CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217006Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABELS AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 27, 2023
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 217006
Product Name, Dosage Form, and Strength:	Abilify Asimtufii (aripiprazole) extended-release injectable suspension, 720 mg/2.4 mL and 960 mg/3.2 mL
Applicant/Sponsor Name:	Otsuka Pharmaceutical Company, Ltd. (Otsuka)
TTT ID #:	2022-67-1
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised syringe labels and carton labeling received on April 26, 2023 for Abilify Asimtufii. The Division of Psychiatry (DP) requested that we review the revised syringe labels and carton labeling for Abilify Asimtufii (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and a follow up recommendation from the Agency communicated to Otsuka via email on April 25, 2023.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Holmes, L. Labels and Labeling Review for Abilify Asimtufii (NDA 217006). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Mar 27. TTT ID No.: 2022-67.

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/s/

LORETTA HOLMES
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MADHURI R PATEL
04/27/2023 12:17:54 PM

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

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

Memorandum

Date: April 17, 2023

To: Roberta Rasetti, Clinical Reviewer, M.D.
Division of Psychiatry (DP)

Tiffanie Taylor, Regulatory Project Manager, DP

Kim Updergraff, Associate Director for Labeling, DP

From: Samuel Fasanmi, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for ABILIFY ASIMTUFII (aripiprazole) extended-release injectable suspension, for intramuscular use

NDA: 217006

In response to DP's consult request dated July 20, 2022, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton labeling for the original NDA submission for ABILIFY ASIMTUFII (aripiprazole) extended-release injectable suspension, for intramuscular use.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling received by electronic mail from DP on April 3, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on April 10, 2023.

Carton Labeling:
OPDP's review of the proposed carton labeling is based on the draft labeling submitted by the Sponsor to the electronic document room on March 2, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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SAMUEL A FASANMI
04/17/2023 11:22:46 AM

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

PATIENT LABELING REVIEW

Date:	April 10, 2023
To:	Tiffanie Taylor, PharmD Regulatory Project Manager **Division of Psychiatry (DP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samuel Fasanmi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ABILIFY ASIMTUFII (aripiprazole)
Dosage Form and Route:	extended-release injectable suspension, for intramuscular use
Application Type/Number:	NDA 217006
Applicant:	Otsuka Pharmaceutical Company, Ltd. c/o Otsuka Pharmaceutical Development & Commercialization, Inc.

1 INTRODUCTION

On June 27, 2022, Otsuka Pharmaceutical Company, Ltd c/o Otsuka Pharmaceutical Development & Commercialization, Inc. submitted for the Agency's review an original New Drug Application (NDA) 217006 for ABILIFY ASIMTUFII (aripiprazole) extended-release injectable suspension, with proposed indications for the treatment of schizophrenia and as a maintenance monotherapy treatment of biopolar I disorder.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DP) on August 22, 2022 and July 20, 2022, for DMPP and OPDP, respectively, to review the Applicant's proposed Medication Guide (MG) for ABILIFY ASIMTUFII (aripiprazole) extended-release injectable suspension.

2 MATERIAL REVIEWED

- Draft ABILIFY ASIMTUFII (aripiprazole) extended-release injectable suspension MG received on November 9, 2022, and received by DMPP and OPDP on April 3, 2023.
- Draft ABILIFY ASIMTUFII (aripiprazole) extended-release injectable suspension Prescribing Information (PI) received on November 9, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 3, 2023.
- Approved ABILIFY MAINTENA (aripiprazole) for extended-release injectable suspension and ARISTADA (aripiprazole lauroxil) extended-release injectable suspension comparator labeling dated February 5, 2020 and August 27, 2020, respectively.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

LAURIE J BUONACCORSI
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SAMUEL A FASANMI
04/10/2023 03:48:12 PM

SHARON R MILLS
04/10/2023 03:55:57 PM

LASHAWN M GRIFFITHS
04/10/2023 03:57:53 PM

MEMORANDUM

HUMAN FACTORS STUDY RESULTS REVIEW MEMO

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 27, 2023
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 217006
Product Name and Strength:	Abilify Asimtufii[a] (aripiprazole) injection 720 mg/2.4 mL and 960 mg/ 3.2mL
Applicant/Sponsor Name:	Otsuka Pharmaceutical Co., Ltd.
TTT ID #:	2022-68-1
DMEPA 1 Safety Evaluator:	Neha Kumar, PharmD
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised quick start guides (QSGs) received on March 17, 2023 for Abilify Asimtufii. The Division of Psychiatry (DP) requested that we review the revised QSGs for Abilify Asimtufii (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to a recommendation that we made during a previous human factors validation results review.[b]

2 CONCLUSION

The Applicant implemented our recommendation, and we have no additional recommendations at this time.

[a] The proprietary name, Abilify Asimtufii, was found conditionally acceptable on February 7, 2023.

[b] Oguntimein, M. Human Factors Validation Study Report Review for Aripiprazole (NDA 217006). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 FEB 06. TTT No.: 2022-68.

APPENDIX A. LABELING RECEIVED ON MARCH 17, 2023

- Abilify Asimtufii (aripiprazole) injection 720 mg/2.4 mL quick start guide available from: \\CDSESUB1\EVSPROD\nda217006\0028\m1\us\114-labeling\draft\labeling\abilify-720mg-qsg.pdf
- Abilify Asimtufii (aripiprazole) injection 960 mg/ 3.2mL quick start guide available from: \\CDSESUB1\EVSPROD\nda217006\0028\m1\us\114-labeling\draft\labeling\abilify-960mg-qsg.pdf

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/s/

NEHA KUMAR
03/27/2023 03:00:59 PM

OLUWAMUREWA OGUNTIMEIN
03/28/2023 01:13:41 PM

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

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

Date of This Review:	March 27, 2023
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 217006
Product Name, Dosage Form, and Strength:	Abilify Asimtufii[a] (aripiprazole) extended-release injectable suspension, 720 mg/2.4 mL and 960 mg/3.2 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Otsuka Pharmaceutical Company, Ltd. (Otsuka)
FDA Received Date:	November 9, 2022 and March 2, 2023
TTT ID #:	2022-67
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

[a] This proposed proprietary name was found conditionally acceptable in the following DMEPA 1 Review: Holmes, L. Proprietary Name Review for Abilify Asimtufii (NDA 217006). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Feb 03. PNR ID No. 2022-1044724837.

