperienced Patient	<u>Use Error:</u> -1 participant did not push the plunger all the way down.  <u>Close Call:</u> -1 participant was able to push the plunger all the way down, but stated it was difficult.	<u>Use Error:</u> -1 participant pressed the plunger down until it touched the safety shield triggers (but not quite far enough to activate them). Participant thought she had delivered a complete dose. She did not read Step 8 in the IFU, so she did not know the needle was supposed to retract. Though it did not correspond to a use error or close call, 1 HCP commented that the PFS does not give very much haptic feedback and that the flange may obscure the view of the plunger moving through the syringe. She is	All of these participants associated with this use issue were able to deliver a full dose, and demonstrated comprehension of the indicators of dose delivery as described in the IFU. The syringes are filled with higher volume than 0.8 mL, the amount for a full dose. Pressing the plunger to touch but not activate the safety shield triggers delivers an expelled volume of 0.8369 mL according to lab testing. In other words, the participant delivered a complete dose in this case, even though the shield did not activate. Results show no pattern in difficulty pressing the plunger due to force (1 comment among 63 participants). The force is partly a function of fixed characteristics – syringe size and formulation	We note the potential harm associated with failure to press the plunger all the way down to deliver the drug includes a partial dose, delay in therapy, pain, and/or needle stick. Based on the subjective feedback and the design features of the PFS, we acknowledge that the participants did not receive a partial dose. Additionally, we note the indicators of dose delivery in Step 7 and 8 in the IFU. Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations at this time.

			<p>concerned about patients' ability to monitor dose delivery, and would teach patients to hold in a position that allows them to see past the flange.</p> <p><u>Close Call:</u> -1 participant was able to push the plunger all the way down, but said it felt like it took a lot of force and she does not have a lot of hand strength/dexterity. She was concerned about the needle slipping (it did not slip during testing).</p>	<p>viscosity. Additionally the syringe has been designed with larger flange with texture, and enhanced larger plunger rod tip with concave surface and texture – all to improve grip and stability, in particular for patients with dexterity issues. As for monitoring the injection, the safety shield, syringe barrel and syringe label are predominately clear in color, to allow users to see the white plunger move through the device as clearly as possible. However the IFU instructs users to look/confirm injection after removing the syringe from the injection site (needle retraction is a more concrete indicator of the plunger position). Changes to the product design would not further mitigate the 2 unique root causes seen in testing.</p>	
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				Results show the risk is low and controlled as far as possible.	
Confirm the Injection is Complete [c]	Close Calls (n=2) -1 PFS Inexperienced Patient -1 HCP	-2 participants expected a click or other completion feedback	Both participants delivered complete injections, however struggled to confirm it. Among them: -1 participant said it was hard to know if the medication had been fully delivered because there was no indication or click. -1 participant said she knew she could not press the plunger any further, but had expected to hear a click and the retraction did not occur as quickly as she thought it would. She said there was no way to really know if the injection was complete because there was no	These close calls would not be mitigated by further syringe design change. The participants were looking for cues that are present in an autoinjector (clicks, medication window). The proposed autoinjector presentation has these cues, and healthcare providers and patients will be given the choice of using the system that works best for them. For both participants, the lack of clicks and medication window did not prevent the them from delivering a complete dose. And the syringe safety shield speed of activation (or the needle retraction speed) is fixed by the safety shield design. Both participants also demonstrated comprehension of the IFU instructions for	We note the potential harm associated with failing to confirm the injection is complete includes a partial dose and/or double dose. We acknowledge both participants were able to complete dose. Additionally, we note the instructions and figure in Step 7 to perform/complete an injection, along with the instructions in Step 8 to confirm the needle has retracted. Therefore, we find the applicant's conclusion and residual risk acceptable and have no recommendations at this time.

			click or window.	confirming a complete dose was delivered. Results show the risk is low and controlled as far as possible.	
Dispose of Product [c]	Use Errors (n=5) -4 PFS Inexperienced Patients -1 Caregiver	-5 participants disposed of PFS in trash	-5 participants disposed of used PFS in trash instead of sharps container. Among them: 1 participant didn't read the IFU, 1 didn't see the instructions on sharps disposal, and 1 skimmed over the instructions. The other 2 participants saw and comprehended the instructions in the IFU, but chose not to since the needle was retracted.	The safety shield locks after injection to cover the needle and prevent accidental sticks. Additionally, the IFU explains and reinforces sharps disposal in several ways. At the beginning of the IFU, text and illustration emphasize that the product is single-use and should be disposed in a sharps container. Also, disposal into a sharps container is included as the final step in the injection process in the IFU. The IFU includes two illustrations to show what a sharps container looks like, and invites users to call the manufacturer help line if they do not have a sharps container. Finally, the IFU tells users NOT to	We note the potential harm associated with failure to dispose of the product or disposing incorrectly includes accidental injection into hand/finger and/or contaminated product. We acknowledge that all participants demonstrated comprehension of the IFU instructions. Additionally, we note the instructions in the IFU to dispose of the used PFS in a sharps container stated in the beginning of the IFU and in Step 8 of the IFU, which also has images. Furthermore, we note the inclusion of the needle safety device which causes the needle to retract into the syringe when activated. Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations at this time.

				dispose of injectors in the household trash, and includes a description of safe alternatives to sharps containers, as well as directs users to the FDA's website on safe sharps disposal. During IFU comprehension testing, all participants demonstrated comprehension of the IFU disposal instructions. Changes to product design would not further mitigate the root causes of these use issues seen in testing. Results show the risk is low and controlled as far as possible.	
Dispose of Product [c]	Use Errors (n=2) -1 PFS Inexperienced Patient -1 Caregiver	-2 participants did not dispose of the PFS	-1 participant said he would put the used PFS in the inner carton, tape it shut, and take it to the doctor's office later. He said he had	The safety shield locks after injection to cover the needle, prevent accidental sticks, and prevent any attempts to reuse the syringe.	We note the potential harm associated with failure to dispose of the product or disposing incorrectly includes accidental injection into hand/finger or contaminated product. We acknowledge the that all participants demonstrated

			<p>not received training in real life on how to dispose of syringes and he knew some people returned them to doctor's offices. He chose not to read the IFU.</p> <p>-1 participant said he would refill the PFS and store it in the refrigerator. He said he knew from TV advertising that some devices are refillable. He said he saw the instruction in the IFU to dispose of the PFS.</p>	<p>The outer carton describes the syringes as "single-dose", as does the cover of the IFU. Inside the IFU booklet, headings emphasize that each syringe is single-dose. There is a warning to users to "Use each syringe only once. Never reuse a syringe." The IFU lists disposal into a sharps container as the last step in the injection process. During IFU comprehension testing, all participants demonstrated comprehension of the IFU disposal instructions. The use error was driven by second-hand experience with medical device disposal, not by the product design, and there is no pattern in this root cause. Results show the risk is low and controlled as far as</p>	<p>comprehension of the IFU disposal instructions in the IFU comprehension testing. Additionally, we note 1 participant chose not to read the IFU, and the other participant, per the subjective feedback, saw the instruction in the IFU to dispose of the PFS. Furthermore, the IFU contains clear steps on how to dispose of PFS (in the introduction and Step 8). Therefore, we find the applicant's conclusion and residual risk acceptable and have no recommendations at this time.</p>
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				possible.	
Dispose of Product [c]	Close Calls (n=1) -1 Caregiver	-1 participant tried to separate PFS from flange when disposing.	-1 participant unscrews his Humalog needle and puts it in the sharps container after injection. At first the participant thought the image in the IFU showed pressing the plunger so the needle would fall off. He saw the needle was not separating, reread the IFU, and disposed of the entire PFS correctly.	The safety shield locks after injection to cover the needle, prevent accidental sticks, and prevent any attempts to reuse the syringe. The outer carton describes the syringes as "single-dose", as does the cover of the IFU. Inside the IFU booklet, headings emphasize that each full syringe is single-dose. There is a warning to users to "Use each syringe only once. Never reuse a syringe." The IFU lists disposal into a sharps container as the last step in the injection process. During IFU comprehension testing, all participants demonstrated comprehension of the IFU disposal instructions. The close call was driven by experience with multi-dose pens. The syringe design and IFU mitigated	We note the potential harm associated with failure to dispose of the product or disposing incorrectly includes accidental injection into hand/finger and/or contaminated product. We acknowledge the participant was able to self-correct due to the device design and the IFU instructions. Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations at this time.

				the risk (to a single close call only.) Results show the risk is low and controlled as far as possible.	
Dispose of Product [c]	Use Error (n=1) -1 PFS Experienced Patient	-1 participant recapped the used needle	-1 Participant said she prefers to recap so no one can get stuck before she puts the PFS in the sharps container. She currently does this with her Enbrel PFS. This was the same single participant who did not trigger the needle shield during the injection.	When activated, the safety shield locks after injection to cover the needle, prevent accidental sticks, and prevent any attempts to recap or reuse the syringe. The IFU lists disposal into a sharps container as the last step in the injection process (with no direction to recap). During IFU comprehension testing, this participant demonstrated comprehension of the IFU disposal instructions. The use error was driven by habit, and there was no pattern of the error in testing. A needle stick did not occur. Results show the risk is low and controlled as far as possible.	We note the potential harm associated with failure to dispose of the product or disposing incorrectly includes accidental injection into hand/finger and/or contaminated product. We acknowledge the participant comprehended the IFU instructions of disposal during IFU comprehension testing. Additionally, we note, per the subjective feedback the participant normally recaps the PFS she uses at home. Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations at this time.

