CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207202Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 207202

Review #2

(with approved Comparability Protocol)

Drug Name/Dosage Form	Abilify Mycite (aripiprazole tablets with sensor)
Strengths	2 mg, 5 mg, 10mg, 15 mg, 20mg, and 30mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Otsuka Pharmaceutical Company, Ltd.
US Agent	Otsuka Pharmaceutical Development & Commercialization, Inc.

Current Review Cycle

SUBMISSION(S) REVIEWED	DOCUMENT DATE	TOPIC
N-0030	**21 APR 2017**	Complete Response
N-0033	**29 AUG 2017**	Software documentation
N-0034	**30 AUG 2017**	Comparability Protocol
N-0035	**3 OCT 2017**	Comparability Protocol
N-0036	**10 OCT 2017**	Carton and Container Labeling
N-0037	**13 OCT 2017**	Comparability Protocol
N-0038	**16 OCT 2017**	PI and labeling
N-0040	**18 OCT 2017**	Comparability Protocol
N-0045	**8 NOV 2017**	Comparability Protocol

Previous Review Cycle

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
N-0000	26 JUN 2015	All
N-0003	3 AUG 2015	Facility
N-0013	2 NOV 2015	Process/Drug Product
N-0014	13 NOV 2015	Facility
N-0017	27 JAN 2016	Process/Drug Product/CDRH
N-0019	24 FEB 2016	Process/Drug Product/CDRH
N-0023	8 MAR 2016	CDRH

Quality Review Team

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

Table of Contents

Table of Contents 2
Quality Review Data Sheet 3
Executive Summary 4

OPQ Facilities Review 12

CDRH OC Review 19

CDRH Device Review 35

CDDRH Software Review 54

Comparability Protocol 62

Reference ID: 4185545

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
29332	Type V	Proteus	IEM	Adequate to support NDA 207202	13 APR 2016	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21436	Abilify Tablets

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH ODE	complete	Approval (see attachment)	1 SEP 2017	Luke Ralston
CDRH OC	Complete	Approval (see attachment)	6 OCT 2017	Katelyn R. Bittleman
CDRH Software	Complete	Approval (see attachment)	13 SEP 2017	Nathalie Yarkony

Reference ID: 4185545

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommendations: Recommend that this application be approved from an OPQ perspective. Each of the consulted CDRH reviewers also made approval recommendations (attached reviews).

The version of the proposed Comparability Protocol submitted on 8 NOV 2017 was found acceptable by a review team which included members from OPQ (ONDP, OLDP, OPF, OPPQ, OPRO), CDRH and DMEPA. Input was also provided from Patrick Raulerson, CDER ORP.

Rationale behind OPQ approval recommendation:

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. A CR action was recommended from an OPQ perspective (b) (4) (b) (4) (b) (4) In their response to the CR action the applicant removed (b) (4) from the app. This changes risk profile of the product (b) (4) to a more passive retrospective diary-type product.

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. If the approved label claim is to 'track drug ingestion', there is some evidence that the product can do so with ca. 90% overall reliability within 30 minutes. Individual results will depend on the patient's ability to use the product correctly as demonstrated by Human Factors testing and the availability of smartphones Bluetooth connection. The risk to the patient will be reduced by the recommended addition to the label of these limitations (Limitations of Use).

Reference ID: 4185545

This will ensure that the patient does not take immediate action based on the ingestion data in the app.

It is in this context that OPQ is making an approval recommendation. Note that the 'Additional OPQ comments' and the manufacturing site deficiencies at Otsuka in the previous CR letter were adequately addressed in the resubmission. A Comparability Protocol (CP) was negotiated with the applicant in this review cycle. (b) (4) The CP underwent significant negotiation with the applicant. The version submitted in the 8 NOV 2017 submission was found to be acceptable.

The regulation of the web-based portal and the impact of the mood and physiological data will be discussed in the CDTL memo.

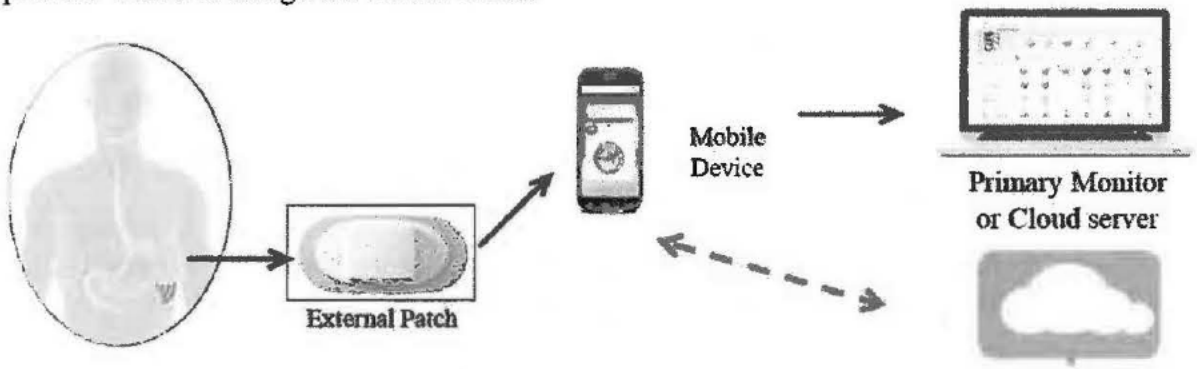
II. Executive Summary of Quality Assessments

The Product: The proposed combination product, Abilify Mycite, is a system that is intended to (b) (4) to aripiprazole and is indicated for the treatment of adults with:

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

The Agency requested that the applicant revise the label claim (b) (4) to "track drug ingestion".

After the tablet is ingested it disintegrates in the stomach, exposing an electronic sensor (ingestible event marker, or IEM) to the gastric fluid. The aqueous gastric environment activates the IEM which sends a signal to the patient's smartphone via a patch (wearable sensor) which is worn on the patient's torso. The smartphone can share the data with the patients' HCPs or caregivers via the Cloud.



The System: The Abilify MYCITE system is a combination product with the following three main components:

Reference ID: 4185545

1. **ABILIFY MYCITE**: Aripiprazole immediate-release **tablets** imbedded with an ingestible event marker (***IEM***) sensor.

2. **MYCITE Patch**: This is a wearable sensor which adheres to the torso, which picks up the signal from the IEM (b) (4) and transmits it to the iPhone (via Bluetooth)

3. **Software** within an iPhone, aka the app, which picks up the signal from the patch and which displays data about the ingestion event for patient. The app can also transmit the data to the Otsuka Cloud-based Server. This allows health care professions and others (at patients' request) to view the data via a web portal. The system also collects other mood and physicological data about the patient which can be viewed on the app and web portal.

The kit is assembled at the (b) (4) This packaging site was found to be acceptable.

ABILIFY MYCITE (aripiprazole) tablets with sensor: The tablet component of the combination products consists of aripiprazole tablets (2, 5, 10, 15, 20 and 30 mg strengths) embedded with an IEM sensor. The composition of the proposed tablets is qualitatively and quantitatively identical to Abilify tablets, except for the addition of the IEM sensor. In addition, the amount of colorant is (b) (4) to distinguish it from Abilify tablets.

The tablets are manufactured by Otsuka in Tokushima, Japan. The site underwent a preapproval inspection and was found to be acceptable. (b) (4)

(b) (4)

The tablets then undergo release and stability testing. Stability data support the proposed 36 month expiry period. The drug product specification is identical to that of Abilify tablets – with the exception of the addition of a test for the functionality of the IEM – called the DFAT test.

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 4185545

(b) (4) The IEM is manufactured by Proteus Digital Health in Hayward, CA. A preapproval inspection of this site was carried out and it was found to be adequate.

Although the details of the IEM were provided in the NDA, more supporting information was provided by Proteus in DMF 29332 (submitted to CDER). This DMF was evaluated CDRH, led by Luke Ralston and found to be adequate to support this application.

(b) (4) 2 configurations:

1. (b) (4) – this was the original model produced by Proteus prior to 2013 and used by Otsuka through most of product development.

2. (b) (4) – this is the proposed commercial version of the IC

Proteus developed the (b) (4) in 2013 (b) (4) This change resulted in challenges during the review process as much of the developmental work and most of the registration stability batches were manufactured with tablets with the older (b) (4) IEM. The two versions are physically identical, just (b) (4) differs. (b) (4)).

(b) (4) These differences added uncertainty to bridging the placebo formulation used in the 206B clinical studies to the commercial formulation.

(b) (4) A shelf life of (b) (4) months was proposed for the IEM when stored at (b) (4) This was found to be acceptable.

MYCITE Patch (wearable sensor): All information for the patch was cross referenced to cleared 510k applications. Two versions of the patch are described in the application.

Reference ID: 4185545

The RP4 version was used through most of development and worked with the (b) (4) version of the IEM. The DW5 version is the proposed commercial version and was designed to work with the commercial (b) (4) version of the IEM. The patch is manufactured for Proteus at Avery Dennison Corp, Mentor, OH. The site underwent a preapproval inspection and was found to be acceptable. Note that the labeling describes this component as 'MYCITE Patch'. Use of the term 'wearable sensor' was considered, as 'patch' could be confused with the commonly used term for a transdermal system drug product. It was decided to use the applicant's term 'MYCITE Patch', mainly because the patients would more intuitively understand the term and there would be less likelihood of it being confused with the IEM 'sensor'. This approach was agreed to by DMEPA, OGD policy, OPQ policy, CDRH and DPP.

Software/Firmware: The software on the app (b) (4) processes this information for display on the phone. This also transmits the data to the Otsuka Cloud based server for sharing with designated parties via a web portal. Nathalie Yarkony and Linda Ricci from CDRH evaluated the app in this review cycle and found it adequate (13 SEP 2017 review attached).

Web Portal: 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 – as it is described as part of the product in product labeling. Software regulation is an evolving topic, especially since the recent passage of the 21st Century Cures Act. This issue together with the patient mood and physiologic data and any disclaimers will be addressed in the CDTL memo.

In Vivo Studies: In the initial review cycle a human factors study tested whether subjects could use the kit, including the patch and the app. This study was evaluated by DMEPA at that time, and found that only one out of 36 subjects successfully used the product. In this review cycle human factors testing results were found acceptable after the applicant modified the instructions. Two in vivo studies were completed to measure the accuracy of IEM detection and determine the data latency throughout the system. These were the Osmitter 316-13-206A and Osmitter 316-13-206B studies. Osmitter 206A used the older (b) (4) IEM. The results found poor detectability (ca 75%) and long lag times. Osmitter 206B study is more relevant to this application as it used the commercial (b) (4) IEM but in a placebo tablet. The results were generally better – out of 116 ingestions 4 were not detected and 7 took greater than 30 minutes to be detected. 90% of the ingestions were detected within 30 minutes and 95% within two hours.

CDRH Hardware Review: In the first review cycle Luke Ralston evaluated the device performance sections of the application and found that "the bench testing and in vitro data has adequately quantified the performance of the device within the tablet *in idealized conditions*." However he found that the Osmitter in vivo studies "demonstrate that the Otsuka software – (b) (4) – has significant data latency that is not consistent with the IEM cleared under 510(k). Even under idealized study conditions

Reference ID: 4185545

a substantial fraction of patients will not receive positive detection confirmation (b) (4) This performance is not adequate to ensure safety and effectiveness for the intended use." However in the resubmission, he concluded that "the data support use of the TRADEMARK system for tracking and trending now that the (b) (4) has been removed from the mobile app". As stated above the removal of the (b) (4) changed the overall risk-benefit profile of this product.

CDRH OC and OPQ Facilities reviews: Katelyn R. Bittleman reviewed the application in this review cycle from a CDRH Office of Compliance perspective. They found the application acceptable from their perspective (6 OCT 2017 review attached). A post approval inspection was recommended for the (b) (4) packaging facility. OPQ facilities made and approval recommendation in this review cycle (18 SEP 2017 review attached).

Comparability Protocol (CP): The CP has undergone several iterations in this review cycle and the most recent version (from 8 NOV 2017 submission) is attached to this review. The CP was agreed upon by members of DMEPA, CDRH, OPQ OLDP, OPQ OPRO, OPQ OPF and OPQ ONDP.

Nonproprietary Name: OPQ OPPQ in consultation with 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. The applicant agreed to this change (N-0036), choosing to place the parentheses around the entire nonproprietary name, i.e. (aripiprazole tablets with sensor).

Biopharmaceutics Considerations:

1. BCS Classification:
    - Drug Substance: 2 (low solubility, high permeability). The absolute BA of Abilify® is ~87%.
    - Drug Product: rapid to very rapid dissolution at pH 1.2 and 4.5, but not pH 6.8

The Applicant's biowaiver request is granted per 21 CFR 320.22(d)(4). The following is the agreed upon dissolution method and acceptance criterion:

USP Apparatus	Spindle Rotation	Medium/ Volume/Temperature	Acceptance Criterion
2, Paddle	60 rpm	900 mL pH 1.2 USP Buffer (degassed), at 37 ± 0.5 °C	Q = (b) (4)% at 30 min

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Reference ID: 4185545

Application Technical Lead Signature: Recommend Approval.

David Claffey.

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4185545

FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
Office of Device Evaluation

Date:	September 1, 2017	**Branch:**	CDDB
To:	David Claffey, Ph.D. Brendan Muoio	**Division:**	DCD
Reviewer:	Luke Ralston, Biomedical Engineer		
File:	NDA 207202 (SN0030) – Resubmission to Complete Response Letter		
Applicant:	Otsuka Pharmaceutical		
Type:	New Drug Application (NDA) – Combination Product		
Linked file:	DMF 029332		
Referenced file:	K150494		

Recommendation: Approve

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Supervisor Concurrence	

I. Overview and Background

Scope of Review

I have been asked to review the design and performance information submitted for the IEM and patch hardware components of the TRADEMARK system. The system is also variously referred to as ABILIFY MYCITE and MIND1 throughout the submission. The documents reviewed for this consult (SN0030) were:

1.2.2	Reviewer Guide
2.5.1	Clinical Overview/Product Development Rationale
2.7.4	Summary of Clinical Safety
5.3.5.4	Comparability Protocol, Software MAF, and Human Factors report

This resubmission of New Drug Application (NDA) 207202 (aripiprazole + ingestible event marker [IEM]) from Otsuka Pharmaceutical is in response to the deficiencies outlined in the FDA Complete Response Letter (CRL) dated April 26, 2016. A subsequent Type A Meeting also provided additional comments to the sponsor on June 28, 2016. The NDA resubmission includes the following information to address the CRL:

Reference ID: 4185545

- As agreed upon with FDA in the June 28, 2016 Type A Meeting, the additional clinical trial requested in the CRL is not necessary given that the (b) (4) has been removed from the system.
- The data previously provided in Section 9.1.3 (Communication Timing) of the Type A Meeting Package are included in Module 2.5.1.2 of SN0030.
- All software documentation has been resubmitted after incorporating the changes to address the human factors deficiencies. These documents are located in Module 5.3.5.4 [Note: software consulting review is provided in a separate memo by Nathalie Yarkony]
- The proposed comparability protocol for postmarket system updates and routine revisions has been updated following completion of the human factors studies and is located in Module 5.3.5.4.

The IEM (Ingestible Event Marker) and patch components are 510(k)-cleared devices manufactured by Proteus Digital Health. Proteus Health has also submitted a Drug Master File (DMF 029332) for their IEM, (b) (4) . Several deficiencies were found in the DMF during review of the original NDA and no updates to the DMF were submitted concurrent with SN0030.

Resubmission Material for NDA 207202

The sponsor reassessed all studies conducted for validation of the IEM, patch, patient app, or HCP web portal as shown in the table below.

