CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207202Orig1s000

OTHER REVIEW(S)

HUMAN FACTORS RESULTS LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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Date of This Review:	October 20, 2017
Requesting Office or Division:	Division of Psychiatry Products
Application Type and Number:	NDA 207202
Product Name and Strength:	Abilify MyCite (aripiprazole + ingestible event marker) tablets 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Otsuka Pharmaceutical Company, Ltd.
Submission Date:	April 21, 2017
OSE RCM #:	2017-969
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
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1 REASON FOR REVIEW

The Division of Psychiatry Products (DPP) consulted the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the human factors (HF) patient interface validation study results (document #DC-001830 ver. 3.0), labels, labeling and packaging submitted for NDA 207202 to determine if they are acceptable from a medication error perspective.

1.1 PRODUCT INFORMATION

The proposed Prescribing Information (PI) states that Abilify MyCite is a drug-device combination product comprised of Abilify tablets (an atypical antipsychotic) embedded with an Ingestible Event Marker (IEM) sensor that communicates with a Patch (wearable sensor) and a medical software application. MyCite is a system that tracks the ingestion of aripiprazole tablets embedded with an IEM, and is indicated for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, and adjunctive treatment of major depressive disorder. The system consists of the following:

- Abilify MyCite (aripiprazole + IEM) tablets
- Mycite Patch (a wearable sensor)
- Mycite App (a compatible mobile patient application)
- Web-based portal for healthcare professionals (HCP)[a]
- Web-based portal for caregiver (CG)[a]

2 REGULATORY HISTORY

NDA 207202 was originally submitted on June 26, 2015. DMEPA reviewed the human factors patient interface validation study results that were submitted at that time and found the study results unacceptable.[b] A Complete Response Letter was issued on April 26, 2016. The NDA was resubmitted (Class II resubmission) on April 21, 2017. As part of the resubmission, Otsuka submitted the results from a new human factors patient interface validation study which is the subject of this review.

3 MATERIALS REVIEWED

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

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[a] Based on the information submitted by Otsuka in the original NDA submission, we determined that the caregiver and healthcare provider portals do not provide clinical decision support features that are intended to alter physician or caregiver behavior. Based on Otsuka's description of the portals, they function as tools which allow for monitoring only. No additional functionality is proposed to the portals in the current submission. Therefore, this review focuses on the human factors patient interface validation study, which includes the aripiprazole with IEM tablets, wearable patch, the App, and associated drug and patch labeling, packaging and electronic instructions for use (IFU).

[b] Holmes L. Human Factors Results Labels and Labeling Review for Abilify MyCite NDA 207202. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Mar 09. RCM No.: 2015-1602.

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

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant conducted a HF validation study to evaluate the changes to the patient user interface of the Abilify MyCite system (also referred to as MIND1 System[c] in this review).

Study Design

A total of 35 representative participants participated in this simulated use HF validation study. There were three distinct user groups based on diagnosis [schizophrenia (12), bipolar 1 disorder (12), and major depressive disorder (11)]. The participants were randomly assigned to an assisted onboarding[d] or unassisted onboarding group. Each participant completed two sessions separated by a period of approximately 24 hours. Onboarding tasks were conducted on Day 1 and the remaining tasks conducted on Day 2. The user groups and use scenarios (assisted and unassisted) are representative of real world use. As such, we agree with the user groups and methodology used in the study (see Appendix C for a more detailed description of the study).

[c] MIND1 System: The MIND1 App, Patch, packaging, aripiprazole + IEM, and labeling. Note that the Abilify MyCite proprietary name was blinded in the study. Instead, the names "MIND1 or "Mindxx" were used.

[d] Onboarding: First-time use of MIND1, including all parts of system setup. The assisted group was introduced to the system by an in-serviced health care provider (HCP) and was assisted, as necessary, in completing the registration and expected first-use with the integrated kit and a study phone. The unassisted group was provided the kit and set up the system for use on their own without assistance.

Critical Tasks Failures and Close Calls

There were 4 failures and 1 close call that occurred with the following critical tasks[e]:

1. Acts on Daily Tile Summary Tile (n=3)
2. Pill registered (n=1)
3. Pill doesn't seem to be registering (n=1)

1. Acts on Daily Summary Tile (Task 25b), n=3

   In the assisted group, two participants failed and indicated that they would take another pill, which is not the intended action that should be taken by the user when viewing the daily summary tile. In addition, there was one participant who experienced a close call with the task:

   - In response to seeing the Daily Summary Tile (DST) for the previous day, one participant stated she would take another pill. The participant did not recognize that the DST contained historical information. The sponsor's root cause analysis indicated that since all the tiles on the Home screen are on the same scroll, it led her to believe that the DST was also referring to that day's information. The participant also demonstrated confusion with the task simulation.

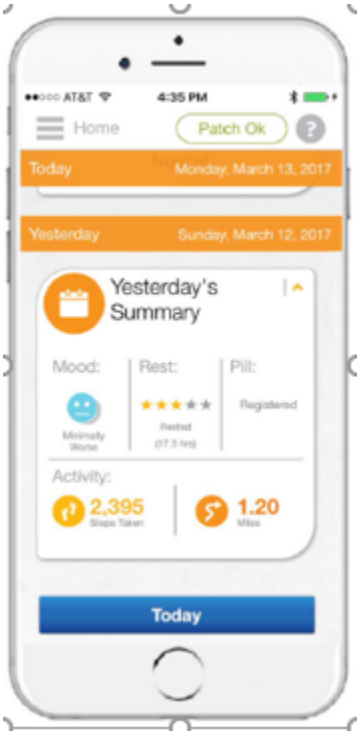
   - The other participant acknowledged and demonstrated understanding that the DST displayed yesterday's information but indicated that she would take another pill "just to get back on track". When probed further, the participant clarified that if she would not take another pill if she had already taken her pill on the present day. The sponsor's root cause analysis indicated that the participant forgot the test scenario regarding having already taken a pill that day and indicated that she might react to taking another pill based on the DST information.

   - One participant had a close call with the task. Upon reviewing the DST, the participant expressed that the pill was not registered and that the pill had not been taken. The participant acknowledged and demonstrated understanding that the DST displayed yesterday's. She stated that she would want to take two pills the next day but then added that she would not do it. The sponsor's root cause analysis indicated that she did not have adequate information about the medication and dosing schedule and her initial assumption that she would want to, if appropriate, compensate for a missed dose.

   Our independent review of the App and the sequencing of tiles as the user scrolls to the DST found that when the DST tile is displayed, the banner above the DST tile reads "Yesterday" and yesterday's date, whereas, the banner at the very top of the screen

[e] Critical Task: User task which, if performed incorrectly or not performed at all, would or could cause serious harm to the patient or user, where harm is defined to include compromised medical care.

reads “Today” and today’s date. Additionally, the “footer” at the bottom of the screen shows “Today” which may be confusing (see screen shot below).[f]



We note that failure to recognize the DST displays information from the previous day and acting on the pill information that the DST displays (i.e., “registered” or “not registered”) may lead to the user not taking a dose or taking an extra dose. For such an error to occur, the user would have to scroll past (and overlook) the present day pill status tile which clearly and prominently indicates whether the present day pill has registered or not registered. Once the user scrolls past the present day pill status tile to the DST on the app display, the user must then overlook the banner that states “yesterday”, overlook the tile title that reads “yesterday’s summary”, and overlook all of the other historical information on the tile from the previous day (mood, rest, activity). The user must then act on the previous pill status in a manner that results in an overdose or dose omission. Additionally, the medication guide, (b) (4), and instruction videos all provide cautionary statements stating that an extra dose should not be taken based on what is shown in the app. Therefore, we find the risk to be minimized to as low as reasonably practical given the multiple points of failure that must occur to result in a medication error. Additionally, based on our discussions with the review team, we understand that infrequent ingestion of an extra dose or dose

[f] The screen shot shown is only intended to be representative of the information that is displayed on the DST. It is not intended to show the specific mood, rest, pill and activity information shown to participants in the study.

omission is unlikely to result in clinically significant harm to the patient. When the task failure root causes are considered in totality with the existing mitigations, and clinical consequences of such error, we find that the residual risk is mitigated to an acceptable level.