Table 5: Analysis of HF Study Results for PFS [Knowledge Comprehension Questions]					
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	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Where should you store your syringes before you're ready to use one? [c]	Incorrect Answers (n=3) -1 PFS Inexperienced Patients -1 Caregiver -1 HCP	-All participants did not understand light, didn't just mean sunlight	All participants understood to store in the refrigerator, however: -1 participant said the IFU should clearly say "sunlight and light from a light bulb or lamp" and provide an icon of a lamp. She was also confused by "direct light" language in the FAQ section of the IFU. -1 participant said "light" on p.4 of the IFU did not indicate room light to her. She assumed the icons were referring to sunlight. She suggested making the icons bigger or moving the icons after the words. -1 participant said she did not pay attention	The room temperature stable time exceeds the time described in the IFU. The outer carton and the IFU both include instructions to store in the refrigerator, within a certain temperature range, out of light and in the box/carton. Additionally, the statements are accompanied by an icon representing both sunlight and light bulb light. For these three use errors, all participants	We note the potential harm associated with failure to store the PFS correctly includes administration of a degraded drug. We acknowledge that the participants' responses indicate they would keep the products away from light as they will be stored in the refrigerator. However, per the subjective feedback, there was some confusion amongst the participants as to how to interpret light. Therefore, we recommend providing further explanation on what "light" includes to improve clarity on this important storage information. We have determined that these changes can be implemented without additional validation testing

			to the light bulb icon in the IFU and thought only the heat from direct sunlight would be the problem. She was not sure why she would need to keep the syringes away from artificial light.	would store in a refrigerator, effectively keeping the products from all direct light. And these participants properly completed the drug integrity check during their injection simulations. Results show the risk is low and controlled as far as possible.	
What if anything should you check about your medication before you use it? [c]	Close Call (n=1) -1 PFS Experienced Patient	-1 participant initially unsure what color the solution should be	All participants correctly answered the question during the IFU comprehension scenario. However, before the IFU comprehension evaluation, 1 participant said that "clear" in Step 3 of the IFU means "free of particles" to her. She did not know what color the liquid was supposed to be, however she assumed colorless was okay.	All participants demonstrated comprehension of the integrity check instructions during the IFU comprehension evaluation. This participant properly checked integrity during injection simulation. There is no pattern in the close call or root cause.	We note the potential harm associated with failure to inspect the PFS includes administration of a degraded/contaminated drug. We acknowledge all participants answered the question correctly during the IFU comprehension testing. Therefore, we find the applicant's conclusion and residual risk acceptable and have no further recommendations at this time.

				Results show the risk is low and controlled as far as possible.	
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### 3.2 HUMAN FACTORS REQUIREMENT FOR JIA

In a February 20, 2019 communication to the Applicant, we requested clarification regarding the intended patient populations for self-administration with both the PFS and the AI, as we noted that JIA is a proposed indication but pediatric participants with JIA were not included in the HF study for the PFS or the AI<sup>c</sup>. On February 27, 2019, the Applicant submitted a response to the IR, including a justification as to why JIA patients did not need to be included in the HF study for the PFS or the AI, but still can be considered for self-administration. The following sections provide our human factors considerations for the PFS and AI.

#### Prefilled Syringe

To address the self-administration of the PFS in pediatric patients with JIA, we sent an IR on March 5, 2019 requesting the Applicant submit an updated Use-Related Risk Analysis (URRA) that incorporates the JIA population<sup>d</sup>. On March 14, 2019, the Applicant submitted an updated URRA; however, it was unclear if the URRA considered the differences in the JIA population (e.g. cognitive and anthropometric differences). Therefore, on April 4, 2019 we sent a follow-up IR for an updated URRA that clearly includes these considerations. The Applicant submitted a full comparative analyses on May 14, 2019, after we sent an IR for the Applicant to include the missing items: injection force and cap removal force. We note there are differences in the injection force and cap removal force. We sought input from our CDRH colleagues and they found these differences to be acceptable in their review.

Based on the updated URRA and the full comparative analyses, we determined that additional data would not be needed to support the PFS user interface for this indication/patient population.

#### Autoinjector

Upon reviewing the Applicant's justification for not including pediatric participants with JIA in the HF validation study for the autoinjector, we disagree with the Applicant's justification and we provide our rationale below:

1. Proportion of patients with JIA is less than 0.1% of adalimumab use in the US.
  - a. DMEPA Comment: JIA patients are still part of the intended user group, and we need HF validation data to support safe and effective use for all intended user groups.
2. Pediatric patients share injection responsibility with caregivers and/or HCPs.
  - a. DMEPA Comment: We acknowledge that pediatric patients may share injection responsibility with caregivers and/or HCPs; however, post-marketing

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<sup>c</sup> Patanavanich, S. FDA Communication: Email Information Request for Hadlima (BLA 761059). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 20.

<sup>d</sup> Patanavanich, S. FDA Communication: Email Information Request for Hadlima (BLA 761059). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 05.

information shows that patients (including pediatric/adolescents) are not always trained in the use of their prescribed medications.

3. The usability study of other products with an indication of JIA did not include patients under age of 18 in a user group.
  - a. DMEPA Comment: The Applicant mentions Cyltezo, Orencia, and Taltz; however, Cyltezo is only licensed in a pre-filled syringe presentation. As for Taltz, this product is currently only indicated for adult patients with Plaque Psoriasis and Psoriatic Arthritis. Finally, although the Orencia ClickJet was approved without JIA data, our thinking has evolved since the time of the HF study results review, which was completed on January 12, 2016. This is also part of DMEPA's effort to ensure consistency moving forward in the scientific thinking with regards to pediatric patients with JIA representing a distinct user group when we evaluate whether HF data are necessary for review to support a marketing application.

In summary, we disagree with the Applicant's justification for not needing HF validation data in JIA patients for self-administration with the autoinjector. From a scientific perspective, we consider pediatric/adolescent JIA patients to be a distinct user group, and therefore consider HF validation data from that user group necessary to support a conclusion that the proposed Hadlima autoinjector can be used safely and effectively by all intended users, in the intended use environments, for its intended uses.

#### **4 CONCLUSION & RECOMMENDATIONS**

For the PFS, we determined that additional data would not be needed to support the PFS user interface for all intended users, in the intended use environments, for its intended uses.

For the autoinjector, we disagree with the Applicant's justification for not conducting a HF validation study with pediatric/adolescent JIA patients as a distinct user group and recommend that the following statement be added to Section 2 of the PI: "Hadlima PushTouch is for adult self-administration or caregiver administration only. Self-administration of Hadlima PushTouch in pediatric patients has not been tested." Therefore, we defer to the Division of Pulmonary, Allergy, and Rheumatology Products on addressing this data gap and determine appropriate labeling for this user group.

Additionally, based on the available data within the submitted HF study results reports, we note that some areas of the Instructions for Use (IFU) that should be revised (see Section 4.2). Given that the modifications are intended to add clarity and/or emphasis to the IFU, we do not require additional human factors validation data.

##### **4.1 RECOMMENDATIONS FOR SAMSUNG BIOEPIS**

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

- A. Autoinjector IFU

1. Based on the use error observed in the HF validation study for the knowledge comprehension question: “What should you do to bring your autoinjector to room temperature”, we recommend revising Step 1 to include (as the first bullet), “Remove your autoinjector from the refrigerator,” to add emphasis and clarity to the correct sequence of steps and proper storage of the proposed product.
  2. Based on two of the use errors observed for the task of confirming the drug delivery and the participants’ subjective feedback in the HF validation study, we recommend revising Step 7 to describe to users what the second click means in order to improve clarity and understanding of the user interface.
- B. Pre-Filled Syringe IFU
1. We recommend revising step 1 to include (as the first bullet), “Remove your pre-filled syringe from the refrigerator,” to add emphasis and clarity to the correct sequence of steps and proper storage of the proposed product.
  2. Based on the subjective feedback from two participants, for the task of inserting the needle into the skin, in the PFS HF study, we recommend revising Step 6, and the related figure, to include the proper angle of insertion/injection to improve clarity of this administration task.
- C. Both Autoinjector and Pre-filled Syringe IFUs
1. Based on the incorrect answers and subjective feedback provided by participants for the knowledge comprehension question: “Where should you store your PFS/autoinjectors,” we recommend revising the storage instructions under “Caring for your...” to provide more clarity as to what “light” refers to.
  2. Based on the use errors for the task of checking the expiration date in the HF study, we recommend revising the image in Step 3 to say “check expiration date” instead of “not expired” to provide further clarity for this task.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Hadlima received on July 23, 2018 from Samsung Bioepis.

