CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217006Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

NDA Executive Summary

1. Application/Product Information

NDA Number.	217006		
Applicant Name	Otsuka Pharmaceutical Company, Ltd.		
Drug Product Name	Aripiprazole 2-Month Ready-to-Use Long-Acting Injectable (Aripiprazole 2M RTU LAI) 300 mg/mL		
Dosage Form.	Injection, extended release		
Proposed Strength(s)	720 mg and 960 mg (300 mg/mL)		
Route of Administration	Intramuscular		
Maximum Daily Dose	960 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of schizophrenia		
Drug Product Description	White suspension in a 5 mL pre-filled syringe (b) (4) 720 mg/syringe and (b) (4) 960-mg/syringe) for intramuscular (IM) injection in the gluteal muscle		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20–25 °C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katie Duncan	Gaetan Ladouceur
	Drug Product/ Labeling	Venkat Pavuluri	Julia Pinto
	Manufacturing	Sateesh Podaralla	Nathan Davis
	Biopharmaceutics	Jia Yin	Ta-Chen Wu

	Microbiology	Peggy Kriger	Elizabeth Bearr
	Other (specify):	N/A	N/A
	RBPM	Teshara Bouie	
	ATL	Valerie Amspacher	
Consults	N/A		

2. Final Overall Recommendation - Approval with QPA(s)

3. Action Letter Information

a. Expiration Dating: The proposed shelf-life of 24 months is acceptable when stored at 20°–25°C (68°–77° F).

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The CMC recommendation is for approval of this application based on reviews from drug substance, drug product, process/facilities, biopharmaceutics and microbiology.

NDA 217006 is aripiprazole 2-month ready-to-use long-acting injectable (2M RTU LAI) for the treatment of schizophrenia and maintenance monotherapy treatment of bipolar I disorder in adults. Aripiprazole 2M RTU LAI is an extended-release aripiprazole formulation intended for administration every 2 months (8 weeks) via gluteal intramuscular (IM) injection by healthcare professionals. FDA approved aripiprazole 1-month LAI (Abilify Maintena IM depot, 300 mg and 400 mg) under NDA 202971.

FDA agreed that pharmacokinetic (PK) bridging to the 1 month product approved under NDA 202971 established effectiveness of aripiprazole 2M LAI (see IND 134612).

As a result of the limited clinical studies, there is no in-vivo/in-vitro correlation for the 2 month drug product.

(b) (4)

This makes setting appropriate particle size specifications especially critical. As a result, after several rounds of negotiation, the applicant tightened the primary and secondary particle size specifications to be in agreement with the particle size range noted for the single clinical batch. Since CMC has no in-vivo data other than the single clinical batch on which to set specifications, the particle size specifications are set based on the specifications approved for the 1 month product and the single clinical batch used for the in-vivo study. These tightened specifications mitigate the risk posed by the limited clinical studies and lack of in-vivo/in-vitro correlation for the dissolution test.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate with QPAs**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Review & EI Statement - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

QPA's
4438-1

The Minimum Quantitation Limit (MQL) for the current leachables methods are greater than the revised AET of (b) (4) mcg/mL. Revalidate the leachables methods such that the MQL is below the revised AET of (b) (4) mcg/mL. Repeat the leachables study on the first 3 batches of each strength manufactured for commercial marketing and use the revalidated method. Test leachables at the timepoints as recommended in ICH Q1A.

4438-2

Identify compounds from the extractables studies with unknown structural formula that are above the revised AET of (b) (4) mcg/mL. Note simulation studies will not be considered accurate identification.

4438-3

No forced degradation studies have been provided to prove the analytical methods are stability indicating. Provide data from forced degradation studies for the formulation in this NDA. Use conditions including acid, base, oxidative, heat, light.

Valerie Amspacher

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: (as submitted in eCTD SN 0007, Dated 09-NOV-2022 and responses received following comments sent to sponsor)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	**ABILIFY ASIMTUFII®** (aripiprazole) extended-release injectable suspension, for intramuscular use.
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Extended-release injectable suspension: 960 mg/3.2 mL and 720 mg/2.4 mL single-dose, pre-filled syringes
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	single-dose, pre-filled syringes.
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	Not a salt form, but monohydrate form of aripiprazole used for formulation.