2. (First) Pill Registered (App Messaging Knowledge Assessment (Task 28), n=1

   One participant in the assisted group failed this task. The participant interpreted the statement correctly in stating, "It is telling me I took my first pill and that it is registered in the system." However, in response to the comprehension question ("Is there anything you would do if you saw this screen") she stated she would take her first pill in response. The sponsor's root cause analysis indicated the failure was due to participant slip. The participant stated she did not intend to take two pills. No mitigation is proposed by Otsuka.

   Our assessment indicates that based on the subjective feedback and the root cause of this failure, the patient clarified she did not intend to take a second pill. Furthermore, the (first) "Pill Registered" screen only appears during onboarding so there is no concern for repeated misinterpretation of the message. Therefore, we find that no further mitigation is needed.

3. Pill Doesn't Seem To Be Registering (App Messaging Knowledge Assessment Task 28), n=1

   One participant in the unassisted group failed this task. The participant noted the "Patch OK" button in the background and added that the screen was telling him to wait but that he did not know how long after taking the pill he needed to wait. The participant also stated he would consider taking a second pill because he misunderstood the task scenario. The sponsor's root cause analysis indicates task confusion since the participant was not clear on the task to be performed. No mitigation has been proposed by Otsuka.

   Our assessment of this failure finds that based on the subjective feedback, the root cause of this failure, and the availability of a call center number on the screen, we do not believe further mitigation is needed. Additionally, this screen only appears during onboarding so there is no concern that repeated misinterpretation of the message would occur.

Necessary Task[g] Failures and Use Difficulties

There were 3 failures and 3 use difficulties that occurred during the performance of paring a replacement patch, which was considered a necessary task.

1. Pairs Replacement Patch (Task 21b), n=6: One participant in the assisted group and two participants in the unassisted group failed this task. One participant in the assisted group and two participants in the unassisted group had difficulty with this task.

   Two participants failed to press the button long enough to activate the patch. One participant stated she did not realize how long she had to keep her finger on the button and added that she read the instructions but she read them "too fast or too quickly...and missed that part." She stated that if "Hold" were bold lettering, that would have helped her notice it. The other participant stated she did not realize "I had to keep my finger on it as long as I should have." Both participants indicated they would call the 1-800 number for assistance with pairing the patch. The sponsor's root cause analysis for both failures indicated there was negative transfer from previous patch experience (the light on the old patch came on instantly when the button was pressed) and insufficiently prominent guidance on the user interface (the instructions did not communicate how long to hold down the button). The third participant that failed to perform this task had a visual impairment. The sponsor's root cause analysis indicated there was insufficiently prominent guidance on the user interface exacerbated by vision impairment.

   Three participants were reported to have difficulty with this task but completed the task.

   - One participant skipped through, did not pay attention to the screens in the App, and received a pairing error. This participant ultimately removed a new patch and paired it successfully. The sponsor's root cause analysis indicated the use difficulty was due to participant inattentiveness.

   - One participant was unable to locate the button on the patch initially but was able to locate the button and to turn the green light on to initiate the pairing process. The sponsor's root cause analysis indicated the button on the patch was not prominent enough to attract the participant's immediate visual/tactile attention.

   - Another participant expected the light to stay on for a longer period of time to indicate successful pairing but the patch had already paired successfully. The sponsor's root cause analysis indicated that the use difficulty was due in part to the participant's initial confusion that the green light would stay on longer to indicate successful pairing.

[g] Necessary Task: User task that is necessary for use, but would not cause serious harm to the user in other ways if performed incorrectly. Could otherwise be referred to as an "essential" task.

We note that failure to pair the patch successfully will result in lack of system functionality but does not result in patient harm. Otsuka did not provide any mitigation for this use error, however, in the "Pairing Your Patch" instructions, the patch button location is enlarged in a separate illustration and is encircled in an orange dotted line to highlight. Our review of the participants' subjective feedback indicates that using bold lettering for the word "Hold" may help users follow the instructions and successfully pair the replacement patch and is a mitigation strategy that can be implemented. We provide recommendations in Section 5.2 of this review.

There were other use errors involving necessary tasks. However, we find the risks associated with these use errors have been mitigated to an acceptable level and we have no additional recommendations. These use errors are described in Appendix E.

Container Labels, Carton Labeling, Packaging, Instructional Videos, (b) (4)

In addition to the recommendations described above, we identified the following areas of concern that should be addressed to promote safe use of the proposed product:

1. There is a discrepancy regarding the number of patches contained in the kit. The paragraph in Section 16.1 *How Supplied* in the Prescribing Information (PI) and the kit carton labeling indicate 7 patches are supplied in the kit whereas Table 17 in Section 16.1 of the PI indicates (b) (4) patches are supplied in the kit. Thus, the information is inconsistent and may cause confusion.

2. The dosage form "tablets" is product identifying information and should follow the established name on the container labels and carton labeling. However, the dosage form is not present in this location and should be added.

3. The Medication Guide (MG) statement on the container labels and carton labeling does not comply with 21 CFR 208.24(d).

4. The statement of strength (i.e., X mg or XX mg) lacks sufficient prominence on the container labels and carton labeling. Increasing its prominence may help minimize product strength selection errors.

We provide recommendations to address these concerns in Section 5.2.

Comparability Protocol

In our review of the Abilify Mycite Comparability Protocol, we identified concerns (b) (4) we recommended that Otsuka address the following (b) (4):

The applicant submitted a revised protocol on October 18, 2017, and we find the revisions acceptable from a human factors and medication error perspective.

5 CONCLUSION & RECOMMENDATIONS

The patient interface HF validation study results showed there were tasks failures where participants indicated they would take or would consider taking an additional pill. Our review of the user interface, HF study results, the sponsor's root cause analysis, and the existing mitigation strategies determined that the risks of extra dose and dose omission have been minimized to as low as reasonably practical. Additionally, based on our discussions with the review team, we understand that infrequent ingestion of an extra dose or dose omission is unlikely to result in clinically significant harm to the patient. Thus, we find that the residual risk is mitigated to an acceptable level.

We also note there is a call center telephone number provided throughout the labeling [e.g., in the (b) (4) inside top panel of the carton labeling] and in the App and is available to users who need assistance or experience a loss of system functionality.[h]

We identified areas in the PI, carton labeling and container label where information is unclear, missing or lacks sufficient prominence. We provide recommendations to address these concerns in Section 5.1 and 5.2.

5.1 RECOMMENDATIONS FOR THE DIVISION

A. Labeling

1. There is a discrepancy regarding the number of patches contained in the kit. Specifically, the paragraph in Section 16.1 *How Supplied* in the Prescribing Information (PI) and the kit carton labeling indicate 7 patches are supplied in the kit whereas Table 17 in Section 16.1 of the PI indicates (b) (4) patches are supplied in the kit. This discrepancy needs to be reconciled for consistency across all labeling.

[h] The effectiveness of the call center was not assessed in this simulated use validation study.

