

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202971Orig1s000**

**OTHER REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: February 11, 2013

Reviewer: Loretta Holmes, BSN, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Abilify Maintena (Aripiprazole) for Extended-release  
Injectable Suspension

Application Type/Number: NDA 202971

Applicant: Otsuka Pharmaceutical Co., Ltd.

OSE RCM #: 2012-2081

**\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\***

## Contents

1	INTRODUCTION .....	3
1.1	Regulatory History .....	3
1.2	Product Information .....	3
2	MATERIALS REVIEWED .....	4
3	RESULTS .....	4
4	CONCLUSIONS AND RECOMMENDATIONS .....	5
	APPENDICES .....	6

## 1 INTRODUCTION

This review evaluates the proposed Sterile Water for Injection container label, Abilify Maintena container labels, carton labeling, insert labeling, and Quick Reference Guide and Instructions for Use (IFU) for Abilify Maintena (Aripiprazole) for Extended-release Injectable Suspension, NDA 202971, for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

This NDA was first submitted on September 26, 2011 but received a Complete Response (CR) action on July 26, 2012. The complete response was issued because GMP deficiencies were found at (b) (4), the manufacturer of the (b) (4) vials of Sterile Water for Injection (SWFI) that were co-packaged in the Abilify Maintena kits.

The Applicant submitted a resubmission after Complete Response on August 31, 2012. Since the Applicant was unable to identify another supplier of (b) (4) SWFI vials, a 5 mL vial is now being proposed. Thus, the labels and labeling have been revised to reflect the new volume of SWFI being supplied in the kits and to update the reconstitution directions.

### 1.2 PRODUCT INFORMATION

The following product information was provided in the August 31, 2012 submission.

- Active Ingredient: Aripiprazole
- Indication of Use: Treatment of schizophrenia
- Route of Administration: Intramuscular injection into the gluteal muscle
- Dosage Form: for Extended-release Injectable Suspension
- Strengths: 300 mg per vial and 400 mg per vial
- Dose and Frequency: The recommended starting and maintenance dose is 400 mg monthly. If there are adverse reactions with the 400 mg dosage, consider reducing the dosage to 300 mg monthly. Dosage adjustments are recommended for patients who are CYP2D6 poor metabolizers and for patients taking CYP2D6 inhibitors, CYP3A4 inhibitors, or CYP3A4 inducers for greater than 14 days. For these patients, the dose is adjusted to 160 mg, 200 mg or 300 mg or Abilify Maintena use is not recommended.
- How Supplied: Kits containing 300 mg per vial or 400 mg per vial of Abilify Maintena; one 5 mL vial of Sterile Water for Injection, USP; one 3 mL Luer Lock syringe with pre-attached 21 gauge, 1.5 inch Hypodermic Needle-Pro® safety needle with needle protection device; one 3 mL BD Luer-Lok™ disposable syringe with BD Luer-Lok tip; one vial adapter; one 21 gauge, 1.5 inch Hypodermic Needle-Pro® safety needle with needle protection device; and one 21 gauge, 2 inch Hypodermic Needle-Pro® safety needle for obese patients with needle protection device

- Storage: Store at 25°C (77°F), excursions permitted between 15°C and 30°C (59°F to 86°F)

## 2 MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) previously evaluated the labels, labeling, and packaging for Abilify Maintena in OSE Review 2011-3916 dated May 18, 2012. Since the primary change with this resubmission is the change in volume for the SWFI vial, we focused our review on the changes in the container labels, carton labeling, insert labeling, Quick Reference Guide and Instructions for Use submitted on August 31, 2012 (see Appendices A, B, and C) since labeling negotiations were previously completed during the first review cycle. Additionally, we reviewed actual samples of the revised 300 mg and 400 mg kits provided by the Applicant.

## 3 RESULTS

Our review of the Sterile Water for Injection (SWFI) vial label, Abilify Maintena vial labels, carton labeling, Quick Reference Guide, IFU, and insert labeling determined that in sections 2.4 and 16.1 of the insert labeling, the Quick Reference Guide (QRG) and Instructions for Use, the information regarding the kit contents has been revised to indicate a 5 mL vial of Sterile Water for Injection is included. This information accurately reflects the newly proposed 5 mL vial of SWFI to be supplied in the kits. The Applicant has also made minor editorial changes that do not raise any new safety concerns.

On the container labels, carton labeling and in section 16.2 of the insert labeling, the storage statement was revised from “(b) (4)” to read: “Store at 25°C (77 °F), excursions permitted between 15°C and 30°C (59°F to 86 °F) [see USP Controlled Room Temperature]”. DMEPA has informed CMC of this change, and we defer to them regarding the storage statement.

Additionally, we have identified the following deficiencies:

### Container Labels

- The container labels for Abilify Maintena are clear see-through labels on clear glass vials which may decrease readability of the information contained on the label.

### Insert Labeling, Quick Reference Guide, and Instructions for Use

- One or both of the following statements regarding the excess amount of SWFI remaining in the vial were added to sections 2.4 and 2.5 of the insert labeling as well as the Quick Reference Guide and Instructions for Use:
  - “The vial will have excess Sterile Water for Injection (b) (4); discard vial with the unused portion.”
  - “Residual Sterile Water for Injection will remain in the vial following withdrawal (b) (4); discard vial with the unused portion.”

The use of dashes in the statements as well as omission of the unit of measure following the number 3 are error prone because the use of dashes and omission of the unit of measure may cause (b) (4) to be misread or misinterpreted as (b) (4), especially if the font size is small. Additionally, the use of (b) (4) may be misread as the amount of SWFI that should be used for reconstitution.

#### 4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes there are areas vulnerable to confusion in the proposed labels and labeling that can lead to medication errors. DMEPA recommends the following be implemented prior to approval of this NDA supplement:

##### A. Abilify Maintena Container Labels

The information on the container labels is very difficult to read because the labels are clear and the glass vials are translucent and clear as well. This decreases the readability of the print on the vial label. We recommend the use of a non-clear vial label that provides sufficient contrast between the text and background color so that the information on the labels can be easily read.

##### B. Insert Labeling, Quick Reference Guide, and Instructions for Use

One or both of the following statements regarding the excess amount of SWFI remaining in the vial were added to sections 2.4 and 2.5 of the insert labeling as well as the Quick Reference Guide and Instructions for Use:

- “The vial will have excess Sterile Water for Injection (b) (4), discard vial with the unused portion.”
- “Residual Sterile Water for Injection will remain in the vial following withdrawal (b) (4) discard vial with the unused portion.”

The use of dashes in the statements as well as omission of the unit of measure following the number (b) (4) are error prone because the use of dashes and omission of the unit of measure may cause (b) (4) to be misread or misinterpreted as (b) (4), especially if the font size is small. Additionally, the use of (b) (4) may be misread as the amount of SWFI that should be used for reconstitution; therefore, we recommend its removal.

We recommend revising the statements as follows:

- “The vial will have excess Sterile Water for Injection; discard any unused portion.”
- “Residual Sterile Water for Injection will remain in the vial following withdrawal; discard any unused portion.”

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sandra Rimmel, Project Manager, at 301-796-2445.

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

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

LORETTA HOLMES  
02/11/2013

IRENE Z CHAN  
02/11/2013



## INTRODUCTION

On September 24, 2011, Otsuka Pharmaceutical Company, Ltd submitted a New Drug Application (202-971) for Abilify Maintena (aripiprazole) extended release suspension for injection for maintenance treatment of schizophrenia.

Aripiprazole is currently available on the market as Abilify<sup>®</sup> in an oral solution, tablet formulation and an injectable IM formulation under NDAs 21-436, 21-713, 21-729 and 21-866. The primary NDA 21-436 for the tablet formulation was first approved November 15, 2002 for schizophrenia. Subsequent NDA supplement approvals followed to include the oral solution approved for schizophrenia on December 10, 2004 (NDA 21-713); the oral disintegrating tablet for schizophrenia Abilify Dismelt<sup>®</sup> (NDA 21-729) on June 7, 2006; and the injectable formulation (NDA 21-866) approved September 20, 2006 for bipolar disorder and schizophrenia.

The Division of Psychiatry Products (DPP) consulted the Pediatric and Maternal Health Staff to review and update the pregnancy and nursing mothers information in the Abilify Maintena labeling.

PMHS - MHT discussed labeling at a meeting with DPP on June 19, 2012 and subsequently, the following information request was sent to the sponsor:

*We are aware of several published case reports concerning the presence of aripiprazole in breast milk. Please provide ASAP any data and a review of the literature [including all references] to support possible inclusion of such information in the label for Abilify Maintena.*

On June 27, 2012, the sponsor responded, submitting results from their clinical safety database search, literature searches, and BMS Corporation safety database search results. The sponsor concluded that data were limited with regard to aripiprazole presence in human breast milk and that the current labeling was adequate and did not recommend changes.

On July 2, 2012, the following information request was sent to the sponsor per the Review Division:

*Regarding your submission for N 202,971 dated 6/27/12 regarding case reports concerning presence of aripiprazole in breast milk. On p. 8 of the submission you state: 'Exposure via breast feeding was reported but limited information was provided regarding the neonates in reports 13421490, 13920624, 14066799, 15240369, 15338056, 15519838, 16464372 and 16691552.' Can you send us the case reports you cite above?*

*Also, why do you think exposure via breast feeding is occurring?*

The sponsor responded on July 3, 2012, summarizing the case reports in question and explaining that they believe that exposure is occurring during breast feeding because patients are using aripiprazole to treat symptoms of their psychiatric illness and not abstaining from breast feeding.

This PMHS- MHT provides a review of the case reports and suggested revisions and re-ordering of existing information related to pregnancy and nursing mothers in the Abilify Maintena

labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

## **BACKGROUND**

### ***Aripiprazole***

Aripiprazole is a second-generation atypical antipsychotic widely used as first line treatment for patients with schizophrenia and bi-polar disorder. Abilify Maintena (aripiprazole IM depot) is made from sterile aripiprazole monohydrate manufactured (b) (4) drug substance that is currently found in the marketed drug product Abilify . Abilify is currently included in the National Atypical Antipsychotic Pregnancy Registry run by Massachusetts General Hospital Center for Women's Mental Health.

### ***Schizophrenia and Pregnancy***

Women with major psychiatric disorders such as schizophrenia have an increased risk of, complications during pregnancy, placental abnormalities and birth complications.<sup>1</sup> Women with schizophrenia displayed more episodes of placental abruption and have infants with neonatal complications at birth, low birth weight and growth, and cases of cardiovascular congenital anomalies.<sup>2</sup>

### ***Aripiprazole and Pregnancy***

There are limited data available with regard to the use of aripiprazole and pregnancy. Several case reports have been published with regard to aripiprazole prenatal exposures. However it is unclear whether aripiprazole poses a risk during pregnancy. The case reports regarding aripiprazole exposure during pregnancy included a varying range of dosage, treatment length and different timing of prenatal exposure.<sup>3</sup> The cases described by Gentile et al. (2011) all resulted in healthy outcomes and were inconclusive as to whether aripiprazole poses a risk during pregnancy.<sup>3</sup> In such cases the benefit of keeping the mother on antipsychotic treatment may outweigh any possible unknown risk to the fetus.

### ***Aripiprazole and Human Breast Milk***

There are limited data available with regard to aripiprazole and human breast milk. Two case reports have been published which demonstrate that aripiprazole levels are present in human milk. Schlotterbeck P et al. (2007) reported approximate 20% breast milk to maternal plasma level concentration ratio which is similarly in range to breast milk measured in other second-generation antipsychotics.<sup>4</sup> Watanabe N et al (2011) reported measuring 38.7 ng/mL of aripiprazole in human breast milk after the mother had been administered 18 mg/day of

---

<sup>1</sup> Jablensky AV, Morgan V, Zubrick SR, Bower C, Yellachich LA. Pregnancy, delivery and neonatal complications in a population cohort of women with schizophrenia and major affective disorders. *Am J Psychiatry*. 2005 Jan;162(1):79-91.

<sup>2</sup> Hizkiyahi R, Levy A, Sheiner E. Pregnancy Outcome of Patients with Schizophrenia. *Am J Perinatol*. 2010 Jan;27(1):19-23.

<sup>3</sup> Gentile S, Tofani S, Bellantuono C. (2011, August). Aripiprazole and Pregnancy A Case Report and Literature Review [Letter to the editor]. *J Clin Psychopharmacology*, p. 531.