<b>Table 2. Relevant Product Information for Hadlima and the Reference Product</b>		
<b>Product Name</b>	Hadlima	US-licensed Humira
<b>Initial Approval Date</b>	N/A	January 31, 2002
<b>Active Ingredient</b>	adalimumab-bwwd	adalimumab
<b>Indication</b>	<ul style="list-style-type: none"> <li>-Rheumatoid Arthritis (RA)</li> <li>-Juvenile Idiopathic Arthritis (JIA) in patients from 4 to 17 years of age</li> <li>-Psoriatic Arthritis (PsA)</li> <li>-Ankylosing Spondylitis (AS)</li> <li>-Adult Crohn’s Disease (CD)</li> <li>-Ulcerative Colitis (UC)</li> <li>-Plaque Psoriasis (Ps)</li> </ul>	<ul style="list-style-type: none"> <li>-Rheumatoid Arthritis (RA)</li> <li>-Juvenile Idiopathic Arthritis (JIA) in patients 2 years of age and older</li> <li>-Psoriatic Arthritis (PsA)</li> <li>-Ankylosing Spondylitis (AS)</li> <li>-Adult Crohn’s disease (CD)</li> <li>-Pediatric Crohn’s disease</li> <li>-Ulcerative Colitis (UC)</li> <li>-Plaque Psoriasis (Ps)</li> <li>-Hidradenitis Suppurativa (HS)</li> <li>-Uveitis (UV)</li> </ul>
<b>Route of Administration</b>	Subcutaneous	Subcutaneous
<b>Dosage Form</b>	Injection	Injection
<b>Strength</b>	40 mg/0.8 mL	<ul style="list-style-type: none"> <li>80 mg/0.8 mL</li> <li>40 mg/0.8 mL</li> <li>40 mg/0.4 mL</li> <li>20 mg/0.4 mL</li> <li>20 mg/0.2 mL</li> <li>10 mg/0.2 mL</li> <li>10 mg/0.1 mL</li> </ul>
<b>Dose and Frequency</b>	<p>Hadlima is administered by subcutaneous injection.</p> <ul style="list-style-type: none"> <li>• Adult RA: 40 mg every week or every other week.</li> <li>• Adult PsA and AS:</li> </ul>	<p>Humira is administered by subcutaneous injection.</p> <ul style="list-style-type: none"> <li>• Adult RA 40 mg every week or every other week</li> </ul>

	<p>40 mg every other week</p> <ul style="list-style-type: none"> <li>• JIA: ≥ 30 kg (66 lbs) and from 4 to 17 years of age: 40 mg every other week.</li> <li>• Adult Crohn's Disease and Ulcerative Colitis: Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every other week</li> <li>• Plaque Psoriasis: Initial dose: 80 mg Then: 40 mg every other week starting one week after initial dose</li> </ul>	<ul style="list-style-type: none"> <li>• Adult PsA, and AS 40 mg every other week</li> <li>• JIA from 2 to 17 years of age: 10 kg to &lt; 15 kg: 10 mg every other week 15 kg to &lt; 30 kg: 20 mg every other week ≥ 30 kg: 40 mg every other week</li> <li>• Adult Crohn's disease and Ulcerative Colitis Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every other week</li> <li>• Pediatric Crohn's disease 17 kg to &lt; 40 kg: Day 1: 80 mg Day 15: 40 mg Day 29: 20 mg every other week ≥ 40 kg: Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every other week</li> <li>• Adult Plaque Psoriasis or Uveitis Initial dose: 80 mg Then: 40 mg every other week starting one week after initial dose</li> <li>• Adult HS Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every week</li> </ul>
<b>Storage</b>	<p>Refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. If needed, may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days</p> <p>Store in original carton until time of administration to protect from light.</p>	<p>Refrigerated at 36° to 46°F (2° to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. If needed, may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days.</p> <p>Store in original carton until time of administration to protect from light.</p>

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

On March 1, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, 118299 and 761059 and SB5<sup>e</sup>. Our search identified one previous reviews<sup>f</sup>, and we considered our previous recommendations to see if they are applicable for this current review.

## **APPENDIX C. HUMAN FACTORS STUDY**

### **C.1 Autoinjector Study Results**

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### **C.2 PFS Study Results**

<\\cdsesub1\evsprod\bla761059\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\rheumatoid-arthritis-ra\5354-other-stud-rep\bimo\sb5-safety-pfs-summative-study-report.pdf>

## **APPENDIX D. ISMP NEWSLETTERS—N/A**

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

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<sup>e</sup> SB5 is the developmental code name used by the Sponsor.

<sup>f</sup> Menos-Grillasca, C. Human Factors Protocol Review for SB5 (IND 118299). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 APR 18. RCM No.: 2017-315.

## **APPENDIX F.— Information Requests and Sponsor Responses**

- **February 20, 2019 IR to the Applicant<sup>g</sup>**
  - **February 27, 2019 Applicant response to the IR**
- **March 5, 2019 IR to the Applicant<sup>h</sup>**
  - **March 14, 2019 Applicant response to the IR**
- **April 4, 2019 IR to the Applicant<sup>i</sup>**
  - **April 17, 2019 Applicant response to the IR**
- **April 25, 2019 IR to the Applicant<sup>j</sup>**
  - **May 3, 2019 Applicant response to the IR**
- **May 9, 2019 IR to the Applicant<sup>k</sup>**

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<sup>g</sup> Patanavanich, S. FDA Communication: Email Information Request for Hadlima (BLA 761059). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 20.

<sup>h</sup> Patanavanich, S. FDA Communication: Email Information Request for Hadlima (BLA 761059). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 05.

<sup>i</sup> Patanavanich, S. FDA Communication: Email Information Request for Hadlima (BLA 761059). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 04.

<sup>j</sup> Patanavanich, S. FDA Communication: Email Information Request for Hadlima (BLA 761059). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 25.

<sup>k</sup> Sinks, M. FDA Communication: Email Information Request for Hadlima (BLA 761059). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAY 14.

## 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,<sup>1</sup> along with postmarket medication error data, we reviewed the following Hadlima labeling submitted by Samsung Bioepis.

- Instructions for Use (image not shown) received on July 23, 2018
  - AI IFU: <\\cdsesub1\evsprod\bla761059\0012\m1\us\mock-up-ai-ifu.pdf>
  - PFS IFU: <\\cdsesub1\evsprod\bla761059\0012\m1\us\mock-up-safety-pfs-ifu.pdf>

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

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/s/  
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MATTHEW J BARLOW  
07/19/2019 03:39:51 PM

MILLIE B SHAH  
07/19/2019 03:42:51 PM

QUYNHNHU T NGUYEN  
07/19/2019 11:40:07 PM

QUYNHNHU T NGUYEN on behalf of MISHALE P MISTRY  
07/19/2019 11:41:25 PM

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

**AMENDMENT TO PATIENT LABELING REVIEW**

Date: July 15, 2019

To: Sally Seymour, MD  
Acting Director  
**Division of Pulmonary, Allergy, and Rheumatology  
Products (DPARP)**

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

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

From: Aman Sarai, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Adewale Adeleye, PharmD, MBA  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)  
Amended Reivew of Patient Labeling: Instructions for Use (IFUs)

Drug Name (nonproprietary name): HADLIMA (adalimumab-bwwd)<sup>1</sup>

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: 761059

Applicant: Cardinal Health on behalf of Samsung Bioepis Co, Ltd.

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<sup>1</sup> The proposed proprietary name (HADLIMA) for this proposed product has been conditionally accepted. Additionally, a four letter suffix for the nonproprietary name has been conditionally accepted until such time that the application is approved.

## 1 INTRODUCTION

On May 29, 2019, DMPP and OPDPs completed collaborative review was entered in DARRTS based on the patient labeling that was attached to the original submission on August 2, 2018. On June 10, 2019, DPARP notified DMPP that the Applicant submitted a new version of the IFUs that required review by DMPP and OPDP. This amended review includes DMPP and OPDPs updated collaborative review of the new version of the IFUs submitted to DMPP on June 10, 2019.