Trial/ Phase	Trial Completion Date	No. Enrolled Subjects, Indication	Trial Design	TRADEMARK Components Assessed in Trial					Treatment Period Duration
				Aripiprazole + IEM	Placebo + IEM	Proteus Patch	Otsuka Medical Software		
							Patient Component (app)	HCP and Caregiver Web Portals	
316-13-204/ Phase 4	26 Feb 2014	58 adults with bipolar disorder or MDD	Open label, single arm	--	X	X	X	X (both portals)	16 weeks
316-13-205/ Phase 1	26 Jul 2013	30 healthy adults	Open label, controlled, randomized (Patch position)	--	--	X	--	--	28 days
316-13-206a/ Phase 4	18 Apr 2014	30 healthy adults	Open label, single arm	X	X	X	X	--	1 day
316-13-206b/ Phase 4	05 Mar 2015	29 healthy adults	Open label, single arm	--	X	X	X	--	1 day
316-13-215/ Phase 2	08 Sep 2016	49 adults with schizophrenia, bipolar I disorder, or MDD	Open label, single arm	X	--	X	X	X (both portals)	8 weeks
316-14-220/ Phase 2a	07 Jul 2015	67 adults with schizophrenia	Open label, single arm	X	X[a]	X	X	X (HCP portal only)	8 weeks

NOTE: Only trial 316-13-215 is new information submitted with SN0030. It did not collect any data on IEM function, event detection rate, or patch performance.

In response to the issues enumerated in FDA's 4/26/2017 CRL, the sponsor recognizes that variable communication times along the data chain to the phone are to be expected. Contributors to communication timing include the patient and Patch being out of the

Reference ID: 4185545

Bluetooth (BT) range of the compatible mobile device, or the mobile device being in an environment with poor data connectivity to the cloud. Other contributors can include the mobile device operating system prioritizing other tasks such as a phone call over cloud or BT data transfer. Date loss is prevented because the Patch is designed to store all data for the device's 7-day lifespan.

The sponsor has resubmitted the data from Trial 316-13-206b which demonstrates that the 95th percentile for communication time for all time points and ingestions ranged from 28.6 to 68.4 minutes (see table below). Most of the ingestions (110 of 116; 94.8%) were recorded in less than 120 minutes. The sponsor believes that the risk of longer communication times causing dosing errors and potential overdose situations will be appropriately mitigated by removing the (b) (4).

Table 2.5.1.2-2 Frequencies of Subjects Who Received Timeline Ingestion Tiles on the Smartphone within Different Timeframes (ITT Sample)

Ingestion Time Point (Hour)	Check Time Point (Minutes)	N[a]	n[b]	Percent
Hour 0	30 Minutes	29	25	86.2
	60 Minutes	29	2	6.9
	> 120 Minutes	29	1	3.4
Hour 2	30 Minutes	29	24	82.8
	60 Minutes	29	1	3.4
	90 Minutes	29	1	3.4
	> 120 Minutes	29	1	3.4
Hour 4	30 Minutes	29	27	93.1
	60 Minutes	29	1	3.4
Hour 6	30 Minutes	29	29	100.0

[a]Number of subjects in ITT Sample ingesting IEM at Hours 0, 2, 4, and 6.

[b]Number of subjects with tiles received by the smartphone within the checking time period for each ingestion time point.

REVIEWER COMMENT: I agree that the data support use of the TRADEMARK system for tracking and trending now that the (b) (4) has been removed from the mobile app. See Section VIII of this memo for the updated review of IEM functionality and validation.

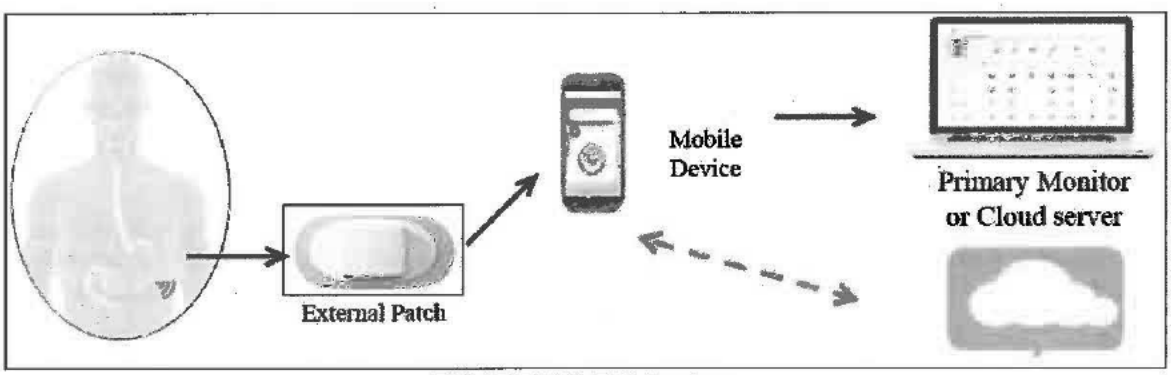
II. Device Description:

This New Drug Application (NDA) requests approval for the TRADEMARK system and the proposed label claim: (b) (4) to aripiprazole and is indicated for the treatment of adults with:

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

Reference ID: 4185545

TRADEMARK is composed of distinct components: (1) the Drug-device Combination (aripiprazole + IEM, which is the investigational product); (2) the Proteus Patch; (3) the Patient Component (app) of the Otsuka Medical Software, (4) the Cloud-based Server; and (5) the Web Portals of the Otsuka Medical Software. The components of TRADEMARK are illustrated in the Figure below.



TRADEMARK System

NOTE: Although the sponsor attempts to describe the Proteus MDDS and the Patient Component (app) as separate components of the system, they both run on the patient's mobile device so have been reviewed as one component.

Table 2.3.1-1 Currently Supported Mobile Devices and Operating Systems

Mobile Devices	Generation	Patient app
iPhone (OMSS App)	6, 6S (iOS 9.X or later)	Version 2.0.0

The Patient Component (app) of the Otsuka Medical Software, which resides on a paired mobile computing device (currently iPhone 6 or later), receives data from the Proteus software also installed on the mobile device. The mobile device transmits data via cellular or Wi-Fi connectivity to the Otsuka Cloud-based Server. The Patient Component (app) of the Otsuka Medical Software has both automatic and optional features; the automatic features include:

- Registration of aripiprazole + IEM ingestion (i.e., after the ingestion of aripiprazole +IEM, the IEM is activated in the stomach, communicates with the Patch, which then registers the IEM's ingestion date and time on the Patient app);
- (b) (4) have been removed from this submission;
- Daily, weekly, and monthly views of medication adherence behavior are automatically available for review by the patient in the Patient Component (app) of the Otsuka Medical Software;
- In addition, these (b) (4) data are automatically transmitted to the Otsuka Cloud-based Server for processing and display on the HCP Web Portal of the Otsuka Medical Software.

Reference ID: 4185545

Optional features of the Patient Component (app) of the Otsuka Medical Software include the options for the patient:

- To share [redacted] (b) (4) data with his/her caregiver;
- To register mood and rest quality, which can be reviewed and, if elected, shared with the patient's HCP and/or caregiver;
- To share Patch-registered activity and rest data with the patient's HCP and/or caregiver.

The Proteus system has been cleared using the product code OZW under the following 510(k) submissions:

- K113070/DEN120011
- K131009
- K131524
- K133263
- K150494

[redacted] (b) (4)

Aripiprazole + IEM tablets (2, 5, 10, 15, 20 and 30 mg strengths) are developed as drug-device combination product. [redacted] (b) (4)

[redacted] (b) (4)

Reference ID: 4185545

(b) (4)

(b) (4) 2 configurations:

1. (b) (4) – this was the original model produced by Proteus prior to 2013 and used by Otsuka in some phases of product development. It is also referred to as (b) (4) in some of the development documents.
2. (b) (4) – this is the current model (b) (4) used in the TRADEMARK system. It is also referred to as (b) (4) in some of the development documents.

(b) (4)

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 4185545

III. Shelf Life/Stability

Some shelf-life/stability data was submitted in Section 2.3.S.7 of the DMF; however, it only included the (b) (4) design and did not contain any drug component.

REVIEWER COMMENT: I defer to the CMC lead review for determination of adequate shelf life/stability of the combination Aripiprazole + IEM.

IV. Biocompatibility

No biocompatibility information is provided in the NDA. I defer to the CDER lead office for the need for a Pharmacology and Toxicology review.

V. Software/Firmware

A software consult was provided by Nathalie Yarkony (CDRH/ODE/DCD/CDDB).

(b) (4)

REVIEWER COMMENT: I defer to the review by Nathalie Yarkony for determination of adequate software development and validation. I defer to CDER Product Jurisdiction team for determination of the final comparability protocol.

Reference ID: 4185545

VI. EMC & Electrical, Mechanical, and Thermal Safety

During the classification of ingestible sensors in 2012, CDRH identified 8 risks to health shown in the table below:

Identified Risks from 2012 classification	Mitigations
Adverse Tissue Reaction	Biocompatibility
Systemic Toxicity	Battery and IC materials
Electromagnetic Incompatibility	VCC transmission
Electrical Safety	Battery design Low-power transmission (heating and tissue stimulation)
Electrical/Mechanical failure	Battery and IC design
Failure to mark event	Animal and Clinical testing
Failure to excrete	Animal and Clinical testing
Usability	Human Factors testing

Mechanical Failure

(b) (4)

NOTE: I defer to the CMC review for the adequacy of these manufacturing controls and implementation for the final finished combination product.

(b) (4)

Electrical Failure

(b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 4185545

(b) (4)



REVIEWER COMMENT: EMC & Electrical, Mechanical, and Thermal safety are adequate.

VII. Manufacturing

Reviewed by CDRH Office of Compliance and not included in this memo.

VIII. Device Verification and Validation

Bench Testing

The bench testing for this product focused on IEM activation after ingestion and IEM functionality. Since activation is dependent upon exposure to the patient's stomach acid, the sponsor performed dissolution studies to demonstrate proper activation. The sponsor also conducted separate testing to demonstrate IEM functionality after the new manufacturing and storage conditions required by the drug substance.

(b) (4)



Reference ID: 4185545



1) Dissolution performance

To confirm that insertion of the IEM had no impact on physicochemical and biological properties of the proposed combination product, two comparative dissolution studies were conducted. It is noted that IEM activation depends more on tablet disintegration than dissolution so this CDRH review focused only on data relevant to disintegration.

The first comparative dissolution study in three different dissolution media, pH 1.2, 4.5 and 6.8, were conducted to demonstrate that the proposed Aripiprazole + IEM would behave equivalently to commercially available Abilify tablets. The second comparative dissolution study was conducted to demonstrate comparability of the final Aripiprazole + IEM formulation which will use (b) (4) colorant in order to distinguish it from current Abilify tablets.

The sponsor concludes that "the presence of an IEM has no adverse impact on the dissolution performance (drug release) from the proposed combination tablet and thus the same

Reference ID: 4185545

dissolution method with the same limit for commercial Abilify tablets (Q= (b) (4)% in 30 minutes) is proposed for this combination product."

These studies did not provide any information about tablet disintegration and the acceptance criteria of Q= (b) (4)% within 30 minutes raised concerns about (b) (4)

NOTE: The results summarized below only include the (b) (4) design with no data submitted for the (b) (4) design.

	2mg	10mg	15mg	30mg
0 months	1:38 – 1:54	1:24 – 1:40	2:30 – 3:00	2:49 – 3:23
3 months	1:26 – 3:03	1:18 – 2:48	2:04 – 2:23	2:54 – 3:31
6 months	1:50 – 3:44	1:30 – 1:48	2:04 – 2:59	3:32 – 3:51
9 months	1:30 – 2:13	1:08 – 2:24	1:57 – 2:14	2:31 – 4:02
12 months	1:33 – 2:16	1:43 – 2:05	2:01 – 3:17	3:04 – 3:48
18 months	1:32 – 1:59	1:06 – 1:41	1:35 – 1:51	2:48 – 6:49

Distribution of Tablet Disintegration Times (minutes:seconds)

(b) (4)

Mean and Minimum IEM Lifetime Measurements (seconds)

IEM + Placebo vs. IEM + Aripiprazole

Section 3.2.P.2.2.1.3 uses DFAT to compare currently cleared IEM + placebo tablet to the proposed IEM + Aripiprazole at all dosages of the API. The results show a slightly longer IEM lifetime in the IEM + Aripiprazole compared to placebo. The smallest difference was in the 2mg Aripiprazole formulation which showed an approximate 50% greater lifetime of the Aripiprazole batches. The mean IEM lifetime was progressively longer for each of the 5mg, 10mg, 15mg, 20mg, and 30mg formulations.

The sponsor explained that the difference in lifetime is because IEM activation depends on (b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 4185545

(b) (4)

CDRH COMMENT: The bench testing and in-vitro data has adequately quantified the performance of the device within the tablet *in idealized conditions*. The sponsor has conducted clinical testing to demonstrate in-vivo performance.

Animal Testing
No animal testing was included in this NDA.

A number of animal studies were submitted in DMF 029332. These were for studies that had been performed for prior product development and partly in support of 510(k) submissions for the stand-alone IEM reviewed by CDRH. Dr. Annabelle Crusan provided a consulting review for the DMF and identified 5 deficiencies which were sent to Proteus. In a 2/8/16 teleconference, Proteus acknowledged the deficiencies in the animal testing but does not plan to submit the requested information. Ultimately, the animal data was not used to support any section of this NDA but did not require resolution since Otsuka submitted clinical testing as discussed in the next section of this memo.

Clinical Testing
Given the difference in performance between the IEM + placebo and IEM + Aripiprazole in bench testing, Otsuka conducted 2 clinical studies under their OSMITTER protocol.

OSMITTER 206A – validate in-vivo performance of IEM ((b) (4) version) + placebo and IEM ((b) (4) version) + Aripiprazole combination
OSMITTER 206B – validate in-vivo performance of IEM (b) (4) version) + placebo

The purpose of these studies was twofold:

1. Validate IEM detection
2. Validate data transmission capabilities of all system components

OSMITTER 206A
This trial was conducted to determine the accuracy of IEM detection by completing a series of patch applications and IEM ingestions in the clinic. The study subjects were not responsible for any aspect of patch placement, pairing to the mobile device, data interpretation, or troubleshooting. Following placement of the patch by clinic staff, subjects ingested one IEM tablet approximately every 2 hours, for a total of 4 ingestions. The subjects ingested one 10-mg aripiprazole-embedded IEM (aripiprazole + IEM) tablet without food (Hour 0), one placebo-embedded IEM (placebo + IEM) tablet without food (approximately Hour 2), one placebo + IEM tablet with a high-fat meal (approximately Hour 4), and one placebo + IEM tablet without food (approximately Hour 6).

Reference ID: 4185545

Results are shown in the table below:

Proportion of Subjects with Ingestible Event Marker Detection			
Timepoint	**Subject Ingestions**	**IEM Detected (%)**	**90% CI (%, %)**
Hour 0[a]	30	22 (73.3)	(57.0, 86.0)
Hour 2[b]	30	19 (63.3)	(46.7, 77.9)
Hour 4[c]	30	23 (76.7)	(60.6, 88.5)
Hour 6[b]	30	28 (93.3)	(80.5, 98.8)
Total	120	92 (76.7)	(69.4, 82.9)

a = aripiprazole + IEM without food; b = placebo + IEM without food; c = placebo + IEM 30 minutes after high-fat meal

This study has a number of limitations and discrepancies:

- Only t = 0 evaluated aripiprazole + IEM
- Only the (b) (4) version was used in this study
- At t = 0, 2, 4 detection is far below 97% historical average
- The study did not use final commercial-release versions of the patch or software

In an attempt to reconcile the poor performance of detection the sponsor conducted a post-hoc analysis of data transmission times. As shown in the table below, there was significant latency noted when sending data from the Proteus patch to the Proteus software application.

Transition	N	Mean	SD	SE of mean	Median	Min	Max
Patch to (b) (4)	94	21.019	30.149	3.110	2.680	0.723	114.428
(b) (4) to Otsuka app.	94	0.356	3.243	0.335	0.021	0.007	31.466

All units are in minutes; (b) (4) – proprietary Proteus software that receives data from the patch and inputs to Otsuka app software

OSMITTER 206B

As a result of the limitations and poor performance in the 206A study, Otsuka conducted the 206B study.

The primary objective was to measure the accuracy of IEM detection using the placebo + IEM, and to evaluate the latency period between site-reported ingestion time and detection of the ingestion event by the Patch. Secondary objectives were to measure the latency period between the Patch detection of the ingestion event and transmission of the event in the Otsuka Cloud-based Server.

Reference ID: 4185545

The trial was conducted with the DW5 Proteus Patch (Patch) and Otsuka application (app) software version 1.5.2.