<sup>4</sup> Schlotterbeck P, Leube D, Kircher T, Hiemke C, Grunder G. (2007, February 12). Aripiprazole in human milk [Letter to the editor]. *International J Neuropsychopharmacology*, p. 433.

aripiprazole.<sup>5</sup> Several other case reports of postpartum women taking aripiprazole were reviewed but did not provide sufficient detail because either the mother decided not to breast feed or breast milk samples were not taken.

## **DISCUSSION AND CONCLUSION**

### **Pregnancy and Nursing Mothers Labeling**

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

Labeling recommendations were made based on a review of the current literature and case reports provided by the sponsor where it was determined that although data are limited, aripiprazole is present in human breast milk.

The sponsor's June 27, 2012, submission included current labeling language for pregnancy and nursing mothers, examples of language used in the protocols for women of childbearing potential, pregnant women and nursing mothers, Otsuka's clinical safety database search results, literature search results, BMS Corporation safety database search results and discussion/conclusion. The sponsor concluded based on their literature search and review of case reports that there was no evidence to suggest that aripiprazole posed a threat to infants or fetuses after exposure during pregnancy or while breast feeding. The sponsor also concluded that there was not enough evidence regarding breast feeding exposure and that the current labeling language be retained.

*Reviewer comment: The PMHS-MHT reviewed the literature and available case reports provided by the sponsor and have determined that aripiprazole concentrations are present in breast milk. The PMHS-MHT believes that although the data are limited, the label should state that aripiprazole is present in human breast milk. In addition, regulatory language was added to the nursing mothers section. This language requires a determination of discontinuing drug or discontinuing breast feeding as opposed to the sponsor's recommendation of not using during breast feeding. The edited labeling excerpts are found below.*

The sponsor's July 2, 2012, response included a more detailed report of the cited case reports from the BMS Corporate safety database that were found in the June 27, 2012, submission. The sponsor concluded that exposure during breast feeding was occurring and that women who

---

<sup>5</sup> Watanabe N, Kasahara M, Sugibayashi R, et al. (2011). Perinatal Use of Aripiprazole A Case Report [Letter to the editor]. *J Clin Psychopharmacology*, p. 377.

continue to breast feed during aripiprazole therapy should be counseled by their doctors. Additionally, the sponsor again stated that the data is limited and the original labeling language should be retained.

*Reviewer comment: The PMHS-MHT agrees with the sponsor's conclusion that aripiprazole is present in human breast milk, however the PMHS-MHT believes that the labeling should be edited as shown below.*

Additionally, the PMHS-MHT recommends that Abilify Maintena be added to the atypical antipsychotic pregnancy registry. Once Abilify Maintena is added to the atypical antipsychotic pregnancy registry then the registry information should be added to Section 8.1 of the labeling.

**PMHS LABELING RECOMMENDATIONS (label excerpts):**

*In addition, the correct regulatory language was added to this section.*

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

-----USE IN SPECIFIC POPULATIONS-----

- *Pregnancy:* Based on animal data, may cause fetal harm (8.1)
- *Nursing Mothers:* Discontinue drug or nursing, taking into consideration importance of drug to the mother (8.3)

**FULL PRESCRIBING INFORMATION: CONTENTS**

**8.1 Pregnancy**

*Pregnancy Category C*

Risk Summary

Adequate and well controlled studies with ABILIFY MAINTENA have not been conducted in pregnant women. Neonates exposed to antipsychotic drugs (including ABILIFY MAINTENA<sup>®</sup>) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits at doses 1 - 10 times the oral maximum recommended human dose [MRHD] of 30mg/day on a mg/m<sup>2</sup>. ABILIFY MAINTENA<sup>®</sup> should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor neonates exhibiting extrapyramidal or withdrawal symptoms. Some neonates recover within hours or days without specific treatment; others may require prolonged hospitalization.

Animal Data

Pregnant rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral maximum recommended human dose [MRHD] of 30mg/day on a mg/m<sup>2</sup> body surface area) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 mg/kg and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased body weights (10 mg/kg and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg. Postnatally, delayed vaginal opening was seen at 10 mg/kg and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rats receiving aripiprazole injection intravenously (3 mg/kg/day, 9 mg/kg/day, and 27 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose, which also caused some maternal toxicity.

Pregnant rabbits were treated with oral doses of 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day (2 times, 3 times, and 11 times human exposure at the oral MRHD of 30mg/day based on AUC and 6 times, 19 times, and 65 times the oral MRHD of 30mg/day based on mg/m<sup>2</sup> body surface area) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 mg/kg and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternbrae at 30 mg/kg and 100 mg/kg), and minor skeletal variations (100 mg/kg).

In pregnant rabbits receiving aripiprazole injection intravenously (3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 10 mg/kg, which produced 5 times the human exposure at the oral MRHD based on AUC and is 6 times the oral MRHD of 30mg/day based on mg/m<sup>2</sup> body surface area.

In a study in which rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral MRHD of 30mg/day on a mg/m<sup>2</sup> body surface area) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg.

An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were seen at this dose.

In rats receiving aripiprazole injection intravenously (3 mg/kg/day, 8 mg/kg/day, and 20 mg/kg/day) from day 6 of gestation through day 20 postpartum, an increase in stillbirths was seen at 8 mg/kg and 20 mg/kg, and decreases in early postnatal pup weights and survival were seen at 20 mg/kg. These doses produced some maternal toxicity. There were no effects on postnatal behavioral and reproductive development.

### **8.3 Nursing Mothers**

Aripiprazole is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### **17.10 Nursing**

Patients should be advised to discontinue nursing or to discontinue ABILIFY MAINTENA, taking into account the importance of the drug to the patient. [*see Use in Specific Populations (8.3)*].

## **APPENDIX A – Recommended revisions for Abilify Maintena Labeling**

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

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

CARRIE M CERESA  
07/16/2012

MELISSA S TASSINARI  
07/18/2012

LISA L MATHIS  
07/18/2012

## SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

<b>Product Title</b>	<b>ABILIFY MAINTENA (aripiprazole) for extended-release injectable suspension, for intramuscular use</b>
Applicant	Otsuka Pharmaceutical Company
Application/Supplement Number	NDA 202971
Type of Application	Original
Indication(s)	Treatment of schizophrenia
Established Pharmacologic Class <sup>1</sup>	Atypical antipsychotic
Office/Division	ODEI/DPP
Division Project Manager	Sonny Saini
Receipt Date	September 26, 2011
PDUFA Goal Date	July 26, 2012
SEALD Review Date	July 12, 2012
SEALD Labeling Reviewer	Debra Beitzell
SEALD Division Director	Laurie Burke

<sup>1</sup> The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

## Selected Requirements of Prescribing Information (SRPI)

### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:** *DPP to grant waiver of 1/2 page HL limit in approval letter.*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 4. White space must be present before each major heading in HL.

**Comment:**

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:** *Under the W&P heading, Delete reference to 5.1 after the Cerebrovascular warning (reference should be to 5.2 only) and after the Dyslipidemia and Weight Gain warnings, add references to 5.5.*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

## Selected Requirements of Prescribing Information (SRPI) Revised

• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

**Comment:**

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

**YES**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

**Comment:**

#### Product Title

**YES**

10. Product title in HL must be **bolded**.

**Comment:**

#### Initial U.S. Approval

**YES**

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning

**YES**

12. All text must be **bolded**.

**Comment:**

**YES**

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

## Selected Requirements of Prescribing Information (SRPI) Revised

### Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

### Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

### Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

### Comment:

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

### Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

### Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

### Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

### Comment:

### Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

### Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

### Comment:

**N/A**

## Selected Requirements of Prescribing Information (SRPI) Revised

24. Each contraindication is bulleted when there is more than one contraindication.

**Comment:**

### Adverse Reactions

- NO** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

**Comment:** *Insert manufacturer's US phone number into the adverse reactions reporting statement.*

### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

**Comment:**

### Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

**Comment:** *Change revision date from June 2012 to July 2012.*

---

## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

**Comment:** *Insert a horizontal line in between the TOC and the FPI.*

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

**Comment:**

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

**Comment:** *Correct heading in TOC for subsection 5.11 to match FPI (i.e., change from “(b)(4)” to “Dysphagia”) and delete subsection 5.12 from TOC. Correct all of the subheadings in TOC under section 17 to match the subheadings in FPI.*

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

**Comment:**

## Selected Requirements of Prescribing Information (SRPI) Revised

- YES** 32. All section headings must be **bolded** and in UPPER CASE.  
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.  
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.  
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”  
Comment:

### Full Prescribing Information (FPI)

#### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.  
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.  
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>

## Selected Requirements of Prescribing Information (SRPI) Revised

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

### Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

### Comment:

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see *Warnings and Precautions (5.2)*]”.

Comment: Correct presentation of cross references under subsections 8.5, 12.3, and 17.1. Cross references should be in sentence case letters (not all uppercase) and should reference the section heading (not subsection heading). See example above.

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

### Comment:

## FULL PRESCRIBING INFORMATION DETAILS

### Boxed Warning

- YES** 42. All text is **bolded**.

### Comment:

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

### Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

### Comment:

### Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

### Comment:

### Adverse Reactions

**YES**

## Selected Requirements of Prescribing Information (SRPI) Revised

46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

**Comment:**

**NO**

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

**Comment:** Text highlighted above needs inserted into statement preceding postmarketing experience adverse reactions.

### Patient Counseling Information

**YES**

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:**

---

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

DEBRA C BEITZELL  
07/12/2012

ANN M TRENTACOSTI  
07/12/2012  
Signing for Laurie Burke

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

**PATIENT LABELING REVIEW**

Date: July 3, 2012

To: Thomas Laughren, M.D.  
Director  
**Division of Psychiatry Products (DPP)**

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

From: Robin Duer, MBA, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: DMPP Review of Patient Labeling (Medication Guide)

Drug Name (established name): Abilify Maintena (aripiprazole)

Dosage Form and Route: extended release suspension for injection

Application Type/Number: NDA 202971

Applicant: Otsuka Pharmaceuticals

## 1 INTRODUCTION

On September 26, 2011, Otsuka Pharmaceuticals submitted for the Agency's review a new drug application (NDA) for Abilify Maintena (aripiprazole) extended release suspension for injection. The purpose of the submission is to provide for an extended release suspension for injection for the maintenance treatment of schizophrenia.

This review is written in response to a request by the Division of Psychiatry Products (DPP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for Abilify Maintena (aripiprazole) extended release suspension for injection.

DPP recommended that DMPP use the approved Abilify (aripiprazole) MG as a comparator for the Abilify Maintena (aripiprazole) extended release suspension for injection MG review. The approved Abilify (aripiprazole) MG is for the tablet, orally disintegrating tablet (ODT), oral solution and short-acting injection formulations for Abilify. We note that the Abilify short-acting injection formulation is not specifically mentioned in the approved Abilify MG and that DMPP has not recently reviewed this MG.

## 2 MATERIAL REVIEWED

- Draft Abilify Maintena (aripiprazole) extended release suspension for injection Medication Guide (MG) received on September 26, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on June 26, 2012
- Draft Abilify Maintena (aripiprazole) extended release suspension for injection Prescribing Information (PI) dated September 26, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on June 26, 2012
- Approved Abilify (aripiprazole) MG dated February 22, 2012

## 3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information

- ensured that the MG 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 on the correspondence.
- Our annotated version of the MG is appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.
- Consult DMPP for a comprehensive review of the approved Abilify (aripiprazole) MG at the next labeling opportunity.

Please let us know if you have any questions.

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

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

ROBIN E DUER  
07/03/2012

MELISSA I HULETT  
07/03/2012

LASHAWN M GRIFFITHS  
07/03/2012

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

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

**Memorandum**

**Date:** June 29, 2012

**To:** **Sonny Saini, PharmD, MBA**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products (DPP)**

**From:** Susannah Hubert, MPH  
Regulatory Review Officer  
Division of Consumer Drug Promotion, OPDP

Jessica Cleck Derenick, PhD  
Regulatory Review Officer  
Division of Professional Drug Promotion, OPDP

**Subject:** **OPDP Comments on ABILIFY MAINTENA (aripiprazole)**  
**extended-release injectable suspension – NDA 202971**

---

OPDP has reviewed the proposed product labeling (PI) and Medication Guide for ABILIFY MAINTENA (aripiprazole) extended-release injectable suspension, using the substantially complete PI and Medication Guide provided by Sonny Saini on June 26, 2012. The following comments are provided below, directly on the attached labeling.

Please feel free to contact Susannah Hubert at 301-796-3245 or Jessica Cleck Derenick at 301-796-0390, or via email, with any questions or clarifications.