On July 23, 2018, Cardinal Health on behalf of Samsung Bioepis Co, Ltd. submitted for the Agency's review a Biologics License Application (BLA) 761059 for SB5 (adalimumab-bwwd), a proposed biosimilar to Humira. BLA 761059 was originally submitted on August 29, 2016 but received a refuse to file (RTF) on October 28, 2016 because SB5 would not be available for inspection at the (b) (4) site listed in the FDA Form 356h of the BLA. The Applicant has resolved the deficiency which was identified in the RTF and has prepared this resubmission after discussing with the Agency.

Cardinal Health on behalf of Samsung Bioepis Co, Ltd is seeking approval of HADLIMA (adalimumab-bwwd) injection, for subcutaneous use for the following indications:

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

- **Plaque Psoriasis (PsO):** The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

Cardinal Health on behalf of Samsung Bioepis Co, Ltd is seeking approval for two HADLIMA presentations: 40 mg/0.8 mL in a single-dose pre-filled glass syringe and 40 mg/0.8 mL in a single-dose autoinjector (PushTouch).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on August 1, 2018 and August 2, 2018, respectively for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for HADLIMA (adalimumab-bwwd) injection, for subcutaneous use.

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

## 2 MATERIAL REVIEWED

- Draft HADLIMA (adalimumab-bwwd) MG and IFUs received on August 2, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 20, 2019.
- Draft HADLIMA (adalimumab-bwwd) Prescribing Information (PI) received on August 2, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 20, 2019.
- Draft revised HADLIMA (adalimumab-bwwd) IFUs received on June 7, 2019 and received by DMPP and OPDP on June 21, 2019.
- Approved HUMIRA (adalimumab) injection MG and IFUs dated December 6, 2018.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%.

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

In our collaborative review of the MG and IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG and IFUs are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- evaluated the MG and IFUs per the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFUs are consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG and IFUs are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

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

Please let us know if you have any questions.

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/s/  
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AMANPREET K SARAI  
07/15/2019 04:08:01 PM

MARCIA B WILLIAMS  
07/15/2019 10:58:31 PM

ADEWALE A ADELEYE  
07/16/2019 08:44:32 AM

LASHAWN M GRIFFITHS  
07/16/2019 08:48:29 AM



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

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**LABELS AND LABELING ASSESSMENT**

Date of review:	July 9, 2019
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Tracy Denison, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research III
Application:	BLA 761059
Applicant:	Samsung Bioepis Co. Ltd
Submission Date:	July 23, 2018
Product:	Hadlima and Hadlima PushTouch (adalimumab-bwwd)
Dosage form(s):	injection
Strength and Container-Closure:	40 mg/0.8 mL single-dose prefilled glass syringe or autoinjector
Purpose of review:	The Applicant submitted a biologics license application for Agency review
<b>Recommendations:</b>	The prescribing information, medication guide, and instructions for use (submitted on June 17, 2019) and container labels and carton labeling (submitted on May 3, 2019) are acceptable from an OBP labeling perspective.

<b>Materials Considered for this Label and Labeling Assessment</b>	
<b>Materials Reviewed</b>	<b>Appendix Section</b>
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

**DISCUSSION**

We evaluated the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations (see Appendix B).

**CONCLUSION**

The prescribing information, medication guide, and instructions for use (submitted on June 17, 2019) and container labels and carton labeling (submitted on May 3, 2019) were assessed and are acceptable from an OBP labeling perspective (see Appendix C).

**APPENDICES**

**Appendix A:** Proposed Labeling

Prescribing Information/Medication Guide/Instructions for Use (submitted on December 31, 2018 <\\cdsesub1\evsprod\bla761059\0012\m1\us\draft-labeling-text-redline.pdf>)



### **Container<sup>4</sup> Label Evaluation**

<b>Proper Name</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices (placement of dosage form below the proper name)</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Comment/Recommendation:</b> We note that the presentation of the dosage form is not consistent between the PFS label and the autoinjector label. Agency preference is for the dosage form to appear in lower case letters. <i>The Applicant revised as requested</i>	
<b>Manufacturer name, address, and license number</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices (U.S license number for container bearing a partial label)</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Lot number or other lot identification</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Expiration date</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices references: USP General Chapters &lt;7&gt; Labeling Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Product Strength</b>	<b>Acceptable</b>
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

<sup>4</sup> Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

<p><i>Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic</i></p> <p><i>USP General Chapters: &lt;7&gt; Labeling</i></p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><b>Multiple-dose containers (recommended individual dose)</b></p> <p>Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55</p>	<p><b>Acceptable</b></p> <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<p><b>Statement: "Rx only"</b></p> <p>Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)</p>	<p><b>Acceptable</b></p> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><i>Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic</i></p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><b>Medication Guide</b></p> <p>Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)</p>	<p><b>Acceptable</b></p> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><b>Comment/Recommendation:</b> <i>container label is too small see carton</i></p>	
<p><b>No Package for container</b></p> <p>Regulation: 21 CFR 610.60(b)</p>	<p><b>Acceptable</b></p> <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<p><b>No container label</b></p> <p>Regulation: 21 CFR 610.60(d)</p>	<p><b>Acceptable</b></p> <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<p><b>Ferrule and cap overseal (for vials only)</b></p> <p><i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: &lt;7&gt; Labeling (Ferrules and Cap Overseals)</i></p>	<p><b>Acceptable</b></p> <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<p><b>Visual inspection</b></p> <p>Regulation: 21 CFR 610.60(e)</p> <p><b>Comment/Recommendation:</b> Confirm that sufficient area of the container remains uncovered for its full length to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located  <i>The Applicant confirms that there is sufficient area on the container to allow for visual inspection when the label is affixed</i></p>	<p><b>Acceptable</b></p> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

(b) (4)

<b><u>NDC numbers</u></b>	<b>Acceptable</b>
Regulations: 21 CFR 201.2, 21 CFR 207.35	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b><u>Route of administration</u></b>	<b>Acceptable</b>
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b><u>Preparation instructions</u></b>	<b>Acceptable</b>
Regulation: 21 CFR 201.5(g)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<i>Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b><u>Package type term</u></b>	<b>Acceptable</b>
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) USP chapter &lt;659&gt; Packaging and Storage Requirements</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Comment/Recommendation:</b> Revise the package type term statement from "Single-Dose Pre-filled Autoinjector" to remove the hyphen in the word pre-filled "Single-Dose Prefilled Autoinjector" <i>The Applicant revised as requested</i>	

<b>Misleading statements</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.6	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Prominence of required label statements</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.15	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Spanish-language (Drugs)</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.16	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Sulfites; required warning statements</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.22	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Bar code label requirements</b>	<b>Acceptable</b>
Regulations: 21 CFR 201.25, 21 CFR 610.67	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Comment/Recommendation:</b> Ensure that a linear bar code appears on the container label <i>The Applicant revised as requested</i>	
<i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.68, 21 CFR 201.26	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Net quantity</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.51	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99) USP General Chapters &lt;1151&gt; Pharmaceutical Dosage Forms (Excess volume in injections).</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

<b>Statement of Dosage</b>	<b>Acceptable</b>
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Comment/Recommendation:</b> <i>partial label see carton</i>	
<b>Inactive ingredients</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.100	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Comment/Recommendation:</b> <i>partial label see carton</i>	
<i>Recommended labeling practices reference: USP General Chapters &lt;1091&gt; Labeling of Inactive Ingredients and USP General Chapters &lt;7&gt; Labeling</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Storage requirements</b>	<b>Acceptable</b>
<i>Recommended labeling practices references: USP General Chapters &lt;7&gt; Labeling, USP General Chapters &lt;659&gt; Packaging and Storage Requirements</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Comment/Recommendation:</b> <i>partial label see carton</i>	
<b>Dispensing container</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.100(b)(7)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A

### **Package<sup>5</sup> Label Evaluation**

<b>Proper name</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Manufacturer name, address, and license number</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.100(e)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Lot number or other lot identification</b>	<b>Acceptable</b>
Regulation: 21 CFR 610.61(c)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

<sup>5</sup> Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

<b>Expiration date</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Preservative</b>	<b>Acceptable</b>
Regulation: 21 CFR 610.61(e)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Number of containers</b>	<b>Acceptable</b>
Regulation: 21 CFR 610.61(f)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Product Strength</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic USP General Chapters: &lt;7&gt; Labeling</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Storage temperature/requirements</b>	<b>Acceptable</b>
Regulation: 21 CFR 610.61(h)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices reference: USP General Chapters: &lt;7&gt; Labeling, USP General Chapters &lt;659&gt; Packaging and Storage Requirements</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><b>Comment/Recommendation:</b> For consistency with the prescribing information, consider revising the storage information to include the alternative storage instructions as follows:  "Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light until time of injection. DO NOT FREEZE. If needed, HADLIMA may be stored at room temperature up to 77°F (25°C) for up to 14 days, with protection from light. Once stored at room temperature, do not place back in the refrigerator. HADLIMA should be discarded if not used within the 14-day period. Write the date removed from the refrigerator ___/___/___."  <i>The Applicant revised as requested</i></p>	
<b>Handling: "Do Not Shake", "Do not Freeze" or equivalent</b>	<b>Acceptable</b>
Regulation: 21 CFR 610.61(i)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Multiple dose containers (recommended individual dose)</b>	<b>Acceptable</b>
Regulation: 21 CFR 610.61(j)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A