5.2 RECOMMENDATIONS FOR OTSUKA PHARMACEUTICAL COMPANY

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

A. Instructional Video

1. When performing Task 21b *Pairs Replacement Patch*, two study participants failed to hold down the patch button long enough for the green light to come on. Failure to pair the patch may lead to loss of system functionality. To help mitigate this error and facilitate patch pairing, consider revising your instructional video such that the words "Press and hold" are in bold font in the "Pairing Your Patch" instructional video.

B. Container Labels and Carton Labeling

1. The established name is not followed by the dosage form "tablets". Add the dosage form statement and place it on the same line as the established name or below the established name.

2. The Medication Guide (MG) statement does not state how the MG is provided. The MG statement should state how the MG is provided. Revise the MG statement to one of the following (or use similar verbiage) in accordance with 21 CFR 208.24(d):

    a. "Dispense the enclosed Medication Guide to each patient." or
    b. "Dispense the accompanying Medication Guide to each patient."

3. The statement of strength lacks sufficient prominence which may pose risk of product strength selection errors. Increase the size of the statement of strength on all panels.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Abilify MyCite that Otsuka Pharmaceuticals submitted on April 21, 2017.

Table 2. Relevant Product Information for Abilify MyCite	
Initial Approval Date	N/A
Active Ingredient	aripiprazole
Indication	Treatment of: schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, and adjunctive treatment of major depressive disorder
Route of Administration	Oral
Dosage Form	Tablets
Strengths	2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg
Dose and Frequency	Dosage range: 2 mg to 30 mg once daily
How Supplied	Kit containing: 30 Abilify MyCite tablets (2 mg, 5 mg, 10 mg, 15 mg, 20 mg or 30 mg) and seven patches
Storage	Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F)
Container Closure	Tablets: HDPE bottles with (b) (4) closure

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 14, 2017, we searched the L:drive and AIMS using the terms, Abilify MyCite and aripiprazole + IEM to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews that are relevant to this current review, and we confirmed that our previous recommendations were implemented or considered.

- Holmes L. Human Factors Validation Study Protocol Review for Abilify MyCite NDA 207202. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Dec 16. RCM No.: 2016-2195.
- Holmes L. Human Factors Results Labels and Labeling Review for Abilify MyCite NDA 207202. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Mar 09. RCM No.: 2015-1602.

APPENDIX C. PATIENT INTERFACE HUMAN FACTORS VALIDATION STUDY [document #DC-001830 ver. 3.0]

C.1 Study Report and System Overview

Link to study report: \\cdsesub1\evsprod\nda207202\0030\m5\53-clin-stud-rep\535-rep-effic-safety-stud\all\5354-other-stud-rep\hf-patient-interface-validation-report\hf-patient-interface-val-report.pdf

System Overview:

C.2 Patient Interface Human Factors Validation Study (Additional Summary of Results)

Necessary Tasks[i]

Although the following tasks were not categorized as critical, they are necessary for the safe use of the product. Overall, there were 13 failures and 8 difficulties that occurred within this group of tasks, below.

1. Download App (Task 2), n=1
2. Peels off large tab (Task 5e), n=1
3. Applies Patch (Task 5b), n=4
4. Ingests First Pill (Task 6c), n=2
5. Remove Patch (Task 19), n=1
6. Applies Replacement Patch (Task 24a), n=2
7. Checks Patch Status (Task 16a), n=1
8. Checks 0-Day Status (Task 16b), n=1
9. Only MIND1 Pills Will Work With System (Task 6b), n=1
10. Do not change your medication unless instructed by your prescribing physician (Task CS-21), n=1
11. Do not take first MIND1 pill until instructed by the App (Task CS-19), n=1
12. Do not stop or change your medication dosage based on information provided by the MIND1 Kit. Consult your healthcare provider. (Task CS-20), n=1
13. Check the expiration date printed on the Patch packaging (Task CS-01), n=1
14. Do not place Patch in a location that overlaps the area where the last Patch was. (Task CS-12), n=2
15. Do not wear the same patch for more than one week (Task CS-24), n=1

The use errors are described in detail below.

1. Download App (Task 2), n=1

One participant in the unassisted group failed this task.

- The participant failed to download the app. The sponsor's root cause analysis attributed the error to negative transfer and task confusion which led the participant to think that he only needed to take a pill during this task as that was the only thing he would typically do when taking his medication.

We find that failure to download the App will result in the inability to use the system as intended. No mitigation has been proposed by Otsuka. (b) (4)

[i] Necessary Task: User task that is necessary for use, but would not cause serious harm to the user in other ways if performed incorrectly. Could otherwise be referred to as an "essential" task.

(b) (4) The root causes and participant feedback do not indicate an issue related to the product user interface. Therefore, we have no additional recommendations at this time.

2. Peels off large tab (Task 5e), n=1

One participant in the unassisted group failed this task.

- The participant took the patch out of the pouch and applied the patch before watching the video that explains how to peel off the patch tabs. He thought he had to peel apart the adhesive layer and foam layer rather than removing only the release liner. The sponsor's root cause analysis indicated the failure was due to insufficiently prominent guidance on the patch.

We find that failure to peel off the large paper tab as instructed may result in lack of patch and system functionality due to poor skin contact. However, the App will alert the user that there is poor skin contact and if not adequately addressed, the App prompts the user to change the patch. Furthermore, the App video that describes patch application provides detailed instructions for and a demonstration of removing the large and small paper backing from the patch. Therefore, we find the risk has been reasonably mitigated and have no additional recommendations.

3. Applies First Patch (Task 5b), n=4

Two participants in the unassisted group failed this task.

- One participant applied the patch to her right forearm before asking for the App. The participant did not appear to be aware that she could move the protective covering to another site. The sponsor's root cause analysis indicated the failure was due to test artifact.
- The other participant failed to apply the patch when instructed by the onboarding[j] video. As she was getting ready to apply the patch, the moderator paused the video to apply the protective covering which drew the participant's attention from the last several seconds of the video. She was unable to navigate back to the patch applying video. The sponsor's root cause analysis indicated the failure was due to test artifact and insufficient guidance on the user interface.

Two participants in the unassisted group had difficulty with this task.

- One participant initially stated she would apply the patch to the upper right side but immediately corrected her response to say "upper left". The sponsor's root cause analysis indicated the difficulty was due to attention slip (participant stated she was "daydreaming").

[j] Onboarding tasks are those tasks associated with first-time use (i.e., account setup, setting up first patch, first pill ingestion, viewing the MIND1 overview video and proceeding to the home screen).

- The other participant initially indicated he might apply the patch to his arm but chose the correct site. The sponsor's root cause analysis indicated the difficulty was due to mental model (participant speculated about placing the patch on the arm based on his exposure to nicotine patch commercials).

Our assessment of the failures and difficulties with applying the first patch find the risks associated with this task have been reduced to an acceptable level. (b) (4) We agree with this justification given there are screen prompts that will help the user to resolve the patch issue. Moreover, in the event a patch is not applied properly, a tile is triggered in the App prompting the user to fix and/or change the patch to resolve the issue. We find the App patch application video, (b) (4), and Patch Box Insert Card clearly describe and show where the patch should be applied. We find the risk for errors with this step have been adequately mitigated to an acceptable level and no further mitigation is needed. Therefore, we have no additional recommendations.

4. Ingests First Pill (Task 6c), n=2

Two participants in the unassisted group failed this task.

- One participant took the first pill before opening the kit and a second pill while completing a patch change after she was done with onboarding. She stated her "prescription" was to take two pills per day. The report also stated she made up a scenario to allow her to take a second pill and that she was unsure what to do during the session. The sponsor's root cause analysis indicated the failure was due to test artifact.