Thank you for the opportunity to comment on this proposed labeling.

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

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SUSANNAH HUBERT  
06/29/2012

**MEMORANDUM**

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

---

**CLINICAL INSPECTION SUMMARY**

**DATE:** June 19, 2012

**TO:** Sonny Saini, Pharm.D., M.B.A., Senior Regulatory Project Manager  
Gregory Dubitsky, M.D., Medical Officer  
Division of Psychiatry Products

**FROM:** John Lee M.D., Medical Officer  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Susan Thompson, M.D., Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Lauren Iacono-Connors, Ph.D., Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**APPLICATION:** NDA 202-971

**APPLICANT:** Otsuka Pharmaceutical Development and Commercialization, Inc.

**DRUG:** Abilify<sup>®</sup> (aripiprazole) Intramuscular Depot Injection

**NME:** No

**INDICATION:** Maintenance treatment of schizophrenia

  

**THERAPEUTIC CLASSIFICATION:** Standard

**CONSULTATION REQUEST DATE:** December 27, 2011

**INSPECTION SUMMARY GOAL DATE:** May 21, 2012

**DPP ACTION GOAL DATE:** June 20, 2012

**PDUFA DUE DATE:** July 26, 2012

## I. BACKGROUND

Schizophrenia is a psychotic disorder associated with profound long-term psychosocial impairments affecting about 0.5% of the United States (U.S.) population. Currently available therapies are only partially effective in alleviating acute and chronic symptoms, and three-fourth of outpatients discontinue medications due to lack of efficacy and/or medication side effects, particularly extrapyramidal symptoms (**EPS**). Very few patients return to baseline psychosocial functioning, even with appropriate therapies.

Abilify® (aripiprazole) is approved in the U.S. for the treatment of schizophrenia, bipolar disorder, and major depressive disorder. Abilify® has an excellent side effect profile: low risks of EPS and prolactin elevation, decreased adrenergic and anticholinergic effects, and minimal weight gain. The favorable side effect profile makes aripiprazole an excellent candidate for a long-acting depot formulation that may significantly enhance treatment compliance and patient outcomes.

### Protocol 31-07-246 (ASPIRE US)

This was a phase 3, randomized, double-blind, placebo-controlled study conducted to evaluate the efficacy, safety, and tolerability of depot IM aripiprazole maintenance therapy in subjects with schizophrenia. The entire study consisted of multiple phases following initial *Screening* to determine potential subjects: (1) *Conversion* from pre-study antipsychotic medications to oral aripiprazole, (2) *Oral Stabilization* on aripiprazole, (3) conversion to depot IM aripiprazole and *Depot Stabilization*, and (4) *Randomization* and long-term depot maintenance, placebo or depot IM aripiprazole. Long-term maintenance depot IM aripiprazole therapy was offered to subjects that advanced to the randomized phase through enrollment in an optional open-label study (Study 31-07-248). Subjects not electing to enroll in (or not eligible for) the open-label study were treated with appropriate antipsychotic medication with safety follow-up.

#### • **Subject Selection**

##### Inclusion Criteria

- Men or women 18 to 60 years of age (inclusive) with schizophrenia (at least 3 years) diagnosed according to the criteria specified in *Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR)*
- History of symptom exacerbation with interruption or discontinuation of antipsychotic medication, currently on an antipsychotic medication other than clozapine

##### Exclusion Criteria

- DSM-IV-TR diagnoses other than schizophrenia
- Demonstrated resistance to antipsychotic medication, or response only to clozapine
- History of seizures, neuroleptic malignant syndrome, or clinically significant tardive dyskinesia
- Electroconvulsive therapy within 180 days of the oral dose stabilization phase
- Clinically significant abnormalities in laboratory tests or electrocardiogram (**ECG**)
- Hospitalization for more than 30 days; uncontrolled thyroid function abnormalities
- Dependence on substances of abuse; two positive drug screens for cocaine; history of incarceration
- Prior participation in a aripiprazole IM depot study; use of an investigational agent within 30 days
- Hypersensitivity to antipsychotic agents, including aripiprazole

#### • **Study Assessment**

- Primary efficacy endpoint: Time from randomization to exacerbation of psychotic symptoms (relapse) or impending relapse during the randomized phase, as defined by any of the following criteria:
  - Clinical Global Impression of Improvement (**CGI-I**) score of  $\geq 5$  (minimally worse), AND an increase in any of the four items on Positive and Negative Syndrome Scale (**PANSS**) to an item score  $> 4$  with an absolute increase of  $\geq 2$  on any given item or  $\geq 4$  combined: (1) conceptual disorganization, (2) hallucinatory behavior, (3) suspiciousness, or (4) unusual thought content

- Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), excluding hospitalization for psychosocial reasons
- Clinical Global Impression of Severity (**CGI-S**) of Suicide (**CGI-SS**) score of 4 (severely suicidal) or 5 (suicide attempt) on Part 1, or score of 6 (much worse) or 7 (very much worse) on Part 2
- Violent behavior resulting in significant injury to self or others, or damage to property
- Key secondary efficacy endpoint: Percentage of subjects meeting the criteria for exacerbation of psychotic symptoms or impending relapse (criteria as described above)
- **Study Phases and General Study Design**
  - *Screening Phase (Days -42 to -2, one or more visits as needed):* If already on (or prescribed) oral aripiprazole monotherapy at screening, the subject continued into the oral stabilization phase directly. Washout of any prohibited medications occurred during the screening phase.
  - *Phase 1, Conversion (4 to 6 weeks, weekly visits):* Any antipsychotic medication (other than oral aripiprazole) was tapered off and replaced with oral aripiprazole monotherapy at a dose of 10 or 15 mg over 4 - 6 weeks. Higher doses were permitted based on investigator judgment of clinical need.
  - *Phase 2, Oral Stabilization (4 to 12 weeks, bi-weekly visits):* If without antipsychotic medication therapy for more than 3 consecutive days at screening, subjects entered this phase directly after being prescribed daily oral aripiprazole not exceeding 30 mg. Subjects continued into the next (depot stabilization) phase if clinically stable on 10 to 30 mg at two consecutive study visits.
  - *Phase 3, Depot Stabilization (12 to 36 weeks, 4 weekly visits then bi-weekly visits):* All subjects initially received aripiprazole IM depot 400 mg. A single decrease to 300 mg was permitted for tolerability, as was a single return to the original 400 mg dose, as clinically required. Oral aripiprazole was continued for the first two weeks (flexible dosing, 10 - 20 mg) to maintain therapeutic plasma concentrations. If stable for 12 consecutive weeks, subjects continued into the main (randomized double-blind) study phase.
  - *Phase 4, Randomized Blinded Depot Maintenance (52 weeks, bi-weekly visits and phone calls):* Eligible subjects were randomized 2:1 to double-blind treatment for 52 weeks with either aripiprazole IM depot (last stabilization dose) or placebo.
    - All injections were administered every four weeks by an unblinded Site Study Drug Manager. Subjects were evaluated bi-weekly for signs of impending relapse or exacerbation of psychotic symptoms, supplemented with weekly phone interviews between visits to determine whether or not the scheduled visit should be moved forward.
    - Any signs of impending relapse or exacerbation of psychotic symptoms resulted in withdrawal from the study for lack of efficacy. The investigational medication was replaced with an alternate antipsychotic medication(s).
- **Prohibited Medications During Study**
  - Antipsychotics, antidepressants, and mood stabilizers
  - CYP2D6 or CYP3A4 inhibitors; CYP3A4 inducers
  - Use of more than one benzodiazepine

## II. GCP INSPECTIONS

This study was completed over 30 months from 2008 to 2011. A total of 1025 subjects were screened at 108 clinical sites in 12 countries: Argentina, Bulgaria, India, Malaysia, Mexico, Philippines, Romania, Russia, Serbia, Slovakia, Taiwan, and United States. Enrollment decreased with advancing study: 1025 at *Screening*, 633 at *Conversion*, 710 at *Oral Stabilization*, 576 at *Depot Stabilization*, and 403 at *Randomization* (269 aripiprazole, 134 placebo). On average per clinical site, fewer than four subjects reached *Randomization*.

The three clinical sites listed in **Table 1** were selected for good clinical practice (GCP) inspection based on large subject enrollment: the two largest US sites and the largest foreign site. For all three sites, no risk factors for GCP non-compliance had been noted.

**Table 1: GCP Inspections of Clinical Study Sites**

	Inspected Entity	Protocol Site Initial Enrollment	Inspection Dates	Outcome Classification
1	Ahmad H. Sulaiman, M.D. Universiti Malaya Medical Centre (UMMC) Department of Psychological Medicine 50603 Kuala Lumpur, Malaysia	31-07-246 Site 218 15 subjects	(b) (4)	Pending (Preliminary VAI)
2	Mark Lerman, M.D. Alexian Brothers Center for Psychiatric Research 1786 Moon Lake Boulevard, Suite 200 Hoffman Estates, IL 60169	31-07-246 Site 007 17 subjects		Pending (Preliminary NAI)
3	Arifulla Khan, M.D. Northwest Clinical Research Center 1951 152nd Place Northeast, Suite 200 Bellevue, WA 98007	31-07-246 Site 002 27 subjects		Pending (Preliminary OAI)

**Outcome Classification:** NAI = no action indicated (no significant GCP deviations); VAI = voluntary action indicated (significant GCP deviations); OAI = official action indicated (serious GCP deviations and/or data unreliable)

**Pending:** Preliminary classification is based on information on Form FDA 483 and preliminary communication with the field investigator. The final establishment inspection report has not been received from the field office and OSI's complete review of the EIR remains pending as of this clinical inspection summary.

### 1. Ahmad H. Sulaiman, M.D. (Site 218)

#### a. What was inspected:

- Scope of Inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable GCP regulations, and data verification
- Data Verification: primary endpoint, adverse events, subject randomization, protocol deviations, subject discontinuations, concomitant medications
- Subjects: 16 subjects were screened, 15 were enrolled, 8 advanced to *Randomization Phase*, and 1 completed the study; 12 were transferred out of the study into the open-label Study 31-07-248 (7 at *Randomization*, 5 at *Conversion*); two subjects were discontinued from the study (withdrew consent) during *Conversion*. Subject records for all 16 screened subjects were completely reviewed, to include informed consent, primary efficacy endpoint, and adverse events.

#### b. General observations and comments:

- Form FDA 483 was issued for 2 minor observations. Specifically:
  - In obtaining informed consent, subject contact information was often (in nine subjects) not collected, making it difficult to rapidly communicate important study-related concerns.
  - The protocol specified subject exclusion for QTc > 475 msec on electrocardiogram, but a subject meeting this exclusion criterion was initially enrolled. The subject was excluded later in the study. The subject suffered no ill effects from being in the study.

- Other observations (isolated, minor, and therefore not cited on Form FDA 483) consisted of: inadequate temperature and calibration logs, incomplete documentation of drug accountability on drug accountability forms, and inadequate documentation of staff training.
  - IRB oversight appeared to be adequate. Study monitoring appeared to be adequate to excellent. Of note, the study monitoring was performed in two parts, blinded and unblinded, to optimally preserve the study blind. Unblinded study monitoring was isolated from other (blinded) study activities.
    - Unblinded activities consisted of pharmacy activities, including study medication handling, dispensing, and accountability. Blinded activities included all other routine study activities.
    - (b) (4) (contract research organization, CRO) performed the study monitoring. The two-part monitoring was performed at different visits by two groups of non-overlapping monitors.
    - In addition to periodic study monitoring, the sponsor also audited the site, as part of overall monitoring and to prepare the site for transitioning into Study 31-07-248 (open-label study).
  - Primary endpoint data were verifiable; the data matched among source records, case report forms (CRF), and data listings reported in the NDA. Underreporting of adverse events was not observed. The list of protocol violations matched those noted in subject records. Source records appeared factual and complete, and matched corresponding case report forms.
  - All subjects had medical records available for review at this university medical center. Medical records were well-maintained, organized, and readily retrievable for review. For all subjects, the study diagnosis (schizophrenia) was verifiable against the subject's medical records. All subjects were recruited from the site's clinic population.
- c. Assessment of data integrity: The observed deficiencies appear minor, isolated, and unlikely to impact study outcome. Data from this study site appear reliable.

**Note:** Observations noted above are based on Form FDA 483 and preliminary communications with the field investigator; an inspection summary addendum will be forwarded to the review division if conclusions change upon receipt and review of the final establishment inspection report (**EIR**).

