CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207202Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	October 20, 2017
From	
Subject	Cross-Discipline Team Leader Review
NDA #	207202
Applicant	Otsuka Pharmaceutical Company Ltd.
Date of Submission	April 21, 2017
PDUFA Goal Date	October 21, 2017
Proprietary Name / Established (USAN) names	Abilify MyCite (aripiprazole tablets with sensor)
Dosage forms / Strength	Tablets with Sensor/ 2, 5, 10, 15, 20 and 30 mg
Proposed Indication(s)	The system is intended to track ingestion of aripiprazole tablets as indicated for schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, and adjunctive treatment of major depressive disorder in adult patients.
Recommended:	*Approval*

1. Introduction and Background

Aripiprazole is an atypical antipsychotic originally approved on November 15, 2002 (tradename Abilify; NDA 021436). It is indicated in adults for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, and adjunctive treatment of major depressive disorder. With this Class 2 resubmission, the Applicant (Otsuka) is seeking approval of Abilify MyCite (aripiprazole tablets with sensor), a system intended (b) (4) for the above indications in adult patients. The Applicant is not pursuing approval for aripiprazole's pediatric indications (i.e., irritability associated with autistic disorder or for the treatment of Tourette's disorder).

The proposed product is a drug-device combination in which the Applicant's product, aripiprazole (Abilify tablets), is combined with a 510(k)-cleared device manufactured by Proteus Digital Health (hereafter, "Proteus"). The Proteus device, cleared in February, 2014, includes an ingestible sensor or ingestible event marker (IEM) and a wearable patch to detect when the IEM has been ingested. The product under review includes the IEM embedded within aripiprazole tablets, the wearable patch, a medical device data system (MDDS) that runs on the patient's smartphone, a smartphone application (app), and a web portal for use by the prescriber if permission is granted by the patient. When used together, the Applicant claims that this system (known as "MIND1" during development) will allow patients in the currently-indicated populations listed above (b) (4); if the patient chooses, he or she can also allow others (e.g., physician, caregivers, etc.) to review the information recorded.

Reference ID: 4180408

This resubmission is a response to the complete response (CR) action taken on April 26, 2016. A CR action was taken mainly due to the risk to the patient [redacted] (b) (4) Another related problem noted in the initial review was the relatively high number of ingested tablets the system failed to detect and the high variability in latency times for data transmission within the system. The CR letter also stated that the Human Factors (HF) study did not provide sufficient data to conclude that the app's user interface supported safe and effective use of this product. The Agency requested improvements to the user interface to mitigate the risk for medication errors and to ensure that the product could be used safely by intended users for intended uses and environments. In the CR letter, the Agency also agreed that the removal of the [redacted] (b) (4) of the app was an acceptable risk-mitigating step to address these concerns.

In response to the CR action, the Applicant:

- Updated the app and removed the [redacted] (b) (4). Because the [redacted] (b) (4) was removed, the Agency agreed in the June 28, 2016, Type A Meeting Preliminary Comments that the additional clinical trial requested in the CR letter was no longer necessary.
- Resubmitted all software documentation after incorporating the changes to address the human factors deficiencies.
- Updated the proposed comparability protocol for postmarketing system updates and routine revisions, following completion of the human factors studies.
- Provided the full commercial drug product manufacturing batch records for each dose strength.
- Conducted another HF validation study to test the app.

2. CMC/Device

The Office of Pharmaceutical Quality (OPQ) and Center for Devices and Radiological Health (CDRH) reviews were conducted by the following team of reviewers:

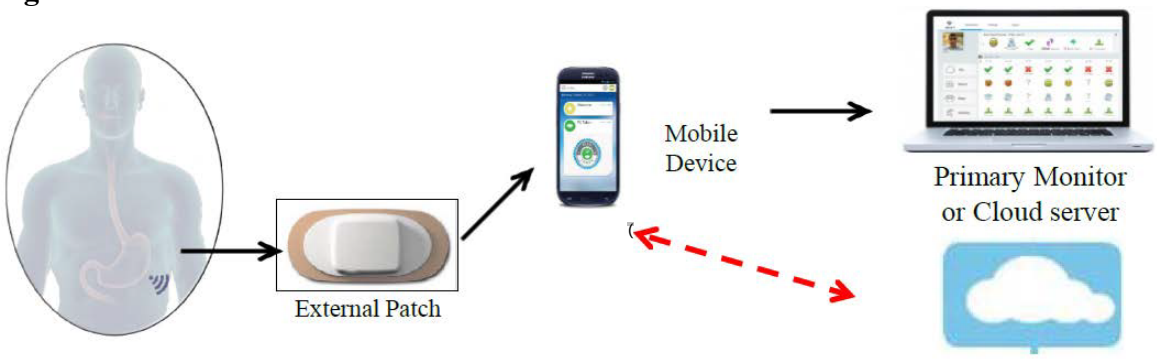
DISCIPLINE	PIMARY/SECONDARY REVIEWER
Drug Substance & Drug Product	Mariappan Chelliah/Wendy Wilson
Process and Microbiology	Hang Guo/Akm Khairuzzaman
Facility	Steven Hertz/Peter Qiu
CDRH Lead Reviewer	Luke Ralston/Shawn Forrest
CDRH Software Reviewer	Natalie Yarkony
CDRH OC reviewer	Katelyn Bittleman/Nazia Rahman
RBPM	Teshara Bouie
Application Technical Lead	David Claffey

All members of the OPQ and CDRH review team and their consultants recommend approval for this resubmission.

In summary, the proposed drug-device combination product is composed of the following main components (see Figure 1):

1. Aripiprazole immediate-release tablets imbedded with an IEM sensor in the same strengths as the approved Abilify tablets (2, 5, 10, 15, 20 and 30 mg). The composition of the proposed tablets is qualitatively and quantitatively identical to Abilify tablets, except for the addition of the IEM sensor and the use of different amounts of colorants to distinguish them from Abilify tablets.
2. MyCite Patch: This is a wearable sensor which adheres to the torso; it picks up the signal from the IEM [redacted] (b) (4) and transmits it to the patient's smartphone (via Bluetooth).
3. Smartphone software (app): Receives data from the patch and displays data about the ingestion event for the patient. The app can also transmit the data to the Otsuka Cloud-based server. This allows the designated healthcare professional (HCP) or caregiver to review the data if the patient grants the necessary permissions.

Figure 1: Product Overview



The OPQ Office of Policy for Pharmaceutical Quality (OPPQ), in consultation with US Pharmacopeia (USP), determined that the nonproprietary name will be "(aripiprazole) tablets with sensor". The term 'with sensor' will be added to an upcoming USP General Chapter to describe products of this type.

In the previous review cycle, the Applicant adequately demonstrated their capability to manufacture the proposed combination product with defined and consistent quality, as demonstrated by the results of in vitro manufacturing controls and bench performance testing. The April, 2016, CR letter included deficiencies related to an Otsuka manufacturing site (FEI:3003808559). The Applicant has resolved these issues.

Luke Ralston from CDRH reviewed the hardware for the original application and for this resubmission. In his latest review, he concludes that "the data support use of the TRADEMARK system for tracking and trending now that the [redacted] (b) (4) has been removed from the mobile app".

It should be noted that the app software [redacted] (b) (4) processes this information for display on the phone. The Otsuka component also transmits the data to the Otsuka Cloud-based server for sharing with designated parties. Nathalie Yarkony and Linda Ricci from CDRH evaluated the app in this review cycle.

Note that the proposed use of the patient's mobile device to perform data analytics changes its classification in the 510(k)-cleared Proteus device as an accessory (under the Mobile Medical Application paradigm) to the primary monitor – a Class II medical device not subject to enforcement discretion.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical data were provided with this resubmission.

4. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was provided with this resubmission.

5. Clinical Microbiology

No clinical microbiology information was submitted with this application.

6. Clinical/Statistical- Efficacy

No new clinical efficacy data were submitted with this application.

7. Safety

The Applicant successfully demonstrated bioequivalence between the approved oral aripiprazole tablets and the proposed product during the original NDA submission. The Applicant relies on the Agency's previous efficacy and safety findings for aripiprazole oral tablets for the proposed product for the intended indications. No new clinical data were submitted in this review cycle.