1 REASON FOR REVIEW

As part of the approval process for Abilify Asimtufii (aripiprazole) extended-release injectable suspension, the Division of Psychiatry (DP) requested that we review the proposed Abilify Asimtufii prescribing information (PI), syringe labels, carton labeling , and Medication Guide for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed prescribing information (PI), syringe labels, carton labeling, and Medication Guide identified areas where the Prescribing Information, syringe labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Otsuka Pharmaceutical Company, Ltd. Our evaluation of the MG did not identify areas of vulnerability that may lead to medication errors.

We note that a Human Factors Validation Study was completed for this product. The study results along with the associated instructions for use of the product (including the Quick Reference Guide) were reviewed under separate cover.[b]

[b] Oguntimein, M. Human Factors Validation Study Report Review for Aripiprazole injection (NDA 217006). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Feb 05. TTT ID No.: 2022-68.

4 RECOMMENDATIONS FOR OTSUKA PHARMACEUTICAL COMPANY, LTD.

Table 2. Identified Issues and Recommendations for Otsuka Pharmaceutical Company, Ltd. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Trade and Professional Sample Syringe Labels and Carton Labeling			
1.	The statement of strength is not consistent across the syringe labels and carton labeling.	The lack of consistency may lead to confusion regarding the product strengths.	Revise the statement of strength to read 720 mg/2.4 mL or 960 mg/3.2 mL as appropriate. Remove the "300 mg/mL" portion of the statement.
Trade Syringe Labels and Trade Carton Labeling			
1.	The NDC numbers on the syringes and carton labeling differ from what is in the Prescribing Information (PI).	It is not clear whether the NDC numbers on the syringe labels and carton labeling or the Prescribing Information are the correct numbers.	Make corrections as needed to the syringe labels/carton labeling or the PI to ensure that the NDC numbers are consistent across the labels and labeling.
2.	The statement "Dosing Frequency: Once Every 2 Months" lacks prominence.	Due to the lack of prominence, users may overlook the statement.	Consider the use of a bold font, or other means, to increase the prominence of the statement.
Trade and Professional Sample Carton Labeling			
1.	The (b) (4) statement is not consistent with Section 2.2 of the PI which states "Recommended Dosage".	The (b) (4) statement should be consistent with the PI.	To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read: "Recommended Dosage: See full Prescribing Information".
2.	The storage statement on the carton labeling is not the same as the storage statement in the PI so it is unclear which is the intended statement. Additionally, some of the numerical temperatures	The lack of consistency between the statements may lead to confusion. Additionally, for clarity, each numerical temperature should be accompanied by the	Ensure that the statement of strength is the same on the carton labeling and in the PI. Revise as appropriate. Additionally, ensure that the numerical temperature is accompanied by the associated temperature scale (e.g., 20°C to 25°C) as appropriate.

Table 2. Identified Issues and Recommendations for Otsuka Pharmaceutical Company, Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	lack their associated temperature scale (e.g., 20 to 25°C).	associated temperature scale.	
Professional Sample Carton Labeling			
1.	There are no NDC numbers on the carton labeling.	The NDC number helps to facilitate product identification and verification.	Per 21 CFR 201.2, the NDC is "requested but not required to appear on all drug labels and in all drug labeling", however, FDA strongly encourages the NDC appear on all drug labels and in all drug labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Abilify Asimtufii that Otsuka Pharmaceutical Company, Ltd. submitted on November 9, 2022.

<table>
<tr><th colspan="2">Table 3. Relevant Product Information for Abilify Asimtufii</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>aripiprazole</td></tr>
<tr><td>Indication</td><td>• Treatment of schizophrenia in adults
• Maintenance monotherapy treatment of bipolar I disorder in adults</td></tr>
<tr><td>Route of Administration</td><td>Gluteal intramuscular injection</td></tr>
<tr><td>Dosage Form</td><td>Extended-release injectable suspension</td></tr>
<tr><td>Strengths</td><td>720 mg/2.4 mL and 960 mg/3.2 mL</td></tr>
<tr><td>Dose and Frequency</td><td>The recommended starting and maintenance dose is 960 mg, administered once every two months (56 days after previous injection). If there are adverse reactions with the 960 mg dosage, consider reducing the dosage to 720 mg once every 2 months.
Dose Adjustments in Patients who are known CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, 3A4 Inhibitors, and/or CYP3A4 Inducers for Greater than 14 days
<table>
<tr><th>Factors</th><th>Adjusted Dose</th></tr>
<tr><td colspan="2">CYP2D6 Poor Metabolizers</td></tr>
<tr><td>Known CYP2D6 Poor Metabolizers</td><td>720 mg</td></tr>
<tr><td>Known CYP2D6 Poor Metabolizers taking concomitant CYP3A4 inhibitors</td><td>Avoid use</td></tr>
<tr><td colspan="2">Patients Taking 960 mg of ABILIFY ASIMTUFII</td></tr>
<tr><td>Strong CYP2D6 or CYP3A4 inhibitors</td><td>720 mg</td></tr>
<tr><td>CYP2D6 and CYP3A4 inhibitors</td><td>Avoid use</td></tr>
<tr><td>CYP3A4 inducers</td><td>Avoid use</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>Single-use kits containing 1 pre-filled syringe and 2 safety needles (a 1.5 inch 22 gauge needle and a 2 inch 21 gauge needle).</td></tr>
<tr><td>Storage</td><td>Store at 25°C (77°F), excursions permitted between 15° and 30°C (59° to 86°F) [see USP Controlled Room Temperature].</td></tr>
</table>

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Abilify Asimtufii labels and labeling submitted by Otsuka Pharmaceutical Company, Ltd.