Proportion of Subjects with Ingestible Event Marker Detection			
Timepoint	**Subject Ingestions**	**IEM Detected (%)**	**95% CI (%, %)**
Hour 0	29	28 (96.6)	(82.2, 99.9)
Hour 2	29	26 (89.6)	(--, --)*
Hour 4	29	28 (96.6)	(82.2, 99.9)
Hour 6	29	29 (100)	(88.1, 100.0)
Total	116	111 (95.6)	

Overall detection accuracy improved in study 206B. Data latency also improved but still showed an extremely large distribution throughout time.

Time from IEM detection at patch to detection at Otsuka server					
Timepoint	**N**	**Mean (minutes)**	**SD**	**Min**	**Max**
Hour 0	28	7.5	23.7	0.5	123.2
Hour 2	26	10.3	20.9	0.5	80.8
Hour 4	27	6.2	10.4	0.4	31.2
Hour 6	29	6.2	8.9	0.8	29.7

REVIEWER COMMENT: Both the 206A and 206B studies demonstrate that the Otsuka software – (b) (4) – has data latency which is minor for the purposes of the intended use. Almost 95% of patients will receive positive detection confirmation by 2 hours after ingestion. This performance is adequate to ensure safety and effectiveness for daily and weekly tracking and trending of medication ingestion.

IX. Limitations and Deficiencies

None

Reference ID: 4185545

MEMO OF

SOFTWARE REVIEW

of a **Moderate** Level of Concern device

Otsuka

Date : September 11, 2017

From : Nathalie Yarkony CDRH\ODE\DCD\CDDB

Sponsor : Otsuka Pharmaceutical Development & Commercialization, Inc.

Device Name : Otsuka Medical Software

Review summary

The sponsor provided information only about the software (SW) application (App), and so this review focused on the App. No information was provided regarding the servers or the web application, in fact despite FDA requests to provide the information the sponsor had decided to remove previous documentation that was provided (server and web-application (b) (4).

The sponsor provided a large amount of documentation (~5000) pages. We have asked the sponsor to provide a narrative to demonstrate how they addressed the issues that FDA raised in the previous round. The sponsor has addressed some issues, while determining that "No further updates to the response provided on 24 Feb 2016" for other issues without providing any explanation or justification.

Furthermore, the sponsor revised the documentation (for example hazard analysis and requirements) without tracing to the previous versions. For example in the hazard analysis the sponsor removed hazards and changed the numbering scheme, therefore I was forced to review the software again.

As the changes to the software are minor it is not clear why the sponsor didn't update the documents version previously provided to FDA. This is not a proper way to document changes; the sponsor should refrain from revamping documents without a proper traceability. This is also related to the comparability protocol, the sponsor has demonstrated (b) (4) (which is an unwanted outcome!). I strongly recommend that a meeting is held with the sponsor to iterate the importance of QM in SW development. To align the expectation of FDA with regards to SW development, and explain how they should address SW deficiencies.

The sponsor removed the (b) (4); eliminating previous concerns that we had, as such and despite the above issues, taking into account the minor risk and the simplicity of the app I recommend approving the app.

Device Description

The sponsor provided the following figure to describe his device. Three of the components are included with the device (marked in blue in the figure.



Software

1. Level of Concern –
   Sponsor indicated a Moderate level of concern, despite the fact that he had answered yes to question #2 in the major level of concern determination table (p.36/2351). In order to rationalize his decision the sponsor noted that *"OMSS App remains a moderate level of concern as it is not for therapeutic intent. It displays medication-taking behavior data of the patient. It does not diagnose, treat, cure, or mitigate any medical or physiological condition. It also does not control the delivery or determine the dosage of aripiprazole. Communication of data to HCP is unidirectional (ie, only to HCP). OMSS App does not provide treatment advice to the patient. HCP cannot initiate communications to the patient through OMSS App."*.
   Based on this rational, and the Content of Premarket Submissions for Software Contained in Medical Devices dated May 11, 2005, we believe that the LOC is adequate.

2. Software Description –

   The OMSS App will capture the following biometric data from the Proteus Patch:
   - Activity
   - Rest - body angle < 30 degrees parallel to the ground
   - Ingestion activity as marked by the Proteus Ingestible Sensor® (IEM), which is embedded in an aripiprazole tablet as part of TRADEMARK The OMSS App enables the patient to enter, record, and keep track of their self-reported mood and quality of rest.

The App transmits patient data to a remote secure web-based server for storage via existing mobile telecommunications and/or internet infrastructure. The web-based server enables HCPs to review (b) (4) information, (b) (4) The OMSS App does not interpret or make any decisions on the data that it conveys, and it is not intended as a replacement for the oversight of HCPs. It also does not provide "real-time" or emergency monitoring. The capabilities of the OMSS App consists of the following:

1) Data is transferred via the Proteus Software located on the mobile device where information is received from the Patch and viewed on the OMSS App
2) Patients can view this information through the app on their smartphone
3) Data are sent to a secure data repository in a private cloud repository
4) A web-based portal allows display of patient(s)' data for the HCP (if elected by the patient for biometric data)
5) A web-based portal allows display of patient(s)' data for the CG (if elected by the patient for biometric data).



Figure 2.3-1 OMSS Data Flow Schematic

The sponsor didn't provide a full SW description that will allow a complete review of the SW. It appears that there are 3 main components to the software: the patient application, the server, and the webportal. The sponsor provided the following table to describe the application functionality; however detailed information regarding the cloud-based server or the webportal wasn't provided.

Table 2.3-1 Summary of Otsuka Medical Software Functions on the User's Smartphone

App Function	Description

Onboarding	☐ "Getting Started" video ☐ Add HCP (required to share ingestion data; sharing data for rest, activity, and mood are optional) ☐ Add caregiver, if applicable, and choose what information to share
Pill Ingestion	(b) (4) ☐ Pill status menu (b) (4)
Activity	☐ Activity (step count) displayed as line graph ☐ Definition of activity capture
Rest	☐ Number of hours of rest displayed ☐ Definition of rest capture ☐ Ability to enter quality of rest
Mood	☐ Ability to enter mood when desired ☐ Log of all mood states throughout the day (5 times total)
Patch Status	☐ Patch status screen to notify patient when patch replacement is needed or skin contact needs to be checked ☐ Step-by-step patch replacement instructions and assistance to ensure proper skin contact
Data Views	☐ Daily, weekly, and monthly view of pill ingestion, mood, rest, and

In addition, the software description should also include information on the following:
(b) (4)

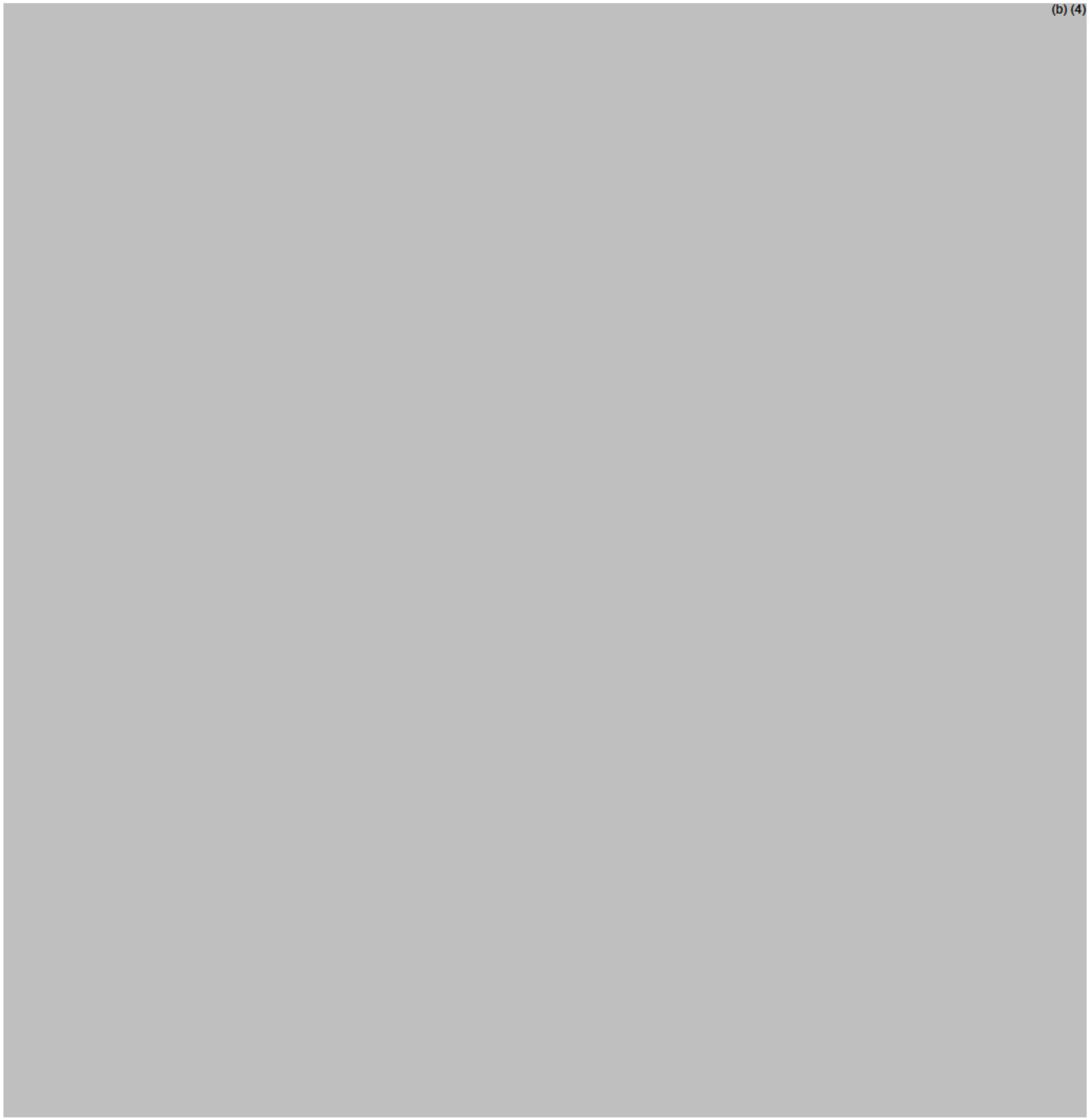
As the sponsor was previously asked to provide this information, the sponsor was asked interactively to provide a reference to his response.
The sponsor referred to appendices 1, 6, 7, 11 and 14 for the missing information. I have reviewed these documents and was able to identify the required data. It should be noted that a short description would suffice and be less burdensome to review.

On p.9/4941 the sponsor noted that "*In the CR Letter, the Agency noted that dosing errors can be attributed to the* (b) (4) *built into the app and recommended that the Sponsor remove this* (b) (4)*. The Agency also recommended improving the user interface to mitigate the risk for medication errors by the intended users and to test their effectiveness in another human factors (HF) validation study. The sponsor has taken the advice of the Agency and has removed the* (b) (4) *from the Otsuka Medical Software System (OMSS) App. We have also updated the OMSS App to version 2.0 with improvements to the patient App and have tested it in both formative and validation trials, the results of which are located in Module 5.3.5.4.* (b) (4)

This is acceptable and resolves previous issues with related risks and their mitigation.

In response to the IR the sponsor provided the following table:

Table 3-1 APIs		
API Name	**Functionality of API**	**Intended Use**



3. Device Hazard Analysis –

The sponsor provided Appendix 2 – AFMEA (VAL-0010409), Appendix 29 – Software Risk Management Plan (VAL-0009208) and Appendix 30 – OMSS App Risk Management Report (VAL-0010250) in which they included a table with identified risk ID, potential hazards, severity, hazardous situation, mitigation measure and risk control, probability of occurrence, total risk

index, additional mitigation controls, verifications of additional mitigation controls, post mitigation probability and risk control, and remarks.

I have reviewed the issues FDA highlighted in the previous review. The following issues remain:

- (b) (4)
- [redacted]

Note to lead:

The sponsor revised the hazard analysis without tracing to the previous versions. As the changes to the software are minor it is not clear why the sponsor didn't update the version previously provided to FDA. This is not a proper way to document changes; the sponsor should refrain from revamping documents without a proper traceability.

4. Software Requirements Specification (SRS)-

SRS was provided in the MAF document:

- Appendix 3 OMSS App System Requirements Specification
- Appendix 4 OMSS App Business Requirement
- Appendix 5 OMSS App Software Requirement Specifications

The sponsor also referred to Appendix 6 - Installation Configuration Specification (VAL-0009906) for the hardware requirements, to Appendix 1 - Software Development Plan (VAL-0009255) for programming language requirements, and to Appendix 7 - Detailed Design Specification (VAL-0009331) for Software performance and functional requirements.

I have reviewed the provided documents and found them to be mostly acceptable.

It should be noted that the Appendix 7 is a combination of requirements and some information about design. The requirements would define what needs to be done and the design would demonstrate how it was done.

5. Architecture Design Chart –

   Architecture design chart was provided in section 4.5 Architecture Design Chart (MAF p.32-33), Appendix 7 OMSS APP Software Detail Design - Patient & Web and Appendix 8 - Detailed Design Specification Appendix A (VAL-0009693)

   The information provided is acceptable.

6. Software Design Specifications (SDS) –

   Software Design Specifications document was provided in appendix 7. *Please refer to my comment is the SRS sections.*

7. Traceability Analysis –

   Traceability analysis was provided in MAF - Appendix 10. While the provided table links together the requirements, testing requirements, identified hazards, and implementation and testing of the mitigations, it doesn't create the link with the design specifications. This link was also not created in the Software Design Specifications. Given the complexity of the software we have determined it to be acceptable.

8. Software Development Environment Description –

   In section 4.8 architecture (MAF p.34) the sponsor referred to the Installation Qualification Protocol and the Installation Configuration Specification (ICS) describe the software Development Environment (Appendix 6) and the Installation Qualification Protocol (Appendix 13), and provided a summary. *The summary included irrelevant information.*

   The SW development environment description was actually provided in section 3 in the MAF, appendix 1- section 4 Software Development Process, in Appendix 11 OMSS App Design and Development Plan, Appendix 12 Appendix A to Design Development Plan. This section provided a description of the process, and the standards that were followed. This is acceptable.

9. Verification and Validation (V&V) Documentation –

   The sponsor detailed their V&V in MAF section 4.9.

   <u>Verification</u>
   Verification documentation are included in the OMSS App System Test Summary Report (Patient), which is presented in Appendix 17, Appendix 18, Appendix 19, Appendix 32, Appendix 33, and Appendix 34.
   The system testing is provided in:
   - Appendix 20 OMSS App System Test Protocol
   - Appendix 21 Appendix A to System Test Protocol
   - Appendix 22 Appendix B to System Test Protocol

   <u>Validation</u>

Validation documentation are included in the OMSS App System Validation Summary Report, which is presented in Appendix 23 and Appendix 24.
The validation testing is provided in:

- Appendix 15 OMSS App Design Validation Protocol
- Appendix 16 Appendix A to OMSS App Design Validation Protocol

The sponsor also provided the Installation Qualification Report in Appendix 14.

(b) (4)

I have reviewed the V&V that was provided and find them to be acceptable.

10. Revision Level History –

Revision level history was provided in the MAF. App version under review is 2.0.
Note that this is just for the App, the sponsor didn't provide any data regarding the other two SW components.

11. Unresolved Anomalies (Bugs or Defects) –

The sponsor indicated that there are no known anomalies; however there are failed test cases in the provided verification testing that appears weren't addressed or tested again. An example is test case1.27.25 in MAF p. 1654.

12. Off-the-shelf Software -

I wasn't able to find a dedicated document for OTS. The sponsor indicated throughout the submission that there are number of OTS components. There is no separate OTS hazard analysis however I was able to ide4ntify related hazard in the hazards analysis. We had asked the sponsor in the previous round to address the issues that may occur with updates of OTS, the sponsor referred to "The process of OTS (includes OS) upgrade is defined in System Support and Governance Plan (VAL-0005782)" for more information, however I wasn't able to find this document in the MAF.

13. Cybersecurity –

Provided in appendix 24. It is acceptable.