## 2. Mark Lerman, M.D. (Site 007)

- a. What was inspected:
- Scope of Inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable GCP regulations, and data verification
  - Data Verification: primary endpoint, adverse events, subject randomization, protocol deviations, subject discontinuations, concomitant medications
  - Subjects: 17 subjects were screened, 17 were enrolled into the study, 10 advanced to *Depot Stabilization Phase*, and 1 completed the study; 6 were transferred out of the study into the open-label Study 31-07-248; 16 subjects were discontinued from the study (withdrew consent). Subject records for all 17 enrolled subjects were reviewed in detail, to include informed consent, primary efficacy endpoint, and adverse events.
- b. General observations and comments:
- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight appeared to be adequate. Study monitoring appeared adequate to excellent: as at Site 218 (see above), (b) (4) performed the study monitoring according to the same monitoring plan and operating procedures.

- Primary endpoint data were verifiable; the data matched among source records, CRFs, and data listings reported in the NDA. Underreporting of adverse events was not observed.
- At this clinical research center, all subjects had well-organized medical records readily available for inspectional review. For all 17 subjects, the study diagnosis (schizophrenia) was verifiable against the subject's medical records.
- All subjects appeared to have signed informed consent properly prior to enrollment. Source records appeared factual and complete, and matched corresponding case report forms. Drug accountability was well documented. No significant objectionable conditions were observed.

c. Assessment of data integrity: Data from this study site appear reliable.

**Note:** Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be forwarded to the review division if conclusions change upon receipt and review of the EIR.

### 3. Arifulla Khan, M.D. (Site 002)

a. What was inspected:

- Scope of Inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable regulations
- Data Verification: primary endpoint, adverse events, subject randomization, protocol deviations, subject discontinuations, concomitant medications
- Subjects: 32 subjects were screened, 27 were enrolled, 13 advanced to *Randomization Phase*, and 6 completed the study; 6 were transferred into the open-label Study 31-07-248 (5 at *Randomization*, 1 at study completion); 21 subjects were discontinued from the study as shown in **Table 2**.

**Table 2: Subject Discontinuation at Site 002**

Subject	Study Phase	Reason	Subject	Study Phase	Reason
0034	2	WC	0078	2	WC
0035	3	WC	0084	1	LFU
0040	2	WC	0091	2	LFU
0041	3	pregnancy	0202	3	LFU
0042	1	medication NC	0203	2	WC
0045	3	SAE	0212	3	LFU
0047	2	WC	0234	1	no efficacy
0054	2	SAE, LFU	0245	1	CI discretion
0068	2	AE	0286	3	WC
0076	3	LFU	0294	1	protocol NC
0077	3	imprisoned			

Study Phases: 1 = Conversion, 2 = Oral Stabilization, 3 = Dopot Stabilization, 4 = Randomized  
 CI = clinical investigator; LFU = lost to follow up; NC = non-compliance; WC = withdrew consent

- Subject Record Review: enrolled subjects for informed consent, primary efficacy endpoint, and adverse events, complete review for the six subjects completing the study
- b. General observations and comments:
- Form FDA 483 was issued for non-compliance with applicable GCP regulations: *General responsibilities of investigators* [21 CFR 312.60] and *Investigator recordkeeping and record retention, case histories* [312.62 (b)]. Specifically:
    - The principal study investigator delegated the initial psychiatric evaluations to physicians not licensed in the United States.
    - During subject screening, 20 physical examinations in 17 prospective subjects were performed by study coordinators who were not delegated to perform physical examinations.
    - For Subject 0084, informed consent was obtained using an incorrect informed consent form (ICF) intended for Study 31-08-248 (open-label study). The subject did not sign the correct ICF until four months after study enrollment.
    - For all subjects, the specific method of double barrier contraception was not documented. For three subjects (0040, 0078, 0091), contraception appeared not to have been evaluated.
    - Three subjects (0035, 0047, 0203) with a recent history of hospitalization were enrolled without verifying that the hospitalization duration was not more than 30 days within 90 days immediately prior to study enrollment, as specified in exclusion criteria. The following subjects were enrolled also in violation of the subject exclusion criteria:
      - Subject 0045 with an apparent history of seizure disorder
      - Four subjects (0035, 0045, 0203, 0286) who participated in previous clinical studies
    - Available medical records indicated that five subjects may not have had schizophrenia and therefore may have been ineligible for the study. **Table 3** shows the primary diagnoses (and the apparent year of initial diagnosis) as documented in the medical records and in the initial study evaluation record (history obtained from subject or subject's family member, as permitted per study protocol).

**Table 3: Conflicting Diagnoses, Current Study vs Medical Records**

Subject	Study Diagnosis Year (1)	MR Diagnosis Year (2), Study (3)	Subject Disposition
0035	paranoid schizophrenia 2000	ADHD 1983, M06-818	WC at Phase 3 (Baseline) subject declined injections
0039	paranoid schizophrenia 2004	bipolar disorder 1998, A1281143	termination at Phase 4 (Week 8), relapse, OLS
0068	paranoid schizophrenia 2005	MDD 2007, CLDA-07-DP-02	discontinuation at Phase 2 (Week 2), AE (headache)
0075	schizophrenia 2004	MDD 1970, CLDA-07-DP-02	termination at Phase 4 (Week 34) impending relapse, OLS
0212	paranoid schizophrenia 2006	MDD unknown, outside MR	discontinuation at Phase 3 (Week 22), LFU

(1) Apparent year of initial diagnosis as documented in study evaluation record

(2) Apparent year of initial diagnosis as documented in available medical records

(3) Prior clinical study that generated the study record as available medical record

ADHD = attention deficit hyperactivity disorder; LFU = lost to follow up; MDD = major depressive disorder; MR = medical record; OLS = subject rolled over into open label study; WC = withdrawal of consent

- Patient-care medical records were typically not available at this Northwest Clinical Research Center. Medical records were not available for inspectional review for 22 of 27 enrolled subjects. Of the five enrolled subjects with prior records, four (Subjects 0035, 0039, 0068, 0075) had "medical" records in the form of previous study records, from previous studies also conducted by Dr. Kahn. In these previous studies, the diagnosis of *schizophrenia had been an exclusion criterion*.
- In the five subjects with available medical records, the primary diagnosis documented in the medical records was inconsistent with Subject Inclusion Criterion 3: schizophrenia for at least three years. Two of the five subjects were among the six who completed the study.

#### Reviewer's Comments

1. *The available medical records of these five subjects consisted of any available health records, including prior clinical study records, and they were not comprehensive clinical care records. The medical record diagnosis does not necessarily rule out the study diagnosis; both may be correct as comorbid diagnoses. Even if not comorbid, it remains unclear which diagnosis is inaccurate.*
  2. *In **Table 3**, Subjects 0039 and 0075 advanced well into Phase 4 of the study (randomized, blinded, depot maintenance) and reached the primary efficacy endpoint of relapse or impending relapse of schizophrenia symptoms. The clinical course in these two subjects suggests that the study diagnosis of schizophrenia was correct, and the medical record diagnoses of bipolar disorder (Subject 0039) and major depressive disorder (Subject 0075) were either comorbid or incorrect.*
  3. *The study protocol permits the primary diagnosis of schizophrenia to be established based on history obtained from the subject or the subject's family member. The protocol also requires, however, that the diagnosis satisfy DSM-IV-TR criteria. Therefore, although not specifically stated, the protocol clearly implies that an unverifiable statement from the subject or the subject's family member should not be used to select subjects with schizophrenia.*
    - *For the five subjects listed in **Table 3**, unverifiable history (statements from subject or family) appears to have been accepted as the study diagnosis without rigorous verification of applicable DSM-IV-TR criteria, verification based on either authoritative medical records or on a formal evaluation by a qualified psychiatrist.*
    - *As cited on Form FDA 483, the principal investigator had delegated the initial psychiatric evaluations to physicians not licensed in the United States, and the evaluations may not have included the rigorous application of DSM-IV-TR criteria.*

*The concern about the lack of rigor in establishing the primary study diagnosis, raised by the availability of medical records in five subjects, may be applicable to other study subjects without any available medical record.*
  4. ***Table 2** shows that Subject 0041 became pregnant during the study (Phase 3, Depot Stabilization). Non-compliance with the protocol-specified subject selection criterion about contraception appears to have contributed directly to this adverse event, an event with unclear (potentially serious) eventual outcome. This deficiency was cited on Form FDA 483, along with others with less serious safety concern.*
- The following minor deficiencies were verbally discussed (not cited on Form FDA 483):
    - Subject 0071: *Investigator's Assessment Questionnaire (IAQ) not completed at Depot Stabilization (Week 10) and at Randomization (Week 14)*
    - Subject 0041: *Resource Utilization Record not completed at Oral Stabilization (baseline) and IAQ not completed at the End of Treatment*

- Subject 0050: *Patient Satisfaction with Medication Questionnaire - Modified* and IAQ not completed during *Randomization* (Week 32)
- *Visual Analog Scale* not assessed:
  - Subject 0045: Current and previous injection sites during *Oral Stabilization* (Week 12)
  - Subject 0050: Previous injection site during *Depot Stabilization* (Week 24), *Randomization* (Week 32), and *Randomization* (Weeks 50 and 52)
- In 13 enrolled subjects: *Authorization to Use or Disclose My Health Care Information* form not signed and/or dated; subject not identified
- Study monitoring appeared adequate: As at Sites 218 and 007 (see above), (b) (4) performed the study monitoring according to the same monitoring plan and operating procedures. A review of the monitoring records showed that (b) (4) had noted many (but not all) of the concerns noted at the FDA inspection, including unavailable medical records and the lack of rigor in confirming the study diagnosis. As monitors specific to the current study, the (b) (4) monitors apparently did not have access to previous study records to verify the study diagnosis.
- Primary efficacy endpoint data were verifiable in that the data matched among source records, CRFs, and data listings reported in the NDA. However, the efficacy data may not be reliable: the study medication may have been administered to ineligible subjects as shown in **Table 3**, to subjects with primary psychiatric diagnoses other than schizophrenia.
- Underreporting of adverse events was not observed. Drug accountability was well documented. IRB oversight (by (b) (4)) appeared adequate.
- c. Assessment of data integrity: Data from this site were verifiable against source records and CRF. However, based on the totality of observations at this site, the data may not be reliable. The possibility that the study medication may have been administered to subjects with psychiatric conditions other than schizophrenia appears to be particularly problematic. Even if non-schizophrenia conditions were comorbid with schizophrenia, subject selection criteria specify subject exclusion for any psychiatric conditions other than schizophrenia, even if they are comorbid with schizophrenia. An assessment of the importance of this exclusion criterion, including the impact of violating this criterion on data reliability, is deferred to the expertise of the review division.

**Note:** Observations noted above are based on Form FDA 483, preliminary communications with the field investigator, and preliminary review of the EIR. An inspection summary addendum will be forwarded to the review division if conclusions change upon completion of the EIR review.

### III. OVERALL ASSESSMENT AND RECOMMENDATIONS

In support of this NDA review, the conduct of Study 31-07-246 (ASPIRE US) was inspected at three clinical study sites with large subject enrollment, two in the U.S. (Sites 002 and 007) and one in Malaysia (Site 218).

No significant deficiencies were observed at two of the three sites. At Site 007 (Lerman; U.S.), a Form FDA 483 was not issued; this site conducted the study in accordance with the study protocol and applicable GCP regulations. At Site 218 (Sulaiman; Malaysia), a Form FDA 483 was issued for two minor isolated deficiencies that are not expected to impact the study outcome; overall compliance with the study protocol and applicable GCP regulations was clearly acceptable. The study data reviewed at these two sites appear reliable with respect to the study protocol as written and submitted to the NDA.

Many GCP violations were observed at Site 002 (Kahn; U.S.) including two with significant potential to compromise data reliability or subject safety: (1) the diagnosis of schizophrenia, the primary condition for which the study medication is being investigated, appeared not to have been rigorously established (without rigorous documented reconciliation with seemingly inconsistent diagnoses in available clinical research records) for five of the 27 subjects (19%) at this site, and (2) the informed consent process appeared to be

inadequate, particularly with respect to assessing the subjects' contraception status. Based on the totality of observations at this site, the data from this site may not be reliable.