- The other participant took a first pill before opening the App and then indicated that he had completed the setup and was done with the task. Once the moderator clarified the task and asked him to restart, he took a second pill at the instruction of the onboarding flow. When asked why he took a second pill, he said, "Because I thought I had to redo the setup". The sponsor's root cause analysis indicated the failure was due to test artifact.

The reported root cause for these failures is test artifact. We agree with this assessment and also considered that the participants took the first pill prior to opening the App. We recognize that in "real life" use of the system, the potential exists for taking an extra dose if a user takes the first pill, downloads the App later on the same day and follows the set up and instructions to take the first pill. We note that the proposed audio portion of the "Taking Your Pill" video states, "(b) (4)." This message may help to prevent an extra dose from being taken. Additionally, we note this risk only exists during the initial onboarding procedure, so there is no concern for a repeated

occurrence of an extra dose being administered. Thus, we find the risk of taking an extra dose during this task has been mitigated to a reasonable level and we have no additional recommendations at this time.

5. Remove Patch (Task 19), n=1

One participant in the assisted group failed this task.

- The participant did not fully remove the patch, leaving the adhesive layer on the simulated skin. When asked why she did not remove the patch completely, she said, "This fake skin is kinda throwing me off base...coz I didn't want to destroy the skin here." The sponsor's root cause analysis indicated the failure was due to test artifact.

Failure to remove the patch may result in skin irritation. Our assessment of this failure finds no further mitigation is needed. We agree with the sponsor's assessment that test artifact contributed to the error since the failure was primarily due to the use of fake skin in a simulated use environment. Thus, we have no additional recommendations at this time.

6. Applies Replacement Patch (Task 24a), n=2

One participant from the assisted group and one participant from the unassisted group failed this task.

- One participant applied the new patch to her arm like she did for the first one and did not apply the patch to her lower left ribs due to completing the task in a simulated environment. The sponsor's root cause analysis indicated the failure was due to test artifact.

- The other participant applied a new patch on the remaining bottom layer of the old patch. The sponsor's root cause analysis indicated the failure was due to error resulting from failure on previous step.

Failure to apply a replacement patch correctly may result in loss of system functionality. We note that the instructional videos and associated labeling clearly depicts the appropriate patch placement site. Our assessment of the root causes of these failures finds that no mitigation is required. Therefore, we have no additional recommendations.

7. Checks Patch Status (Task 16a), n=1

One participant in the assisted group had difficulty with this task.

- The participant did not respond to the patch status tile until prompted because he was focused on the task assigned. He stated, "the App didn't say anything...there's no voice telling me 'check your patch, check your patch', there's no alarm system". The sponsor's root cause analysis indicted the difficulty was due to test artifact.

We note that a loss of system functionality may result from not responding to the patch status tile. We acknowledge the participant's subjective feedback regarding the lack of a voice prompt or alarm system. However, the tile would continue to appear until addressed which we find provides adequate mitigation for this task and we have no further recommendations.

8. Checks 0-Day Status (Task 16b), n=1

One participant in the unassisted group failed this task.

- The participant did not react to the patch status tile and stated he was done with the task. On being asked about the tile, the participant stated he did notice the tile but did not want to put on a new Patch because his pill for the day registered in the system (based on the "All is Good" tile). This indicated to him that his patch was still working and that he did not need to replace the patch yet. According to the study report, the participant indicated that he understood the prompt in the App and chose not to act on it based on his own assumption and judgment. The sponsor's root cause analysis indicated the failure was due to intentional misuse.

The report also stated, *it should be noted also that due to the simulated nature of the test, the "All is good" tile that signals pill registration was triggered by the moderator almost immediately upon the participant's "taking" the pill. In actuality, while a pill could register quickly, it could also take several minutes for the registration to appear in the App, meaning that it is quite possible that in a similar real-world scenario, the participant would have proceeded to act while the pill was still registering. This, and waiting until a patch was no longer functional to exchange it would have resulted in at most one pill not registering in the system before resuming normal system functionality. At no point during the session did the participant indicate that he would take more than one pill in the event a pill did not register, therefore indicating that this scenario would have resulted in no more than the negligible harm associated with temporary loss of system functionality or user confusion.*

We note that failure to respond to the 0-day patch status may result in loss of system functionality if the patch is worn for more than 7 days. This may potentially lead to the infrequent ingestion of an extra dose if the patch is not functioning as intended. However, based on the subjective feedback of intentional misuse, the root cause of this failure, and the limited potential for an infrequent extra dose to result in clinically significant harm to the patient, we do not find that further mitigation is indicated.

Additional Observations: Extra Pill(s) Taken

Per the HF validation report, in addition to the aforementioned failures and difficulties noted during the Patch Maintenance group of tasks, there were three other participant observations made of taking an extra pill. First, two participants were observed taking an extra pill during a patch change sequence although one participant indicated that while she didn't realize she took an additional pill, did so because she thought the next day had arrived. Secondly, one participant took two pills during the 0-Day status scenario. He indicated that he did not remember that he took two pills during the task.

Our assessment determined that the extra dose observations may be attributed to study artifact due to the simulated nature of the study. While there is a residual risk of patients taking an extra dose, we find the risk has been sufficiently minimized to an acceptable level.

App Messaging Knowledge Assessment Questions

All participants were required to evaluate the App messaging linked to necessary or critical tasks within the App.

9. Only MIND1 Pills Will Work With System (Task 6b) n=1

One participant in the untrained group failed this task.

- The participant initially answered that the non-MIND1 pills would work. The participant was confused regarding what pills he was being asked about. On subsequent questioning, he verbalized correct understanding. The sponsor's root cause analysis indicated the failure was due to task confusion.

Taking a non-MIND1 pill would result in the pill not registering. Acting upon a pill not registering screen may lead to an overdose if an additional pill is taken.

We note the MIND1 pills and patches will be provided together in a single kit which may help to limit the potential use of "regular" pills with the system. (b) (4) Thus, we have no additional recommendations.

Cautionary Statements Knowledge Assessment Questions

10. Do not change your medication unless instructed by your prescribing physician (Task CS-21), n=1

One participant in the assisted group had difficulty with this statement.

- The participant stated her confusion was due to not understanding if the statement was referring to the medication or dosage. The participant stated her confusion was due to not understanding if the statement was referring to the medication or dosage. The sponsor's root cause analysis indicated the difficulty was due to misunderstanding based on questions asked.

The report also stated that several participants interpreted the statement as meaning that only MIND1 would work with the system or that only MIND1 pills should be taken unless specified by the doctor. Furthermore, the report stated that since responses like "don't take any other pill unless instructed" could possibly be interpreted as "discontinue other medications", the statement "Do Not Change Your Medication Unless Instructed By Your Prescribing Physician" was changed to statement CS-20 ("Do not stop or change your medication dosage based on information provided in the MIND1 kit. Consult your healthcare provider") which seemed to be clear to participants and did not cause similar confusion. We agree with the applicant's mitigation and have no additional recommendations.

11. Do not take first MIND1 pill until instructed by the App (Task CS-19), n=1

One participant in the assisted group had difficulty with this task.

- When the participant was asked the follow up question "...is it okay to take your first pill before you open the app" she said "no." The sponsor's root cause analysis indicated the difficulty was due to participant inarticulateness.

We note that difficulty with understanding this statement may subsequently lead to taking an extra pill. However, we agree with the sponsor's assessment of the root cause; the participant appears to have understood the messaging but was unable to articulate the response correctly. The subjective feedback from the participant indicated she would not take an extra pill. Thus, no additional mitigation is necessary and we have no additional recommendations.

12. Do not stop or change your medication dosage based on information provided by the MIND1 Kit. Consult your healthcare provider. (Task CS-20), n=1

One participant in the assisted group had difficulty with this task.