<b>Route of administration</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Known sensitizing substances</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Inactive ingredients</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.61, 21 CFR 201.100	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices references: USP General Chapters &lt;1091&gt; Labeling of Inactive Ingredients, USP General Chapters &lt;7&gt; Labeling</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><b>Comment/Recommendation:</b> Revise the ingredient list to read as follows:  "Each 0.8 mL single-dose prefilled syringe [or prefilled autoinjector] contains 40 mg adalimumab, citric acid monohydrate (0.544 mg), L-histidine (0.96 mg), L-histidine hydrochloride monohydrate (8.64 mg), polysorbate 20 (0.64 mg), sodium citrate dihydrate (1.6 mg), sorbitol (20 mg), and Water for Injection, USP" to ensure that the net quantity appears on the carton labeling, to distinguish the active ingredient from the inactive ingredients, to remove the hyphen from within the word "prefilled", and to include USP nomenclature.  <i>The Applicant revised as requested</i></p>	
<b>Source of the product</b>	<b>Acceptable</b>
Regulation: 21 CFR 610.61(p)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Minimum potency of product</b>	<b>Acceptable</b>
Regulation: 21 CFR 610.61(r)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Rx only</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Divided manufacturing</b>	<b>Acceptable</b>
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	<input type="checkbox"/> Yes <input type="checkbox"/> No

	<input checked="" type="checkbox"/> N/A
<b>Distributor</b>	<b>Acceptable</b>
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Bar code</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.67, 21 CFR 201.25	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Comment/Recommendation:</b> Ensure that a linear bar code appears on the inner carton labeling for both the prefilled autoinjector and prefilled syringe <i>The Applicant revised as requested</i>	
Recommended labeling practices references: <i>Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.68, 21 CFR 201.26	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>NDC numbers</b>	<b>Acceptable</b>
Regulations: 21 CFR 201.2, 21 CFR 207.35	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Preparation instructions</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.5(g)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic</i> <i>USP General Chapters &lt;7&gt; Labeling</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Package type term</b>	<b>Acceptable</b>
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter &lt;659&gt; Packaging and Storage Requirements</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Misleading statements</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.6	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Prominence of required label statements</b>	<b>Acceptable</b>

Regulation: 21 CFR 201.15	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Spanish-language (Drugs)</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.16	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Phenylalanine as a component of aspartame</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.21(c)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Sulfites; required warning statements</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.22(b)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Net quantity</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.51	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Comment/Recommendation:</b> <i>see ingredient list comment</i>	
Recommended labeling practices reference: <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463)</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Statement of Dosage</b>	<b>Acceptable</b>
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Comment/Recommendation:</b> Revise the statement of dosage from "See the enclosed prescribing information for dosage information" to read as follows: "Dosage: See Prescribing Information" <i>The Applicant revised as requested</i>	
<b>Dispensing container</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.100	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>Medication Guide</b>	<b>Acceptable</b>
Regulations: 21 CFR 610.60, 21 CFR 208.24	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

**Prescribing Information and Patient Labeling Evaluation**

**PRESCRIBING INFORMATION**

<b>Highlights of Prescribing Information</b>	
<b>PRODUCT TITLE</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.57(a)(2)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>DOSAGE AND ADMINISTRATION</b>	<b>Acceptable</b>
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>DOSAGE FORMS AND STRENGTHS</b>	<b>Acceptable</b>
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) USP chapter &lt;659&gt; Packaging and Storage Requirements USP General Chapters: &lt;7&gt; Labeling</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Full Prescribing Information</b>	
<b>2 DOSAGE AND ADMINISTRATION</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.57(c)(3)(iv)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>3 DOSAGE FORMS AND STRENGTHS</b>	<b>Acceptable</b>
Regulation: 21 CFR 201.57(c)(4)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Comment/Recommendation:</b> We added the identifying characteristics of the dosage form per 21 CFR 201.57(c)(4) <i>The Applicant revised as requested</i>	

<p><i>Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i>  <i>USP chapter &lt;659&gt; Packaging and Storage Requirements</i>  <i>USP General Chapters: &lt;7&gt; Labeling</i></p> <p><b>Comment/Recommendation:</b> we revised for readability and to remove information that is not required for this section. The syringe size and needle description are not required and are already provided in the more appropriate section 16 (How Supplied/Storage and Handling).  <i>The Applicant revised as requested</i></p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><b>11 DESCRIPTION</b></p>	<p><b>Acceptable</b></p>
<p>Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)</p> <p><b>Comment/Recommendation:</b>  We deleted this portion of the sentence, “<span style="background-color: #cccccc; padding: 2px;">(b) (4)</span>”, since the mechanism of action is already stated in the more appropriate section 12.1 below.  <i>The Applicant revised as requested</i></p> <p>We added the dosage form per 21 CFR 201.57(c)(12)  <i>The Applicant revised as requested</i></p> <p>We revised the identifying characteristics of the dosage form per 3.2.P.1, “clear to opalescent, and colorless to pale brown”  <i>The Applicant revised as requested</i></p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><i>Recommended labeling practices references: USP General Chapters &lt;1091&gt;, USP General Chapters &lt;7&gt;</i></p> <p><b>Comment/Recommendation:</b>  We relocated the proper name to appear after the proprietary name.  <i>The Applicant revised as requested</i></p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><b>16 HOW SUPPLIED/ STORAGE AND HANDLING</b></p>	<p><b>Acceptable</b></p>
<p>Regulation: 21 CFR 201.57(c)(17)</p> <p><b>Comment/Recommendation:</b>  We added identifying characteristics of the drug product per 21 CFR 201.57(c)(17)  <i>The Applicant revised as requested</i></p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<p><i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i></p> <p><b>Comment/Recommendation:</b>  We deleted “package insert, medication guide and instructions for use” since this information is more appropriate for the contents statement on the carton labeling.</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

<i>The Applicant revised as requested</i>	
<b>MANUFACTURER INFORMATION</b>	<b>Acceptable</b>
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>MEDICATION GUIDE, PATIENT INFORMATION LABELING, INSTRUCTIONS FOR USE</b>	
<b>TITLE (NAMES AND DOSAGE FORM)</b>	<b>Acceptable</b>
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: &lt;1&gt; Injections, Nomenclature and Definitions, Nomenclature form).</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>STORAGE AND HANDLING</b>	<b>Acceptable</b>
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>Recommended labeling practices for Patient Labeling or IFU: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Comment/Recommendation:</b> <i>ensure consistency with prescribing information</i>	
<b>INGREDIENTS</b>	<b>Acceptable</b>
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters &lt;1091&gt;)</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>MANUFACTURER INFORMATION</b>	<b>Acceptable</b>
21 CFR 201.1, 19 CFR 134.11, 21 CFR 208.20(b)(8)(iii)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<i>21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

**APPENDIX C. Acceptable Labels and Labeling**

Prescribing Information/Medication Guide/Instructions for Use (submitted on June 17, 2019

[\\cdsesub1\evsprod\bla761059\0058\m1\us\draft-labeling-text-clean.pdf](#))



(b) (4)



Tracy  
Denison

Digitally signed by Tracy Denison  
Date: 7/09/2019 04:36:30PM  
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Vicky  
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill  
Date: 7/09/2019 10:00:28AM  
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**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

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

**Memorandum**

**Date:** June 5, 2019

**To:** Brandi Wheeler, Pharm.D., Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

**From:** Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Kathleen Klemm, Pharm.D., Team Leader, OPDP

**Subject:** OPDP Labeling Comments for HADLIMA (adalimumab-bwwd)

**BLA:** 761059

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In response to DPARP's consult request dated August 1, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide/Instructions for Use (IFU), and carton and container labeling for the original BLA submission for HADLIMA (adalimumab-bwwd) injection, for subcutaneous use.

**PI and Medication Guide/IFU:** OPDP's comments on the proposed labeling are based on the attached draft PI and Medication Guide/IFU received by electronic mail from DPARP (Brandi Wheeler) on March 20, 2019, and we do not have any comments.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide/IFU were sent under separate cover on May 29, 2019.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 3, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or [adewale.adeleye@fda.hhs.gov](mailto:adewale.adeleye@fda.hhs.gov).