The significance of the observations at Site 002 was discussed with the review division (April 10 - 30, 2012) in the context of the overall NDA review:

- The study protocol allows the diagnosis of schizophrenia to be established based on history alone (medical record verification not required), *provided* that the diagnosis satisfies DSM-IV-TR criteria. The major deficiency at Site 002, the acceptance of a potentially unreliable diagnosis based on history without rigorous confirmation, does not appear to be a deficiency of the study protocol itself applicable to other study sites. The deficiency was not seen at the other two clinical site inspections.
- As evaluated at the other two FDA inspections conducted for this NDA, oversight monitoring of Study 31-07-246 (by (b) (4)) appears to have been adequate to excellent, and GCP compliance at these two sites were accordingly adequate to excellent. The quality of oversight monitoring and GCP compliance at other FDA-uninspected sites may be expected to be similar.
- Acceptable GCP compliance confirmed at Sites 007 and 218 appears to be representative for the study as a whole. The deficiencies at Site 002 appear to be limited to this site. Sensitivity analyses conducted by the review division showed that removing Site 002 has little impact on the overall efficacy outcome.

The efficacy data reported in the NDA from Sites 007 and 218 appear reliable. Based on joint (DPP and OSI) review findings, additional GCP inspections in follow up of the findings at Site 002 were not pursued.

**Note:** For all three inspections, the final EIR has not been received from the field office (Sites 007 and 218) or the EIR review has not been completed at OSI (Site 002). The final classification of the inspection outcomes remains pending. The observations noted above are based on preliminary communications with the field investigator or preliminary EIR review. An addendum to this clinical inspection summary will be forwarded to DPP if the final classification changes from the pending classification, or if additional observations of clinical or regulatory significance are discovered after completing the EIR review.

{See appended electronic signature page}

John Lee, M.D.

Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

Susan Thompson, M.D.

Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

{See appended electronic signature page}

Lauren C. Iacono-Connors, Ph.D.

Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

JONG HOON LEE  
06/19/2012

LAUREN C IACONO-CONNORS  
06/19/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Usability Study, Label, and Labeling Review**

Date: May 18, 2012

Reviewer: Yelena Maslov, Pharm.D., Acting Team Leader  
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, Pharm.D., MPH, Deputy Director  
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Abilify Maintena (Aripiprazole)  
Extended-release Suspension for Injection,  
300 mg per vial and 400 mg per vial

Application Type/Number: NDA 202971

Applicant/sponsor: Otsuka American Pharmaceutical, Inc.

OSE RCM #: 2011-3916

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1 INTRODUCTION

This review evaluates Usability Studies for Aripiprazole Extended-release Suspension for Injection and product's design. Additionally, this review evaluates the vial labels as well as carton, prescription information, instructions for use (IFU), and quick reference guide (QRG) labeling for the potential to contribute to medication errors.

### 1.1 BACKGROUND

The Applicant proposed to market Aripiprazole extended release Suspension for Injection for the maintenance treatment of schizophrenia in adults. This product will be administered to the patients once (b) (4) intramuscularly. Currently, there are several Abilify products on the market that are used for the same indication. See Table 1 below for detailed description of marketed Abilify formulations.

Table 1: Marketed Abilify Formulations

Names and Strengths of the Products	NDA Number	Date of Approval	Dosing and Frequency	Sponsor
Abilify Tablets, 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg	NDA 021436	11/15/2002	2 mg to 30 mg orally once daily	Otsuka
Abilify Oral Solution, 1 mg/mL	NDA 021713	12/10/2004	2 mg to 30 mg orally once daily	Otsuka
Abilify Orally Disintegrating Tablet, 10 mg and 15 mg	NDA 021729	06/07/2006	10 mg to 30 mg once daily	Otsuka
Abilify Injection, 9.75 mg/1.3 mL (7.5 mg/mL)	NDA 21866	09/20/2006	5.25 mg to 15 mg intramuscularly one time for agitation. Dose can be repeated in 2 hours to a maximum of 30 mg per day.	Otsuka

### 1.2 REGULATORY HISTORY

The Applicant submitted the New Drug Application (NDA 202971) for Aripiprazole extended release Suspension for Injection on September 26, 2011. The proposed indication for this product is the maintenance treatment of schizophrenia in adults.

During

May 9, 2011 and June 7, 2011 pre-NDA meetings DMEPA recommended the Applicant conduct Usability Study to validate that the users can safely and accurately deliver the drug as labeled. The Applicant submitted Use Hazard Analysis and Use FMEA Report on September, 26, 2011 with original Application and Usability Study on December 21, 2011.

### 1.3 PRODUCT INFORMATION

The following product information is provided in the September 26, 2011 NDA submission.

- Active Ingredient: Aripiprazole
- Indication of Use: The maintenance treatment of schizophrenia in adults.
- Route of Administration: Intramuscular
- Dosage Form: Extended-release Suspension for Injection
- Strength: 300 mg per vial and 400 mg per vial
- Dose and Frequency: 300 mg to 400 mg intramuscularly once (b) (4) administered only by the healthcare professional. Dose should be adjusted to 200 mg if the patient is also on a strong, moderate, or weak inhibitor of CYP3A4 or CYP2D6, or on a strong CYP3A4 or CYP2D6 inhibitor.
- How Supplied: Aripiprazole Extended release Suspension for Injection is supplied in a kit consisting of the following:
  - 300 mg per vial or 400 mg per vial
  - (b) (4) vial of diluent (Sterile Water for Injection, USP)
  - One 3-mL Luer Lock syringe with pre-attached 21 g-1.5 Hypodermic Needle-Pro with needle protection device (for diluent withdrawal)
  - One vial adapter
  - (b) (4)
  - One 21 gauge, 1.5-inch Hypodermic Needle-pro safety needle with needle protection device (for gluteal administration to not obese patients)
  - One 21 gauge, 2-inch (50 mm) Hypodermic Needle-Pro safety needle with needle protection device (for gluteal administration to obese patients at the clinical judgment).
- Storage: The kit should be stored below (b) (4).
- Brief Instructions for Use (See Appendix B for the IFU labeling):
  - For 400 mg dose: Reconstitute with 1.9 mL of diluent to the active ingredient vial (out of (b) (4) provided in the diluent vial), withdraw 2 mL using the adapter, inject intramuscularly into gluteus muscle by using the correct size syringe (depending whether or not a patient is obese)
  - For 300 mg dose: Reconstitute with 1.5 mL of diluent to the active ingredient vial (out of (b) (4) provided in the diluent vial), withdraw 1.5 mL using the adapter, inject intramuscularly into gluteus muscle by using the correct size syringe (depending whether or not a patient is obese)
  - For 200 mg dose [For use with 300 mg vial only]: Reconstitute with 1 mL of diluent to the active ingredient vial (out of (b) (4) provided in the diluent vial),

withdraw 1 mL using the adapter, inject intramuscularly into gluteus muscle by using the correct size syringe (depending whether or not a patient is obese).

- Container and Closure System: Both vials containing Aripiprazole Extended-release Suspension for Injection have (b) (4) overage (b) (4)

Additionally, the use of the vial adapter is recommended to facilitate the consistent withdrawal of the milky-white reconstituted drug from the vial. The Applicant studied what may occur if: 1) the adapter is not used and 2) if the entire amount of diluent is used for 300 mg and 400 mg doses. The results were the following:

- If the 21-gauge needle is used instead of adapter, the maximum deliverable amount from both vials is close to the desired 300 mg or 400 mg dose (b) (4).
- If the entire diluent vial is used (approximately (b) (4) to reconstitute 300 mg dose, then the maximum extractable volume of approximately (b) (4). According to the clinical team, this overdose is not clinically significant because it is within the (b) (4) of the desired dose. Furthermore, since 1.9 mL is needed to reconstitute 400 mg, if 2 mL of diluent is used, the maximum extractable volume is very close to 400 mg.
- The Applicant did not study the implications of the overfill in 300 mg vial or 400 mg vial on the 200 mg dose. The CMC team expressed concern that the Applicant did not perform such evaluation for 200 mg dose from 300 mg vial.

## 2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis<sup>1</sup> and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Validation Summative Usability Study submitted on December 21, 2011 (See Appendix E for the summary of the Usability Study)
- Use Hazard Analysis and Use FMEA Report submitted on September 26, 2011 (no image)
- Aripiprazole Extended-release Suspension for Injection Vial Labels submitted on March 27, 2012 (Appendix A)
- Sterile Water for Injection, USP Vial Label submitted on March 27, 2012 (Appendix A)

---

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

- Kit Carton Labeling submitted on March 27, 2012 (Appendix A)
- Prescriber Information Labeling submitted on March 27, 2012 (no image)
- Instructions for Use (IFU) for the kit submitted on March 27, 2012 (Appendix B)
- Quick Reference Guide (QRG) submitted on March 27, 2012 (Appendix C)
- Instructions for Use for the Needle-Pro Syringe and Needle submitted on January 9, 2012. (Appendix D)

Although there are other Abilify products that are currently marketed, their product characteristics as well as labeling and labeling are different from the proposed Aripiprazole Extended-release Suspension for Injection. Thus, we did not search AERS database for errors related to other Abilify products, because identification of those errors will not inform this review. However, Aripiprazole extended release Suspension for Injection will have similar product kit and similar instructions for use to the currently marketed product in the same pharmacological class, Zyprexa Relprevv. Thus, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Zyprexa Relprevv. The January 11, 2012 AERS search used the following search terms: active ingredient “Olanzapine%”, trade name “Zyprexa%”, and verbatim terms “Zyprexa%” and “Olanzapine%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. No time limitations were set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error (i.e., adverse events and allergic reactions not related to medication errors) or described medication error not related to the labels, labeling, IFU, or product design such as intentional overdoses as a suicide attempt, dose omission due to patient refusing the dose, missing an appointment, or being hospitalized.

Following exclusions, no relevant cases were identified.

### **3 RESULTS**

The following section describes the findings of DMEPA’s evaluation of the summative Validation Summative Human Factors Study and the risk assessment of the Aripiprazole Extended-release Suspension for Injection product design as well as the associated labels and labeling (i.e. vials labels, carton, prescriber information labeling, kit IFU, QRG, and IFU for Needle-Pro Syringe and Needle).

### 3.1 VALIDATION SUMMATIVE HUMAN FACTORS STUDY

- The Applicant identified appropriate critical steps of the preparation and administration process of Aripiprazole Extended release Suspension for Injection that included 1) using the correct volume of diluent, 2) withdrawing the correct amount of drug suspension, and 3) using the correct size of the needle to inject the product into the gluteal muscle.
- Fourteen (14) of 16 participants completed all critical tasks successfully without committing a single error. Two (2) participants who did not use the IFU or QRG or did not finish reading the IFU or Quick Reference Guide (QRG) committed 4 errors. One participant who did not read the IFU, failed 3 critical steps (i.e., used the entire vial of diluent, entire vial of suspended product, and proposed that injection should be administered to deltoid muscle). One participant who partly read the IFU committed one error (i.e., withdrew the entire amount of suspended product for injection). As a result, the placement of the colorful, easy to read and comprehend QRG, and kit IFU inside the kit carton on top of the kit items represent an effective means of preventing the errors associated the product's use.
- User Population:
  - 1) The Applicant recruited only healthcare practitioners (nurses and nurse practitioners) employed by psychiatric facilities and clinics, but did not include general medicine healthcare practitioners. This user population for the study is acceptable, because the FDA clinical team anticipates that Aripiprazole Extended-release Suspension for Injection will be administered almost exclusively at the psychiatric inpatient and outpatient facilities.
  - 2) The study did not include physicians as part of the user population. Although not ideal, it is acceptable, because the study focused on ability of healthcare providers to reconstitute the product correctly and withdrawn the correct dose and did not focus on the correct injection technique. These actions are primarily performed by nursing staff and we have no reason to believe that these practices vary among different groups of healthcare practitioners (i.e., doctors and nurses).
- Subjective data regarding the ease of the device use, readability and clarity of the IFUs and QRG should be obtained from the post-test questions and answers to help optimize the device and labeling. However, since all the participants who read the QRG and the kit IFU completed all the tasks successfully without errors (n=14), we can rely on objective data without significant need for subjective data.
- The Usability Study did not test whether healthcare practitioners (HCPs) would choose the correct vial strength to obtain the 200 mg dose from (i.e., 300 mg vial) and did not test whether HCPs can successfully reconstitute and extract 200 mg dose from that vial. Preparing a dose of 200 mg can result in clinically significant overdose, if the intended 200 mg dose is extracted from the wrong vial (i.e., 400 mg) and/or reconstituted or extracted incorrectly (see discussion). Thus, Applicant's results related to the correct preparation of 300 mg dose or 400 mg dose can not be extrapolated to the extraction and preparation of 200 mg dose.

## 3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

We identified the following areas of the vial labels, carton, prescribing information, IFUs, and QRG labeling are vulnerable to confusion and may lead to medication errors.