Nathalie Yarkony

26 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

QUALITY ASSESSMENT

Recommendation: Complete Response

NDA 207202

Review #1

Amended on 21 APR 2016 with final OPF Facilities recommendation

Drug Name/Dosage Form	Aripirazole Tablets with Ingestible Event Marker Sensor
Strengths	2 mg, 5 mg, 10mg, 15 mg, 20mg, and 30mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Otsuka Pharmceutical Company, Ltd.
US Agent	Otsuka Pharmaceuctical Development & Commercialization, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
N-0000	26 JUN 2015	All
N-0003	3 AUG 2015	Facility
N-0013	2 NOV 2015	Process/Drug Product
N-0014	13 NOV 2015	Facility
N-0017	27 JAN 2016	Process/Drug Product/CDRH
N-0019	24 FEB 2016	Process/Drug Product/CDRH
N-0023	8 MAR 2016	CDRH

Quality Review Team

DISCIPLINE	REVIEWER
Drug Substance & Drug Product	Mariappan Chelliah
Process and Microbiology	Hang Guo
CDRH Lead Reviewer	Luke Ralston
Facility	Donald Obenhuber
Biopharmaceutics	Gerlie Gieser
RBPM	Grafton Adams & Dahlia Woody
Application Technical Lead	David Claffey

Table of Contents

Table of Contents **2**

Quality Review Data Sheet **3**

Executive Summary **4**

Primary Quality Review **13**

ASSESSMENT OF THE DRUG SUBSTANCE 13

2.3.S DRUG SUBSTANCE 13

ASSESSMENT OF THE DRUG PRODUCT 17

2.3.P DRUG PRODUCT 17
R.2 Comparability Protocols 77

ASSESSMENT OF THE PROCESS 78

2.3.P DRUG PRODUCT 78
R.2 Comparability Protocols 129

ASSESSMENT OF THE FACILITIES 130

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION 136

ASSESSMENT OF MICROBIOLOGY 145

2.3.P.7 Container/Closure System 145

A APPENDICES 146

ASSESSMENT OF ENVIRONMENTAL ANALYSIS 148

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1 150

Labeling & Package Insert 150

II. List of Deficiencies To Be Communicated 150

III. Attachments CDRH REVIEWS 150

Reference ID: 4185545

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
29332	Type V	Proteus	IEM	Adequate to support NDA 207202	13 APR 2016	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21436	Abilify Tablets

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH ODE	complete	CR (see attachment)	4 MAR 2016	Luke Ralston
CDRH OC	Complete	Approval (see attachment)	19 APR 2016	Crystal Lewis

Reference ID: 4185545

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommendations: Recommend that this application not be approved from an OPQ perspective. CDRH also made a CR action recommendation (attached review).

Rationale behind recommendation: The applicant has adequately demonstrated that they can manufacture the proposed combination product with defined and consistent quality as demonstrated by in vitro manufacturing controls and bench performance testing. The OPQ and CDRH reviewers have generally made approval recommendations based on the individual components' performances. However the proposed product is designed to work with patients as an integrated combination product. The in vivo performance of the final commercial product has not been adequately demonstrated.

Although the individual components' manufacturing and bench testing were found to be adequate, of interest to the patient is that the entire kit adequately functions as designed. Although the proposed indication is to (b) (4)

(b) (4)

Clinical study design is outside of OPQ's purview; therefore we cannot recommend how the applicant should address this deficiency. However it is our view, given the totality of the data and the risk of dosing errors, that insufficient data were provided to support the performance of the entire to-be-marketed product.

Reference ID: 4185545

Note that should the applicant redesign the app to deactivate the (b) (4) it will function more passively and will be more consistent with the proposed label claim (b) (4) The risk to the patient of dosing errors is reduced as the patient would view the data in a retrospective manner and would not act in real-time on the information supplied by the app. Given the reduced risk, the 206B studies could possibly support the adequacy of the performance of the product – though this will require reevaluation of these data in the context of future changes in the app.

Note also that the OPQ facilities review team did not recommend approval as the drug substance manufacturer (Otsuka, Saga, Japan) has a 'withhold' recommendation after a recent surveillance inspection.

Draft Action letter language (as clinical studies are being requested, this will require revision and finalization by DPP):

1. Considering the risk of dosing errors that the product presents to the patient and the variable results seen with the placebo product in 316-13-206B study, we request that you carry out a similar study which unambiguously tests the to-be-marketed formulation under the conditions in which it is likely to be used. We request that the study have a predetermined and justified endpoint, e.g. positive detection rate after a certain time period. We recommend that the tablets studied represent or bracket the commercial tablet sizes/strengths, that you study with/without food and consider using aged tablets. The Agency is prepared to provide advice/feedback on such a study.

   We acknowledge your 24 Feb 2016 IR response where you state that " (b) (4)
   (b) (4)

Reference ID: 4185545

(b) (4)



2. During a recent inspection of the OTSUKA PHARMACEUTICAL CORPORATION LTD, FEI: 3003808559 manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Additional comments for CR letter:

1. The proposed comparability protocol is not approved as it cannot be evaluated due to the user interface (Human Factors) deficiencies identified. We recommend that if continue to wish to pursue a CP, that it be included in a resubmission/response to the CR.

2. We acknowledge receipt of the full commercial drug product manufacturing batch records at the preapproval inspection, please submit these to the application.

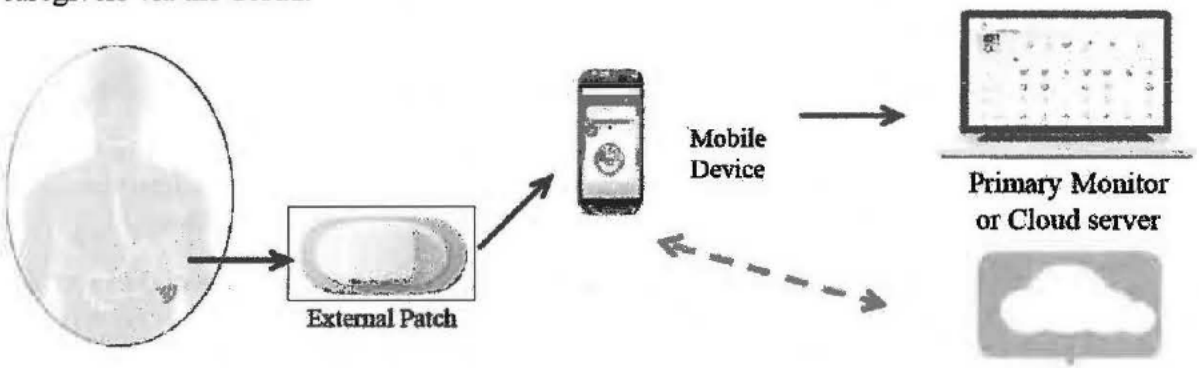
Reference ID: 4185545

II. Executive Summary of Quality Assessments

The Product: The proposed combination product, Abilify Mycite, is a system that is intended to [redacted] (b) (4) to aripiprazole and is indicated for the treatment of adults with:

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

After the tablet is ingested it disintegrates in the stomach exposing an electronic sensor (ingestible event marker, or IEM) to the gastric fluid. The aqueous gastric environment activates the IEM which sends a signal to the patient's smartphone via a patch which is worn on the patient's torso. The smartphone can share the data with the patients' HCPs or caregivers via the Cloud.



The Kit: Abilify Mycite, aripiprazole tablets with IEM sensor is a combination product with the following three main components:

1. Aripiprazole immediate-release **tablets** imbedded with an ingestible event marker (***IEM***) sensor.
2. A wearable sensor which adheres to the torso, aka the **patch**, which picks up the signal from the IEM [redacted] (b) (4) and transmits it to the iphone (via Bluetooth)
3. **Software** within an iphone, aka the app, which picks up the signal from the patch and which displays data about the ingestion event with patient. The app can also transmit the data to the Otsuka Cloud-based Server (also part of the application). This allows health care professions and others (at patients' request) to view the data.

The kit is assembled at the [redacted] (b) (4) This packaging site was found to be acceptable.

Tablets: The tablet component of the combination products consists of aripiprazole tablets (2, 5, 10, 15, 20 and 30 mg strengths) embedded with an IEM sensor. The composition of the proposed tablets is qualitatively and quantitatively identical to Abilify

Reference ID: 4185545

tablets, except for the addition of the IEM sensor. In addition, the amount of colorant is (b) (4) to distinguish it from Abilify tablets.

The tablets are manufactured by Otsuka in Tokushima, Japan. The site underwent a preapproval inspection and was found to be acceptable. (b) (4)

(b) (4)

The tablets then undergo release and stability testing. Stability data support the proposed 36 month expiry period. The drug product specification is identical to that of Abilify tablets – with the exception of the addition of a test for the functionality of the IEM – called the DFAT test.

(b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 4185545

(b) (4)

[redacted] This was found to be acceptable.

Patch: All information for the patch was cross referenced to cleared 510k applications. Two versions of the patch are described in the application. The RP4 version was used through most of development and worked with the (b) (4) version of the IEM. The DW5 version is the proposed commercial version and was designed to work with the commercial (b) (4) version of the IEM. The patch is manufactured for Proteus at Avery Dennison Corp, Mentor, OH. The site underwent a preapproval inspection and was found to be acceptable.

Software/Firmware: The software on the app (b) (4) [redacted] processes this information for display on the phone. This 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 and found it adequate.

In Vivo Studies: A human factors study tested whether subjects could use the kit, including the patch and the app. This study was evaluated by DMEPA and found that only one out of 36 subjects successfully used the product. Two in vivo studies were completed to measure the accuracy of IEM detection and determine the data latency throughout the system. These were the Osmitter 316-13-206A and Osmitter 316-13-206B

Reference ID: 4185545

studies. Osmitter 206A used the older [(b) (4)] IEM. The results found poor detectability (ca 75%) and long lag times. Osmitter 206B study is more relevant to this application as it used the commercial [(b) (4)] IEM but in a placebo tablet. The results were generally better – out of 116 ingestions 4 were not detected and 7 took greater than 30 minutes to be detected. Therefore 10% of the ingestions were not detected within 30 minutes – the point in which the app reminds/instructs the patient to take a tablet.

CDRH Review: Luke Ralston evaluated the device performance sections of the application and found that "the bench testing and in vitro data has adequately quantified the performance of the device within the tablet *in idealized conditions*." However he found that the Osmitter in vivo studies "demonstrate that the Otsuka software – [(b) (4)] - has significant data latency that is not consistent with the IEM cleared under 510(k). Even under idealized study conditions a substantial fraction of patients will not receive positive detection confirmation [(b) (4)] This performance is **not adequate** to ensure safety and effectiveness for the intended use." Crystal Lewis and Viky Verna reviewed the application from a CDRH Office of Compliance perspective. They found the application acceptable from their perspective (review attached).

A. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: 2 (low solubility, high permeability). The absolute BA of Abilify® is ~87%.
   - Drug Product: rapid to very rapid dissolution at pH 1.2 and 4.5, but not pH 6.8

2. Biowaivers/Biostudies
   - Biowaiver Request: Granted per 21 CFR 320.22(d)(4), based on meeting the following criteria: (1) the reformulated product is identical, except for different color, flavor, or preservative that could not affect the relative bioavailability (BA) of the reformulated product to another product for which the same manufacturer has obtained approval, (2) the BA of the reference product has been measured, and (3) both drug products meet an appropriate *in vitro* test approved by the FDA.

From a Biopharmaceutics perspective, NDA 207-202 for aripiprazole + IEM is recommended for APPROVAL. The Applicant's biowaiver request is granted. The following dissolution method and acceptance criterion agreed upon with the Applicant should be used for the routine QC of the tablets at batch release and during stability testing:

Reference ID: 4185545

USP Apparatus	Spindle Rotation	Medium/ Volume/Temperature	Acceptance Criterion
2, Paddle	60 rpm	900 mL pH 1.2 USP Buffer (degassed), at 37 ± 0.5 °C	Q = (b) (4) % at 30 min

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature: Recommend CR.

David J. Claffey -S

Digitally signed by David J. Claffey -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300225565, cn=David J. Claffey -S
Date: 2016.04.21 20:19:20 -04'00'

123 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4185545

(b) (4)

[redacted]

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

This Biopharmaceutics review focuses on the evaluation of (1) the biowaiver request for all the proposed strengths of aripiprazole + IEM (Ingestible Event Marker) tablets, (2) the proposed dissolution method and acceptance criterion, and the (3) adequacy of the bridging information provided for the primary stability and the proposed commercial batches of the aripiprazole + IEM tablets. Otsuka received approval for 2, 5, 10, 15, 20, and 30 mg Abilify® (aripiprazole) tablets in November 2002. More recently, Otsuka developed the same strengths of IEM-embedded aripiprazole tablets for the same indications; the IEM -- along with the wearable patch sensor and medical software application - is said to allow for the [redacted] (b) (4) to aripiprazole (patient compliance). Like Abilify™ oral tablets, the proposed drug-device combination product is an immediate release formulation of aripiprazole. Although aripiprazole exhibits low solubility at pH >5, the absolute bioavailability of Abilify® tablets is approximately ~87%.

11. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Yes.

Reference ID: 4185545

As proposed, the FDA dissolution method already approved for Abilify® (aripiprazole) tablets is acceptable for the routine QC testing of aripiprazole + IEM tablets. At the time of the NDA review of the Abilify® tablets, the parameters of this dissolution method were determined to be optimal, (b) (4)

The Applicant is (b) (4) , based on the cumulative dissolution data provided in this NDA for the primary registration lots and the representative proposed commercial lots of aripiprazole + IEM tablets at batch release and during 24 months of long-term stability storage at 25 °C/60%RH, the dissolution acceptance criterion should be "Q = (b) (4)% at 30 minutes".

Therefore, the following dissolution method and acceptance criterion are recommended for the routine QC testing of the proposed aripiprazole + IEM tablets at batch release and stability testing.

USP Apparatus	Spindle Rotation	Medium/ Volume/Temperature	Acceptance Criterion
2 (Paddle)	60 rpm	900 mL pH 1.2 USP Buffer (degassed), at 37 ± 0.5 °C	Q = (b) (4)% at 30 min

a. Is the Applicant's biowaiver request acceptable?

Yes.

The Applicant cited 21 CFR 320.22(d)(4) which states that the *in vivo* [bioavailability or bioequivalence] data requirement may be waived if the drug product is a reformulated product that is identical, except for a different color, flavor, or preservative that could not affect the bioavailability of the reformulated product to another drug product for which the same manufacturer has obtained approval and (i) the bioavailability of the other product has been measured; (ii) both drug products meet an appropriate *in vitro* test approved by FDA.

To support the request to waive *in vivo* BA/BE studies for all proposed strengths of the aripiprazole + IEM tablets, the following information were provided for FDA review: (1) a side-by-side comparison of the chemical compositions of all strengths of the aripiprazole + IEM tablet and all the approved strengths of Abilify™ oral tablets (Tables 38.1-1 and 38.1-2), (2) comparative *in vitro* dissolution profiles in three pH media (pH 1.2, 4.5, and 6.8; 50 rpm) and using the FDA approved pH 1.2 [60 rpm] dissolution QC method for Abilify® tablets, and (3) data supporting the functionality of the IEM device and the time to trigger the signal to the computing device (e.g., as part of routine dissolution testing).