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)

[redacted]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Instructions for obtaining uniform suspension prior to injection into the gluteal muscle included.
Important administration instructions supported by product quality information (e.g., do not crush or chew	Adequate	Reconstitution not applicable. However, the instructions for preparation of pre-filled syringes containing suspension for intramuscular injection into the gluteal

extended-release tablets, instructions for mixing with food)		muscle are included in section 2.5 and in "Instructions for Use" (IFU).
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	Only drug substance has USP monograph.
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

[redacted]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	Not a salt, but monohydrate form of aripiprazole used for formulation.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	The term "sterile" was included before "aqueous extended-release…" in the description and other sections of Labeling, where product description is present, in response to comments sent.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Pre-filled syringe
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	Single dose pre-filled syringe

Section 11 (DESCRIPTION)

11 DESCRIPTION

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	Not a salt. Monohydrate form of Aripiprazole is used.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	No alcohol present in the drug products.
Sterility statement (if applicable)	Adequate	The term "sterile" was included in revised PI, before "aqueous extended-release…" in the description and other sections of Labeling, where product description is present.
Pharmacological/Therapeutic class	Adequate	atypical antipsychotic
Chemical name, structural formula, molecular weight	Adequate	Molecular weight and structural formula for aripiprazole monohydrate used in the drug product are included.
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	N/A	No information provided

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	Drug Substance has a USP monograph.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

16 HOW SUPPLIED/STORAGE AND HANDLING

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Revised product identification in section 16 (b) (4) How Supplied, adding color of the (b) (4) wrap for tip cap used for the two dosage strengths.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	single-dose, pre-filled syringes
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	(b) (4)

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Store at 25°C (77°F), excursions permitted between 15° and 30°C (59° to 86°F) [see USP Controlled Room Temperature].
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	No information on whether the product is latex free or not included in the PI
Include information about child-resistant packaging	N/A	Pre-filled syringe for administration by a healthcare professional.

1.2.5 Other Sections of Labeling

NONE

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING (Medication Guide and Instructions for Use)

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	Medication Guide and IFU
Special preparation instructions (If applicable)	Adequate	IFU contains adequate instructions for healthcare professionals to prepare the PFS with uniform dispersion of suspension, prior to injection.
Storage and handling information (If applicable)	N/A	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	Medication Guide and IFU
Alphabetical listing of inactive ingredients (if applicable)	Adequate	Medication Guide
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