### 3.2.1 Kit Design

- The diluent vial and the active ingredient vial contain overfill which may lead to overdoses, particularly if 200 mg dose is intended.

### 3.2.2 Prescribing Information

- The prescribing information labeling uses inconsistent terms related to the frequency of administration [REDACTED] (b)(4) which may be confusing.
- The dosing and administration information is grouped together in one paragraph, decreasing clarity of this important information.
- The prescribing information uses negative statements that may be misinterpreted and errors may occur (e.g., “[REDACTED] (b)(4)”, etc.).
- The complicated instructions regarding missed doses are described in paragraph format and are lengthy and difficult to follow.
- The prescribing information uses trailing zeros and hyphens that can be misinterpreted and result in medication errors.

### 3.2.3 Aripiprazole Extended release Suspension for Injection IFU

- The IFU in the prescribing information (Section 2.7) is not consistent with the IFU located on the back side of the sheet with the QRG.
- The IFU uses trailing zeros and hyphens that can be misinterpreted and result in medication errors.
- The IFU uses the generic words “[REDACTED] (b)(4)” and “product” which may be misleading.
- The figures depicting steps of the preparation and administration process lack visibility due to gray-and-white color font and small size, leading to wrong preparation and administration technique errors.
- The IFU lacks important instructions related to placement of the Needle-Pro needle on the syringe and engagement of the needle in the safety device.
- The IFU uses negative statements such as “[REDACTED] (b)(4)” which may be misinterpreted as “[REDACTED] (b)(4)” and result in errors.

### 3.2.4 Quick Reference Guide (QRG)

- The QRG also uses trailing zeros and hyphens, which may be misinterpreted and lead to errors.

- The QRG uses incorrect term “(b) (4)” instead of “Sterile Water for Injection, USP” and generic term “product” which may be misleading.
- Step 4 does not state what steps should be taken if the drug is not administered immediately. However, this information is important and should be noted in QRG.
- The needle size is not prominently displayed in Step 8, which may lead to use of the wrong needle.

### **3.2.5 Needle-Pro Syringe and Needle IFU**

- The IFU uses two languages, English and French, and thus, does not follow 21 CFR 201.15 (c)(1)
- The word “Ensure” is misspelled with the letter “I”.
- The text font size is small and difficult to read.
- No illustrations are included to help visualize the process of connecting the needle to the syringe.

### **3.2.6 Aripiprazole Extended release Suspension Carton Labeling**

- The yellow color font for 300 mg overlaps with the color font used for Abilify Immediate release Injection, 9.75 mg/1.3 mL, which may lead to the use of the wrong product.
- The medication guide statement per 21 CFR 208.24(d) is missing.
- The proprietary name appears in different font size text, which may lead to confusion.
- The graphic of the two twisted lines is prominent and decreases the readability of the most important information on the top panel such as proprietary and established names and route of the administration.
- The carton labeling does not contain the important statement “For Single Use Only” to reinforce that this product should not be used more than once.
- The carton labeling contains hyphens that can be misinterpreted, and thus, should be deleted.

### **3.2.7 Aripiprazole Extended release Suspension Vial Label**

- The different types of boxing around the strengths (i.e., black box around 300 mg strength and white box around 400 mg) do not provide sufficient differentiation between the two strengths of the product. Thus, additional differentiation between the two strengths should be utilized.
- The route of administration can be increased to be made more prominent.

### 3.2.8 Sterile Water for Injection, USP Vial Label

- The vial label uses incorrect term [REDACTED] <sup>(b) (4)</sup>” and should be changed to “Sterile Water for Injection, USP”.
- The vial label contains product’s proprietary name, established name, and dosage form and thus, may be misinterpreted that the vial actually contains the active ingredient.
- The statement “For single use only. Discard the remainder” should be added to ensure the diluent is used only once.

## 4 MEDICATION ERROR RISK ASSESSMENT DISCUSSION

Due to the overfill of the diluent and the active ingredient as well as the use of the adapter, the amount of the reconstituted product that can be extracted from the vial is larger than the intended dose. Although this may not result in clinically significant overdose for 300 mg or 400 mg doses (See Section 1.3 for explanation), it can result in clinically significant overdose, if the intended dose is 200 mg extracted from 300 mg vial or 400 mg vial.

Dosing errors for 300 mg or 400 mg doses can be prevented by following the Quick Reference Guide or the Instructions for Use as demonstrated by the Validation Summative Human Factors Study. Additionally, having the colorful Quick Reference Guide with Instructions for Use on the back side of the same sheet prominently placed on top of the kit items may help ensure that healthcare practitioners will follow the QRG and IFU prior to the preparation of the product and thus, prevent errors. However, HCPs may also overlook or not attend to Quick Reference Guide or the Instructions for Use as was demonstrated in the Validation Summative Human Factors Study when two participants avoided the Instructions for Use and Quick Reference Guide, which led to wrong usage technique errors (i.e., use of the entire diluent and entire reconstituted product amounts). However, the usability study did not test whether participants would choose the correct vial strength to obtain the 200 mg dose from (i.e., 300 mg vial) and prepare the 200 mg dose correctly. Thus, it is unknown whether healthcare practitioners would make errors while preparing this dose.

Additional dosing instructions, such as the amount of diluent to use and the amount of reconstituted product to withdraw, can be added to the carton labeling to help prevent dosing errors; however, the labels and labeling are not the most effective means to prevent overdoses of 200 mg strength in this case. Instead, redesign of the product (i.e., addition of the kit containing vials of 200 mg strength of the active ingredient and the appropriate amount of diluent) should be considered.

In addition to dosing errors that may occur due to product design, wrong drug errors may also occur between Aripiprazole extended-release Suspension for Injection, 300 mg and Abilify Injection, 9.75 mg/1.3 mL due to similar appearance of labels and labeling. The 300 mg and 9.75 mg products overlap in background color of the carton labeling and vial labels as well as overlapping product characteristics such as the same root name “Abilify”, similar dosage forms (injection vs. Extended-release Suspension for Injection), and the same route of the administration (intramuscular). Potential wrong drug errors can

be prevented by changing the background color for Aripiprazole Extended-release Suspension for Injections, 300 mg, so that it does not overlap with the immediate release injectable Abilify or with extended-release, 400 mg, product.

## **5 CONCLUSIONS**

The usability study demonstrated that the 300 mg dose and 400 mg dose of the product can be prepared correctly if the Instructions for Use (IFU) or Quick Reference Guide (QRG) is followed. However, the study did not test whether participants are able extract and prepare a 200 mg dose correctly.

The usability study also demonstrated that the product design is prone to dosing errors due to overfill of the active ingredient, diluent, and the use of the adapter if the IFU or QRG is not used. This is particularly concerning for 200 mg dose, especially since it was not evaluated and there is risk of significant overdose.

Our evaluation of the vial labels, carton, prescribing information, product IFU, QRG, and Needle-Pro syringe and needle IFU identified areas that introduce vulnerability that can lead to medication errors.

## **6 RECOMMENDATIONS**

Based on this review, DMEPA recommends the following recommendations should be implemented prior to approval of this NDA.

Please copy the Division of Medication Errors Prevention on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sandra Griffith, project manager, at 301-796-2445.

### **6.1 COMMENTS TO THE DIVISION**

#### **A. Product Design**

The product design of Aripiprazole Extended-release Suspension for Injection, 200 mg strength is prone to clinically significant overdose errors due to overfill of the active ingredient, diluent, and the use of the adapter if the Instructions for Use (IFU) or Quick Reference Guide (QRG) is overlooked or not attended to. The usability study did not test whether participants would choose the correct vial strength to obtain the 200 mg dose from (i.e., 300 mg vial) and/or prepare the 200 mg dose correctly. Thus, it is unknown whether healthcare practitioners would make errors while preparing this dose. As a result, we recommend the Applicant redesign the product to add the 200 mg strength kit (i.e., kit containing vials of 200 mg strength of the active ingredient and the appropriate amount of diluent to reconstitute 200 mg dose).

#### **B. Prescriber Information Labeling**

1. *Dosage and Administration* Section, Highlights of Prescribing Information
  - a. Revise the phrase “administered monthly” to state administered “every 4 weeks” because Section 2.2, *Missed Dose* states that the product should be administered [REDACTED]<sup>(b) (4)</sup> (i.e., 4 weeks). Thus, the inconsistency in the frequency of administration is confusing and misleading.
2. *Dosage Forms and Strengths, Highlights of Prescribing Information*

Revise the strengths to start from lower strength to the higher as follows: 300 mg per vial and 400 mg per vial.

3. *Dosage and Administration* Section, Full Prescribing Information

Revise the statement “(b) (4)” to state “For intramuscular use only. Do not administer by any other route” in Section 2.3, Administration Instructions and Section 2.7 Instructions for Use. Negative statements such as (b) (4)” may have an opposite of the intended effect and inadvertently encourage the wrong route of administration. Thus, revising this statement to omit the incorrect route of administration such as “Do not administer by any other route” may help minimize the wrong route of administration error.

4. Section 2.1, *Recommended Dosing*

In the third paragraph dosing information is not grouped together and administration information is placed in between dosing statements leading to reduced clarity of this important information. Additionally, the first paragraph of Section 2.1, *Missed Dose*, should be added in this section because it provides the information regarding the recommended dosing frequency and not regarding missed dose. Thus, we recommend revising the paragraph as follows:

*The recommended starting and maintenance dose of Abilify Maintena is 400 mg administered every 4 weeks. Some patients may benefit from a treatment reduction to a 300 mg dose based on individual patient tolerability. The first dose should be accompanied by 14 consecutive days of concurrent treatment with 10 mg to 20 mg of oral Aripiprazole (or current oral antipsychotic). Treatment should be initiated by a healthcare professional as a single injection in the gluteal muscle.*

5. Section 2.2 *Missed Dose*

The complicated instructions regarding missed doses are described in a paragraph format and are lengthy and difficult to follow. Thus, we recommend revising the second and third paragraph of this section to simplify the instructions and increase the readability by using bullet points as follows:

*After initiation, the recommended dosing interval is once every 4 weeks.*

*For the missed **second or third** doses:*

- *If 5 weeks or less elapsed since the last injection: administer the dose as soon as possible. Follow by injections once every 4 weeks.*
- *If more than 5 weeks elapsed since the last injection: reinstate as per Section 2.1 with 14 days of concurrent oral Aripiprazole.*

*For the missed **forth and subsequent** doses:*

- *If 6 weeks or less elapsed since the last injection: administer the dose as soon as possible. Follow by injections every 4 weeks.*

- *If more than 6 weeks elapsed since the last dose: reinstate as per section 2.1 with 14 days of concurrent oral Aripiprazole.*

6. Section 2.3 *Administration Instructions*

Delete the statement in parentheses stating “(b) (4)”. Negative statements such as “(b) (4)” may have an opposite of the intended effect and inadvertently encourage the wrong technique of administration.

7. Section 3, *Dosage Forms and Strengths*

Revise the first sentence of this section to state “Abilify Maintena is available in a 300 mg per vial and 400 mg per vial and is provided as a lyophilized powder for reconstitution”.

8. Section 16.1, *How Supplied*

- Trailing zero is a dangerous dose designation that appears on ISMP list of Error-Prone Abbreviations, Symbols, and Dose Designations because “(b) (4) vial” can be misinterpreted as a “(b) (4) vial” if the decimal point is not seen. As a part of a national campaign to reduce medication errors related to error-prone medical abbreviations, symbols, and dose designations, the FDA agreed not to approve labels and labeling that include error-prone abbreviations, symbols, and dose designations. Thus, delete the trailing zero after the number (b) (4) in a sentence (b) (4) vial of diluent (sterile water for injection).
- Delete the hyphen between the numeric characters and the words ‘mL’, ‘gauge’, or ‘inch’ in the kit contents (e.g., (b) (4), 21 gauge, 1.5 inch, etc.) as these hyphens may be misinterpreted and result in confusion.

**C. Instructions for Use (IFU) for Aripiprazole Extended release Suspension for Injection Kit (300 mg and 400 mg)**

- Ensure the IFU on the back side of the sheet with Quick User Guide is consistent with the IFU used in the professional labeling, *Section 2.7, Full Prescribing Information*.
- Delete trailing zeros throughout the Instructions for Use because trailing zero is a dangerous dose designation that appears on ISMP list of Error-Prone Abbreviations, Symbols, and Dose Designations. For example, “1.0 mL” may be misinterpreted as “10 mL” if the decimal point is not seen.
- Delete the hyphen between the numeric characters and the words ‘mL’, ‘gauge’, or ‘inch’ in the kit contents (e.g., (b) (4), 21 gauge, 1.5 inch, etc.) as these hyphens may be misinterpreted and result in confusion.
- To improve readability of the volume of diluent to add or of the final volume to injection, insert a space between the numerical characters and measurement units such as follows: 1.5 mL, 1 mL, or 2 mL.
- Revise the word (b) (4) with the phrase “Sterile Water for Injection” throughout the IFU.
- Replace the word “(b) (4)” with the proprietary name of the product.