- Immediately before being asked to interpret this statement, the participant was asked to read, "Do not take your first MIND1 pill until instructed by the App." She demonstrated understanding of this statement, but when asked to read the statement saying "Do not stop or change dosage based on information from the MIND1 App. Consult your doctor", immediately said "Now that's just confusing. You just said don't take it unless the App tells you to, and told me to not take your pill until the App told me to, and now you are telling me do not stop or change your medication dosage based on information provided by the MIND1 kit". The sponsor's root cause analysis indicated the difficulty was due to misunderstanding based on the order of questions asked.

Based on the participant's subjective feedback, we agree with this assessment. We note that (b) (4) and when presented out of context likely resulted in confusion that can be attributed to study artifact. Thus, we have no additional recommendations.

13. Check the expiration date printed on the Patch packaging (Task CS-01), n=1

One participant in the assisted group failed this task.

- The participant initially interpreted the statement to mean that the medication would not work effectively if it was expired. The sponsor's root cause analysis indicated the failure was due to mental model (participant may have operated initially with the understanding that an expiration date is associated with pills, not patches) and task sequence (exposure to a series of statements about pills right before this one is likely to have influenced initial misreading).

Failure to check the patch expiration date and subsequent use of expired patches may lead to loss of system functionality because the patch may not function properly. Our review of the

failure and the labeling finds the statement appears to be clear, therefore, no additional mitigations are necessary.

14. Do not place Patch in a location that overlaps the area where the last Patch was. (Task CS-12), n=2

Two participants in the assisted group had difficulty with this task.

- One participant verbalized confusion but answered correctly. The sponsor's root cause analysis indicated the difficulty was due to participant fatigue.

- One participant answered incorrectly. However, upon hearing a follow up question from the moderator, the participant sought clarification and answered the question correctly. The sponsor's root cause analysis indicated the difficulty was due to misunderstanding terminology.

Our review finds the statement is clearly communicated and no additional mitigations are necessary. We have no additional recommendations.

15. Do not wear the same patch for more than one week (Task CS-24), n=1

One participant in the assisted group failed this task.

- The participant struggled to communicate his response to the moderator and his initial answer was incorrect, however, when asked the follow up question, he answered correctly. The sponsor's root cause analysis indicated the failure was due to inarticulateness and mental model.

Our review finds the warning statement is clearly communicated. Additionally, the system has built in alerts to notify the patient when the patch needs to be changed. We have no additional recommendations.

APPENDIX F. OTHER SUPPORTING DOCUMENTS REVIEWED FOR BACKGROUND INFORMATION (INCLUDING LINKS)

Human Factors Engineering/Usability Engineering Report: \\cdsesub1\evsprod\nda207202\0030\m5\53-clin-stud-rep\535-rep-effic-safety-stud\all\5354-other-stud-rep\hfe-ue-report\human-factors-engineering-ue-report.pdf

Use-Related Risk Assessment Analysis: \\cdsesub1\evsprod\nda207202\0030\m5\53-clin-stud-rep\535-rep-effic-safety-stud\all\5354-other-stud-rep\hf-use-related-risk-analysis\use-related-risk-assessment-analysis.pdf

MIND1 Videos and Scripts/MIND1 System User Interface/MIND1 System Intended Use: Application 207202 - Sequence 0030 - Protocol or Amendment -

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,[k] along with postmarket medication error data, we reviewed the following Abilify MyCite labels and labeling submitted by Otsuka Pharmaceutical Company on April 21, 2017.

- Commercial Container Labels
- Commercial Carton Labeling
- Professional Sample Container Labels
- Professional Sample Carton Labeling
- Tablet Bottle Tray
- Top Card
- Patch Pouch
- Patch Box Insert Card
- Patch Box Front Panel
- Patch Box Back Panel
- (b) (4)
- Prescribing Information (Image not shown)

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

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/s/

LORETTA HOLMES
10/20/2017

LOLITA G WHITE
10/20/2017

QUYNHNHU T NGUYEN
10/23/2017

DANIELLE M HARRIS
10/25/2017

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

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

Memorandum

Date: October 16, 2017

To: Brendan Muoio, PharmD, RAC, Regulatory Project Manager
Division of Psychiatry Products (DPP)

Kimberly Updegraff, RPh, MS, RAC, Associate Director for Labeling, DPP

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, RAC, Team Leader, OPDP

Subject: **NDA 207202**
OPDP labeling comments for ABILIFY® MYCITE™ (aripiprazole) tablets with sensor, for oral use

---

In response to DPP's consult request dated May 25, 2017, OPDP has reviewed the proposed carton and container labeling, and Instructions for Use (IFU) for Abilify Mycite.

Carton and Container Labeling and IFU

OPDP's comments on the proposed carton and container labeling are based on draft carton and container labeling submitted to DPP on April 21, 2017, and October 9, 2017, and are provided below.

OPDP's comments on the proposed IFU are based on the draft IFU obtained from DPP's Sharepoint on September 15, 2017, and our comments are provided below.

Please note that OPDP's review of these materials was limited to content pertaining to the drug product, and we defer to CDRH for the review of non-drug related content.

PI and Medication Guide

OPDP's comments on the proposed PI were sent under separate cover on October 8, 2017. A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on October 6, 2017.

Thank you for your consult. If you have questions, please contact Aline Moukhtara at (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

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/s/

ALINE M MOUKHTARA
10/16/2017

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

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

Memorandum

Date: October 8, 2017

To: Brendan Muoio, PharmD, RAC, Regulatory Project Manager
Division of Psychiatry Products (DPP)

Kimberly Updegraff, MS, RAC, Associate Director for Labeling, DPP

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, RAC, Team Leader, OPDP

Subject: **NDA 207202**
OPDP labeling comments for ABILIFY® MYCITE™ (aripiprazole) tablets with sensor, for oral use

---

In response to DPP's consult request dated May 25, 2017, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for Abilify Mycite.

PI

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPP on October 5, 2017, and are provided below.

Medication Guide

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on October 6, 2017.

Carton and Container Labeling and Instructions for Use (IFU)

OPDP's comments on the proposed carton and container labeling, and IFU will be provided under a separate cover.

Thank you for your consult. If you have questions, please contact Aline Moukhtara at (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

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/s/

ALINE M MOUKHTARA
10/08/2017

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:	October 6, 2017
To:	Mitchell Mathis, MD Director **Division of Psychiatry Products (DPP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)** Mathilda Fienkeng, PharmD, RAC Team Leader **Office of Prescription Drug Promotion (OPDP)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Aline Moukhtara, RN, MPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ABILIFY MYCITE (aripiprazole)
Dosage Form and Route:	Tablets with sensor, for oral use
Application Type/Number:	NDA 207202
Applicant:	Otsuka Pharmaceutical Company, Ltd.

1 INTRODUCTION

On April 21, 2017, Otsuka Pharmaceutical Company, Ltd., resubmitted for the Agency's review an original New Drug Application (NDA) 207202 for ABILIFY MYCITE (aripiprazole) tablets with sensor, for oral use. This resubmission of NDA 207202 was to fully address the deficiencies identified in the Complete Response (CR) letter issued by the Agency on April 26, 2016.

ABILIFY MYCITE (aripiprazole) tablets with sensor, for oral use, is a drug-device combination of aripiprazole tablets, an atypical antipsychotic, embedded with an Ingestible Event Marker (IEM) sensor used for the proposed indication of:

- The treatment of adults with schizophrenia
- Acute treatment of adults with manic and mixed episodes associated with bipolar I disorder
- Adjunctive treatment of adults with major depressive disorder

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 Psychiatry Products (DPP) on May 25, 2017 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG), for ABILIFY MYCITE (aripiprazole) tablets with sensor, for oral use.