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

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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.**  
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/s/  
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ADEWALE A ADELEYE  
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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: May 29, 2019

To: Sally Seymour, MD  
Acting Director  
**Division of Pulmonary, Allergy, and Rheumatology  
Products (DPARP)**

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

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

From: Aman Sarai, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Adewale Adeleye, Pharm.D., MBA  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

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

Drug Name (nonproprietary name): HADLIMA (adalimumab-bwwd)<sup>1</sup>

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: 761059

Applicant: Cardinal Health on behalf of Samsung Bioepis Co, Ltd.

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<sup>1</sup> The proposed proprietary name (HADLIMA) for this proposed product has been conditionally accepted. Additionally, a four letter suffix for the nonproprietary name has been conditionally accepted until such time that the application is approved.

## 1 INTRODUCTION

On July 23, 2018, Cardinal Health on behalf of Samsung Bioepis Co, Ltd. submitted for the Agency's review a Biologics License Application (BLA) 761059 for SB5 (adalimumab-bwvd), a proposed biosimilar to Humira. BLA 761059 was originally submitted on August 29, 2016 but received a refuse to file (RTF) on October 28, 2016 because SB5 would not be available for inspection at the (b) (4) site listed in the FDA Form 356h of the BLA. The Applicant has resolved the deficiency which was identified in the RTF and has prepared this resubmission after discussing with the Agency.

Cardinal Health on behalf of Samsung Bioepis Co, Ltd is seeking approval of HADLIMA (adalimumab-bwvd) injection, for subcutaneous use for the following indications:

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

Cardinal Health on behalf of Samsung Bioepis Co, Ltd is seeking approval for two Hadlima presentations: 40 mg/0.8 mL in a single-dose pre-filled glass syringe and 40 mg/0.8 mL in a single-dose autoinjector (PushTouch).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on August 2, 2018 and August 1, 2018, respectively for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for HADLIMA (adalimumab-bwwd) injection, for subcutaneous use.

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

## 2 MATERIAL REVIEWED

- Draft HADLIMA (adalimumab-bwwd) MG and IFUs received on August 2, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 20, 2019.
- Draft HADLIMA (adalimumab-bwwd) Prescribing Information (PI) received on August 2, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 20, 2019.
- Approved HUMIRA (adalimumab) injection MG and IFUs dated December 6, 2018.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%.

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

In our collaborative review of the MG and IFUs we:

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

## 4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

## **5 RECOMMENDATIONS**

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

Please let us know if you have any questions.

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**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.**  
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/s/  
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AMANPREET K SARAI  
05/29/2019 12:12:56 PM

MARCIA B WILLIAMS  
05/29/2019 12:14:40 PM

ADEWALE A ADELEYE  
05/29/2019 01:17:35 PM

LASHAWN M GRIFFITHS  
05/29/2019 02:22:44 PM

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

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

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<b>Date of This Review:</b>	April 25, 2019
<b>Requesting Office or Division:</b>	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
<b>Application Type and Number:</b>	BLA 761059
<b>Product Name and Strength:</b>	Hadlima (adalimumab-bwwd) Injection, 40 mg/0.8 mL
<b>Product Type:</b>	Single Ingredient Combination Product (Biologic-Device)
<b>Rx or OTC:</b>	Prescription (Rx)
<b>Applicant/Sponsor Name:</b>	Samsung Bioepis Co., Ltd.
<b>FDA Received Date:</b>	July 23, 2018
<b>OSE RCM #:</b>	2016-1974
<b>DMEPA Safety Evaluator:</b>	Carlos M Mena-Grillasca, BS Pharm
<b>DMEPA Team Leader:</b>	Idalia E. Rychlik, PharmD

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## 1 REASON FOR REVIEW

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that DMEPA review the proposed carton, container, Prescribing Information (PI), and Instructions for Use (IFU) labels and labeling for Hadlima (adalimumab-bwwd) BLA 761059, to determine if they are acceptable from a medication error perspective. On July 23, 2018 Samsung Bioepis submitted a Resubmission/After Refuse to File Biologics License Application 351(k) as a proposed biosimilar to the Reference Product US-licensed Humira.

## 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.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C*
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)**	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

\*Human Factor review under RCM# 2016-1978

\*\*We do not typically search FAERS 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

The Applicant is proposing to package the autoinjector and the prefilled syringe in 2 count packs. We note that these packaging configurations are the same as those marketed for the reference product, US-licensed Humira.

Our review of the proposed labels and labeling identified areas which may be improved to decrease risk of medication error.

1. The NDC numbers are currently presented as "XXXXX-XXX-XX" on the container label and carton labeling, and as "0000-0000-00" in Section 16 How Supplied/Storage and Handling of the Prescribing Information (PI) labeling. Therefore, we were unable to assess the appropriateness of the NDC numbers from a safety perspective.
2. We note that the dosage statement "See the enclosed prescribing information for the dosage information" does not follow current labeling practices.

## 4 CONCLUSION & RECOMMENDATIONS

We find the proposed packaging configuration for the autoinjector and prefilled syringe adequate. However, we identified areas in the labels and labeling that are vulnerable to medication errors. We provide recommendations in section 4.1. for Samsung and recommend that they be implemented prior to the approval of this BLA application.

### 4.1 RECOMMENDATIONS FOR SAMSUNG BIOEPIS CO., LTD

#### A. General Comments (All container labels and carton labeling)

1. The NDC numbers are currently presented with the placeholders "XXXXX-XXX-XX" on the container labels and carton labeling. Therefore, we were unable to assess the appropriateness of the NDC numbers from a safety perspective. Revise the container labels and carton labeling to include the actual NDC numbers.

2. Revise the dosage statement from "See the enclosed prescribing information for dosage information" to read "Dosage: See Prescribing Information".
3. Per our General Advice letter dated April 25, 2019, your proposed suffix -bwwd was found conditionally acceptable. Revise the nonproprietary name to read "adalimumab-bwwd".

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Hadlima received on February 1, 2019 from Samsung Bioepis Co., Ltd., and the listed drug (LD).

<b>Table 2. Relevant Product Information for Hadlima and the Reference Product</b>		
<b>Product Name</b>	<b>Hadlima</b>	<b>US-licensed Humira</b>
<b>Initial Approval Date</b>	n/a	January 31, 2002
<b>Active Ingredient</b>	Adalimumab-bwwd	adalimumab
<b>Indication</b>	<ul style="list-style-type: none"> <li>• Rheumatoid Arthritis (RA)</li> <li>• Juvenile Idiopathic Arthritis (JIA) in patients 4 years of age and older</li> <li>• Psoriatic Arthritis (PsA)</li> <li>• Ankylosing Spondylitis (AS)</li> <li>• Adult Crohn's disease (CD)</li> <li>• Ulcerative Colitis (UC)</li> <li>• Plaque Psoriasis (Ps)</li> </ul>	<ul style="list-style-type: none"> <li>• Rheumatoid Arthritis (RA)</li> <li>• Juvenile Idiopathic Arthritis (JIA) in patients 2 years of age and older</li> <li>• Psoriatic Arthritis (PsA)</li> <li>• Ankylosing Spondylitis (AS)</li> <li>• Adult Crohn's disease (CD)</li> <li>• Pediatric Crohn's disease</li> <li>• Ulcerative Colitis (UC)</li> <li>• Plaque Psoriasis (Ps)</li> <li>• Hidradenitis Suppurativa (HS)</li> <li>• Uveitis (UV)</li> </ul>
<b>Route of Administration</b>	Subcutaneous	Subcutaneous
<b>Dosage Form</b>	Injection, solution	Injection, solution
<b>Strength/How Supplied</b>	40 mg/0.8 mL PFS 40 mg/0.8 Autoinjector	80 mg/0.8 mL Humira Pen 40 mg/0.8 mL Humira Pen 40 mg/0.4 mL Humira Pen 80 mg/0.8 mL PFS 40 mg/0.8 mL PFS 40 mg/0.4 mL PFS 20 mg/0.4 mL PFS 20 mg/0.2 mL PFS 10 mg/0.2 mL PFS 10 mg/0.1 mL PFS 40 mg/0.8 mL vial for institutional use only
<b>Dose and Frequency</b>	Hadlima is administered by subcutaneous injection. <ul style="list-style-type: none"> <li>• Adult RA 40 mg every week or every other week</li> <li>• Adult PsA, and AS 40 mg every other week</li> <li>• JIA ≥ 30 kg: 40 mg every other week</li> <li>• Adult Crohn's disease and Ulcerative Colitis Day 1: 160 mg</li> </ul>	Humira is administered by subcutaneous injection. <ul style="list-style-type: none"> <li>• Adult RA 40 mg every week or every other week</li> <li>• Adult PsA, and AS 40 mg every other week</li> <li>• JIA 10 kg to &lt; 15 kg: 10 mg every other week 15 kg to &lt; 30 kg: 20 mg every other week ≥ 30 kg: 40 mg every other week</li> </ul>

	<p>Day 15: 80 mg Day 29: 40 mg every other week</p> <ul style="list-style-type: none"> <li>• Adult Ps Initial dose: 80 mg Then: 40 mg every other week starting one week after initial dose</li> </ul>	<ul style="list-style-type: none"> <li>• Adult Crohn's disease and Ulcerative Colitis Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every other week</li> <li>• Pediatric Crohn's disease 17 kg to &lt; 40 kg: Day 1: 80 mg Day 15: 40 mg Day 29: 20 mg every other week ≥ 40 kg: Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every other week</li> <li>• Adult Ps or Uveitis Initial dose: 80 mg Then: 40 mg every other week starting one week after initial dose</li> <li>• HS Adults: Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every week Adolescents (12 yrs and older) ≥60 kg: Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every week Adolescents (12 yrs and older) 30 kg to &lt;60 kg: Day 1: 80 mg Day 8: 40 mg every other week</li> </ul>
<b>Storage</b>	Refrigerated at 36° to 46°F (2° to 8°C). If needed, may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days.	Refrigerated at 36° to 46°F (2° to 8°C). If needed, may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days.