7. Provide the illustrations depicting steps of the IFU in color to help to increase readability and comprehension of instructions. Currently, the gray-and-white figures are small, blend in with the background, and difficult to see, which may lead to the wrong preparation and administration techniques.
8. Revise the statement “(b) (4)” to read “Do not administer by any other route”. Negative statements such as “(b) (4)” may have an opposite of the intended effect and inadvertently encourage the wrong route of administration. Thus, revising this statement to omit the incorrect route of administration such as “Do not administer by any other route” may help minimize the wrong route of administration error.
9. Add the statement “Administer once every 4 weeks” prior to Step 1, after the sentence “Inject immediately after reconstitution”. We recommend addition of this statement to ensure that HCPs are aware of the dosing differences between the immediate release Abilify Injection and this product.

10. *Step 1, Preparing the Materials*

Add the statement “for obese patients” next to 2 inch needle to ensure the correct needle is used for obese patients. It is important that the correct needle is used for product administration due to shorter needle may result in subcutaneous administration of the product, which may lead to adverse events.

11. *Step 2, Determining Reconstitution Volume*

Revise the second sentence to be more concise and bolded to ensure the prominence and clarity of this important information as follows:

***Important: There is more Sterile Water for Injection, USP in the vial than is needed to reconstitute Aripiprazole Extended-release Suspension for Injection.***

12. *Step 3, Reconstituting Product*

- a. Revise item #4 to replace the phrase “(b) (4)” with the phrase “1.5 mL” or “1.9 mL” for 300 mg strength and 400 mg strength respectively to increase the clarity of the statement.
- b. Revise item #7 to explain what steps should be taken to engage the needle safety device and include additional illustrations consistent with the Needle-Pro IFU. Although separate Needle-Pro IFU is included, healthcare practitioners may not refer to it as demonstrated in Formative and Validation Usability Studies. We recommend revising item #1 as follows (Example):

*Remove the needle from the vial. Engage the safety device by using one-handed technique. Gently press the sheath against a flat surface until the needle is firmly engaged into the sheath. Visually confirm that the needle is fully engaged into the needle protection sheath.*

- c. In item #10, revise the last negative sentence “(b) (4)” to read “Store the suspended product only in vials”. Negative statement such as “(b) (4)” may be misinterpreted

as positive (b) (4) and have an opposite of the intended effect. Thus, this approach may encourage wrong storage of the medication and lead to additional errors.

- d. Add illustrations to item #13 to help with visualizing how to use syringe BD to remove the vial adapter from the package.

### 13. Step 4, *Injecting Product*

- a. Revise item #4 explaining how to attach the Hypodermic Needle-Pro to the syringe BD since this is important information. Additionally place illustrations to help visualize the process. Although separate Needle-Pro IFU is included, healthcare practitioners may not refer to it as demonstrated in Formative and Validation Usability Studies. We recommend revising item #4 as follows (Example):

*Attach the selected Hypodermic Needle-Pro safety needle to the syringe BD containing the suspension for injection. Ensure the needle is firmly seated on the Needle-Pro safety device with the push and a clockwise twist, and then pull the needle cap straight away from the needle.*

- b. Revise the second sentence in item #4 (b) (4) to read “Inject the recommended volume immediately”. The first part of this sentence is not relevant because by the time item #4 should be performed the suspension should already be in the syringe.
- c. In item #4, revise the statement “(b) (4)” to state “Do not administer by any other route”.
- d. In item #4, revise the statement “Engage the needle safety device” to refer to the above item #7 in step 3 that explains how to engage the needle safety device.

### D. Quick Reference Guide (300 mg and 400 mg)

1. See Comments C.2 through C.4 and revise the QRG accordingly.
2. Add a prominent statement “Administer once every 4 weeks” to the QRG to ensure that HCPs are aware of the dosing differences between the immediate release Abilify Injection and this product.
3. Revise the statement (b) (4) to state “Sterile Water for Injection”.
4. Revise the word (b) (4) to state the proprietary name of the product.
5. Revise step 4 to include what steps should be taken if Aripiprazole Extended-release Suspension for Injection is not administered immediately as follows (Example):

*“If the product not administered immediately, the reconstituted suspension is can be stored in the vial for up to 12 hours. Shake the vial vigorously for at least 1 minute to re-suspend prior to injection.”*

6. Increase prominence of the needle sizes and the word “Obese” in step 8 by using bigger-size font or bolding.

#### **D. Instructions for Use for Hypodermic Needle-Pro Syringe and Needle**

1. Use only English language for the IFU for Hypodermic Needle-Pro Syringe and Needle in accordance with 21 CFR 201.15(c)(1).
2. Correct the spelling error of the word “Ensure” in section 6.2.
3. Increase the font size of the text to improve readability of the information.
4. Include illustrations to help visualizing how to attach the Needle-Pro safety needle device to the syringe.

### **5.2 COMMENTS TO THE APPLICANT**

#### **A. Carton Labeling (300 mg per vial and 400 mg per vial)**

##### **Top Panel**

1. Ensure the size of the established name is at least ½ size of the letters comprising the proprietary name and has prominence consistent with the proprietary name including type, size, color, and font in accordance with 21 CFR 201.10(g)(2).
2. Revise the presentation of the root name ‘Abilify’ from all upper case letters (ABILIFY) to title case (Abilify) to improve readability.
3. To be consistent with other lyophilized powders, add the phrase “per vial” after the product’s strength such as “300 mg per vial” and “400 mg per vial”.
4. The yellow color used to represent 300 mg strength overlaps with the color font used for Abilify (Aripiprazole) Injection. The visual similarity can lead to selection of the wrong product. Thus, revise the color font used for 300 mg, so that the carton labeling does not overlap or appear similar to Abilify Injection.
5. Add the medication guide statement to the top panel above the “Single use only” statement per 21 CFR 208.24(d). Consider using the statement as follows: “Attention: Dispense an enclosed Medication Guide to each patient”.
6. Revise the presentation of the proprietary name to appear in the same font size, color, and type size. This presentation will emphasize the full name of the product. Currently, the root name is more prominent than the modifier, which may lead to confusion if modifier is overlooked due to decreased prominence.
7. Delete the graphic of the twisted lines on the top panel as this graphic is prominent and intervenes with readability of the important information such as proprietary and established names and route of administration.
8. Increase the prominence of the route of administration by using bigger font size as this information is very important and should be emphasized.
9. To reinforce that this product is packaged in a single-use vial, add the statement “Discard Unused Portion” immediately after the statement “Single use only”.
10. If space permits, add the following table to the 300 mg strength product:

Intended Dose	Amount of diluent for reconstitution	Amount to inject by using adapter
300 mg	1.5 mL	1.5 mL
200 mg	1.5 mL	1 mL

And to the 400 mg strength:

Intended Dose	Amount of diluent for reconstitution	Amount to inject by using adapter
400 mg	1.9 mL	2 mL

If space does not permit or addition of the tables to the top panel greatly clutters the most important information such as proprietary and established names, dosage form, strength, and route of administration, add these tables to the front panel of the carton labeling.

### **Side Panel**

1. Revise the statement “(b) (4)” to state “One (b) (4) vial of diluent: Sterile Water for Injection, USP”.
2. Delete the hyphen between the numeric characters and the words ‘mL’, ‘gauge’, or ‘inch’ in the kit contents (e.g., (b) (4), 21 gauge, 1.5 inch, etc.) as these hyphens may be misinterpreted and result in confusion.
3. In the Usual Dosage, add the statement “Administer once every 4 weeks” before the statement “See Package Insert”. We recommend addition of the statement to ensure the correct dosing schedule is followed and to ensure that HCPs are aware of the dosing differences between the immediate release Abilify Injection and this product.

### **B. Aripiprazole Vial Label (300 mg per vial and 400 mg per vial)**

1. See Comments A.1 through A.4 and revise the vial labels accordingly.
2. The different types of boxing around the strengths (i.e., black box around 300 mg strength and white box around 400 mg) do not provide sufficient differentiation between the two strengths of the product. Thus, vial labels look too similar to each other and to the diluent (i.e., Sterile Water for Injection, USP) containing black writing on the white background. As a result, the wrong strength of the product may be selected. Please provide additional differentiation between the strengths by employing different colors consistent with the carton labeling or additional means to help prevent selection errors.
3. Increase the prominence of the route of administration by using bold and/or larger font.

### **C. Sterile Water for Injection, USP Vial Label (Diluent)**

1. Revise (b) (4)” to state “Sterile Water for Injection, USP” as “(b) (4) (b) (4)” was not identified in USP monograph.

2. Delete the statement “ [REDACTED] (b) (4) [REDACTED] as this prominent statement may be misinterpreted that this vial actually contains the active ingredient.
3. Add the statement “For single use only” after the word “Sterile” to emphasize that the product should be used only once.

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

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

YELENA L MASLOV  
05/18/2012

KELLIE A TAYLOR  
05/18/2012

CAROL A HOLQUIST  
05/18/2012



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: February 28, 2012

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID

THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID

CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID

TO: Greg Dubitsky, Medical Officer, CDER/OND/ODE1/DPP
Sonny Saini, Project Manager, CDER/OND/ODE1/DPP

SUBJECT: NDA 202971, Otsuka, Injector (for treatment of schizophrenia)

[Handwritten signature] 3/5/2012

[Handwritten signature] 3/5/2012

Review Memo - Table of Content

CDRH HUMAN FACTORS REVIEW ..... 2
OVERVIEW ..... 2
REVIEW MATERIALS ..... 2
CDRH HUMAN FACTORS REVIEW ..... 2
Combination Product Device Information ..... 2
CDRH Human Factors Involvement History ..... 2
Review of Human Factors Related Information ..... 2
REVIEW RECOMMENDATIONS ..... 4
APPENDIX A ..... 6

## **CDRH Human Factors Review**

### ***Overview***

The Division of Psychiatry Products, Office of Drug Evaluation I, Office of New Drugs, requested a Human Factors consultative review of the NDA 202971 submitted by Otsuka Pharmaceuticals, Inc. The Applicant seeks FDA's approval for the intramuscular injection of Abilify which is used for treatment of schizophrenia. This review provides CDRH's review and recommendations on the Human Factors related information contained in the NDA.

Please note that there are two requests for additional clarification/information that can be found in the recommendation section. Please transmit these requests to Otsuka.

### ***Review Materials***

NDA Submission:

\\CDSESUB1\EVSPROD\NDA202971\202971.enx

Submission dated 12/22/2012

## ***CDRH Human Factors Review***

### **Combination Product Device Information**

Submission Number: 202971

Applicant: Otsuka Pharmaceutical, Inc.

Drug Constituent: Aripiprazole/Abilify

Device Constituent: Aiguille Hypodermic Needle-Pro and vials

Intended Treatment: Schizophrenia

### **CDRH Human Factors Involvement History**

- 24-Jan-2012: CDRH HF team was requested to provide a review on the Human Factors information contained in the NDA

### **Review of Human Factors Related Information**

Otsuka submitted a Human Factors Engineering/Usability Engineering report dated December 20, 2011 as a result of the Agency's response to a Type-B pre-NDA meeting request on June 7, 2011.

The combination product is the Abilify IM Depot kit, which is intended for schizophrenia via intramuscular (IM) injections. Human Factors considerations for the use of this product include the following:

- The primary user population will be healthcare professionals (HCP) who work in a Mental Health (Depot Clinic), psychiatric in-patient facility, or in a Psychiatrist's Office who have responsibility for administering intramuscular (IM) injections.
- The kit will be primarily used in the clinical environment in a treatment room of a Mental Health Clinic or psychiatric office.
- It is not expected that users will receive any formal training on the use of the Abilify® extended release suspension for injection kit. During commercial use the HCP will be

expected to use the enclosed Instructions for Use and the Quick Reference Guide along with their HCP and/or nursing and intramuscular injection training to use the kit. The Applicant stated that they are developing plans to provide additional support to HCP's regarding the use of the kit through their commercial operations, in line with all regulatory requirements.