Reference ID: 4185545

Table 38.1-1. Quantitative composition of the proposed commercial aripiprazole + IEM tablets

Ingredient		2-mg tablet		5-mg tablet		10-mg tablet		15-mg tablet		20-mg tablet		30-mg tablet	
		mg	%w/w	mg	%w/w	mg	%w/w	mg	%w/w	mg	%w/w	mg	%w/w
Aripiprazole	NC	(b) (4)											
Lactose monohydrate	NF												
Starch (Corn)	NF												
Microcrystalline cellulose	NF												
Hydroxypropyl cellulose	NF												
Magnesium stearate	NF												
(b) (4)	USP												

Total weight (Aripiprazole tablet)	---	95.0		95.0		95.0		95.0		189.76		285.0	
IEM[3]	NC	1		1		1		1		1		1	
Total Aripiprazole+IEM tablet target weight (Combination product)[4]	---	99.0		99.0		99.0		99.0		193.76		289.0	
Tablet Color and Shape	---	Pale green, modified rectangular		Pale blue, modified rectangular		Pale pink, modified rectangular		Pale yellow, round		White to pale yellowish white, round		Pale pink, round	

NC: Non Compendial, NF: National Formulary, USP: U.S. Pharmacopeia, q.s.: quantity sufficient

1 (b) (4)

2

3 (b) (4)

4

Source: Table 3.2.P.1-1

Table 38.1-2. Composition of the current Abilify® tablets

Ingredient		2-mg tablet		5-mg tablet		10-mg tablet		15-mg tablet		20-mg tablet		30-mg tablet	
		mg	%w/w	mg	%w/w	mg	%w/w	mg	%w/w	mg	%w/w	mg	%w/w
Aripiprazole	NC	(b) (4)											
Lactose monohydrate	NF												
Starch (Corn)	NF												
Microcrystalline cellulose	NF												
Hydroxypropyl cellulose	NF												
Magnesium stearate	NF												
(b) (4)	USP												

Total (Tablet composition)	---	95.0		95.0		95.0		95.0		189.76		285.0	
Tablet Color and Shape	---	Green, modified rectangular		Blue, modified rectangular		Pink, modified rectangular		Yellow, round		(b) (4) (b) (4) white round		Pink, round	

NC: Non Compendial, NF: National Formulary, USP: U.S. Pharmacopeia, q.s.: quantity sufficient

1 (b) (4)

2

Source: Table 2.3.P.1-3

The qualitative and quantitative composition of the drug component of the Applicant's drug-device combination tablet is identical to that of the currently marketed Abilify® tablets, with the exception of (b) (4) colorant and the debossing letters (to allow for visual distinction between the approved and the IEM-embedded tablets of aripiprazole,

Reference ID: 4185545

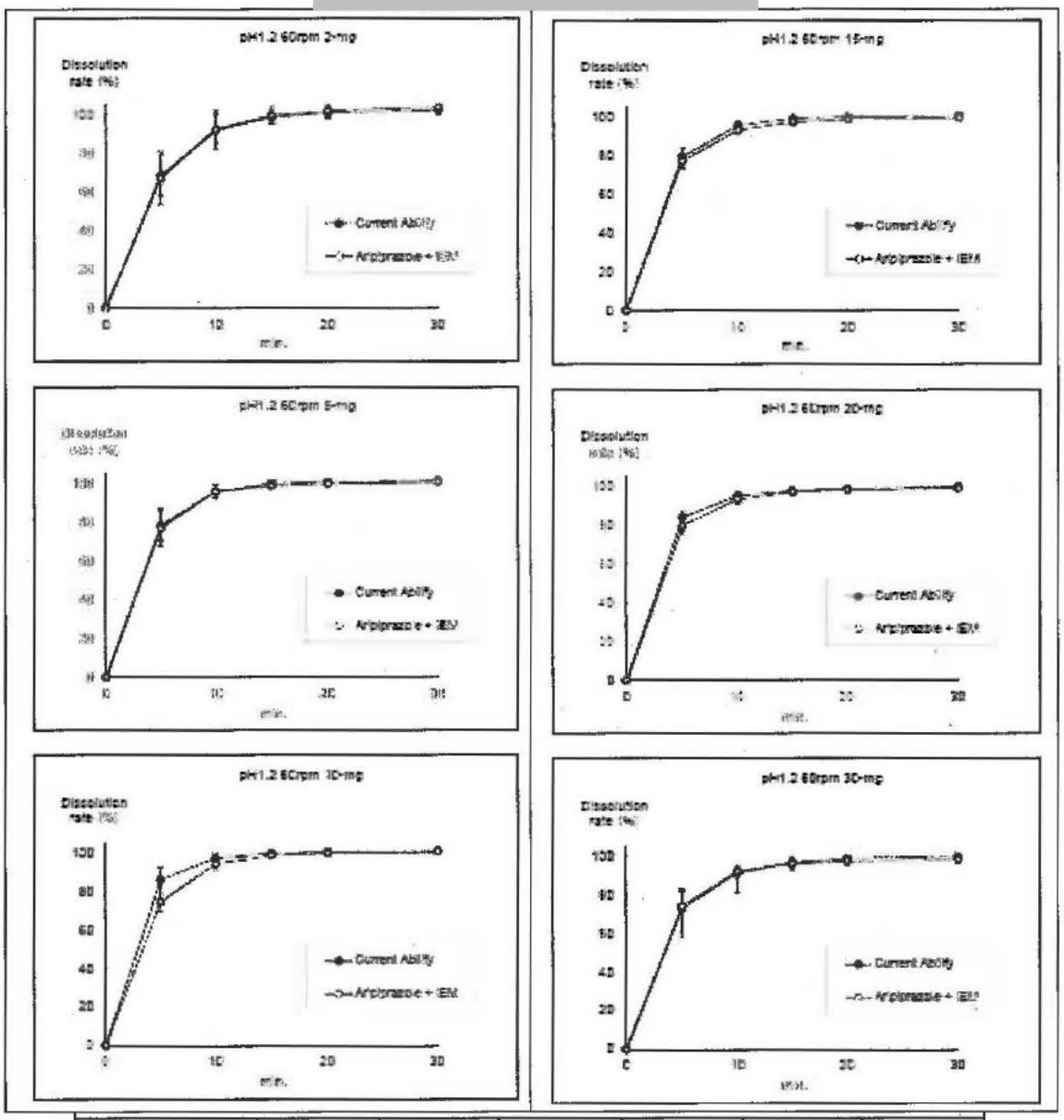
considered less than a Level III process change per the SUPAC Guidance). Per the Applicant, the manufacturing methods and operating principles are comparable between Abilify® tablets and the proposed commercial aripiprazole + IEM tablets.

The *in vitro* dissolution profiles of the proposed commercial aripiprazole + IEM versus the corresponding strengths of Abilify® tablets using the FDA dissolution QC method approved for Abilify® tablets are reproduced below (Figure 38-1.1); f_2 analysis was not needed due to very rapid dissolution (i.e., >85% dissolved in 15 minutes) of both the test and the reference tablets. Additionally, comparative *in vitro* dissolution data were provided for all the proposed strengths of aripiprazole + IEM tablets (three primary stability lots per strength) versus all the approved strengths of Abilify™ oral tablets, at pH 1.2, 4.5, and pH 6.8, as well as using the FDA dissolution QC method for Abilify® tablets. Whenever f_2 calculation was appropriate, the values were > 50 (Table 38-1.3), suggesting significant dissolution profile comparability.

Figure 38-1.1
Comparative Dissolution Profiles for Proposed Commercial Aripiprazole + IEM Tablets versus current Abilify® Tablets (using Approved Dissolution QC Method for Abilify® Tablets)

Reference ID: 4185545

Best Available Copy



Sample tablets	2-mg	5-mg	10-mg	15-mg	20-mg	30-mg
Abilify	4K90YUF1	4J00YUE2H	4L77YUD1 H	4I77YUC2H	4K83YUB1	4L80YUA1 H
Commercial tablet[1]	14K95A002	14K95A005	14K95A010	14K95A015	14K95A020	14K95A030

[1] one (b) (4) colorant batch from each strength for aripiprazole+IEM tablets

Table 38-1.3
Profile similarity factor (f_2) values calculated from the in vitro dissolution study comparing the primary stability batches (3 lots per strength) of the aripiprazole + IEM tablets versus current Abilify® tablets

Reference ID: 4185545

Table 3.2.P.2.2.3-3 f_2 Values in Comparative Dissolution Study

Strength	pH Media	f_2 Calculated		
		Lot A	Lot B	Lot C
2 mg	1.2	NA	NA	NA
	4.5	65	96	85
	6.8	93	81	82
5 mg	1.2	NA	NA	NA
	4.5	88	84	76
	6.8	88	87	85
10 mg	1.2	NA	NA	NA
	4.5	68	77	71
	6.8	98	97	99
15 mg	1.2	68	80	64
	4.5	76	79	69
	6.8	99	99	100
20 mg	1.2	NA	NA	NA
	4.5	90	84	81
	6.8	99	99	97
30 mg	1.2	NA	NA	NA
	4.5	81	97	87
	6.8	100	100	100

NA: f2 was not calculated as dissolution rate at 15 minutes was above 85%

Source: Table 3.2.P.2.2.3-3

Reviewer's Assessment:

The drug component of the aripiprazole + IEM tablets is essentially of the same chemical composition as the approved Abilify™ tablets. Because the Applicant was required to demonstrate that the embedded IEM device does not negatively impact the release of aripiprazole from the oral tablet, it is justified to use (per FDA advice) the already approved FDA dissolution method for Abilify® tablets in the comparative *in vitro* studies. Additional dissolution method development studies specific for the drug-device combination tablets were not warranted. The validation parameters of the dissolution method were satisfactory.

Based on the results of these *in vitro* comparative dissolution studies, it can be concluded that the addition of the IEM to the aripiprazole tablet (the same or essentially the same as that of the approved Abilify® tablets) does not result in a change in *in vitro* drug dissolution profile. Therefore, from a Biopharmaceutics perspective, the Applicant's biowaiver request for all strengths of the proposed aripiprazole + IEM tablet is granted.

Of note, per FDA advice, the Applicant conducted human factors studies to establish the safe and effective use of the proposed drug-device combination product. Specifically, the safety of aripiprazole + IEM oral tablets (10, 15, 20 or 30 mg) administered once daily for 8 weeks to schizophrenia patients was investigated in Phase 2a Study 316-14-220. Refer to the Medical Review for the evaluation of the findings of these human studies.

This CDER Biopharmaceutics reviewer defers to the CDRH reviewer regarding the evaluation of IEM functionality in the proposed drug-device combination tablet. Based on the dissolution information of primary stability and proposed commercial batches at release and during 24 months of long-term stability (25 °C/60%RH) storage, the minimum cumulative amount of drug release at 30 minutes for individual units is (b) (4)%. Thus, the FDA recommended acceptance criterion of Q = (b) (4)% at 30 minutes is

Reference ID: 4185545

reasonable for the proposed aripiprazole + IEM tablets.

On 01/21/2016, the following information request was sent to the Applicant:

Based on our review of cumulative in vitro dissolution data generated for all strengths of the proposed aripiprazole + IEM tablet, the recommended acceptance criterion for routine QC testing of all tablet strengths is ***"Q = (b)(4)% at 30 minutes."*** *Provide a revised drug product specification table accordingly.*

It is pertinent to mention that the recommended dissolution acceptance criterion (for aripiprazole + IEM tablets) is also adequate for Abilify® tablets; we therefore strongly suggest that you consider revising the dissolution acceptance criterion for Abilify® tablets to "Q = (b)(4)% at 30 minutes".

In response to the 01/21/2016 Information Request, the Applicant agreed to (b)(4) the dissolution specification for the aripiprazole + IEM tablet to "Q = (b)(4)% at 30 minutes", and update the relevant NDA sections including the long-term stability protocol. With respect to Abilify®, the Applicant committed to review the dissolution data for the commercial batches produced to date; any change in the dissolution acceptance criterion will be provided under NDA 21-436 as a reportable change in the next NDA Annual Report. The Applicant's response to the Biopharmaceutics Information Request is adequate.

12. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Yes.

In vitro dissolution studies were conducted by the Applicant to bridge several aripiprazole tablet formulations, namely, (1) the approved Abilify® tablets, (2) the original aripiprazole + IEM tablets (used in the primary stability studies and which have exactly the same drug product composition including tablet color as the current Abilify® tablets), and (3) the proposed commercial aripiprazole + IEM tablets (manufactured in the proposed commercial manufacturing site using the proposed production equipment, and are only different from the primary stability batches in terms of (b)(4) colorant and debossing letters used). See Tables 39-1 and 39-2 for the lot numbers of the aripiprazole + IEM tablets with *in vitro* dissolution profile data compared to Abilify® tablets. As discussed above, the *in vitro* dissolution profiles of the Applicant's three tablet formulations of aripiprazole at batch release were comparable.

Table 39-1. Primary stability lots of aripiprazole + IEM tablets compared to Abilify® tablets

Reference ID: 4185545

Sample tablets		2-mg	5-mg	10-mg	15-mg	20-mg	30-mg
Abilify		3D77595	3C73YUE3 H	3C84YUD3 H	3C89YUC4 H	0H94YUB1	3C77YUA3 H
Primary batch	Lot A	13A84A002 A	13C87A005 A	13B73A010 A	13A84A015 A	13C87A020 A	13B73A030 A
	Lot B	13A84A002 B	13C87A005 B	13B73A010 B	13A84A015 B	13C87A020 B	13B73A030 B
	Lot C	13A84A002 C	13C87A005 C	13D70A010	13D70A015	13C87A020 C	13B73A030 C

Source: Table 3.2.P.2.2.3-1

Table 39-2. Proposed commercial lots of aripiprazole + IEM tablets compared to Abilify® tablets

Sample tablets	2-mg	5-mg	10-mg	15-mg	20-mg	30-mg
Abilify	4K90YUF1	4J00YUE2H	4L77YUD1 H	4I77YUC2H	4K83YUB1	4L80YUA1 H
Commercial tablet[1]	14K95A002	14K95A005	14K95A010	14K95A015	14K95A020	14K95A030

[1] one (b) (4) colorant batch from each strength for aripiprazole+IEM tablets

Source: Table 3.2.P.2.2.3-2

Reviewer's Assessment:

In the minutes of the Type C Meeting held on February 10, 2014, the FDA agreed that based on data from previous submissions to the IND, an *in vivo* BE trial between Abilify® and aripiprazole + IEM tablets is not needed. Additionally, per prior agreement with FDA (in a Type B meeting held August 14, 2014), *in vitro* comparative dissolution testing using the QC method approved for Abilify® tablets was determined to be a suitable strategy to support the (b) (4) colorant and debossing changes in the aripiprazole + IEM tablets.

Based on the results of *in vitro* dissolution studies, the (b) (4) in colorant and the difference in debossing letters, plus the insertion of the IEM into the aripiprazole tablet (that has the same chemical composition as the Applicant's Abilify® tablets), did not result in significant alterations in *in vitro* aripiprazole dissolution profiles.

Of note, the reported maximum *in vitro* disintegration times for the individual aripiprazole + IEM tablets included in the primary stability batches at release and during 24 months of long-term storage at 25 °C/60%RH were NMT (b) (4) minutes, and NMT (b) (4) minutes, respectively. Currently, disintegration time is to be collected for the aripiprazole + IEM tablets for informational purposes only, which [per the Applicant] is also the case for Abilify® tablets. This CDER Biopharmaceutics Reviewer defers to the CDRH Reviewer regarding the need to include disintegration time in the Drug Product specifications of the aripiprazole + IEM tablets as a means to ensure IEM functionality.

Reference ID: 4185545

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Recommendation and Signature:

From a Biopharmaceutics perspective, NDA 207-202 aripiprazole + IEM Tablet is recommended for APPROVAL. The following dissolution method and acceptance criterion should be implemented for the routine QC of the tablets at batch release and during stability testing.

USP Apparatus	Spindle Rotation	Medium/ Volume/Temperature	Acceptance Criterion
2, Paddle	60 rpm	900 mL pH 1.2 USP Buffer (degassed), at 37 ± 0.5 °C	Q = (b) (4)% at 30 min

1/22/2016

Gerlie Gieser, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Peroducts/OPQ

Secondary Review Comments and Concurrence:

I concur with Dr. Gieser's review and approval recommendation for NDA 207-202.

1/31/2016

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Peroducts /OPQ

Reference ID: 4185545

ASSESSMENT OF MICROBIOLOGY

1. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Reviewer's Assessment: Satisfactory

The firm proposes microbial limit test for long term stability at the following time points: 0 month, 12 months, 24 months, 36 months, and 48 months. The microbial limit test would be 'for information only'. The test items would be TAMC, TYMC, and *Escherichia coli.* The test method is USP. Stability data for 12 months stability at long term storage, for all strengths, has shown that the samples are not susceptible to microbial growth.

The proposed product has the same materials as the approved commercially available product, Abilify tablets, under NDA 021436. The only addition to this product is the addition of an IEM (b) (4). This addition, along with the manufacturing process associated with IEM addition, is not expected to introduce microbial burden into this proposed product. The applicant also will be conducting microbial limit test on a yearly basis for tablets stored at long term stability conditions, but for information only. Given the history of Abilify and the low risk of microbial burden posed by the introduction of the IEM, this appears acceptable.

2.3.P.7 Container/Closure System

2. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Reviewer's Assessment: Satisfactory

For the proposed container/closure system of the drug product, please refer to question 23 and the assessment provided by the drug product reviewer (Mariappan Chelliah).

Reference ID: 4185545

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

3. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Lactose monohydrate is sourced from [redacted] (b) (4) is not included as source of BSE risk in the list of United States Department of Agriculture-recognized animal health status of countries/regions regarding specific livestock or poultry diseases, or acceptable commodities.