**APPENDIX B. PREVIOUS DMEPA REVIEWS**

On April 10, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Hadlima. Our search did not identify any previous reviews.

**APPENDIX C. HUMAN FACTORS STUDY**

N/A

**APPENDIX D. ISMP NEWSLETTERS**

N/A

**APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)**

N/A

**APPENDIX F. OTHER SOURCES**

N/A

**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,<sup>a</sup> along with postmarket medication error data, we reviewed the following Hadlima labels and labeling submitted by Samsung Bioepis Co., Ltd..

- Container label received on July 23, 2018 and April 19, 2019
- Carton labeling received on July 23, 2018 and April 19, 2019
- Instructions for Use received on February 1, 2019
- Prescribing Information (Image not shown) received on February 1, 2019

**G.2 Label and Labeling Images (not to scale)**



<sup>a</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Food and Drug Administration  
Office of New Drugs, ODE-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:** February 20, 2019

**From:** Denise N. Johnson-Lyles, Ph.D.  
Senior Regulatory Project Manager  
Division of Pediatric and Maternal Health (DPMH)

**Subject:** Pregnancy and Lactation Labeling Rule (PLLR) consult request

**BLA Number:** BLA 761059

**Drug:** SB5

**Applicant:** Samsung Bioepis Co., Ltd.

**Indication(s):** Rheumatoid arthritis, juvenile idiopathic arthritis in patient 4 years of age and older and  $\geq 30$  kg (66 lbs.), psoriatic arthritis, ankylosing spondylitis, adult Crohn's Disease, ulcerative colitis, and plaque psoriasis

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) submitted a consult request to DPMH on February 20, 2019, asking for assistance with the review of labeling language for the pregnancy and lactation sections of the Prescribing Information (PI) for the above referenced BLA.

DPMH participated in applicable team and labeling meetings and provided labeling recommendations to DPARP for subsequent negotiation with the applicant. There are no further comments at this time.

This memorandum will close out the consult request.

DPMH Maternal Health MO Reviewer- Carrie Ceresa  
DPMH Maternal Health Team Leader- Miriam Dinatale  
DPMH Division Director- Lynne Yao  
DPMH RPM- Denise Johnson-Lyles

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DPMH RPM Closeout

## CLINICAL INSPECTION SUMMARY

<b>Date</b>	March 1, 2019
<b>From</b>	Min Lu, M.D., M.P.H., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
<b>To</b>	Raj Nair, M.D., Medical Officer Nikolay Nikolov, M.D., Associate Director for Rheumatology Brandi Wheeler, Regulatory Project Manager Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
<b>BLA</b>	761059
<b>Applicant</b>	Samsung Bioepis Co., Ltd.
<b>Drug</b>	SB5, proposed biosimilar to Humira (adalimumab)
<b>NME</b>	BLA Original for a biosimilar
<b>Therapeutic Classification</b>	Tumor necrosis factor (TNF) blocker
<b>Proposed Indication</b>	Treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis in patients 4 years of age and older and $\geq 30$ kg (66 lbs.), psoriatic arthritis, ankylosing spondylitis, adult Crohn's Disease, ulcerative colitis, and plaque psoriasis
<b>Consultation Request Date</b>	October 5, 2018
<b>Summary Goal Date</b>	March 15, 2019
<b>Action Goal Date</b>	July 23, 2019
<b>BsUFA Date</b>	July 23, 2019

### 1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Niebrzydowski and Sokolovic) were selected for inspections for Protocol SB5-G31-RA, entitled "A Randomized, Double-blind, Parallel Group, Multicenter Clinical Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity of SB5 Compared to Humira® in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy." The study data derived from these clinical sites, based on the inspections, are considered reliable and the studies in support of this application appear to have been conducted adequately.

The final classification for the inspection for Dr. Niebrzydowski's site is No Action Indicated (NAI). The preliminary classification for the inspection of Dr. Sokolovic's clinical site is NAI. Inspection classification becomes final when the Establishment Inspection Report (EIR) is received from the field, has been reviewed, and a letter is issued to the inspected entity.

## 2. BACKGROUND

SB5, a human monoclonal antibody, is developed as a biosimilar product to the reference product US-licensed Humira® (adalimumab). Humira® (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF) approved for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa, and uveitis. The reference product was originally approved in the United States (US) in 2002 (BLA 125057) and also approved and marketed European Union (EU).

In this application, the sponsor proposes SB5 as a biosimilar product to the US-licensed Humira® reference product under section 351(k) of the Public Health Service Act (PHS Act). For this initial BLA, the Applicant intends to claim the same therapeutic indications for the proposed biosimilar SB5 as those granted for Humira® in the US, with the exception of those indications protected by orphan exclusivity (pediatric Crohn's disease, hidradenitis suppurativa, and uveitis). In addition, as SB5 is currently only available as 40 mg pre-filled syringe (PFS) and autoinjector (AI) presentations, the Applicant intends to claim the Juvenile idiopathic arthritis (JIA) indication only for patients aged 4 years and older who can administer the full 40 mg dose, i.e. patients weighing at least 30 kg (66 lbs).

The sponsor's clinical development program for SB5 included a Phase 1 study in healthy subjects and a Phase 3 study in subjects with RA. The Phase 1 study was a randomized, single-blind, three-arm, parallel group, single dose study to compare the pharmacokinetics (PK) profiles, safety, tolerability and immunogenicity of SB5, US Humira®, and EU Humira® in healthy subjects. The Phase 3 study (SB5-G31-RA) was a multicenter, randomized, double-blind, parallel group study to evaluate the efficacy, safety, PK, and immunogenicity of SB5 compared to EU Humira® in patients with moderate to severe RA.

### Protocol SB5-G31-RA

Protocol Title: A Randomized, Double-blind, Parallel Group, Multicenter Clinical Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity of SB5 Compared to Humira® in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy

This was a multicenter, randomized, double-blind, parallel group study to evaluate the efficacy, safety, PK, and immunogenicity of SB5 compared to EU Humira® in patients with moderate to severe RA despite methotrexate (MTX) therapy.

The primary objective of this study was to demonstrate the equivalence of SB5 to EU Humira® at Week 24, in terms of American College of Rheumatology 20% response criteria (ACR20) response rate in subjects with moderate to severe RA despite MTX therapy. The secondary objectives were to evaluate other relevant efficacy endpoints, safety and tolerability, PK, and immunogenicity of SB5 in subjects with moderate to severe RA despite MTX therapy.

The primary efficacy endpoint was the ACR20 response between SB5 and EU Humira® at Week 24. The primary endpoint (ACR20 response at Week 24) was assessed in all subjects who completed 24

weeks of study treatment. Secondary endpoints included other relevant efficacy parameters, safety, PK and immunogenicity parameters.

The study main inclusion criteria included subjects aged 18-75 years old, had been diagnosed as having RA according to the revised 1987 American College of Rheumatology (ACR) criteria for at least 6 months but not exceeding 15 years prior to Screening, had moderate to severe active disease despite MTX therapy, had been treated with MTX for at least 6 months prior to randomization and must have been on both: a stable route of administration (oral or parenteral) and stable dose of MTX (10-25 mg/week) for at least 4 weeks prior to Screening.

Study subjects were randomized in a 1:1 ratio to receive either SB5 40 mg or EU sourced Humira® 40 mg every other week via subcutaneous injection. Subjects were enrolled in the study for up to 60 weeks after randomization, consisting of 52 weeks of active treatment and 8 weeks of safety follow-up.

The study screened 744 subjects and randomized 544 subjects from 51 centers in seven countries (Bosnia, Bulgaria, Czech Republic, Korea, Lithuania, Poland, and Ukraine). The study screened the first subject on May 12, 2014 and the last subject completed the last visit on Oct 19, 2015.