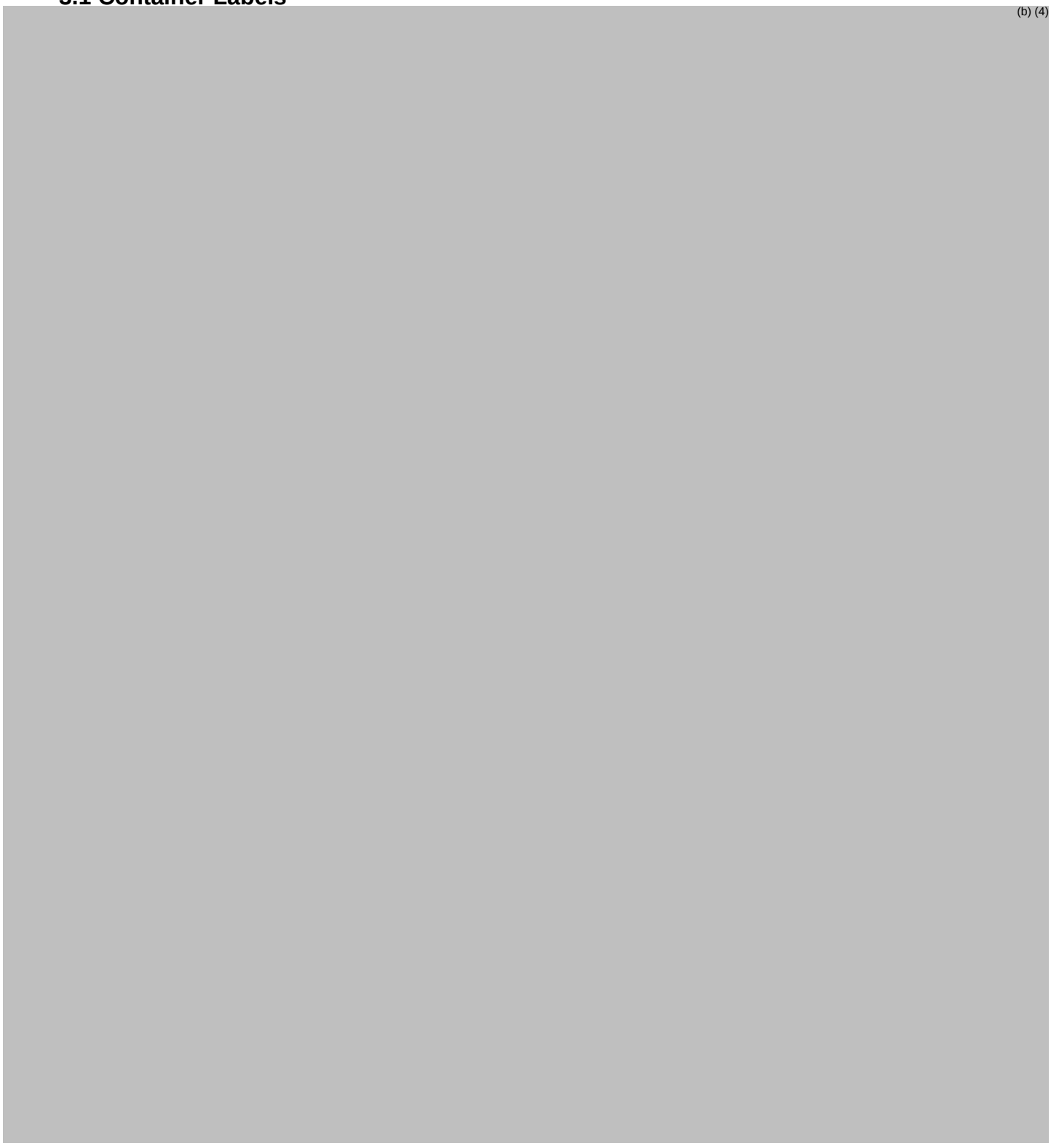
Deficiencies listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT" section.

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(b) (4)



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	Final determination on prominence of the Established name in relation to the Proprietary name is deferred to DMEPA.
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	FOR GLUTEAL INTRAMUSCULAR INJECTION ONLY
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	(b) (4)
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Storage information included on the outer carton only. Small label on prefilled syringe (PFS) is exempt from the provision, per 21 CFR 201.10(i).
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	Adequate	Single-dose injection

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	Complete text included on side panel of carton, acceptable per 21 CFR 201.10(h)(2). Small label on PFS is exempt from this requirement, per 21 CFR 201.10(i).
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Linear Bar code present on PFS and QR code given on Carton.

Item	**Items in Proposed Labeling** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments about Carton Labeling** (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Though medication Guide is included, the drug product is not meant for self-administration. To be administered to patients by healthcare professionals only.
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	No USP monograph exists as of this review date, for the drug product.
And others, if space is available.	Adequate	DOSING FREQUENCY: ONCE EVERY 2 MONTHS

Assessment of Carton and Container Labeling: Adequate.

ITEMS FOR ADDITIONAL ASSESSMENT

Prescribing Information and Medication Guide: None.

Overall Assessment and Recommendation:

Adequate As of this review, the labeling information is deemed ready for approval, from the CMC labeling/labels perspective.