2 MATERIAL REVIEWED

- Draft ABILIFY MYCITE (aripiprazole) tablets with sensor, MG received on April 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 3, 2017.
- Draft ABILIFY MYCITE (aripiprazole) tablets with sensor, Prescribing Information (PI) received on April 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 3, 2017.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we:

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

4 CONCLUSIONS

The MG is 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 is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
10/06/2017

ALINE M MOUKHTARA
10/06/2017

BARBARA A FULLER
10/06/2017

LASHAWN M GRIFFITHS
10/06/2017

HUMAN FACTORS VALIDATION STUDY PROTOCOL REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	December 16, 2016
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 207202
Product Name and Strength:	Abilify MyCite (aripiprazole + Ingestible Event Marker) 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Otsuka Pharmaceutical Company, Ltd.
Submission Date:	September 19, 2016
OSE RCM #:	2016-2195
DMEPA Primary Reviewer:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, M.S.

1 REASON FOR REVIEW

The Division of Psychiatry Products (DPP) requested a review of the human factors (HF) patient interface validation protocol submitted to NDA 207202 on September 19, 2016.

1.1 PRODUCT INFORMATION

Abilify MyCite is comprised of aripiprazole with an ingestible event marker (IEM), referred to as the Proteus Ingestible Sensor, inside each tablet, wearable patches (the Proteus patch, DW5), and a set of local and cloud-based applications. The system is intended for use by patients with major depressive disorder (MDD), bipolar 1 disorder (BP1) or schizophrenia (SCZ) and their caregivers and treatment team to (b) (4).

Specifically, the user interface of Abilify MyCite consists of:

- Abilify MyCite application (app)
- A set of disposable patches (Proteus patch DW5), comprised of an adhesive layer and an electronics module to communicate between the pill and the patient app
- A bottle of pills to be taken orally, comprised of an aripiprazole medication tablet (2 mg, 5 mg, 10 mg, 15 mg, 20 mg, or 30 mg tablets), and an IEM (the Proteus Ingestible Sensor), embedded within the tablet (b) (4)
- Device labeling, packaging, package inserts, (b) (4) and electronic instructions for use (electronic IFU)

Abilify MyCite will be available as an integrated kit consisting of 30 tablets, (b) (4) patches, labeling, and prescribing information. The contents of the kit will be used with the accompanying app, (b) (4)

1.2 REGULATORY HISTORY

NDA 207202 for aripiprazole + IEM was initially submitted by Otsuka on June 26, 2015. On April 26, 2016, a Complete Response Letter was issued that requested improvements be made to the user interface to mitigate the risk for medication errors observed in the 2015 study and that those changes should be validated in another HF validation study. Some of the proposed changes include the addition of a (b) (4); revisions to the app user interface, instructions for use and product labeling; and removal of (b) (4).

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Human Factors Protocol	C
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other—Associated Documents	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for 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 HF validation study protocol focuses on evaluating those changes that were made in order to address the task failures and difficulties that were observed in the previous 2015 HF validation study.

A summary of the HF validation study protocol is provided in Appendix C. Our review of the proposed HF validation study protocol and associated labels and labeling identified the following areas of concern:

- The study methodology does not clearly identify the knowledge tasks used to assess cautionary statements in the (b) (4) patch card insert, and patch pouch label (b) (4)
- In the (b) (4) Pill Bottle Tray labeling, (b) (4) lack sufficient contrast and may be difficult to read.

4 CONCLUSION & RECOMMENDATIONS

Our review of the human factors validation study protocol and associated labels and labeling identified areas that need improvement. We recommend that Otsuka address the identified concerns before commencing with the validation study. We provide recommendations in Section 4.1, below.

4.1 RECOMMENDATIONS FOR OTSUKA PHARMACEUTICAL COMPANY

Our review of the human factors validation study protocol and associated labeling identified several areas of concern. Please address the following prior to conducting your human factors validation study for NDA 207202:

1. Your protocol methodology does not clearly identify how cautionary statements in the (b) (4) patch card insert, and patch pouch label (b) (4) Understanding of cautionary statements in the (b) (4) is considered as critical task. As such, we expect that you incorporate in your study protocol specific knowledge tasks to assess the user's understanding of these cautionary statements. Update your protocol to include the knowledge assessment of the cautionary statements.

2. Your product packaging includes colors that lack contrast and visibility which may decrease readability of important product information. In the (b) (4) Pill Bottle Tray labeling (b) (4) lack sufficient contrast and may be difficult for some to read. We recommend that you consider the use of colors that provide better contrast and promote readability.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Abilify MyCite that Otsuka submitted on September 19, 2016.

Table 2. Relevant Product Information for Abilify MyCite	
Initial Approval Date	N/A
Combination Product	Aripiprazole embedded with an Ingestible Event Marker (IEM) that communicates with a patch (wearable sensor) and medical software application
Device	Ingestible Event Marker (IEM)
Indication	Treatment of: • Schizophrenia • Acute Treatment of Manic and Mixed Episodes associated with Bipolar I Disorder • Adjunctive Treatment of Major Depressive Disorder
Route of Administration	Oral
Dosage Form	Tablets
Strengths	2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg
Dose and Frequency	2 mg to 30 mg once daily
How Supplied	Kits containing one 30-count bottle of tablets and (b) (4) wearable sensors
Storage	Tablet bottle: Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Do not store in conditions where tablets are exposed to humid conditions. Wearable Sensor: Store between 15°C and 30°C (59°F to 86°F), 15% to 93% relative humidity
Container Closure	Tablet bottle: (b) (4) closure

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 23, 2016, we searched the L:drive and AIMS using the terms, aripiprazole, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews that are relevant to this review.

1. Holmes L. Human Factors Usability Study Protocol Review for Abilify + Ingestible Event Marker IND 115927. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Nov 25. RCM No. 2014-2108.
2. Holmes L. Human Factors Results Labels and Labeling Review for Abilify MyCite. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Mar 9. RCM No.: 2015-1602.

APPENDIX C. HUMAN FACTORS STUDY PROTOCOL (Excerpted from the Human Factors Validation Study Protocol and Associated Documents)

(b) (4)

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APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

We reviewed the following Abilify MyCite study protocol labels and labeling submitted by Otsuka on September 19, 2016.

- Container Labels and Carton Labeling
- (b) (4)
- Patch Card Insert
- Draft Human Factors PI (no image)

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

(b) (4)

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LORETTA HOLMES
12/16/2016

LOLITA G WHITE
12/17/2016

QUYNHNHU T NGUYEN
12/21/2016

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

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

Memorandum

Date: **April 8, 2016**

To: Simran Parihar, PharmD, RPh
Regulatory Health Project Manager
Division of Psychiatry Products (DPP)

From: Susannah K. O'Donnell, MPH, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 207202**
Aripiprazole + Ingestible Event Marker (IEM)

OPDP acknowledges receipt of the July 31, 2015, consult request from DPP for proposed product labeling (PI) for aripiprazole + IEM. OPDP notes DPP indicated that final labeling negotiations will not be initiated during the current review cycle because a Complete Response letter will be issued. Therefore, OPDP will not provide comments on the proposed PI during this review cycle.

OPDP requests that DPP submit a new consult request during a subsequent review cycle to provide comments regarding labeling for this application.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

Thank you!