Reference ID: 4185545

(b) (4)

[redacted]

Reviewer's Assessment: Satisfactory

No materials of biological origin or derived from biological sources are used in the manufacture of the drug product.

Lactose monohydrate is derived from [redacted] (b) (4) and is not likely to present any risk of TSE contamination. The firm has also provided a declaration from [redacted] (b) (4) who supplies the lactose monohydrate. In addition, the same excipients, with the exception of the IEMs, are used in the approved product Abilify, which has been approved under NDA 021436.

Reference ID: 4185545

4. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Reviewer's Assessment: Satisfactory

No materials of biological origin or derived from biological sources are used in the manufacture of the drug product.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

The NDA is Approvable from a microbiology perspective.

Hang Guo
March 30, 2016

Secondary Review Comments and Concurrence:
I concur
Sharmista Chatterjee
April 8, 2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

5. Is the applicant's claim for categorical exclusion acceptable?

Reference ID: 4185545

6. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:
Otsuka has requested categorical exclusion from environmental assessment for the following reasons:

1) Active Moiety: The consumption of aripipirazole in all dosage form in 2014 was less than (b) (4) kg. The projected maxium consumption is (b) (4) kg, if the Aripiprazole + IEM tablets area approved. Based on the consumption of (b) (4) kg per year, the *'expected introduction concentration'* (EIC) of the aripiprazole active moiety into the aquatic environment is (b) (4) ppb/day. This amount is below the NMT 1 ppb limit required for environmental assessment exemption under 21 CFR § 25.31(b). In addition, no extraordinary circumstance exist as per 21 CFR § 25.15(d).
2) IEM: The 510(k) cleared IEMs are exempted under 21 CFR § 25.34. The sponsor also cites Agency's response regarding the EA categorical exclusion in the pre-NDA meeting held on 05-May-2015 under IND 115927.

Reviewer's Assessment: Categorical exclusion may be granted

1) *Sponsor's proposal of EA for the active moiety under 21 CFR § 25.31(b) appears reasonable and therefore, it may be granted.*
2) *As part of the pre-NDA meeting, FDA has already agreed with the sponsor's claim that the device component is exempted from environmental analysis as per 21 CFR 25.34 (please refer to Q6 from the p-NDA meeting minutes).*

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

Categorical exclusion from the environmental analysis may be granted.

Mariappan Chelliah
24-Mar-2016

Secondary Review Comments and Concurrence: I concur.

Wendy I. Wilson-Lee

Reference ID: 4185545

Branch Chief (Acting), ONDP	01-APR-2016

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Not Reviewed

Several outstanding deficiencies remain to be resolved in this application. The clinical team decided that the labeling will not be reviewed in this cycle. Therefore, this reviewer did not review the CMC related sections of the labeling.

Mariappan Chelliah
23-Mar-2016

Secondary Review Comments and Concurrence: I concur.

Wendy I. Wilson-Lee
Branch Chief (Acting), ONDP 01-APR-2016

Reference ID: 4185545

FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
Office of Device Evaluation

Date:	March 4, 2016	**Branch:**	CDDB
To:	Simran Parihar, Pharm.D David Claffey, Ph.D.	**Division:**	DCD
Reviewer:	Luke Ralston, Biomedical Engineer		
File:	NDA 207202		
Applicant:	Otsuka Pharmaceutical		
Type:	New Drug Application (NDA) – Combination Product		
Linked file:	DMF 029332		

Recommendation: Not Approvable [CDER: Complete Response (CR)]

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Supervisor Concurrence	

I. Overview and Background

I have been asked to provide a consulting review of device information submitted by Otsuka Pharmaceutical Development & Commercialization, Inc. for combination product Aripiprazole + IEM product. The following sections were reviewed:

3.2.P.2.2.1	Formulation Development
3.2.P.2.2.3	Physiochemical and Biological Properties
3.2.P.5.2.7	IEM Activation Test (DFAT)
3.2.P.8.3.6	Data tables for Long-term stability Studies
SN0013	Response to CMC Information Request 02NOV2015

Validation Report for IEM Activation Test (Method No.: P20-031-TUD-002)
1/11/2016 Amendment to DMF 029332
2016-01-21 Aripiprazole + IEM CMC FDA Response

The IEM (Ingestible Event Marker) device is a 510(k)-cleared device manufactured by Proteus Digital Health. Proteus Health has also submitted a Drug Master File (DMF 029332) for their Ingestible Event Marker (IEM), (b) (4) . Several deficiencies were also found in the DMF and are noted in this memo when applicable.

Reference ID: 4185545

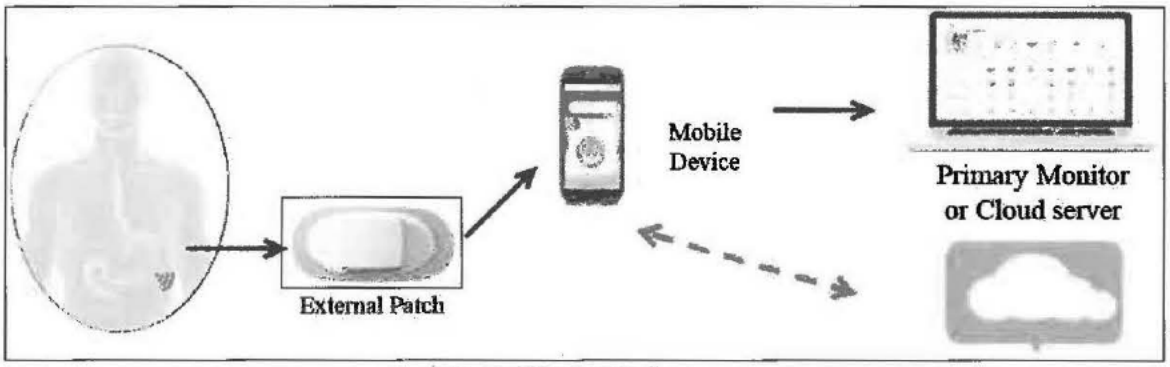
Information Requests (IR) were sent to the sponsor on October 23, 2015, December 29, 2015, and February 12, 2016.

II. Device Description:

This New Drug Application (NDA) requests approval for the TRADEMARK system and the proposed label claim: (b) (4) to aripiprazole and is indicated for the treatment of adults with:

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

TRADEMARK is composed of distinct components: (1) the Drug-device Combination (aripiprazole + IEM, which is the investigational product); (2) the Proteus Patch; (3) the Patient Component (app) of the Otsuka Medical Software, (4) the Cloud-based Server; and (5) the Web Portals of the Otsuka Medical Software. The components of TRADEMARK are illustrated in the Figure below.



TRADEMARK System

NOTE: Although the sponsor attempts to describe the Proteus MDDS and the Patient Component (app) as separate components of the system, they both run on the patient's mobile device so have been reviewed as one component.

The Patient Component (app) of the Otsuka Medical Software, which resides on a paired mobile computing device, receives data from the Proteus software also installed on the mobile device. The mobile device transmits data via cellular or Wi-Fi connectivity to the Otsuka Cloud-based Server. The Patient Component (app) of the Otsuka Medical Software has both automatic and optional features; the automatic features include:

- Registration of aripiprazole + IEM ingestion (i.e., after the ingestion of aripiprazole +IEM, the IEM is activated in the stomach, communicates with the Patch, which then registers the IEM's ingestion date and time on the Patient Component [app]);

Reference ID: 4185545

- [redacted] (b) (4)
- Daily, weekly, and monthly views of medication adherence behavior are automatically available for review by the patient in the Patient Component (app) of the Otsuka Medical Software;
- In addition, these [redacted] (b) (4) data are automatically transmitted to the Otsuka Cloud-based Server for processing and display on the HCP Web Portal of the Otsuka Medical Software.

Optional features of the Patient Component (app) of the Otsuka Medical Software include the options for the patient:

- To share [redacted] (b) (4) data with his/her caregiver;
- To register mood and rest quality, which can be reviewed and, if elected, shared with the patient's HCP and/or caregiver;
- To share Patch-registered activity and rest data with the patient's HCP and/or caregiver.

The Proteus system has been cleared using the product code OZW under the following 510(k) submissions:

- K113070/DEN120011
- K131009
- K131524
- K133263
- K150494

Aripiprazole + IEM tablets (2, 5, 10, 15, 20 and 30 mg strengths) are developed as drug-device combination product. [redacted] (b) (4)

(b) (4)

4 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 4185545

III. Shelf Life/Stability

Some shelf-life/stability data submitted in Section 2.3.S.7 of the DMF; however, it only included the [redacted] (b) (4) design and did not contain any drug component.

REVIEWER COMMENT: I defer to the CMC lead review for determination of adequate shelf life/stability of the combination Aripiprazole + IEM.

IV. Biocompatibility

No biocompatibility information is provided in the NDA.

V. Software/Firmware

A combined software consult was provided by Nathalie Yarkony (CDRH/ODE/DCD/CDDB) and Linda Ricci (CDRH/ODE). The review identified 11 deficiencies that were conveyed to the sponsor in a February 12, 2016 IR letter. Otsuka responded with additional information on February 24, 2016. The combined software review is attached to this memo for reference.

REVIEWER COMMENT: All software deficiencies were resolved and the information provided by Otsuka is adequate. NOTE: [redacted] (b) (4)

VI. EMC & Electrical, Mechanical, and Thermal Safety

During the classification of ingestible sensors in 2012, CDRH identified 8 risks to health shown in the table below:

Identified Risks from 2012 classification	Mitigations
Adverse Tissue Reaction	Biocompatibility
Systemic Toxicity	Battery and IC materials
Electromagnetic Incompatibility	VCC transmission
Electrical Safety	Battery design Low-power transmission (heating and tissue stimulation)
Electrical/Mechanical failure	Battery and IC design
Failure to mark event	Animal and Clinical testing
Failure to excrete	Animal and Clinical testing
Usability	Human Factors testing

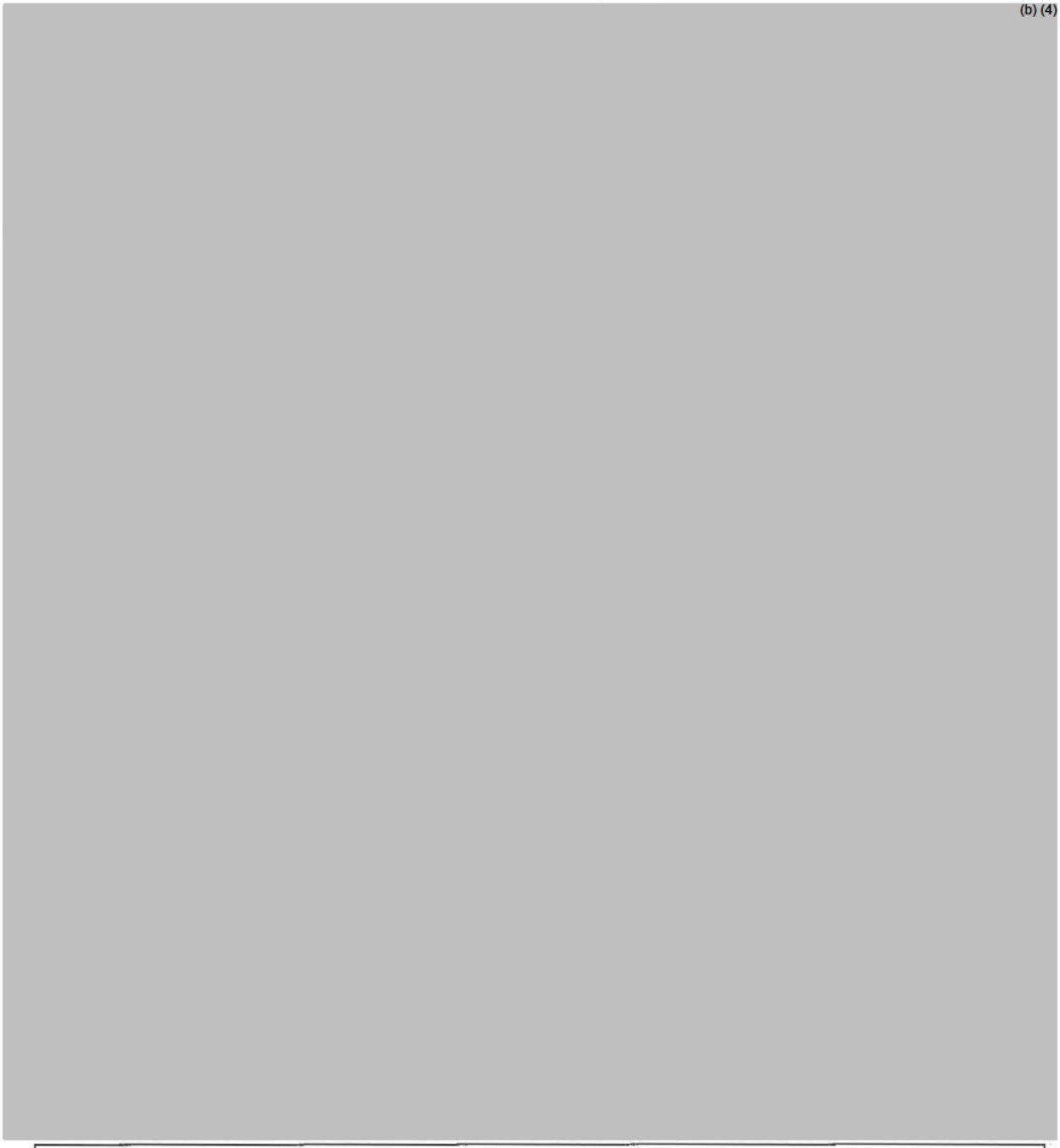
Mechanical Failure

[redacted] (b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 4185545

(b) (4)



REVIEWER COMMENT: EMC & Electrical, Mechanical, and Thermal safety are adequate.

VII. Manufacturing

Reviewed by CDRH Office of Compliance and not included in this memo.

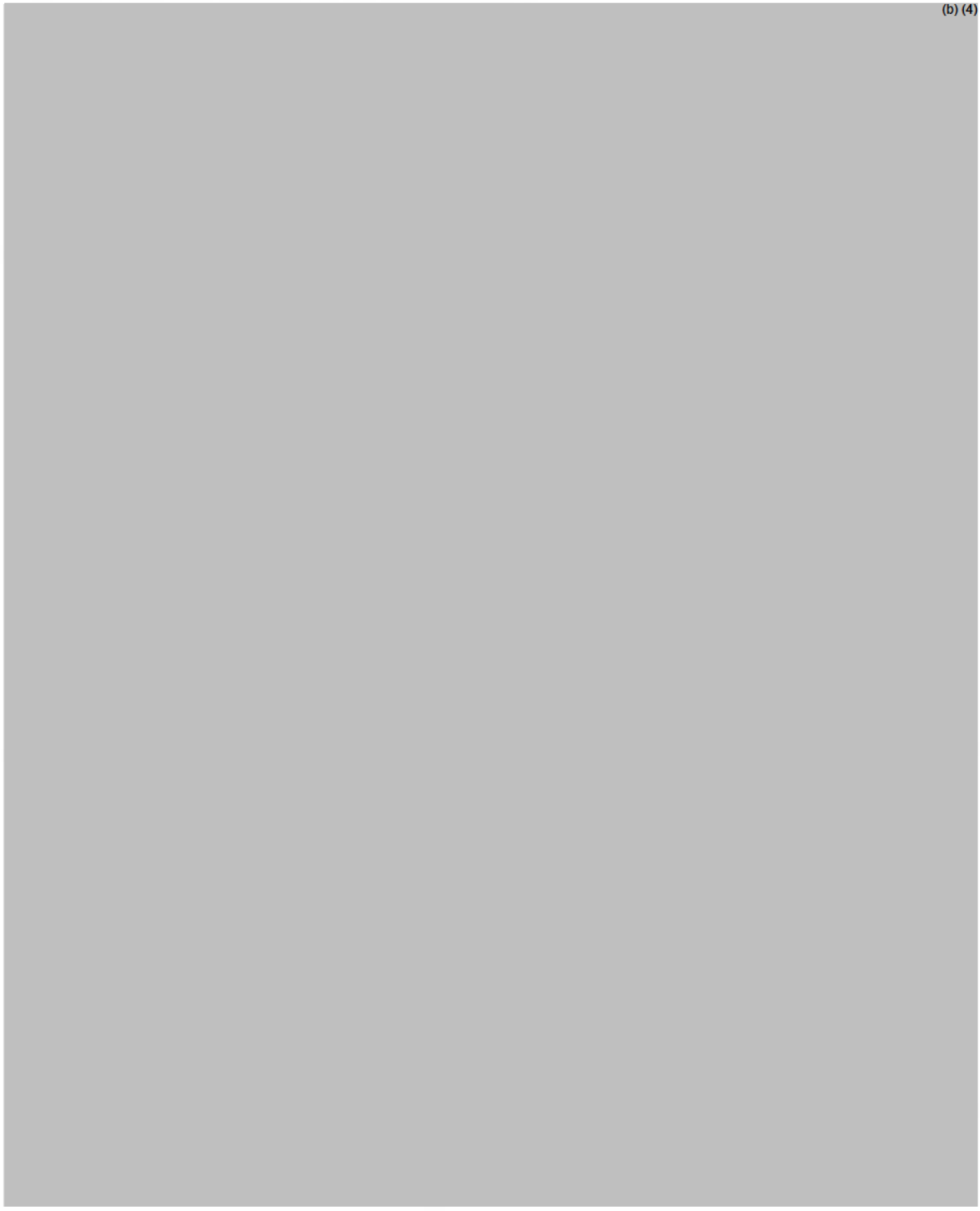
VIII. Device Verification and Validation

Bench Testing

Reference ID: 4185545

The bench testing for this product focused on IEM activation after ingestion and IEM functionality. Since activation is dependent upon exposure to the patient's stomach acid, the sponsor performed dissolution studies to demonstrate proper activation. The sponsor also conducted separate testing to demonstrate IEM functionality after the new manufacturing and storage conditions required by the drug substance.