### 3. RESULTS (by site):

Name of CI, Address	Site #, Protocol #, and # of Enrolled Subjects	Inspection Date	Classification
Jaroslawn Niebrzydowski, M.D. Medica Pro Familia Sp. Z o.o. S.K.A., ul., Oddzial w Gdyni Bernarda Chrzanowskiego 3/5 Gdynia, 81338 Poland	Site #1007 Protocol SB5-G31-RA 54 Subjects	January 21-25, 2019	NAI
Sekib Sokolovic, M.D. University Clinical Center Sarajevo, Bolnicka 25 Canton Sarajevo, 71000 Sarajevo Bosnia and Herzegovina	Site #1401 Protocol SB5-G31-RA 14 Subjects	February 4-7, 2019	NAI*

#### Key to Compliance Classifications

NAI (No Action Indicated) = No deviation from regulations.

VAI (Voluntary Action Indicated) = Deviation(s) from regulations.

OAI (Official Action Indicated) = Significant deviations from regulations. Data unreliable.

\* Pending = Preliminary classification is based on communication with the field investigator.

EIR is pending at present time. Final classification occurs after EIR is reviewed and when the post-inspectional letter has been sent to the inspected entity.

## **Clinical Study Site Investigators**

### **1. Jaroslaw Niebrzydowski, M.D. (Site #1007, Gdynia, Poland)**

The site screened 70 subjects and enrolled 54 subjects in Study Protocol SB5-G31-RA. Among the 54 enrolled subjects, 44 subjects completed the study and ten subjects discontinued the study. Of the ten subjects, seven subjects discontinued the study prior to Week 24 and three subjects discontinued between Weeks 24 and 52. The reasons for discontinuation prior to Week 24 included withdrawal of consent due to lack of efficacy in four subjects (Subjects (b) (6) in the SB5 group and Subject (b) (6) in the in the EU Humira group), adverse events (Subject (b) (6) due to dizziness in the SB5 group and Subject (b) (6) due to hypertension/dizziness in the EU Humira group), and unavailable neutrophils count for exclusion criterion due to sample quality in one subject (Subject (b) (6)). Three additional subjects (Subjects (b) (6)) withdrew consent between Weeks 24 and 52 due to lack of efficacy during SB5 treatment period (all were treated with EU Humira prior to Week 24 and rerandomized to the SB5 group).

The inspection evaluated the following documents: source records, screening and enrollment logs, Ethics Committee approvals (EC), site signature and responsibility logs, financial disclosures, Form FDA 1572s, data management and electronic case forms (eCRF), study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and correspondence with the ethics committee, monitors, and sponsor were also inspected. There were no limitations during conduct of the clinical site inspection.

Source records for 30 of 54 enrolled subjects were reviewed for protocol adherence, inclusion/exclusion criteria, adverse event reporting, informed consent form (ICF), and PK sampling time. Raw source data to evaluate the primary efficacy endpoint of ACR 20 were reviewed in 41 of 54 enrolled subjects including swollen and tender joint counts, subject pain assessment using visual analogue scale (VAS), subject global assessment of disease activity using VAS, physician global assessment of disease activity using VAS, the health assessment questionnaire disability index (HAQ-DI), and acute phase reactant level (CRP) values. The primary study endpoint was verifiable against the case report forms and BLA subject line listings at the study site.

At the end of this inspection, the following findings were discussed with the investigator:

1. The regulatory binder did not contain information/documentation indicating the EC granted ongoing approval of the study. The site received the initial approval letter and didn't receive any additional letter for protocol amendments/changes. The study coordinator explained the EC would only provide documentation if the committee disapproved continuation of the study.
2. Lack of documentation indicating FDA could review subject records. The ICF did not contain specific wording that the FDA may review subject records. However, it contained language indicating regulatory authorities could review subject records.
3. Failure to report a non-serious adverse event.

Subject (b) (6) (EU Humira group) reported a non-serious adverse event (cystitis) at Visit 5 and was treated with antibiotics. This event was not recorded in the case report form and data listings.

4. Subjects meeting exclusion criteria were enrolled into the study.

Specifically,

- Subject (b) (6) (EU Humira group) had lab test results of hepatitis B virus DNA level of 1.63 log IU/ml (upper limit 1.46 log IU/ml, which is equivalent to upper limit of 29 IU/ml specified in the protocol) and hepatitis B core antibody reactive at screening visit. Subject (b) (6) was randomized and treated with the first dose of study drug although the subject met exclusion criterion #7. The repeat test of HBV-DNA was subsequently requested by the sponsor and the result was within the normal limit.
- Subject (b) (6) (SB5 group) was randomized without neutrophils count result (due to sample quality) against exclusion criterion #6c. Repeat tests were done and had the same issue. The subject discontinued the study subsequently due to this prior to any study treatment.
- Subject (b) (6) (SB5 group) is screened 3 days earlier than the specified 5-year window after uterus removal surgery for malignancy against exclusion criterion #12e.

5. Inaccurate record in the eCRF.

Specifically, for Subject (b) (6) (EU Humira group), the pain assessment using the Visual Analogue Scale (VAS Scale) was measured 27mm at baseline in source documents and it was also recorded as 27mm on the physician's notes. However, the VAS was recorded as 43 mm in the subject's case report form and on subject data listings at baseline. Subject (b) (6)'s pain assessment using VAS at Week 24 was 13mm (52% improvement from baseline) and the data transfer error didn't change the subject's primary efficacy endpoint (ACR20) response category.

Although the clinical investigator should have conducted the study in accordance to the investigational plan, the findings noted above appear unlikely to have significant impact on the overall efficacy and safety of the study. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

## 2. Sekib Sokolovic, M.D. (Site #1401, Sarajevo, Bosnia and Herzegovina)

The site screened 17 subjects and enrolled 14 subjects in Study Protocol SB5-G31-RA. An audit of all enrolled subjects' records was conducted. Among the 14 enrolled subjects in Study Protocol SB5-G31-RA, 13 subjects completed the study and one subject (Subject (b) (6)) discontinued due to an adverse event (mycobacterium tuberculosis complex test positive).

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and correspondence with the ethics committee, monitors, and sponsor were also inspected. Source documents for enrolled subjects whose

records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No significant observations were identified. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

*{See appended electronic signature page}*

Min Lu, 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}*

Kassa Ayalew, M.D., M.P.H.  
Branch Chief, Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

**cc:**

Central Doc. Rm.  
Review Division /Medical Team Leader/ Nikolay Nikolov  
Review Division/Medical Officer/ Raj Nair  
Review Division /Project Manager/ Brandi Wheeler  
OSI/DCCE/ Division Director/ Ni Khin  
OSI/DCCE/Branch Chief/Kassa Ayalew  
OSI/DCCE/GCP Reviewer/Min Lu  
OSI/ GCP Program Analyst/Yolanda Patague

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/s/  
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MEMORANDUM

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

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DATE: 10/9/2018

TO: Division of Pulmonary, Allergy and Rheumatology Products  
Office of New Drugs

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

SUBJECT: **Decline to conduct biopharmaceutical inspection**

RE: BLA 761059

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) declines to conduct a biopharmaceutical inspection for the sites specified below.

**Rationale**

**PAREXEL International GmbH** – Office of Regulatory Affairs (ORA) inspected the site in August 2016 under NDA 021292/S004.

The inspectional outcome was Voluntary Action Indicated (VAI) because reserve samples of test and reference articles were not retained. However, after further review and the Strategic Action Meeting (SAM), OSIS recommended that the data be accepted for Agency review. Therefore, OSIS recommends that an inspection is not warranted at this time.

(b) (4) – OSIS inspected the site in (b) (4).  
The inspection outcome was VAI. The following five observations were documented for BLA (b) (4) only and no observations for NDA (b) (4) were documented on the FDA Form 483:

(b) (4)



After reviewing the written response from the sponsor, OSIS recommended that the data be accepted for Agency review. For additional details, please consider the OSIS Establishment Inspection Report (EIR) Review submitted to DARRTS on 3/22/2018.

OSIS would like to inform the review division that studies in support of BLA (b) (4) were also inspected at this site in (b) (4). Although the final classification for the inspection was No Action Indicated (NAI), there were several discussion items that OSIS requested the review division to consider. These considerations are outlined in the OSIS EIR Review in DARRTS submitted on 4/13/2017.

Therefore, OSIS recommends that an inspection is not warranted at this time because the site has been inspected 3 times in the last 2.5 years and the previously inspected PK/immonuogenecity studies are similar to, and were conducted within 1 to 2 years of the current studies.

#### Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	PAREXEL International GmbH	Klinikum Westend, Haus 31, Spandauer Damm 130, 14059, Berlin, Germany
Analytical	(b) (4)	

(b) (4)

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ANGEL S JOHNSON  
10/09/2018