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/s/

SUSANNAH O'DONNELL
04/08/2016

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

REVIEW DEFERRAL MEMORANDUM

Date:	April 5, 2016
To:	Mitchell Mathis, M.D. Director **Division of Psychiatry Products (DPP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Medication Guide (MG)
Drug Name (established name):	Aripiprazole and Ingestible Event Marker (IEM)
Dosage Form and Route:	Tablets
Application Type/Number:	207202
Applicant:	Otsuka Pharmaceutical Company, Ltd.

1 INTRODUCTION

On June 26, 2015, Otsuka Pharmaceutical Company, Ltd. submitted for the Agency's review an original New Drug Application for aripiprazole + Ingestible Event Marker (IEM) tablets and associated components. The product is a combination of Abilify (aripiprazole) embedded with an IEM that communicates with a Patch (a wearable sensor) and a medical software application. It is a system that (b) (4) to aripiprazole and is indicated for the treatment of:

- Schizophrenia;
- Acute treatment of manic and mixed episodes associated with bipolar I disorder;
- Adjunctive treatment of major depressive disorder (MDD)

On August 3, 2015 the Division of Psychiatry Products (DPP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for aripiprazole + IEM.

This memorandum documents the DMPP review deferral of the Applicant's proposed Medication Guide (MG) for aripiprazole + IEM.

2 CONCLUSIONS

Due to outstanding clinical deficiencies, DPP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

AMANPREET K SARAI
04/05/2016

SHAWNA L HUTCHINS
04/05/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

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

TO: NDA 207202

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

SUBJECT: Division of Psychiatry Products (DPP) consult request to DPMH requesting maternal health labeling review, DARRTS Reference ID: 3807372

DRUG: Aripiprazole with IEM

DPP submitted a consult request to DPMH dated August 17, 2015, asking for maternal health (pregnancy and lactation) labeling review for the above referenced, NDA 207202.

DPMH participated in internal team meetings for this application, including a labeling planning meeting held on December 9, 2015. Review issues identified to date were discussed in this December meeting and per advice from DPP, the team was asked to hold labeling edits, pending the outcome of discussion of identified review issues at a CDER Regulatory Briefing Meeting. A CDER Regulatory Briefing Meeting for this NDA was held on February 26, 2016. On March 15, 2016, DPMH received information by e-mail from DPP (via DPP Regulatory Health Project Manager, Danbi Lee) that based on feedback from the regulatory briefing a Complete Response action is pending for this NDA. If labeling review resumes upon resubmission of the NDA, DPMH may be re-consulted for maternal health labeling review. DPMH has no further comment at this time. This memorandum will close out the consult request.

DPMH Maternal Health MO Reviewer– Leyla Sahin
DPMH Maternal Health Team Leader – Tamara Johnson
DPMH Division Director - Lynne Yao
DPMH RPM – Denise Johnson-Lyles

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/s/

DENISE N JOHNSON-LYLES
03/17/2016
DPMH RPM closeout memo

HUMAN FACTORS RESULTS LABELS AND LABELING REVIEW

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

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

Date of This Review:	March 9, 2016
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 207202
Product Name and Strength:	Abilify Mycite (aripiprazole + Ingestible Event Marker)[1] 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Otsuka Pharmaceutical Company, Ltd.
Submission Date:	June 26, 2015
OSE RCM #:	2015-1602
DMEPA Primary Reviewer:	Loretta Holmes, BSN, PharmD
Human Factors Specialist:	Quynh Nguyen, MS
DMEPA Team Leader:	Danielle Harris, PharmD, BCPS
DMEPA Deputy Director:	Irene Z Chan, PharmD, BCPS
DMEPA Division Director	Todd Bridges, RPh

(b) (4)

1 REASON FOR REVIEW

The Division of Psychiatry Products (DPP) consulted the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the human factors (HF) validation studies' (HFS) results, labels and labeling and packaging submitted for NDA 207202 to determine if they are acceptable from a medication error perspective.

Otsuka Pharmaceutical Company submitted an NDA for aripiprazole tablets plus the ingestible event marker (IEM) system. The IEM System is comprised of aripiprazole oral tablets with an embedded IEM, adhesive wearable sensors (i.e., the patches[2]), and a set of local and cloud-based applications, including the patient mobile application and caregiver and healthcare provider dashboards. The system is intended for use by patients with Major Depressive Disorder (MDD), Bipolar 1 Disorder (BP1) or Schizophrenia (SCZ) and their caregivers and treatment team to (b) (4) of patients with their aripiprazole treatment regimen. (b) (4) data is shared with a healthcare provider and/or caregiver only if the patient chooses to share the data.

Based on the information submitted by Otsuka, we have determined that the caregiver and healthcare provider dashboards do not provide clinical decision support features that are intended to alter physician or caregiver behavior. Based on Otsuka's description of the dashboards, they function as tools which allow for monitoring only. Based on the proposed functionality, we have determined that this review will focus only on the HFS that evaluates the patient interface, which includes the aripiprazole with IEM tablets, wearable patch, local mobile application (hereafter referred to as the "app"), and associated drug and device labeling, packaging and electronic instructions for use (IFU).

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Human Factors and Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A

[2] The Applicant and HFS report utilize the term "patch" (although we note the "patch" does not contain medication). Therefore, we are using this term throughout the review for consistency with the HFS report findings.

[3] Indication statement submitted by Applicant is (b) (4) however, the exact wording of this statement is still under discussion

Table 1. Materials Considered for this Human Factors and Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Previous DMEPA Reviews	B (N/A)
Human Factors Study Report	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
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Patient Interface Human Factors Study Review

We evaluated the human factors (HF) validation study results for the patient interface and disagree with Otsuka that the study demonstrated that the user interface supports the safe and effective use of the product by the intended user population. Of note, 35 out of 36 participants encountered difficulties or failed a critical task (~97%). Standalone HF validation studies are generally qualitative and not designed to capture rates of error; however, we note that the large number of failures and difficulties seen in this study is a departure from similarly designed studies with other products seen by the Agency. In a small sample size, a finding of this magnitude is especially concerning since this serves as an indicator for performance expected in actual use. Multiple participants encountered more than one difficulty or committed more than one failure with a critical task in the course of the Human Factors Study (HFS). Thus, the study results indicate that further improvements should be made to the user interface, including the instructions for use, to further mitigate the risk for medication errors to occur with the use of the product. The raw data study results from all evaluated tasks (necessary and critical)[4] are presented in Appendix C.2. DMEPA identified areas of concern where participants failed or had difficulty completing critical tasks (see Appendix C.3 for more detail).

The inability for patients to correctly use the app and other components of the system, including the patch, (b) (4) which is the proposed indication for this product. Additionally, difficulty or failures with critical tasks are expected to lead to extra doses and/or missed doses

[4] Categorization of tasks as "necessary" or "critical" was determined by the researchers who conducted the HFS.

[5] Indication statement submitted by Applicant is (b) (4) however, the exact wording of this statement is still under discussion

of aripiprazole, and it is unclear based on the submitted data if these will be limited to singular events or could lead to multiple incidences because the HFS did not provide data on performance over time. Per discussion with the Division of Psychiatry Products (DPP), our understanding is that though it is not common, some patients are sensitive to missed doses and have a narrow therapeutic window with regard to plasma levels and will become symptomatic when doses are missed. These symptoms increase the likelihood that they will further miss doses since the medication is to improve their thinking/perception ability. This pattern is the typical pattern that leads to hospitalizations for relapse. Thus, this is the target population for this product. Safety wise, doubling the dose on a population level may not be bad for the schizophrenia population but on an individual level may lead to increased extrapyramidal symptoms (EPS), especially for the bipolar population.