Daniel Lee, MD, was the clinical reviewer for this resubmission; he recommends approval. As previously discussed, a major concern during the initial review cycle was the potential for patients to take additional tablets, [redacted] (b) (4) if the system failed to register an ingestion. Dr. Lee agrees with other review team members that the removal of this function sufficiently mitigates this risk. In reviewing the entire safety data provided by the Applicant during the first review cycle, Dr. Lee notes frequent but mild and self-limited rashes at patch application site in trials extending up to 12 weeks. However, he believes the risks for skin irritation can be mitigated with labeling.

Finally, Dr. Lee is concerned that 21 (12.1%) of 174 subjects exposed to the proposed product in three trials experienced infections. These infections varied widely from gastroenteritis, sinusitis, fungal, urinary tract, upper respiratory tract, and tooth or gum infections. He compared his observation to the infection rates seen in previous aripiprazole trials and post-marketing data and found the MyCite rates to be "9-18 times the predicted percentage of total adverse events." Dr. Lee recommends that postmarketing studies further evaluate this risk. In my opinion, the low number and high variability of infection-related adverse events (AEs) in these trials do not allow us to draw any substantive conclusions regarding an increased risk of infection. Furthermore, one must be careful in comparing MyCite trials with other oral aripiprazole trials, due the significant differences in trial design and subject characteristics. Finally, a direct comparison against postmarketing data is also difficult to interpret due to multiple confounding factors. I remain unconvinced that an increased risk exists for infection-related AEs in patients using MyCite..

8. Advisory Committee Meeting

No Advisory Committee meeting was held. This resubmission was discussed internally at a Medical Policy Council (MPC) on October 20, 2017. In summary, it was decided that the application could be approved with appropriate disclaimers in product labeling (to be discussed in detail in the following sections).

9. Pediatrics

The Applicant has an agreed Pediatric Study Plan (June 11, 2014). No changes to the agreed pediatric plan were proposed with this resubmission.

10. Other Relevant Regulatory Issues

Comparability Protocol

Still outstanding is the issue of post-approval software design control. A comparability protocol (CP) is being negotiated between the Agency and the Applicant. The CP will delineate (b) (4). The CP has undergone several iterations in this review cycle and a final CP has not yet been agreed upon.

Web Portal Regulation

The web portal is the website used by the caregiver or HCP to access the patient's ingestion data. Questions arose over whether the software was subject to Agency regulation, because it is described as part of the product in the product's labeling. Software regulation is an evolving topic, especially since the recent passage of the 21st Century Cures Act. Ashley Boam, Director of OPQ OPPQ, determined that the web portal software does not need to be regulated in its present form, as the user is the healthcare provider and the information being provided merely summarizes the patient-level information and provides no treatment recommendations.

Human Factors Studies

In the previous review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) found the results of the HF patient interface validation study unacceptable, as just one out of 36 participants successfully used the product.

As requested in the CR letter, this resubmission includes the results from a new simulated-use HF validation study. The study included 35 patients who represented three distinct user groups based on diagnosis [schizophrenia (n=12), bipolar I disorder (n=12), and major depressive disorder (n=11)]. The participants were randomly assigned to an assisted onboarding or an 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) were considered representative of real-world use by DMEPA.

The results showed there were tasks failures where participants indicated they would take or would consider taking an additional tablet. DMEPA evaluated the task failures, the Applicant's root cause analyses of these, and the existing mitigation strategies and they concluded that the risks of extra dose and dose omission have been sufficiently minimized. Based on discussions with the review team, DMEPA understands that infrequent ingestion of an extra dose or dose omission is unlikely to result in clinically significant harm to the patient. While it is possible that additional changes to the app user interface could further reduce the residual risk, they found that the residual risk is mitigated to an acceptable level and changes to the app user interface are not necessary prior to approval.

Office of Prescription Drug Promotion

The Office of Prescription Drug Promotion (OPDP) reviewers, Aline Moukhtara and Shawna Hutchins found the Medication Guide (MG) acceptable after their feedback was incorporated. Because the Agency did not consider the web-based portal for HCPs and caregivers to be approved labeling, OPDP recommended that the portal be removed from the label. However, the rest of the review team considered the portal to be a purposeful component of the MyCite system and disagreed with this recommendation.