Applicant provided updated prescribing information, incorporating the following changes recommended from CMC perspective:

1. Include the 'color' of syringe tip caps, in sections 3 Dosage Form and Strengths and 16 (b)(4) How Supplied of prescribing information (PI), to differentiate the two dosage strengths which are otherwise filled in same 5 mL prefilled syringes, with different nominal volume of suspension.
2. Include the term "sterile" before "aqueous extended-release…" in section 11. Description of PI, and other sections of Labeling, where product description is present.
3. Revise the statement of identification, in section 16 (b)(4) How Supplied of, as "ABILIFY ASIMTUFII (aripiprazole) is available as white to off-white, sterile aqueous extended-release injectable suspension in single-dose, pre-filled syringes in 720 mg/2.4 mL or 960 mg/3.2 mL strengths." Also add a statement of identification of the two dosage strengths by the irrespective syringe tip cap's colors.

Primary Labeling Assessor Name and Date: **Venkateswara Pavuluri, PhD; R. Ph.; 05-APR-2023**

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Julia C. Pinto, PhD; __-APR-2023

Venkateswara Pavuluri

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Julia Pinto

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FDA U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	NDA 217006
Assessment Cycle Number	01
Drug Product Name/ Strength	Aripiprazole Ready-to-Use (RTU) 2-Month Long-Acting Injectable (LAI) / 720 mg/2.4 mL and 960 mg/3.2 mL
Route of Administration	Intramuscular injection
Applicant Name	Otsuka Pharmaceutical Company, Ltd.
Therapeutic Classification/ OND Division	Neurologic Disorders /DN1
RLD/RS Number	Not Applicable
Proposed Indication	Treatment of schizophrenia
Primary Reviewer	Jia Leo, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant seeks approval for Aripiprazole 2-Month Ready-to-Use Long-Acting Injectable (Aripiprazole 2M RTU LAI) 720 mg and 960 mg via 505(b)(1) pathway. Aripiprazole 2M RTU LAI was developed as a suspension for intramuscular (IM) injection every 2 months in addition to the currently approved Abilify Maintena® (aripiprazole IM depot), a prolonged-release suspension for once monthly IM injection. The aripiprazole 2M RTU LAI is provided in a prefilled syringe which does not require reconstitution prior to use. This new formulation provides a stable aripiprazole suspension at 300 mg/mL, (b) (4) As the suspension passes through the needle during administration or after tapping and shaking the syringe, it becomes a uniform suspension (b) (4) and provides ease and comfort of dosing. Key findings of the Biopharmaceutics review are summarized below.

Dissolution Method:

The Applicant provided data to support the selection of USP Apparatus IV (flow-through cells) closed system flow rate (4 mL/min), medium pH (pH 5.0 acetate buffer), 1000 mL volume, and sample amount. (b) (4) (b) (4) Applicant proposed an IVR method using closed system with 5 mg sample amount. The selection of the in vitro release (IVR) parameters is acceptable. The Applicant evaluated and demonstrated the discriminating ability of the proposed IVR method against mean primary API particle size, mean secondary API particle size, (b) (4). The proposed IVR method was shown to be discriminating and can reject batches with mean primary API particle size outside the specification range (b) (4) (b) (4) and batches with mean secondary API particle size outside the

specification range [redacted]. The final agreed-upon dissolution acceptance criteria can reject a variant batch [redacted]

Dissolution Acceptance Criteria:
The originally proposed dissolution acceptance criteria of "0.5 hr [redacted], 2 hr [redacted]" were deemed permissive and the Applicant was requested to tighten the dissolution acceptance criteria in the IR dated 1/19/2023. In response, the Applicant tightened the dissolution acceptance criterion at the 2 hr time point to 2 hr [redacted]. Subsequently, the Agency requested that the Applicant tighten the dissolution acceptance criterion at the last time point from [redacted] to 8 hr NLT [redacted] based on the provided IVR data of the clinical batches and to be in line with the Agency's current guideline. The Applicant accepted the Agency's recommendation. The final agreed-upon dissolution acceptance criteria are "0.5 hr [redacted], 2 hr [redacted], 8 hr NLT [redacted]".