- Trade and Professional Sample Syringe Labels received on 11/09/2022[d]
- Trade Carton labeling received on 11/09/2022[e]
- Professional Sample Carton Labeling received on 03/02/2023[f]
- Prescribing Information (image not shown) received on 11/09/2022[g]

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

(b) (4)

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

[d] Available at: \\Cdsesub1\evsprod\NDA217006\0007\m1\us\114-labeling\draft\carton-and-container

[e] Available at: \\Cdsesub1\evsprod\NDA217006\0007\m1\us\114-labeling\draft\carton-and-container

[f] Available at: \\Cdsesub1\evsprod\NDA217006\0025\m1\us\114-labeling\draft\carton-and-container

[g] Available at: \\Cdsesub1\evsprod\NDA217006\0007\m1\us\114-labeling\draft\annotated

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LORETTA HOLMES
03/27/2023 02:32:28 PM

MADHURI R PATEL
03/27/2023 03:31:49 PM

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

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

Date of This Review:	March 23, 2023
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 217006
Product Type:	Combination Product (Drug-Device)
Product, Name, Dosage Form and Strength:	Aripiprazole injection 720 mg/2.4 mL and 960 mg/ 3.2mL
Device Constituent:	Prefilled Syringe (PFS)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Otsuka Pharmaceutical Co., Ltd. (Otsuka)
FDA Received Date:	June 27, 2022; November 07, 2022
OSE TTT #:	2022-68
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

This is a corrected review that does not change the overall recommendations/conclusions of the original review dated February 06, 2023.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report submitted under NDA 217006 for Aripiprazole injection.

1.1 PRODUCT INFORMATION

Initial Approval Date	N/A
Therapeutic Drug Class	Second Generation Atypical Antipsychotic
Active Ingredient	Aripiprazole
Indication	• Treatment of schizophrenia in adults • Maintenance monotherapy treatment of bipolar I disorder in adults
Route of Administration	Intramuscular (gluteal)
Dosage Form	Injection
Strength	720 mg and 960 mg
Dose and Frequency	To be administered by intramuscular injection in the gluteal muscle, once every two months, by a healthcare professional.
How Supplied	pre-filled syringes in 720 mg/2.4 mL or 960 mg/3.2 mL strengths. The single-use kit contains 1 pre-filled syringe and 2 safety needles (a 1.5-inch 22-gauge needle and a 2-inch 21-gauge needle). • 720 mg aripiprazole kit (NDC 59148-114-80) • 960 mg aripiprazole kit (NDC 59148-102-80)
Storage	Store at 25°C (77°F), excursions permitted between 15° and 30°C (59° to 86°F) [see USP Controlled Room Temperature].
Container Closure/Device Constituent (including figure)	 (b) (4)

<table>
<tr><td>Intended Users</td><td>Healthcare professionals</td></tr>
<tr><td>Intended Use Environment</td><td>Clinical Setting</td></tr>
<tr><td>Relevant Information</td><td>The proposed product is the same as Abilify (b) (4) which was approved on November 15, 2002, under NDA 021436. The following are the differences between the two products.
<table>
<tr><td>Difference</td><td>Abilify (b) (4)</td><td>Proposed Product</td></tr>
<tr><td>Dosage Form</td><td>Tablet</td><td>Injection</td></tr>
<tr><td>Indications</td><td>- Treatment of schizophrenia
-Treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years).
-Maintenance adjunctive treatment of Bipolar I disorder with lithium or valproate.
-Pediatric maintenance study for irritability associated with autism.</td><td>-Treatment of schizophrenia in adults
-Maintenance monotherapy treatment of bipolar I disorder in adults</td></tr>
</table></td></tr>
</table>

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

- On November 4, 2021, the Applicant submitted a Human Factors (HF) Validation Study protocol under 134612 for Aripiprazole injection 720 mg/2.4 mL and 960 mg/ 3.2mL PFS for administration by healthcare providers (HCPs). We reviewed the protocol and provided recommendations.[a]
- On February 04, 2022, the Applicant submitted clarifying questions regarding the acceptability of their human factors (HF) validation study methodology under 134612 for Aripiprazole injection 720 mg/2.4 mL and 960 mg/ 3.2mL PFS for administration by

[a] Birkemeier, D. HF Validation Study Protocol Review for Aripiprazole Injection (IND 134612). FDA, CDER, OSE, DMEPA (US); 2021 DEC 23. RCM No.: 2021-2177.

HCPs. These clarifying questions are in response to recommendations that we made during a review of their HF validation study protocol submitted on November 04, 2021.We provided responses to their clarifying questions. [b]

- On June 27, 2022, the Applicant submitted a New Drug Application (NDA) for Aripiprazole injection 720 mg/2.4 mL and 960 mg/ 3.2mL PFS under NDA 217006. This submission included the results of their HF validation study for administration by HCPs, which is the subject of this review.

1.3 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

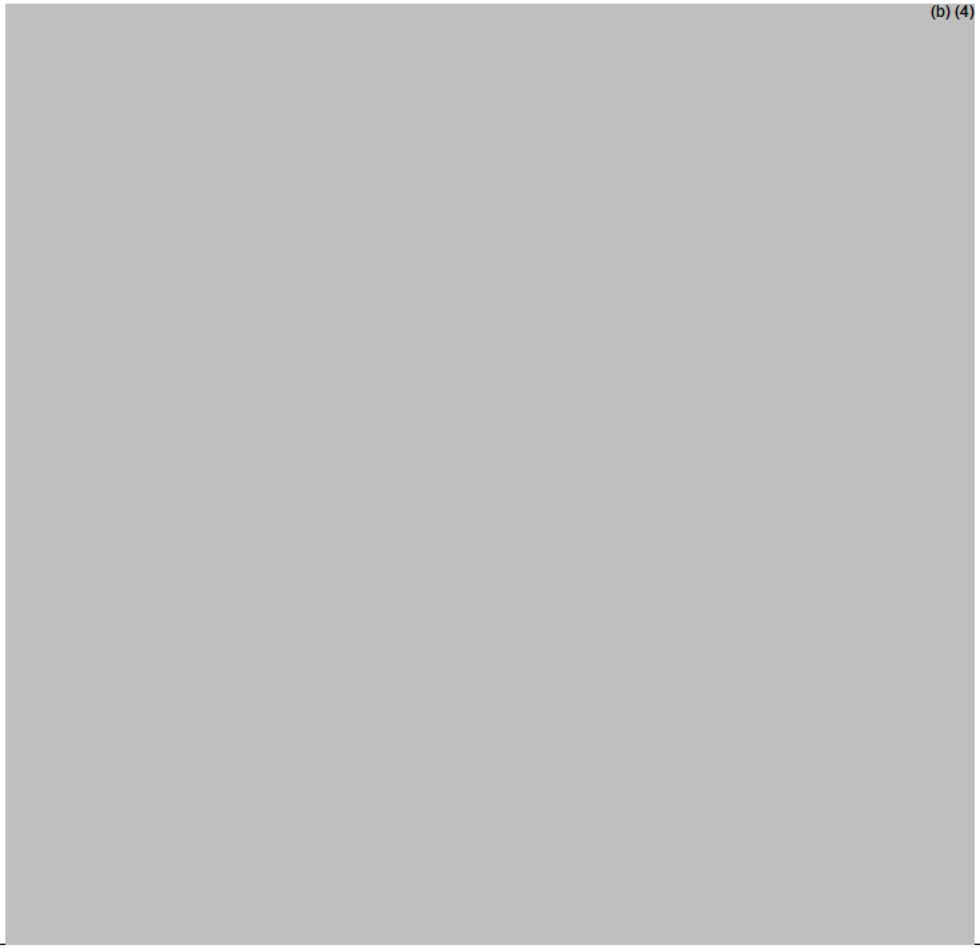
2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