We hypothesize that the intended population might inherently experience more difficulty compared to other adult populations in using this type of technology. The study contractor may have also had the same thinking as page 40 of 285 in their study reports noted "Conducting probing in close proximity to the task was important, particularly given the cognitive limitations of the participant population." Schizophrenics appeared to do slightly worse compared to bipolar or MDD patients; however, the study was not designed to evaluate differences between these subgroups.

Our detailed evaluation of all of the necessary and critical steps determined that one participant out of 36 performed all the tasks successfully without difficulty or failure[6]. The remaining 35 out of 36 participants encountered at least one difficulty or committed a failure during their simulation. Multiple participants encountered more than one difficulty or experienced more than one failure, with 46 total difficulties and 104 total failures observed during the HFS. Necessary tasks are those that are required in order to complete the use process, such as downloading the app and entering account information, whereas critical tasks are those required to ensure safe and effective use of the system. Therefore we evaluated critical tasks carefully. When the analysis was limited to just those tasks deemed critical[7], 29 total difficulties and 88 failures with critical tasks were observed during the HFS, and only one participant successfully completed the simulation without difficulty or failure.

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[6] Data discussed in this report only reflects the data retrieved on participants' first attempt at the task. In some cases, participants were afforded multiple attempts at certain tasks. We note that in some cases performance improved when the task was repeated but in others, performance was worse. This, along with the fact that not all participants repeated tasks multiple times, made analysis of repeated attempts difficult to interpret.

[7] The HFS report provided the following definitions of what were considered "critical" or "necessary tasks". Critical tasks: those that are required for safe and effective use of the product. Necessary tasks: those that are required in order to complete the use process, but if omitted or performed incorrectly do not constitute a safety risk. Independent analysis by DMEPA determined that one of these tasks would not in fact be deemed critical for the Agency.

We conducted secondary analyses of the data to looks for trends with differences in diagnosis or training, and were unable to find a particular subgroup or identify a particular intervention that would lead us to conclude that the specific subgroups of patients could be expected to use this product correctly. We note that trained participants generally performed better than the untrained group; however, though this trend was observed, the study was not designed to evaluate differences between these subgroups. Additionally, failures and difficulties occurred in both groups for many of the same tasks suggesting that training was unable to overcome the risk for user errors to occur with this product. We note the HFS report identified study artifact as a contributing factor to some of the failures and difficulties; however, our independent review determined that this would not alter our overall findings that the HFS did not demonstrate the interface supports safe and effective use of this product by patients.

We provide our assessment of the HF validation study in further detail below. The following sections focused only on failures or difficulties encountered with critical tasks.

(b) (4)

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4 CONCLUSION & RECOMMENDATIONS

We find that the Human Factors validation study report does not provide sufficient data to conclude that the user interface supports safe and effective use of this product by the Major Depressive Disorder (MDD), Bipolar 1 Disorder (BP1) or Schizophrenia (SCZ) patient population. Given the observed critical task failures spread across all user groups, it is not apparent that training intervention or labeling the product for specific subgroups of patients in actual use would be an option to improve use-related performance.

Improvements to the user interface are needed to mitigate the risk for medication error and ensure the system can achieve its goal (b) (4) . We recommend that Otsuka re-evaluates the critical task failures and difficulties and the associated root causes, update their use-related risk analysis,

[13] Indication statement submitted by Applicant is (b) (4) however, the exact wording of this statement is still under discussion

implement additional mitigations and demonstrate their effectiveness by conducting another human factors validation study.

Additionally, we determined that improvements to the labels and labeling are necessary to ensure safe use of the product. We provide recommendations in Section 4.1. that should be conveyed to the Applicant at this time.

4.1 RECOMMENDATIONS FOR TO OTSUKA

A. General Comment

We find that the Human Factors validation study report does not provide sufficient data to conclude that the user interface supports safe and effective use of this product by the Major Depressive Disorder (MDD), Bipolar 1 Disorder (BP1) or Schizophrenia (SCZ) patient population. There were multiple failures and difficulties observed with critical tasks. These failures can lead to dosing errors (e.g., missed dose or extra dose) and/or render the system ineffective (b) (4) .

Improvements to the user interface are needed to mitigate the risk for medication errors and ensure the product can be used by intended users for intended uses and environments. We recommend you re-evaluate the critical task failures and difficulties and their associated root causes, update your risk analysis accordingly, implement additional risk mitigation strategies, and demonstrate their effectiveness by conducting another human factors (HF) validation study. We provide some label and labeling recommendations below that we recommend are implemented with any other changes you plan to make to the user interface so they can also be validated in your HF validation study.

B. Aripiprazole + IEM Labels and Labeling

1. General Comment
    a. We recommend that you consider providing printed patient labeling that provides a brief overview of the system, instructions for critical use elements of the app, including system set up, critical patch tasks, description of some of the app features, cautions, etc. Based on the results of your HF validation study, we believe that printed patient labeling will be helpful to some patients and may minimize the risk for some errors seen in your HF validation study (e.g., (b) (4)).

b. All labels and labeling should be updated with the conditionally acceptable proprietary name, Abilify Mycite.

2. Carton Labeling
   a. To help minimize the risk of wrong strength selection errors, increase the prominence of the statement of strength on the top panel of the labeling. Additionally, add the statement of strength to the front panel (see the example below).

   b. (b) (4) Reference the entire conditionally acceptable proprietary name, “Abilify Mycite”, in order to minimize potential confusion.

3. Patch Pouch Label

4. Top Card, Patch Box Front Panel, and Pill Bottle Tray

   To help minimize confusion, place the word (b) (4)" in front of the numbers so that patients are clear that a sequence of steps is being referred to rather than the number of tablets to take (a failure seen in your HF validation study). For example:

   (b) (4)
   1: The App

   2: The Patches

   3: The Tablets

5. Patch Box Front Panel and Patch Pouch Labeling

   The statement "Patches do not contain medication" does not have sufficient prominence and could be overlooked. Relocate the statement to a central location on the patch box front panel in order to give it more prominence. Additionally, add the statement to the Patch Pouch label to decrease the chance of this information being overlooked.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Aripiprazole + IEM that Otsuka submitted on June 26, 2015.

Table 2. Relevant Product Information for Aripiprazole + IEM	
Initial Approval Date	N/A
Active Ingredient	Aripiprazole
Device	Ingestible Event Marker (IEM)
Indication	(b) (4) is indicated for the treatment of: schizophrenia; acute treatment of manic and mixed episodes associated with bipolar I disorder; and adjunctive treatment of major depressive disorder.
Route of Administration	Oral
Dosage Form	Tablets
Strengths	2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg
Dose and Frequency	2 mg to 30 mg once daily
How Supplied	Kits available in 2mg, 5mg, 10mg, 15mg, 20mg and 30mg strengths. Each kit contains a bottle of 30 tablets and (b) (4) patches.
System Components	Aripiprazole + IEM Tablets Patch (a wearable sensor) App (a compatible mobile patient application) Web-based software for health care professionals/caregiver
Storage	Tablet bottle: Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not store in conditions where tablets are exposed to humid conditions. Wearable Sensor: Store between 15°C and 30°C (59°F to 86°F), 15% to 93% relative humidity
Container Closure	Tablets: HDPE bottles with (b) (4) closure

APPENDIX C. PATIENT INTERFACE HUMAN FACTORS STUDY REPORT

(b) (4)

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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,[16] along with postmarket medication error data, we reviewed the following Aripiprazole + IEM labels and labeling submitted by Otsuka Pharmaceutical Company on June 26, 2015.

- Container Labels
- Professional Sample Container Labels
- Carton Labeling Professional Sample Carton Labeling
- Patch Pouch
- Patch Box
- Prescribing Information (no image)
- Medication Guide (no image)

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G.2 Labels and Labeling Images (not to scale)

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

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/s/

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