Formulation bridging:
Composition of batch 18C95A300 (used in the pivotal clinical trial 031-201-00181 and the supportive clinical trial 031-201-00279) is the same as the proposed commercial products, except the dose strength and container closure system. Composition of batch 14C93A400 (used in the supportive clinical trial 031-201-00104) is identical to batch 18C95A300, except the filling volume and container closure system (syringe versus vial). The IVR/dissolution comparison was provided for the clinical batch 18C95A300 and the proposed commercial product in multi-pH medium (pH 1.2, 4.5, 6.8, and 5) using USP Apparatus IV. Additional comparisons were performed using the proposed IVR method in pH 5.0 medium and particle size (primary and secondary) between clinical batches and the commercial product, including long-term stability study (LTSS) batches and the process validation (PV) batches. The clinical batches and the proposed commercial formulation are adequately bridged by supporting dissolution comparison data and particle size comparison data.

Recommendation:
From a Biopharmaceutics perspective, NDA 217006 for Aripiprazole Ready-to-Use (RTU) 2-Month Long-Acting Injectable (LAI) / 720 mg/2.4 mL and 960 mg/3.2 mL is ADEQUATE.

FDA-approved dissolution method and acceptance criteria:

USP Apparatus	Flow rate	Medium/Temperature	Volume (mL)	Sample Amount	Acceptance Criteria
IV (Flow-through Cells) closed system	4 mL/min	pH 5.0 acetate buffer/ 37°C ± 0.5°C	1000	5 mg	0.5 hr [redacted] 2 hr [redacted] 8 hr NLT [redacted]

List Submissions being assessed:

Document(s) Assessed	Date Received
Sequence 0001 /Original submission	6/27/2022
Sequence 0015 /Response to Biopharmaceutics IR	2/20/2023
Sequence 0029 /Response to Biopharmaceutics IR	3/16/2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment:
Not Applicable. No BCS designation was requested.

Solubility:

Table 1. Solubility of drug substance, aripiprazole monohydrate, across pH 3.0 – 5.0

Buffer pH		Solubility of Aripiprazole Drug Substance (µg/mL)			
		Shaking for 30 min		Shaking for 24 hr[a]	
		Monohydrate	Anhydrous	Monohydrate	Anhydrous
Acetate Buffer	pH 3.0	787	1862	850	879
	pH 3.5	365	1189	379	388
	pH 4.0	139	580	146	148
	pH 4.5	44	189	41	47
	pH 5.0	12	56	12	13

[a]30 min at 37°C, 30 min at 45°C, and 23 hours at 37°C.

The provided solubility data showed decrease in solubility of aripiprazole monohydrate with increase in pH value. As the highest strength and dose is 960 mg/3.2 mL, based on the provided solubility data, the drug substance is considered having low solubility, per BCS criteria.

According to the Applicant, under strongly acidic conditions such as pH 1.2 buffer, the drug substance forms hydrochloride. In addition, the solubility at pH 5.0 is 70 times lower than that at pH 3.0. Therefore, this Reviewer determines that the evaluation of the drug substance solubility is adequate and accepts that the solubility data at pH 1.2 and pH 6.8 were not provided.

Permeability:
No permeability data were provided.

Dissolution: Refer to B.2 section

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *{Adequate}*

1. In Vitro Release (IVR) Method

The Applicant (b) (4) (b) (4) (b) (4) proposed an IVR method using closed system with 5 mg sample amount. The proposed IVR method is shown in **Table 2**.

Table 2. Proposed IVR method and acceptance criteria

USP Apparatus	Flow rate	Medium/Temperature	Volume (mL)	Sample Amount	Acceptance Criteria
IV (Flow-through Cells) closed system	4 mL/min	pH 5.0 acetate buffer/ 37°C ± 0.5°C	1000	5 mg	30 min (b) (4) 2 hr (b) (4)

(b) (4)

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Evaluation of discriminating ability:
The Applicant evaluated the discriminating ability of the IVR method against API particle size and drug product (b) (4).