(b) (4)



Reference ID: 4185545

1) Dissolution performance
To confirm that insertion of the IEM had no impact on physicochemical and biological properties of the proposed combination product, two comparative dissolution studies were conducted. It is noted that IEM activation depends more on tablet disintegration than dissolution so this CDRH review focused only on data relevant to disintegration.

The first comparative dissolution study in three different dissolution media, pH 1.2, 4.5 and 6.8, were conducted to demonstrate that the proposed Aripiprazole + IEM would behave equivalently to commercially available Abilify tablets. The second comparative dissolution study was conducted to demonstrate comparability of the final Aripiprazole + IEM formulation which will use (b) (4) colorant in order to distinguish it from current Abilify tablets.

The sponsor concludes that "the presence of an IEM has no adverse impact on the dissolution performance (drug release) from the proposed combination tablet and thus the same dissolution method with the same limit for commercial Abilify tablets (Q= (b) (4)% in 30 minutes) is proposed for this combination product."

These studies did not provide any information about tablet disintegration and the acceptance criteria of Q= (b) (4)% within 30 minutes raised concerns about (b) (4)

NOTE: The results summarized below only include the (b) (4) design with no data submitted for the (b) (4) design.

	2mg	10mg	15mg	30mg
0 months	1:38 – 1:54	1:24 – 1:40	2:30 – 3:00	2:49 – 3:23
3 months	1:26 – 3:03	1:18 – 2:48	2:04 – 2:23	2:54 – 3:31
6 months	1:50 – 3:44	1:30 – 1:48	2:04 – 2:59	3:32 – 3:51
9 months	1:30 – 2:13	1:08 – 2:24	1:57 – 2:14	2:31 – 4:02
12 months	1:33 – 2:16	1:43 – 2:05	2:01 – 3:17	3:04 – 3:48
18 months	1:32 – 1:59	1:06 – 1:41	1:35 – 1:51	2:48 – 6:49

Distribution of Tablet Disintegration Times (minutes:seconds)

(b) (4)

Mean and Minimum IEM Lifetime Measurements (seconds)

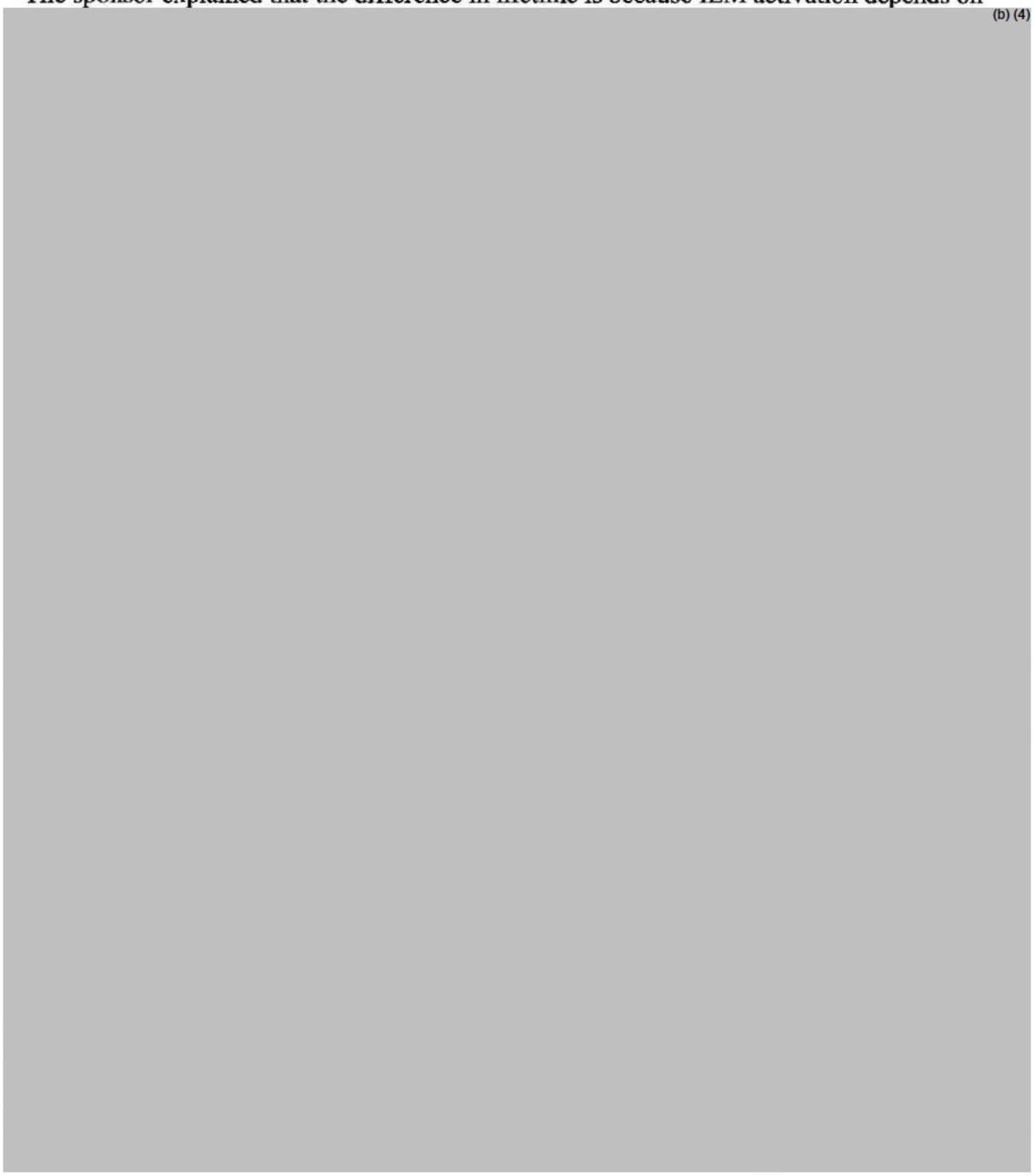
Reference ID: 4185545

IEM + Placebo vs. IEM + Aripiprazole

Section 3.2.P.2.2.1.3 uses DFAT to compare currently cleared IEM + placebo tablet to the proposed IEM + Aripiprazole at all dosages of the API. The results show a slightly longer IEM lifetime in the IEM + Aripiprazole compared to placebo. The smallest difference was in the 2mg Aripiprazole formulation which showed an approximate 50% greater lifetime of the Aripiprazole batches. The mean IEM lifetime was progressively longer for each of the 5mg, 10mg, 15mg, 20mg, and 30mg formulations.

The sponsor explained that the difference in lifetime is because IEM activation depends on

(b) (4)



Reference ID: 4185545

(b) (4)

CDRH COMMENT: The bench testing and in-vitro data has adequately quantified the performance of the device within the tablet *in idealized conditions*. The sponsor has conducted clinical testing to demonstrate in-vivo performance.

Animal Testing
No animal testing was included in this NDA.

A number of animal studies were submitted in DMF 029332. These were for studies that had been performed for prior product development and partly in support of 510(k) submissions for the stand-alone IEM reviewed by CDRH. Dr. Annabelle Crusan provided a consulting review for the DMF and identified 5 deficiencies which were sent to Proteus. In a 2/8/16 teleconference, Proteus acknowledged the deficiencies in the animal testing but does not plan to submit the requested information. This issue is being resolved separately but is not the basis for disapproval since Otsuka submitted clinical testing as discussed in the next section of this memo.

Clinical Testing
Given the difference in performance between the IEM + placebo and IEM + Aripiprazole in bench testing, Otsuka conducted 2 clinical studies under their OSMITTER protocol.

OSMITTER 206A – validate in-vivo performance of IEM (b) (4) version) + placebo and IEM (b) (4) version) + Aripiprazole combination
OSMITTER 206B – validate in-vivo performance of IEM ((b) (4) version) + placebo

The purpose of these studies was twofold:

1. Validate IEM detection
2. Validate data transmission capabilities of all system components

Reference ID: 4185545

OSMITTER 206A

This trial was conducted to determine the accuracy of IEM detection by completing a series of patch applications and IEM ingestions in the clinic. The study subjects were not responsible for any aspect of patch placement, pairing to the mobile device, data interpretation, or troubleshooting. Following placement of the patch by clinic staff, subjects ingested one IEM tablet approximately every 2 hours, for a total of 4 ingestions. The subjects ingested one 10-mg aripiprazole-embedded IEM (aripiprazole + IEM) tablet without food (Hour 0), one placebo-embedded IEM (placebo + IEM) tablet without food (approximately Hour 2), one placebo + IEM tablet with a high-fat meal (approximately Hour 4), and one placebo + IEM tablet without food (approximately Hour 6).

Results are shown in the table below:

Proportion of Subjects with Ingestible Event Marker Detection			
Timepoint	**Subject Ingestions**	**IEM Detected (%)**	**90% CI (%, %)**
Hour 0[a]	30	22 (73.3)	(57.0, 86.0)
Hour 2[b]	30	19 (63.3)	(46.7, 77.9)
Hour 4[c]	30	23 (76.7)	(60.6, 88.5)
Hour 6[b]	30	28 (93.3)	(80.5, 98.8)
Total	120	92 (76.7)	(69.4, 82.9)

a = aripiprazole + IEM without food; b = placebo + IEM without food; c = placebo + IEM 30 minutes after high-fat meal

This study has a number of limitations and discrepancies:

- Only t = 0 evaluated aripiprazole + IEM
- Only the (b) (4) version was used in this study
- At t = 0, 2, 4 detection is far below 97% historical average
- The study did not use final commercial-release versions of the patch or software

In an attempt to reconcile the poor performance of detection the sponsor conducted a post-hoc analysis of data transmission times. As shown in the table below, there was significant latency noted when sending data from the Proteus patch to the Proteus software application.

Transition	N	Mean	SD	SE of mean	Median	Min	Max
Patch to (b) (4)	94	21.019	30.149	3.110	2.680	0.723	114.428
(b) (4) to Otsuka app.	94	0.356	3.243	0.335	0.021	0.007	31.466

(b) (4)- proprietary Proteus software that receives data from the patch and inputs to Otsuka app software

Reference ID: 4185545

ISSUE: [redacted] (b) (4) [redacted]. The system did not meet this performance requirement.

OSMITTER 206B

As a result of the limitations and poor performance in the 206A study, Otsuka conducted the 206B study. The primary objective was to measure the accuracy of IEM detection using the placebo + IEM, and to evaluate the latency period between site-reported ingestion time and detection of the ingestion event by the Patch. Secondary objectives were to measure the latency period between the Patch detection of the ingestion event and transmission of the event in the Otsuka Cloud-based Server. The trial was conducted with the DW5 Proteus Patch (Patch) and Otsuka application (app) software version 1.5.2.

Proportion of Subjects with Ingestible Event Marker Detection			
Timepoint	**Subject Ingestions**	**IEM Detected (%)**	**95% CI (%, %)**
Hour 0	29	28 (96.6)	(82.2, 99.9)
Hour 2	29	26 (89.6)	(--, --)*
Hour 4	29	28 (96.6)	(82.2, 99.9)
Hour 6	29	29 (100)	(88.1, 100.0)
Total	116	111 (95.6)	

Overall detection accuracy improved in study 206B. Data latency also improved but still showed an extremely large distribution throughout time. It also did not include the time from tablet ingestion to IEM activation.

Time from IEM detection at patch to detection at Otsuka server					
Timepoint	**N**	**Mean (minutes)**	**SD**	**Min**	**Max**
Hour 0	28	7.5	23.7	0.5	123.2
Hour 2	26	10.3	20.9	0.5	80.8
Hour 4	27	6.2	10.4	0.4	31.2
Hour 6	29	6.2	8.9	0.8	29.7

REVIEWER COMMENT: Both the 206A and 206B studies demonstrate that the Otsuka software – [redacted] (b) (4) – has significant data latency that is not consistent with the IEM cleared under 510(k). Even under idealized study conditions a substantial fraction of patients will not receive positive detection confirmation [redacted] (b) (4) [redacted]. This performance is **not adequate** to ensure safety and effectiveness for the intended use.

Reference ID: 4185545

IX. Limitations and Deficiencies

1. You have submitted clinical testing in the OSMITTER 316-13-206A and 316-13-206B studies to measure the accuracy of IEM detection and determine the data latency throughout the MIND1 system. Both of these studies demonstrate that the system performance is substantially degraded by addition of the drug tablet. FDA identified the following deficiencies with these studies:
    a. OSMITTER 206A
        i. At least 26 (and possibly as many as 28) of the 120 ingested sensors were never detected by the Otsuka app; (b) (4)
        ii. For IEMs detected during the study, there was significant data latency observed which put time to detection beyond the default time of 30 minutes (b) (4)
        iii. This study was conducted with versions of the wearable sensor (patch) and software that are not representative of the final finished device
        iv. Only a single time point (Hour 0) evaluated the final finished combination of aripiprazole + IEM
        v. Only a single time point (Hour 4) evaluated the performance when taken with food
    b. OSMITTER 206B
        i. This study used only placebo + IEM for testing and did not include any data for the proposed combination aripiprazole + IEM
        ii. At Hour 0 and Hour 2 the mean time to detection plus standard deviation show that a significant fraction of patients will be at or slightly beyond the 30 minute default (b) (4)
        iii. Data latency between the Patch and Otsuka app is significantly longer (b) (4) (b) (4)

Reference ID: 4185545

Attachments

- 3/2/2016 Software Review from Nathalie Yarkony

Reference ID: 4185545

MEMO OF

SOFTWARE REVIEW

of a **Moderate** Level of Concern device

Otsuka

Date : March 2, 2016

To : Luke Ralston CDRH\ODE\DCD\CDDB

From : Nathalie Yarkony CDRH\ODE\DCD\CDDB

Sponsor : Otsuka Pharmaceutical Development & Commercialization, Inc.

Device Name : Otsuka Medical Software

Review summary

Device Description

The sponsor provided the following figure to describe his device. Three of the components are included with the device (marked in blue in the figure), however the sponsor only provided description for the App.



Software

1. Level of Concern –**Acceptable**
   Sponsor indicated a Moderate level of concern, despite the fact that he had answered yes to question #2 in the major level of concern determination table (p.36/2351). In order to rationalize his decision the sponsor noted that "*OMS remains a moderate level of concern as it is not for therapeutic intent. It displays medication-taking behavioral data of the patient. It does not diagnose, treat, cure, or mitigate any medical or physiological condition. It also does not control the delivery or determine the dosage of aripiprazole. Communication of data to HCP is unidirectional (ie, only to HCP). OMS does not provide treatment advice to the patient. HCP cannot initiate communications to the patient through OMS*".
   Based on this rational, and the Content of Premarket Submissions for Software Contained in Medical Devices dated May 11, 2005, we believe that the LOC is adequate.