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

2.1 SUMMARY OF STUDY DESIGN

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

[b] Birkemeier, D. Memorandum Review of Responses to Human Factors Validation Study Protocol Review for Aripiprazole injection (IND 134612). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 FEB 22. RCM No.: 2021-2177-1.

Table 3. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	**Details**
Participants	A total of 16 participants completed the human factors validation study: 14 registered nurses 1 psychiatrist 1 nurse practitioner
Training	No training was provided to the participants.
Test Environment & Materials	Testing was conducted at a market research facility in a room equipped with a two-way mirror. Set-up for the facility simulated the HealthCare setting use environments where this medication is administered. Light, furnishings and ambient noise simulated a typical hospital or community mental health setting, simulating what is typical in this environment. There was no alteration of lighting or noise conditions in the test environment and no additional distractions were introduced. The figure 1 below shows a diagram of the space in the research setting.  (b) (4)

	The room contained equipment the clinician would need to complete the task including: • 720 mg Ari-2M PFS kit (containing the pre-filled syringe with active medication, Quick Start Guide (QSG), 2 needles, Prescribing Information (PI) for kit, PI for needles) • 960 mg Ari-2M PFS kit (containing the pre-filled syringe with active medication, Quick Start Guide (QSG), 2 needles, PI for kit, PI for needles) • Sharps container • Alcohol prep pads • Band-Aids • A medical mannequin with embedded injection pads • Gloves • Tray • Mayo Medical Table
Sequence of Study	• Consent/ Enrollment • Introduction • Background • Simulated Use Task: The order in which dose strength (720 mg or 960 mg) and needle size were presented was counterbalanced so that not all received the same dose strength in the same order and both needle sizes were tested. • Post-use interview (general debrief on use-related safety and root cause investigation, if needed) • Knowledge Assessment • Post-use interview • Wrap-up

3 RESULTS AND ANALYSIS

We have carefully reviewed each observed event, the Applicant's URRA, the participants' subjective feedback, the Applicant's RCA, and the Applicant's comments below. For our analyses see Table 4 and Section 3.1 below.

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Table 4. Focused Analysis of Use Errors, Use Difficulties and Close Calles AND DMEPA's Recommendations

Legend: **UE** = use error; **CC** = close call; **UD** = use difficulty; **URRA** = use-related risk analysis; **RCA** = root cause analysis

Information Supplied by Applicant	DMEPA's Findings and Recommendations
Task: "Do not massage injection site" <table><tr><td>Total number of UE, CC, and UD</td><td>Type of Participants</td></tr><tr><td>UE (n=2)</td><td>P06, P02</td></tr></table>	
Observed event(s): Participant massaged the injection site after giving the injection.	
Risk associated with Task Errors (Per Applicant uFMEA): if this task is omitted or not performed correctly, there is a risk of impact on drug particle dispersion in injection site which might have an impact on drug absorption rate.	No identified concerns with the risks identified. However, we note the risks are not complete because the Applicant did not specify the clinical impact of drug particle dispersion in the injection site and the impact on drug absorption rate.
Relevant RCA/Subjective Feedback/Observation: • The participant missed the instructions in the QSG to not massage the injection site. He stated that he typically applies "gentle pressure" to an injection site to minimize the effects of injecting into a large muscle, however he was observed slightly rubbing the area. When asked about this during the root cause probing, he stated that the "Do not Massage injection site" did not stand out to him as the text was small. • Another participant was unable to complete this step due to activating the safety shield prior to attempting this task.	No identified concerns.
Applicant Comment and Proposed Mitigations: none	Our review of the Quick Start Guide indicates that step 6 Inject into gluteal muscle includes instructions to not massage injection site. However, based on subjective feedback (participant indicated the instruction did not stand out to him as the text was small), and our overall assessment, we find that the instructions not to massage the injection site lacks prominence. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.

3.1 ANALYSIS OF OTHER TASK ERRORS

The HF validation study showed use errors, use difficulties, and close calls with the tasks listed below in this section; however, based on our review of the available assessment of these use error/use difficulties/close calls, the available participants' subjective feedback, and the Applicant's root cause analysis, we determined the residual risk is acceptable. Specifically, we find that the labeling mitigations in place include information that is prominently placed within the labels and labeling to address the tasks below. We also find the labels and labeling are in alignment with best labeling practices. In addition, we considered the use tasks of the proposed product as compared with the use tasks in similar marketed products with the same indication, use groups and use environment to determine if there are any known concerns of vulnerability to use error and did not identify any concern. Subsequently, we did not identify further need for risk mitigation strategies at this time to address the use errors related to the following tasks and find the residual risks are acceptable:

- Select Correct Dose Strength Kit
- Tap/Shake Syringe: There were eight use errors observed in this task. Seven out of the eight participants tapped 10 times or more but only shook between 6 to 9 seconds instead of 10 seconds as instructed in the IFU. The last participant did not tap or shake at all. The Applicant categorized this task as non-critical. Per the uFMEA, if the tapping and shaking tasks are omitted or performed incorrectly there are risks of underdose (not requiring hospitalization) and delayed treatment. We reached out to our Division of Psychiatry (DP) clinical colleagues for their feedback on the abovementioned categorization and they noted that the Applicant did not provide any data or published scientific literature supporting their claim that underdose is not associated with hospitalization. As such we issued an information request on November 03,2022 to ask the Applicant to provide data or published scientific literature supporting their claim that underdose is not associated with hospitalization. Additionally, we asked the Applicant to provide information on how much less drug (underdose) is injected if the PFS is not tapped 10 times and/or shook for 10 seconds as indicated in the IFU. In the Applicant's response dated November 07, 2022, they indicated that the laboratory testing study results confirmed that deliverable assay, particle size distribution, and viscosity complied with the specifications for the aripiprazole 2M RTU LAI PFS under all redispersion conditions evaluated, including when no tapping or shaking was done. The study showed that the minimum of one of the following methods are required to receive a full dose:
  - Tapping 5 times (tapping only);
  - Shaking for 5 seconds (shaking only);
  - Tapping 3 times and shaking for 3 seconds (tapping and shaking).