- The device user interface includes printed materials (quick reference guide, drug prescription insert, and safety needle IFU). The device constituent consists of a drug vial containing lyophilized drug, a diluent vial (water for injection), and several injection device. The complete list of the kit components includes drug vial, diluent vial, vial adapter, 3-ml Luer lock syringe with pre-attached 21g x 1.5 inch safety needle, 3-ml syringe with Luer lock connector, 21-gauge, 1.5 inch (38 mm) safety needle, and 21-gauge, 2-inch (50 mm) safety needle.
- The expected user tasks are:
  - Determining/Selecting a dose kit to use based on a prescription scenario
  - Determining the correct volume of diluent to reconstitute the drug\*
  - Drawing diluent into the syringe
  - Injecting diluent into the drug vial
  - Shaking/mixing the drug to acquire a homogeneous suspension
  - Determining the correct amount of drug suspension to withdraw for injection and administration\*
  - Selecting the appropriate length needle for injection\*
  - Indicating the correct site of injection
- A use-related risk assessment was used to identify risks associated with user interaction with the kit. Based on this risk assessment, task priority was assigned to three critical tasks (those with \* from the list above) that could cause dosing errors (under dosing and over dosing). A complete use-related risk assessment was not submitted, and therefore, the reviewer is not clear on how the Applicant designated specific tasks to be critical.
- In addition, an exploratory (formative) study was conducted prior to validation. This study was conducted with 16 nurses and nurse practitioners. Half of the participants were requested to review the printed labeling prior to proceeding with using the device, and half of the participants were allowed to proceed with the use of the device without reviewing the printed labeling. The study identified two use issues:
  - The first was that users did not use, could not find or used the incorrect IFU (needle safety syringe).
  - The second was that even when the IFU was read there were still two critical steps that were subject to use errors

The major mitigations to address these issues was to create a separate quick reference guide (QRG). In addition, the Instructions for Use for the safety needles was reduced in size by eliminating multiple (12 original) languages, leaving only English and French, and placed lower in the kit to further avoid confusion with the QRG and PI.

- The validation study consisted of 16 nurses and nurse practitioners. There were four use errors among two participants.
  1. One participant refused to refer to the instructions at all, committed three of the use errors. First error occurred on the he withdrawal of the correct diluent. The participant assumed that all of the diluent was required. Second error occurred when the participant did not use the vial adapter for extracting the specified dose. Third

error occurred when the the participant decided that they would choose the needle based on their assessment of the patients injection depth requirements rather than any that was recommend by the kit label. The participant stated that they routinely use a 2-inch needle for IM injection into the gluteus. The inclusion of needles in the kit is not meant to override the clinical judgment of the HCP and although the choice of needle length could affect drug adsorption, this is a clinical decision. As a result, this user would have prepared a syringe that could have resulted in an overdose.

2. The other participant did not withdraw the correct drug volume. In most cases this use error would NOT lead to dosing error due to two mitigations implemented prior to the exploratory study. The first change was to reduce the volume of diluent (b) (4) to 2 ml) and the second change was to include the vial adapter as the method of extracting the drug.

The Applicant indicated that dosing errors (overdose and underdose) can occur in instances where the HCP commits a combination of three separate use errors (withdraws too much diluent; fails to use the vial adapter and does not withdraw the specified drug volume). This was clearly the case for the first participant. The Applicant further stated that these participants had established behaviors that overrode their ability to follow directions which resulted in their following previous patterns of professional training and experience.

### ***Review Recommendations***

The use-related risk was not submitted, and therefore, the reviewer is not clear on how the Applicant designated specific tasks to be critical. The validation study identified four use errors among the two participants in the study. One participant refused to review the IFU and committed three of the four use errors that could result in dosing error (overdose). The other participant committed a use error where the Applicant argued that the design of the product "would have" ensured that they have prepared the correct dose without clearly stating if the participant did successfully administer a correct dose. The reviewer is concerned that there is still a potential risk for dosing error. Further clarification and information is necessary to complete CDRH Human Factors review.

Please transmit the following questions to the Applicant:

1. Your Human Factors Engineering/Usability Engineering report dated December 20, 2011 did not include a comprehensive use related risk assessment for all tasks associated the use of this product. As a result, the Agency is not clear on how you designated which tasks to be critical. Please submit a comprehensive use related risk assessment for all tasks associated the use of this product including your rationale for identifying tasks that are critical tasks.
2. Your Human Factors Engineering/Usability Engineering report dated December 20, 2011 identified four use errors among two test participants.
  - a. One participant did not refer to the instructions for use and committed three of the use errors. First error occurred on the withdrawal of the correct diluent where the participant assumed that all of the diluent was required. Second error occurred when the participant did not use the vial adapter for extracting the specified dose.

Third error occurred when the participant did not choose the correct needle based on the recommendation in the kit label. As a result, this user committed a dosing error (overdose). It might be possible that this participant had a different mental model based on their training and/or experience. Please evaluate the error sequence to determine if it represents the potential for other users to commit that error or if you have reason to believe this is an isolated event and explain your findings. If this same error scenario is likely to be repeated by other users, the Agency believes that the device labeling should be designed to better convey the importance of proper use and to minimize the risk of dosing error scenario. You stated that you are developing plans to provide additional support to HCP's regarding the use of the kit through their commercial operations. Please provide a description of how you plan to address the potential of dosing error in these efforts.

- b. The other participant did not withdraw the correct drug volume. You emphasized that the design of the product "would have" ensured that they have prepared the correct dose. Please state whether this participant successfully administered a correct dose, how the user recognized that they committed an error, and whether or not they were able to self-correct. Please review and consider this error as with the previous error discussed above to include determination of how the error occurred, whether it is likely to be repeated and, if so, the corrective measures that you will use to reduce or eliminate its likelihood of being repeated by actual users.

## Appendix A

### Device Description

The commercial presentation of Aripiprazole IM Depot is lyophilized product in a (b) (4)-mL Type-I (b) (4) glass vial. The vials are stoppered with an (b) (4) rubber stopper and sealed with a flip-off aluminum cap. The individual vial will be packaged in a convenience kit package along with reconstitution devices.

The syringes, vial adapter, needles are commercial products and are purchased as off-the shelf items, and are not custom packaged or labeled for the Aripiprazole IM Depot convenience kit. 3 mL luer-lock syringe with pre-attached 21G × 1 1/2" Hypodermic Needle-Pro® is manufactured by Smiths Medical ASD Inc. Detailed information is provided in 510(k) K923127.

### Indications for Use

ABILIFY (b) (4) (aripiprazole) is indicated for the maintenance treatment of schizophrenia in adults.

### Instructions for Use

See page 9-14 of the attachment.



NDA 202971  
innotated-draft-lab..

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SANDEEP S SAINI

06/28/2012

Intercenter consult review entered into DARRTS for CDRH

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information	
NDA # 202971 BLA#	NDA Supplement #:S- BLA STN #
Efficacy Supplement Type SE-	
Proprietary Name: Abilify (b) (4) Established/Proper Name: aripiprazole extended release suspension for injection Dosage Form: powder for suspension Strengths: 300 mg/vial and 400 mg/vial	
Applicant: Otsuka Pharmaceuticals Agent for Applicant (if applicable): David Goldberger,	
Date of Application: 9/26/11 Date of Receipt: 9/26/11 Date clock started after UN:	
PDUFA Goal Date: 7/26/12	Action Goal Date (if different):
Filing Date: 11/25/11	Date of Filing Meeting: 11/14/11
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3	
Proposed indication(s)/Proposed change(s): maintenance treatment of schizophrenia	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>	
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input checked="" type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 67380				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			S
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			X																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			X																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			X																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  <i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															X	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></p>		X																		

<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  If yes, # years requested: 3  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?		X		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
If electronic submission, does it follow the eCTD guidance? <sup>1</sup> If not, explain (e.g., waiver granted).	X			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 ( <i>NDAs/NDA efficacy supplements</i> ) or under 21 CFR 601.2 ( <i>BLAs/BLA efficacy supplements</i> ) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			X	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?		X		Sponsor submitted the form on 11/3/11 after we contacted them.
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>	X			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>			X	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>	X			
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>			X	
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	X			CDRH - 10/11/11 DMEPA – 10/12/11 DRISK – 10/24/11 DDMAC – 10/13/11
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>  <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 06/15/11, 05/27/11 - CMC  <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 11/14/2011

**BLA/NDA/Supp #:** 202,971

**PROPRIETARY NAME:** Abilify (b) (4)

**ESTABLISHED/PROPER NAME:** aripiprazole extended release suspension for injection

**DOSAGE FORM/STRENGTH:** 300 mg/vial; 400 mg/vial

**APPLICANT:** Otsuka Pharmaceuticals

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** maintenance treatment of schizophrenia

**BACKGROUND:**

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sonny Saini	Y
	CPMS/TL:	Steve Hardeman/Keith Kiedrow	N
Cross-Discipline Team Leader (CDTL)	Jing Zhang		Y
Clinical	Reviewer:	Greg Dubitsky	N
	TL:	Jing Zhang	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:	Steven Fong	N
	TL:		

Clinical Pharmacology	Reviewer:	Huixia Zhang	Y
	TL:	Hao Zhu	N
Biostatistics	Reviewer:	Andrejus Parfionovas	Y
	TL:	Peiling Yang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sonia Tabacova	Y
	TL:	Aisar Atrakchi	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	David Claffey	Y
	TL:	Chhagan Tele	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Jessica Cole	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Joe Duran	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Yelena Maslov	Y
	TL:	Irene Chan	N
OSE/DRISK (REMS)	Reviewer:	Shawna Hutchins	Y
	TL:	Mary Dempsey	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Pharmcometrics – Satjit Brar, Yaning Wang – TL; DSI – John Lee, Susan Thompson – TL; ONDQA Biopharmaceutics – Zedong Dong, Angelica Dorantes – TL; DDMAC – Jessica Click Derenick, Susannah Hubert – TL, OSE DRISK Labeling Reviewer – Robin Duer		Y
Other attendees			

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	
<p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO

<p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
------------------	--

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b>	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
Comments:	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> </ul>

<input type="checkbox"/>	• notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

Sonny Saini	11/16/11
Regulatory Project Manager	Date
Paul David	11/4/11
Chief, Project Management Staff	Date

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SANDEEP S SAINI  
11/16/2011

PAUL A DAVID  
11/17/2011

# REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

**Application:** N 202971

**Name of Drug:** Abilify <sup>(b) (4)</sup> (aripiprazole extended release suspension for injection)

**Applicant:** Otsuka Pharmaceuticals

## Labeling Reviewed

**Submission Date:** 9/26/11

**Receipt Date:** 9/26/11

## Background and Summary Description

Aripiprazole is a second generation antipsychotic, currently available in tablet (NDA 21-436), oral solution (NDA 21-713), orally disintegrating tablet (NDA 21-729), and injectable formulation (NDA 21-866). Aripiprazole has been widely used since its initial approval in 2002 for the treatment of schizophrenia. The current approved indications for oral formulations of aripiprazole include: treatment of schizophrenia; acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate; maintenance treatment of bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate; adjunctive treatment of major depressive disorder; and treatment of irritability associated with autistic disorder. The current approved indication for injectable formulation of aripiprazole is acute treatment of agitation associated with schizophrenia or bipolar I disorder. The proposed indication for aripiprazole extended release suspension for injection is maintenance treatment of schizophrenia.

## Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

## **Conclusions/Recommendations**

All labeling deficiencies identified in the SRPI section of this review will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by December 23, 2011. The resubmitted labeling will be used for further labeling discussions.

Sonny Saini, PharmD, MBA, Senior Regulatory Project Manager	11/8/11
Regulatory Project Manager	Date
Steve Hardman, RPh, CPMS	11/8/11
Chief, Project Management Staff	Date

# Selected Requirements for Prescribing Information (SRPI) N 202,971

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances.

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**
  - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
- **Product Title**
  - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
- **Initial U.S. Approval**
  - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
- **Boxed Warning**
  - All text in the boxed warning is **bolded**.
  - Summary of the warning must not exceed a length of 20 lines.
  - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
  - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
- **Recent Major Changes (RMC) – n/a**
  - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
  - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
  - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI. – n/a

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).** – Does not state “[See 17 for Patient Counseling Information and Medication Guide.](#)”

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication. – *n/a*

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. – “adverse events” term was used in this section.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.” [Section does not contain this sentence.](#)

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SANDEEP S SAINI  
11/08/2011

STEVEN D HARDEMAN  
11/08/2011