2. Software Description –**Acceptable with information provided in IR**
   In the original review, the following concern was raised:

   > *The sponsor didn't provide a full SW description that will allow a complete review of the SW. It appears that there are 3 main components to the software: the patient application, the server, and the webportal. The sponsor provided the following table to describe the application functionality; however no information regarding the cloud-based server or the webportal was provided.*

   In the response to the interactive review, the sponsor provided links to the description of the information in the original application. In addition, they provided a summary of the functionality provided by the web portal and the server. The information provided is adequate

for this review. As described, the web portal and server functions will be considered MDDS as the patient app is the primary viewer.

Table 2.3-1 Summary of Otsuka Medical Software Functions on the User's Smartphone	
App Function	**Description**
Onboarding	☐ "Getting Started" video ☐ Add HCP (required to share ingestion data; sharing data for rest, activity, and mood are optional) ☐ Add caregiver, if applicable, and choose what information to share
Pill Ingestion	(b) (4) ☐ Pill status menu (b) (4)
Activity	☐ Activity (step count) displayed as line graph ☐ Definition of activity capture
Rest	☐ Number of hours of rest displayed ☐ Definition of rest capture ☐ Ability to enter quality of rest
Mood	☐ Ability to enter mood when desired ☐ Log of all mood states throughout the day (5 times total)
Patch Status	☐ Patch status screen to notify patient when patch replacement is needed or skin contact needs to be checked ☐ Step-by-step patch replacement instructions and assistance to ensure proper skin contact
Data Views	☐ Daily, weekly, and monthly view of pill ingestion, mood, rest, and

The original review also noted the following items that were missing from the description:

In addition, the software description should also include information on the following:
(b) (4)

The IR provided the appropriate information on these items. (b) (4)

The additional information provided answers the questions and issues raised in the Device Description (question 1 for the software).

3. Device Hazard Analysis –**Acceptable**

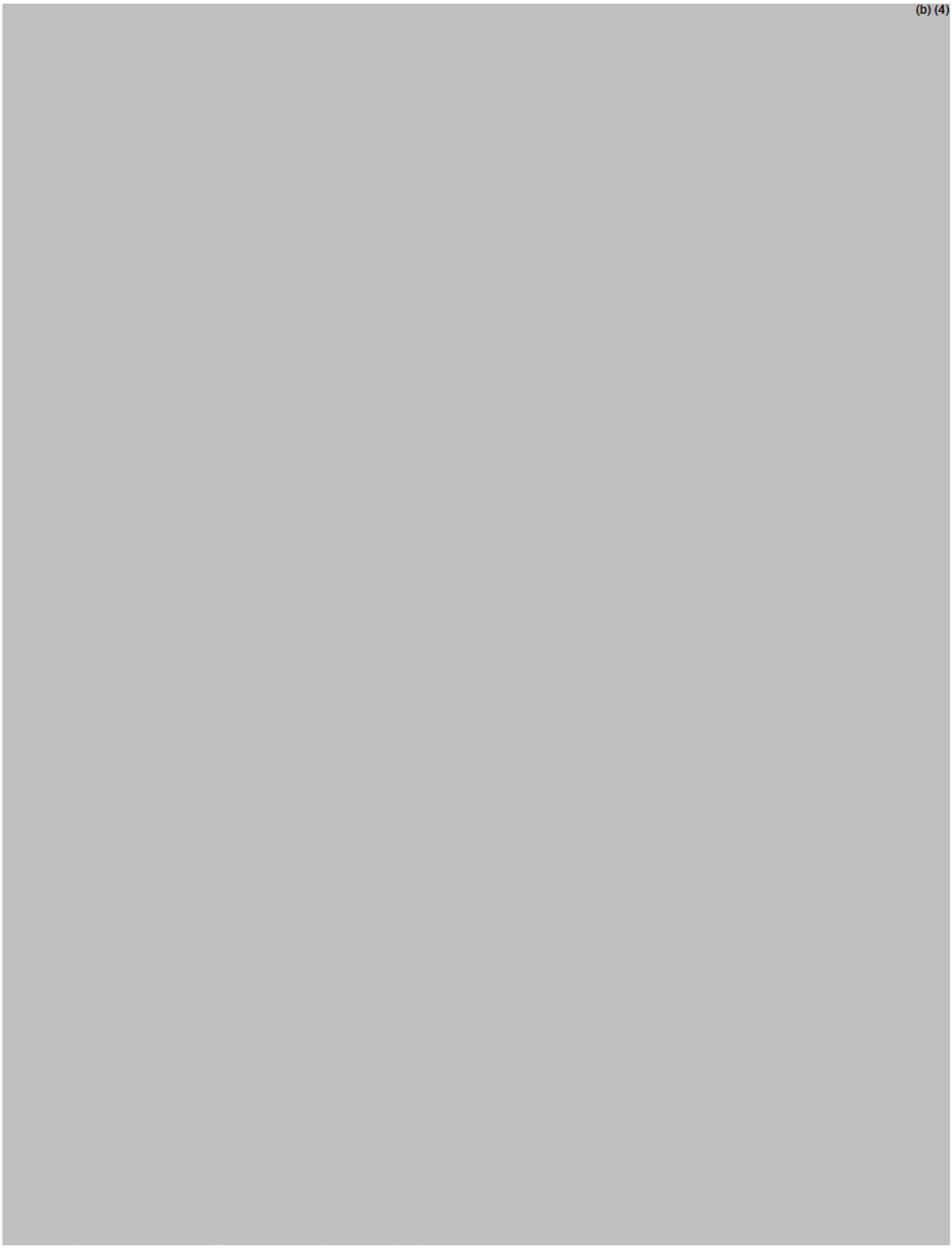
The sponsor provided Appendix 2 - Application Failure Modes Effects Analysis in which they included a table with identified hazards, potential hazards, severity, potential cause, probabilities, risk control index, mitigation type, mitigation controls, verifications, post mitigation probability and risk control, and remarks. The table collates several hazardous situations under the same entry, several causes under the same entry, and mitigations under the same entry. The sponsor should revise the table and separate the hazards into different

entrees, when there are multiple causes to the hazard where each cause has its own appropriate mitigation.

For example [redacted] (b) (4)

[redacted] (b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page



4. Software Requirements Specification (SRS)- **Acceptable**



In the IR response, the sponsor has provided adequate information on these items.

5. Architecture Design Chart –**Acceptable**

   Architecture design chart was provided in section 4.5 Architecture Design Chart (p.39), and Appendix 6 Infrastructure Configuration Specification. However figure 4.5-1 - Presentation, Application and Data Layers Contained in the Otsuka Medical Software is not readable and we can't review its content. The sponsor should provide a readable version. The information provided in Appendix 6 is acceptable. – In the IR response, the sponsor has provided a readable version of this chart. It is acceptable.

6. Software Design Specifications (SDS) –**Acceptable**

   Software Design Specifications document was provided in appendix 7. It is acceptable.

7. Traceability Analysis –**Acceptable**

   Traceability analysis was provided in appendix 8. While the provided table links together the requirements, testing requirements, identified hazards, and implementation and testing of the mitigations, it doesn't create the link with the design specifications. This link was also not created in the Software Design Specifications. Given the complexity of the software we have determined it to be acceptable.

8. Software Development Environment Description –**Acceptable**

Was provided is section 3 Software Development Process (p.32). This section provided a description of the process, and the standards that were followed. This is acceptable.

9. Verification and Validation Documentation –**Acceptable**

The verification plans were included in Appendix 10 - OMSS Software Design Verification Plan and Appendix 11 - OMSS App Design Validation Plan, describe the validation and verification processes followed for the OMS. Verification results are included in the OMSS App System Test Summary Report, which is presented in Appendix 12. Please note that the integration testing was included as part of the whole system testing in appendix 12.

The OMS System validation process is documented in protocols and reports.

System Test Protocols - The system testing process were included in Appendix 13 - General Test Protocol, Appendix 14 - Caregiver Test Protocol, Appendix 15 - Healthcare Professional Test Protocol and Appendix 16 Patient Test Protocol.

Validation Test Results - Results from the validation testing activities are included in the OMSS App Design Validation Summary Report included in Appendix 17. Test results for the validation activities for the patient, HCP, and caregiver are described above are included in Appendix 12.

Installation Qualification Report - Installation is performed by the user; refer to labeling in Module 1, Section 1.14.

Appendix 12

(b) (4)



1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)



10. Revision Level History –**Acceptable**

(b) (4)



11. Unresolved Anomalies (Bugs or Defects) –**Acceptable**

(b) (4)



1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

12. Cyber Security –**Acceptable**

Was included is section 5 (p.45) and appendix 2 and appendix 19. The spreadsheet in Appendix 2 lists all the cybersecurity risks identified during the development of the OMS and the implemented controls.

Appendix 19 Cybersecurity Controls Justification includes a list of identified risks and justifications to their mitigation (or why they were not specifically addressed). The sponsor provided promissory notes to address some of the identified risks, this is not acceptable.

(b) (4)

13. Responses to 05 May 2015 Pre-NDA Meeting Questions (p.48)

QUESTION 1: Does the (b) (4)" button appear each time the App is launched?

(b) (4)

QUESTION 2: What happens if the patient takes the pill and then the Patch battery dies?

Otsuka Response: *If the Patch battery dies before the pill ingestion data are transmitted to the Otsuka Cloud-based Server, then those data are lost. The Patch battery lasts for approximately 1 week. There will be an automatic reconnection/re-synching of data when Patch connectivity is restored.*

This is acceptable

QUESTION 3: What is the role of the (green) Patch status icon and what indicators would trigger this icon to turn red, signally poor connectivity?

Otsuka Response: *The indicator would show as "red" (poor connectivity) for 1 of 4 reasons: (1) connectivity to Bluetooth is poor, (2) poor skin contact, (3) Patch needs to be replaced, or (4) there is no Patch paired with the app.* (b) (4)

This is acceptable from SW aspect.

QUESTION 4: Does the App have to be on all the time to ensure connectivity to the Patch?

Otsuka Response: *The App does not have to be open and running in the foreground all of the time. Once the App is launched, it reconnects to the Patch in the background whereby data is synced and downloaded.* (b) (4)

Note : App on and App in the foreground are two different things. I would ask the sponsor to clarify that they indeed meant app on.

QUESTION 5: Can the data stored in the cloud and pushed to the App be accessed by the HCP/caregiver without prior patient approval?

Otsuka Response: *No, allowing the HCP and/or caregiver access to this information is at the patients' discretion. Moreover, the HCP and/or caregiver can only access the respective portal upon email invitation from the patient through the patient App.*

This is acceptable

QUESTION 6: What occurs to the data if the phone is lost?

Otsuka Response: *Data can be recovered from the Cloud-based Server and synced to a new phone. This is only for data that has been uploaded to the Cloud-based Server.*

This is acceptable

QUESTION 7: Can the patient willingly disconnect/stop sharing information with the HCP/caregiver?

Otsuka Response: *Yes, patient can opt to disconnect from the HCP and/or caregiver at any time. The patient has autonomy to discontinue sharing all or some of the parameters, though medication adherence information is automatically shared with the HCP unless the patient has disconnected from the HCP.*

QUESTION 8: Is the Patch: ☐ water proof ☐ resistant to sweat from exercise ☐ submersion in water (such as soaking in a tub) ☐ wearable during magnetic resonance imaging (MRI)?

Otsuka Response: The Patch is designed to be water resistant and wearable during bathing, etc. The proposed labeling includes guidance on the handling of the Patch during an MRI, (b) (4) (b) (4)

QUESTION 9: Will the lag time for information transmitted from the Patch to the App be communicated to the patient?

Otsuka Response: *The Patch records all information and there may be a delay of up to a few minutes when the data is pushed to the App (see synoptic Clinical Study Report [CSR] 316-13-206B). Patients will be informed of this delay in the counseling section of the label.* (b) (4) *these concerns are addressed in the electronic instructions for use (IFU).*

This is not under the SW review scope [redacted] (b) (4)

QUESTION 10: [redacted] (b) (4)

[redacted] (b) (4)

QUESTION 11: During the Patch pairing process, if you forget to pair the Patch, prior to adhering it to your torso, can a subject pair the Patch while it is on the body?

Otsuka Response: *For ease of use, it is better to pair the Patch before the patient applies it; however, while not described in the electronic IFU, it can be paired when it's on the body.*

The sponsor should describe the paring process while the patch is on the body, and include it in the labeling.

QUESTION 12: Was the knowledge of the "Patch Status" icon, and various other icons tested during human factors testing?

Otsuka Response: *Yes, knowledge/comprehensibility of these icons was tested.*

What were the results of this test?

QUESTION 13: What is the HCP/caregiver training process?

Otsuka Response: *As described in the patient counseling section of the PI, HCPs will assist in onboarding of patients when the patients are initially prescribed the product. Training for the HCP will be provided during routine in-service presentations by Otsuka. Caregiver training is provided on the Caregiver Web Portal.*

Not under SW scope

QUESTION 14: Can the Patch be paired with more than 1 phone?

Otsuka Response: [redacted] (b) (4)
The Patch can be paired with only one phone at a time. [redacted] (b) (4)

This is acceptable

QUESTION 15: Is information lost, if the phone becomes impaired or lost?

Otsuka Response: *During the time period that the phone is lost, whatever information captured by the existing Patch will be lost until a new Patch is paired. The proposed labeling will provide guidance on steps which must be taken if the patient's phone is lost or nonfunctional.*

The sponsor should clarify that the information that is lost is only the information that wasn't sent to the server. Also, the sponsor should provide measures to limit the amount of data lost by using timely backups.

QUESTION 16: If 2 patients are in close proximity while activating and pairing their Patch, will the phones pick up multiple Patches?

(b) (4)

It is not clear whether the sponsor meant current specification of (b) (4) separation between patients. If so, why is it needed when there is a unique serial number.

(b) (4)

QUESTION 18: (b) (4)

(b) (4)

This is acceptable.

QUESTION 19: What occurs if a patient accidentally disconnects from the HCP? Are they able to reconnect, and is data lost during the process?

Otsuka Response: *Subjects are able to reconnect to the HCP by sending a new invite; however,* (b) (4) *No data will be lost if you reconnect to the same HCP; however, if you connect to a new HCP, historic information provided to the previous HCP will not be shared.*

Note to the lead: The sponsor should provide instructions in the labeling for such scenario.

Also, the sponsor should clarify if the patient asks to transfer the data from one HCP to another, is there a possibility to do so.

14. **Off-the-shelf SW - Acceptable**

Not included.

The sponsor has adequately documented the Software Description section (please refer to SW description section above)

Deficiencies

1. In your device description you indicated that your device has 3 software components: the patient component (app) of the Otsuka Medical Software, the Otsuka cloud-based server of the Otsuka Medical software and the Web Portals of the Otsuka Medical software. In the software description you included table 2.3-1 to describe the application functionality; however you didn't include any information regarding the cloud-based server or the webportals.
    a. Please revise your software description to include information about the cloud based server and the webportals. Please note that upon review of the functionalities of these software components if they are determined to be under active regulation, then you will need to provide all of their relevant software documents as requested by the Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, issued 2015.
    b. Please also update your software description to include information on the following: (b) (4) .

IR Response: The sponsor has adequately responded to this question as documented in the discussion for the Software Description section above.

2. (b) (4)

IR Response: In the IR response, the sponsor has indicated that they are only planning on (b) (4) for this submission. While this does not answer all of the questions (b) (4) it is adequate in response to this specific part of this question.

b. Throughout the submission you referred to changes that will be made (b) (4) please provide the appropriate documents to support it.

IR Response: The sponsor has further described the changes made (b) (4) and believes that these are minor. In the area of cybersecurity, they have provided additional information on the steps they are taking to secure their software. This will be discussed in more detail in other parts of the review. For this question, this response is considered adequate.

3. You provided Appendix 2 - *Application Failure Modes Effects Analysis* in which you included a table with identified hazards, potential harm, severity, potential cause, probabilities, risk control index, mitigation type, mitigation controls, verifications, post mitigation probability and risk control, and remarks.

7 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Recommendation

The IR responses are adequate.

Nathalie Yarkony -S

Digitally signed by Nathalie Yarkony -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001332288, cn=Nathalie Yarkony -S
Date: 2016.03.04 12:59:58 -05'00'