  The study also confirmed that 10 taps and 5 seconds of shaking does not cause a problem with the quality of the expelled drug suspension. Our DP clinical colleagues agreed with the Applicant that the use errors seen in the HF validation study results

would not result in harm based on the Applicant's IR response. The RCA indicated that all participants said they were counting in their heads to at least 10 seconds to ensure they had shaken for enough time. They all thought they counted for at least 10 seconds. We note the user interface includes instructions and images to support this task. Based on our review, we did not identify areas of improvement and have no recommendations at this time.

- Expel Air
- Recapping the Needle
- Select Injection Site
- Inject Via Correct Route (IM): One participant was unable to complete this step due to activating the safety shield prior to attempting to inject.
- Activates Plunger by Depressing Plunger Rod Slowly: One participant was unable to complete this step due to activating the safety shield prior to attempting to inject.
- Disposes of Used Needles/ Syringe
- Storage

4 LABELS AND LABELING

Table A below includes the identified medication error issue with the submitted instructions for use (IFU) based on the HF study results, our rationale for concern, and the proposed recommendation to minimize the risk for medication error. Additionally, we note that the DMEPA 1 primary review team will evaluate product specific label and labeling under separate cover and label and labeling comments may be forthcoming based on the outcome of that review.

Table A. Identified Issues and Recommendations for Otsuka Pharmaceutical Co., Ltd. (Otsuka) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Quick Start Guide			
1.	The instruction in Step 6 "Do not massage injection site" lacks prominence.	Per the uFMEA, if the user massages the injection site, there is risk of impact on drug particle dispersion in injection site which might have an impact on drug absorption rate. The human factors (HF) validation study identified subjective feedback that indicated that one participant stated the instruction did not stand out to him as the text was small.	Increase the prominence of the instructions in Step 6 to not massage injection site. For example consider bolding the instruction.

5 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors, close calls, use difficulties with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified an additional risk mitigation to address the use errors. Above, we have provided recommendations in Table A for the Applicant. We ask that the Division of Psychiatry (DP) convey Table A in its entirety to the Applicant. These changes can be implemented without submitting additional HF validation testing data for Agency review.

5.1 RECOMMENDATIONS FOR OTSUKA PHARMACEUTICAL CO., LTD. (OTSUKA)

Our evaluation results of your human factors (HF) validation study indicates that there is an additional mitigation that can be implemented to address use errors that occurred with a task. We provide recommendations in Table A, and we recommend that you implement the recommendation and submit the revised label and labeling for our review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX B. PREVIOUS REVIEWS

B.1.1 Methods

On January 2, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, “217006”, “134612” and “ Aripiprazole” .

B.1.2 Results

Our search identified two previous reviews[ab] and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The Aripiprazole 2M Prefilled Syringe HFE/UE Report can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda217006\0001\m1\us\111-information-amendment\info-amend-ari-2m-hfe-ue-report.pdf

The Aripiprazole 2- Month RTU Use Risk Assessment (uFMEA) can be accessed in EDR via:

\\CDSESUB1\EVSPROD\nda217006\0001\m1\us\111-information-amendment\ari-2m-rtu-ufmea.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda217006\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophrenia\5354-other-stud-rep\mma-344\mma-344-report-body.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On 11/3/2022, we issued an Information Request (IR) stating the following: We note in your human factors (HF) Validation study report you state, “the largest use error was in the Tap & Shake task (non-critical), where a total of 7 participants did not shake for the listed 10 seconds”. Additionally, you indicated in your Aripiprazole 2-Month RTU USE Risk Assessment (uFMEA) that if the tapping and shaking tasks are omitted or performed incorrectly there are risks of underdose (not requiring hospitalization) and delayed treatment. However you did not provide the following:

- data or published scientific literature supporting your claim that underdose is not associated with hospitalization.

• How much less drug (underdose) is injected if the prefilled syringe is not tapped 10 times and/or shook for 10 seconds as indicated in the instructions for Use (IFU)
As such, we are unable to fully review your HF validation study report. Please provide the following:
• data or published scientific literature supporting their claim that underdose is not associated with hospitalization.
• An estimated amount of underdose if the prefilled syringe is not tapped 10 times and/or shook for 10 seconds as indicated in the IFU

On 11/7/2022, the Applicant did provide an acceptable response that can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda217006\0010\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophrenia\5354-other-stud-rep\mma-344\response-hf-ufmea.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Aripiprazole labels and labeling submitted by Otsuka Pharmaceutical Co., Ltd. on June 27, 2022.

720 mg Syringe Label	\\CDSESUB1\EVSPROD\nda217006\0001\m1\us\114-labeling\draft\carton-and-container\draft-syringe-label-720mg.pdf
720 mg Carton Labeling	\\CDSESUB1\EVSPROD\nda217006\0001\m1\us\114-labeling\draft\carton-and-container\draft-carton-720mg.pdf
960 mg Syringe Label	\\CDSESUB1\EVSPROD\nda217006\0001\m1\us\114-labeling\draft\carton-and-container\draft-syringe-label-960mg.pdf
960 mg Carton Labeling	\\CDSESUB1\EVSPROD\nda217006\0001\m1\us\114-labeling\draft\carton-and-container\draft-carton-960mg.pdf
720mg Quick Start Guide (Instructions for use)	\\CDSESUB1\EVSPROD\nda217006\0001\m1\us\114-labeling\draft\labeling\abilify-720mg-qsg.pdf