Numerous questions also arose in relation to the app. OPDP had concerns regarding what was to be considered promotional vs. approved labeling, whether promotional labeling could coexist with approved labeling electronically, and how to differentiate between these within the app. In this product, the Instructions for Use (IFU) are electronic and in the app (considered approved labeling). In addition to tracking medication ingestion, the app has features to track mood, activity, and rest; these are considered promotional labeling and are subject to regulation. OPDP recommended that these additional features be completely removed from the app. These recommendations were discussed internally at the MPC meeting held on October 20, 2017. During this meeting, it was decided that these features (i.e., mood, rest, and activity tracking) could remain functional within the app provided than an adequate disclaimer (i.e., that these features have not been evaluated by the FDA) is clearly displayed in the app and the label. The exact language for this disclaimer should appear in the Limitations of Use (see Section 11) in the product's label, the app's login screen, physician web portal login screen, and web portal summary screen.

11. Labeling

The proprietary name Abilify MyCite was conditionally accepted by DMEPA. OPQ, in consultation with USP, determined that the nonproprietary name would be "(aripiprazole tablets with sensor)" or "(aripiprazole) tablets with sensor". The Applicant proposed a label claim that this product is (b) (4) Given that there are no controlled trials to support this claim and the known limitations of the proposed product, the review team thought the term (b) (4) would have promotional implications and that a more appropriate claim would be that it is "intended to track drug ingestion."

The following Limitations of Use (LOU) were added to the label:

- The (b) (4) of ABILIFY MYCITE to improve patient compliance or modify aripiprazole dosage has not been established.
- The use of ABILIFY MYCITE to track drug ingestion in "real-time" or during an emergency is not recommended because detection may be delayed or not occur.

Additionally, language related to the functions not evaluated by the FDA will be included in the app and web portal. The final language is being negotiated at the time of this writing but will be similar to the following statement:

- (b) (4)

The Applicant has agreed to these changes.

12. Recommendations/Risk Benefit Assessment

The Applicant demonstrated substantial evidence of Abilify Mycite usability in one simulated use trial. When used in conjunction with the Medical Information Device #1 (MIND1) system, 97% of Abilify + IEM ingestions are detected by the wearable sensor and detection is accurately communicated to both the MyCite app and the clinician/caregiver web portal. However, the product's known limitations remain. Although under the idealized conditions of the 316-13-206B study the app detected 90% of tablets within 30 minutes, it took over two hours to detect two tablets and it failed to detect 50% of one subject's tablets. (b) (4)

Individual results will depend on the patient's ability to use the product correctly. This greatly depends on the IFU, both printed and electronic. DMEPA's evaluation of the task failures in the HF study and the Applicant's root cause analyses, and the existing mitigation strategies concluded that the risks of extra dose and dose omission have been sufficiently minimized. The risk of extra doses was greatly mitigated by the removal of the (b) (4) in this review cycle. Addition of LOU statements to the labeling further mitigates the risk and ensures that the patient does not take immediate action based on the recorded ingestion data in the app.

It also states that, as noted above, the product has not been demonstrated to increase compliance.

If the MyCite system fails, patients will not incur additional risk; they will continue to receive the exact treatment benefits of aripiprazole tablets without tracking. If the system works as intended and the patient choses to share the data with the HCP, the drug ingestion data could potentially help guide the prescribing physician on treatment interventions. No new safety signals were identified in the development program and the overall benefit-risk ratio for the proposed product remains similar to that of aripiprazole oral tablets.

Although the novelty of the proposed product and its components led to unique questions during the review process, the review team has reached a consensus to approve Abilify MyCite with the LOU highlighted in Section 11. Decisions regarding the contents and regulation of the app and the web portal are highlighted in Section 10. The labeling and MG have been negotiated with the Applicant to satisfaction. I agree with the review team's decision to approve this product.

Recommendation for Postmarketing Risk Evaluation and Management Strategies:
None.

Recommendation for other Postmarketing Requirements and Commitments:
The final postmarketing requirements are being finalized as of the time of this writing. The final language and dates will be included on the Approval Letter.

1. Conduct a human factors usability study using the to be marketed product in pediatric patients with bipolar I disorder and irritability with autistic disorder ages 10 to 12 years and 6 to 12 years, respectively.
2. Conduct a human factors usability study using the to be marketed product in pediatric patients ages 13 to 17 years with schizophrenia, bipolar I disorder, and irritability with autistic disorder.

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/s/

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11/13/2017

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11/13/2017