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

960 mg Quick Start Guide (Instructions for use)	\\CDSESUB1\EVSPROD\nda217006\0001\m1\us\114-labeling\draft\labeling\abilify-960mg-qsg.pdf
Prescribing Information	\\CDSESUB1\EVSPROD\nda217006\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-clean.pdf

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

/s/

OLUWAMUREWA OGUNTIMEIN
03/23/2023 04:16:19 PM

JASON A FLINT
03/24/2023 08:56:26 AM

M E M O R A N D U M

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

DATE: February 22, 2023

TO: Tiffany Farchione, MD
Director
Division of Psychiatry
Office of New Drugs

FROM: Melkamu Kebtie Getie, Ph.D., R.Ph.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Routine inspection of Howard A. Hassman (Hassman Research Institute), Marlton, NJ, Peter P. Ventre (Research Centers of America), Oakland Park, FL, and David P. Walling (Collaborative Neuroscience), Garden Grove, CA

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged inspections of study 031-201-00181 (NDA 217006 conducted under IND 134612, Aripiprazole) conducted by Clinical Investigators a) Dr. Howard A. Hassman at Hassman Research Institute, Marlton, NJ, b) Dr. Peter P. Ventre at Research Centers of America, LLC., Oakland Park, FL, and c) Dr. David P. Walling at Collaborative Neuroscience Network, LLC., Garden Grove, CA.

Form FDA 483 was not issued at the inspection close-out of all the three sites, but discussion items were addressed at all sites.

After reviewing the inspectional findings, I conclude the data from the audited study are reliable. However, I recommend that the review division consider the following for activities performed at Research Centers of America, LLC and Collaborative Neuroscience Network.

For the Research Centers of America,

- The CGI-S assessment for subject (b) (6) visit 29, and potentially for subject (b) (6), visit 57, were performed after PK blood draw, deviating from the protocol. I recommend that the review division evaluate whether CGI-S assessment data for these subjects for the visit dates mentioned should be excluded from efficacy assessment.
- There were changes in dates for medications that could potentially affect the eligibility of subjects (b) (6) (b) (6) to be enrolled in study 031-201-00181. Therefore, I recommend that the review division determine whether the eligibility of subjects (b) (6) should be further evaluated.

For the Collaborative Neuroscience Network,

- I recommend that the review division evaluate the impact of the unreported AE and/or concomitant medication for subjects (b) (6).

2. Inspected Studies:

NDA 217006

Study Number: 031-201-00181
Study Title: "A Phase 1b, Open-label, Multiple-dose, Randomized, Parallel-arm, Safety, Tolerability, and Pharmacokinetic Trial of Aripiprazole Intramuscular Depot Administered in the Gluteal Muscle in Adult Subjects with Schizophrenia or Bipolar I Disorder"
Dates of conduct: 8/1/2019 (first informed consent signed) – 7/8/2020 (last trial observation)

Clinical Investigator 1: Dr. Howard A. Hassman
Hassman Research Institute
401 Route 73 North, 30 Lake Center
Suite 100, Marlton, NJ 08053

Clinical Investigator 2: Dr. Peter P. Ventre
Research Centers of America, LLC.
5757 North Dixie Highway,
Oakland Park, FL 33334

Clinical Investigator 3: Dr. David P. Walling
Collaborative Neuroscience
Network, LLC.
12772 Valley View Street, Suite 3
Garden Grove, CA 92845

3. Inspectional Findings

3.1 Dr. Howard A. Hassman (Hassman Research Institute)

ORA investigators Michael Serrano and Tyanna N Hadley inspected Clinical Investigator Dr. Howard A. Hassman at Hassman Research Institute, Marlton, NJ from January 3-6, 2023, and January 17, 2023.

The previous FDA inspection of Dr. Howard A. Hassman was conducted from April 15, 2021, to May 31, 2021, at 175 Cross Keys Road, Berlin, NJ. At the conclusion of the 2021 inspection, Form FDA-483 was not issued. However, one discussion item was addressed regarding a discrepancy between the source record and the data line listing for one of the subject’s Montgomery-Asberg Depression Rating Scale (MADRS) evaluation. The EIR did not specify whether this issue was followed up during the current inspection. However, the studies audited during the current inspection did not have similar findings.

The current inspection included auditing the following items:

- Informed consent process
- Protocol
- Primary efficacy endpoint verification
- Inclusion and exclusion criteria
- Training records
- Delegation log
- Financial disclosure forms
- Institutional review board approvals
- Test article accountability
- Randomization

- Adverse events

At the conclusion of the inspection, investigators Serrano and Hadley did not issue Form FDA 483, but the following were discussed with the management.

Discussion item 1: Discrepancy on the eligibility criteria evaluation for Subject (b) (6)

Per "Clinical Discharge" document collected during inspection, Subject (b) (6) was discontinued from the study on (b) (6) (b) (6)(**Attachment 1, page 2**), due to positive drug screening test results read on (b) (6) (meeting exclusion criteria #2). The subject was previously dosed on (b) (6) (b) (6) (baseline visit), before the drug screening test results were read. The EIR further stated that Dr. Hassman changed the subject's information (b) (6) (about 11 months later), indicating this subject met exclusion criteria #2 on (b) (6) (b) (6) (the day of dosing). Audit history showing the change was collected during the inspection (**Attachment 2**). The ORA investigator is concerned that the updated information incorrectly implied that the subject was dosed on (b) (6) (b) (6), irrespective of meeting exclusion criteria.

Firm's response: The EIR did not state the firm's response.

OSIS Evaluation: The information documented in **Attachment 1** indicates that the subject was appropriately discontinued from the study on (b) (6) once the drug screening results came up positive. However, the initial eligibility information noted in the e-source document as recorded on (b) (6) is accurate and should not have been changed. Given that the protocol did not specify how additional information, such as drug screening results, after the completion of the study visit should be recorded in the source document and that the initial information was accurately reflected in the source documents, this finding has no impact on reliability of the study data.

Discussion item 2: Lack of good clinical practice (GCP) corrections to source documentation

The EIR stated that, for subjects (b) (6) there were discrepancies of visit days for sample collection between two document types. The two document types were a) requisition forms for PK laboratory forms and b) corresponding laboratory reports.

- For subject (b) (6) requisition form copies for sample collections on (b) (6) both indicated a Day 201 visit. The corresponding laboratory reports indicated the Day 199 visit was on (b) (6) and the Day 201 visit was on (b) (6)
- For subject (b) (6) the Day 15 visit occurred on (b) (6) (b) (6) but the requisition form for samples collected on (b) (6) also indicated a Day 15 visit (should have been Day 18 visit). The Day 18 visit requisition form had a collection date of (b) (6) (should have been Day 22 visit).

The EIR also stated discrepancy between the date subject (b) (6) discontinued from the study and the date the subject was contacted for adverse event follow-up documented on progress notes. The subject discontinued from the study (b) (6) (b) (6) but the progress note indicates that the subject was contacted for adverse event follow up on (b) (6). The progress note recorded on (b) (6) stated that the subject reported the event of akathisia stopped on (b) (6) (b) (6) (about a month after the date of documentation).

Firm's response: The EIR did not state the firm's response about the discrepancies for subjects (b) (6) Per the EIR, the site explained that the discrepancy for the akathisia event for subject (b) (6) was due to data entry error and that the subject was followed up in (b) (6).

OSIS Evaluation: The firm's practice of inaccurate/non-contemporaneous documentation of study events is unacceptable. However, the EIR stated that the dates were appropriately captured in the lab reports for subjects (b) (6) and (b) (6) where discrepancies were observed. The site's response for subject (b) (6) appears plausible. Therefore, this finding does not impact reliability of the study data.

3.2 Dr. Peter P. Ventre (Research Centers of America, LLC.)

ORA investigator Angelica M Chica inspected Clinical Investigator Dr. Peter P. Ventre at Research Centers of America, LLC., Oakland Park, FL from January 9-12, 2023, and January 18, 2023.

Dr. Peter P. Ventre has not been previously inspected by FDA.

The current inspection included auditing the following items:

- Informed consent process
- Protocol
- Subject selection criteria
- Institutional review board approvals
- Source data evaluation
- Electronic data capture (EDC) systems
- Adverse event reports
- Randomization
- Investigational drug accountability
- Retention samples
- Monitoring
- Concomitant therapies

At the conclusion of the inspection, investigator Chica did not issue Form FDA 483, but the following were discussed with the management.

Discussion item 1: Information documented in the query section of the electronic source record (e-Source) is not documented in the subject's progress note section in the e-Source and the paper source documents for the study visit.

Per Exhibits provided with the EIR,

1) for Subject (b) (6) ECGs were collected at the screening visit (b) (6) and a finding of "Ectopic Supraventricular Rhythm" was documented on the ECG Analysis Report (paper source record). The Clinical Investigator's response to the query dated (b) (6) requesting for assessment of the clinical significance of the ectopic supraventricular rhythm was documented on the query section of the e-source document.
2) for Subject (b) (6) ECGs were collected at the screening visit (b) (6) and a finding of "First Degree AV Block" was documented on the ECG Analysis Report. The Clinical Investigator's response to the query dated (b) (6) requesting for assessment of the clinical significance of the

First Degree AV Block was documented on the query section of the e-source document.

3) for Subject (b) (6) ECGs were collected at the Day 29 visit on (b) (6) and the Day 57 visit on (b) (6) and a finding of "Left Anterior Hemiblock" was documented on the ECG Analysis Report for both visits. The Clinical Investigator's response to the queries dated (b) (6) (Day 29 visit) and (b) (6) (Day 57 visit) to assess the clinical significance of the finding were documented on the query section of the e-source document.

The ORA Investigator's concern is that the clinical significance assessment outcome for all the three subjects mentioned above was not documented on a) the 12-Lead ECG note section of the e-source document signed by the investigator or co-investigator and b) the ECG Analysis Report (except for Subject (b) (6)). For Subject (b) (6), the ECG report included with the EIR as an exhibit has a comment similar to the query response regarding the ECG findings.

Firm's response: The EIR did not state the firm's response for this discussion item.

OSIS Evaluation: The EIR did not state whether the site's SOP or protocol has a specific requirement on where the outcome of the ECG assessment needs to be documented. Therefore, this finding has no impact on reliability of the study data.

Discussion item 2: Deviation of protocol section 3.7.5. – Clinical Global Impression - Severity (CGI-S), one of the efficacy assessments, was performed after PK blood draw.
Contrary to the protocol which states that all efficacy assessments should be performed prior to PK blood draws, CGI-S was done after PK samples were collected for the following subjects.

- Subject (b) (6), visit 29 on (b) (6) CGI-S was performed at 11:09 am after PK sample was collected at 11:04 am.
- Subject (b) (6), visit 57 on (b) (6) CGI-S was performed 11:07 am after PK sample was collected at 10:17 am. The PK sample collection time was changed to 11:47 am on (b) (6) but per the EIR, no documentation was provided on how the new time was determined.

Firm's response: The EIR did not state the firm's response for this discussion item.

OSIS Evaluation: The CGI-S assessment was performed for subject (b) (6) visit 29, and potentially for subject (b) (6) visit 57, after PK blood draw, deviating from the protocol. I recommend that the review division evaluate whether CGI-S assessment data for these subjects for the visit dates mentioned should be excluded from efficacy assessment.

Discussion item 3: Deviation of protocol sections 3.4.2 (Inclusion criteria) and 3.4.3. (Exclusion criteria).

1. Per protocol section 3.4.3, subjects enrolled to the robust sampling schedule must not have taken oral aripiprazole (Abilify) for 30 days, prior to screening. Subject (b) (6) (screened on (b) (6)) was enrolled in robust sampling schedule. The audit history of the e-source documentation shows that the end date for Abilify was originally documented as (b) (6) (entry date: (b) (6)), but later changed to (b) (6) (entry date: (b) (6)) without documentation of how the new date was determined. Note that the end date (b) (6) was entered on (b) (6) (about 3 months earlier).
2. Per protocol section 3.4.2, subjects must be on a stable dose of one of the oral atypical antipsychotic medications (e.g., quetiapine) for at least 2 months prior to screening. Subject (b) (6) screened on (b) (6) was originally documented to have been taking Seroquel (quetiapine) starting (b) (6) (recorded on (b) (6) (b) (6). This information was later changed to indicate a start date of (b) (6) (recorded on (b) (6)) without documentation of how the new date was determined.

Firm's response: The EIR did not state the firm's response for this discussion item.

OSIS Evaluation: While these may be errors in entering the data (b) (6), I recommend that the review division determine whether the eligibility of these 2 subjects should be further evaluated.

Discussion item 4: Investigational product (IP) was kept in an area with access to hospital personnel other than the study staff.

The EIR stated that although the IP was segregated from the main pharmacy medication, they were housed in an open area in bins (not double locked in a locked cabinet), which can be accessed by hospital personnel other than the study staff. The EIR also stated that one bottle of IP was missing after drug accountability was performed. A note to file included with the EIR states that a missing bottle was noted during the study closeout visit.

Firm's response: The EIR stated that the site implemented corrective action to limit accessibility of IP to only study staff. The IP will be kept in labeled plastic bins with lids and locks around the lids. The keys to these locks will be only accessible to study staff.

OSIS Evaluation: The protocol stipulated that investigational product is stored in a locked cabinet. Therefore, this finding is a protocol violation. However, there is no indication that the IP were accessed by unauthorized people during the conduct of the study. Therefore, this finding has no impact on reliability of the study data. The site's proposed changes appear appropriate.

Discussion item 5: Discrepancies in the informed consent form (ICF) log with regards to the dates of when the ICFs were obtained.

The EIR stated that for the subjects listed in the table below, discrepancies were noted in the date when the ICF was obtained between the ICF and the subject enrollment log.

Subject number	Date on the ICF	Date of IC on the enrollment log	Date of screening per individual data listing
(b) (6)			
			page 4074 (PDATA-20.3)
(b) (6)			
			page 4072 (PDATA-20.3)

(b) (6)			Screening failure (b) (6) (b) (6), page 4714 (PDATA-24)
(b) (6)			Screening failure (b) (6) (b) (6), page 4714 (PDATA-24)
(b) (6)			Screening failure (b) (6) (b) (6), page 4714 (PDATA-24)
(b) (6)			page 4073 (PDATA-20.3)

Firm's response: The EIR did not state the firm's response for this discussion item.

OSIS Evaluation: The firm's practice of inaccurate documentation of the dates of informed consent on the enrollment log is unacceptable However, audit trails of the e-source data included with the ICF document for each subject, collected during inspection, confirm the dates of consent indicated on the electronically signed ICF. Based on information from individual subject data listing, these subjects were screened on or after the date of informed consent. Therefore, this finding is a minor recording deviation and has no impact on neither the reliability of the study data nor safety of the subjects.

3.3 Dr. David P. Walling (Collaborative Neuroscience Network, LLC.)

ORA investigators Julian C Hanson and Samson O Oluseye inspected Clinical Investigator Dr. David P. Walling at Collaborative Neuroscience Network, LLC., Garden Grove, CA, from January 9-13, 2023.

Dr. David P. Walling was previously inspected by FDA at the same site in May 2021. No Form FDA 483 was issued; however, a discussion item regarding lack of documentation of protocol required diagnosis of schizophrenia for one subject was discussed. The EIR did not specify whether this issue was followed up during the current inspection. However, the current inspection did not have similar finding.

The current inspection included auditing the following items:

- Subject eligibility,
- Informed consent
- Dosing
- Test article accountability and storage
- PK sample collections
- Protocol required activities
- Concomitant medications
- Adverse events
- Investigational review board oversite
- Communications
- Monitoring
- Electronic data capture (EDC) systems
- Retention samples

At the conclusion of the inspection, investigators Hanson and Oluseye did not issue Form FDA 483, but the following was discussed with the management.

Discussion item: Adverse events (AE) and concomitant medications documented in the paper source records were not documented in the electronic case report forms (eCRF)

The EIR stated that for the subjects listed in the table below the AE and concomitant medication were documented in paper source records, but not in eCRF.

Subject #	AE	Concomitant medication
(b) (6)	Rash	Benadryl
	Neck stiffness, Upper respiratory infection	
	Right shoulder strain	

Firm's response: The EIR stated that Dr. Walling acknowledged the importance of reporting adverse events and explained that during the COVID pandemic the site lost their QA personnel, which is now back in place. The site also stated paper documents were not uploaded for the audited study, but now photographs of paper notes are attached to eCRF, which allows for remote review and monitoring of the documents. The EIR also stated that the site will use adverse event logs for all trials, which will help ensure that adverse events are not missed.

OSIS Evaluation: With implementation of adequate QA procedures, the proposed corrective action can help prevent occurrence of similar issues in the future. The AE and concomitant medication were not reported in data listings. The concomitant medication diphenhydramine (Benadryl), as a CYP2D6 Inhibitor, is prohibited per protocol, Table 4.1-1. The adverse events are indicated as mild in the paper source records. I recommend that the review division evaluate the impact of these unreported AE and concomitant medication on study data and subject safety. The documents collected during the inspection are included in **Attachment** (b) (6) .

Melkamu Getie-Kebtie, Ph.D., R.Ph
Pharmacologist

Attachments

1. Clinical Discharge for (b) (6)
2. Audit history for e-Source document for (b) (6)
3. Progress note – Subject (b) (6)
4. Progress note – Subject
5. Progress note – Subject

Draft: MG 2/13/2023, 2/14/2023, 2/16/2023, 2/17/2023, 2/21/2013
Edit: SA 02/13/2023,2/14/23, 2/16/23, 2/17/23, 2/21/23, 2/22/23; JC 2/17/2023, 2/22/2023

OSIS File #: BE 9553

eNSpect Assignment ID: 202256
eNSpect OpID: 230691 (Howard A. Hassman), 228299 (Peter P. Ventre) and 230677 (David P. Walling)

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

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/s/

MELKAMU GETIE KEBTIE
02/22/2023 11:35:23 AM

STANLEY AU
02/22/2023 12:44:39 PM
Team Lead

SEONGEUN CHO
02/22/2023 12:50:34 PM

M E M O R A N D U M

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

DATE: 1/18/2023

TO: Division of Psychiatry (DP)
Office of Neuroscience (ON)

FROM: Office of Study Integrity and Surveillance (OSIS)

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

RE: NDA 217006

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS conducted an inspection of the site in (b) (4) The inspection was conducted under the following submissions: NDAs non-responsive and non-responsive

The following items were discussed with the site:

NON-RESPONSIVE

After review if the discussion items and the site's response, OSIS concluded that data from the reviewed studies were reliable.

Site

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

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/s/

WENDY NG
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