API particle size:
As part of the mitigation strategy to ensure batch-to-batch consistency, the Applicant tightened the specification for API particle size (**Table 3**). Varian batch 23A82A300-2 has mean primary and secondary particle sizes smaller than lower limit of the specification for API particle size and variant batch 18E85A300-2 has mean primary and secondary particle sizes larger than the upper limit of the specification for API particle size (**Table 4**). The dissolution results (**Figure 6**) showed no discriminating ability of the IVR method using one dosage unit against API particle size.

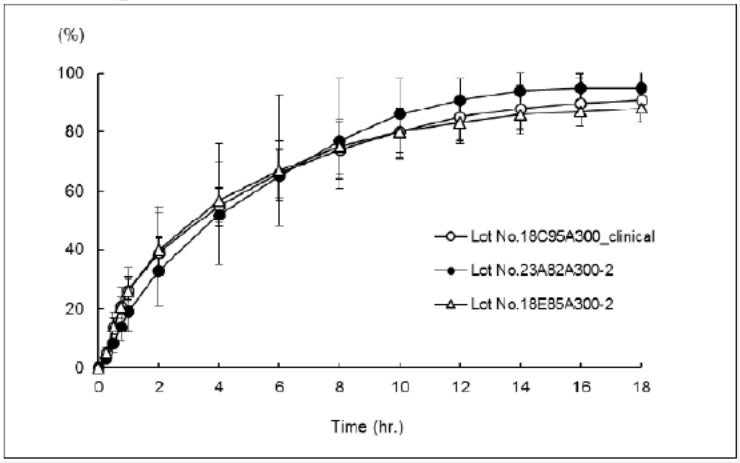
Table 3. Updated (tightened) specification of primary and secondary API particle size

Primary Particle Size Distribution	Mean Particle Size : (b) (4) 10%D : (b) (4) 90%D : (b) (4)	(b) (4)
Secondary Particle Size Distribution	Mean Particle Size : (b) (4) 10%D : (b) (4) 90%D : (b) (4)	

Table 4. Batches used in the evaluation of the discriminating ability

Lot Number (Purpose)	Mean primary particle sizes (Secondary particle sizes)	Primary particle sizes (μm) (Secondary particle sizes (μm))			Preparation processes
		10%D	50%D	90%D	(b) (4)
18C95A300[a] (Clinical Batch)	(b) (4)				
14C93A400[b] (Clinical Batch for supportive study)					
23A82A300-2[c] (i)					
18E85A300-2[c] (ii)					
19C74A300-4A[c,d] (iii)					
21B80A960[e] (LTSS Lot)					
22I76YRA[e] (PV Lot)					

Figure 6. Dissolution profiles of batches with different mean particle size (Aripiprazole 960 mg, 0.7 N acetic acid solution, flow rate of 16 mL/min, n=12)



(b) (4)

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(b) (4)

Evaluation of the discriminating ability:

In the original submission, the Applicant evaluated the impact of the mean primary API particle size (**Figure 13, Table 5 and 6**), the mean secondary API particle size (**Figure 14, Table 7 and 8**), (b) (4) (**Figure 15 and Table 9**) on the drug product dissolution using the proposed IVR method. Based on the dissolution results and the originally proposed dissolution acceptance criteria, the IVR method is able to reject batches with 1) mean primary API particle size larger than specification upper limit (b) (4) (b) (4) and 2) (b) (4)

(b) (4)

(b) (4). The method is not able to reject mean primary API particle size smaller than the specification lower limit (b) (4)

(b) (4). The method's discriminating ability against mean secondary API particle size larger than the specification upper limit (b) (4)

(b) (4) is marginal. The discriminating ability against mean secondary API particle size smaller than the specification lower limit was not evaluated.

In the IR dated 1/19/2023, the Applicant was requested to further evaluate the discriminating ability against (i) mean primary API particle size smaller than the proposed specification lower limit, and (ii) mean secondary API particle sizes smaller than the proposed specification lower limit and larger than the proposed specification upper limit. The Applicant was also requested to provide full dissolution profile comparison instead of dissolution data comparison at the proposed specification time points. In response to the IR, the Applicant manufactured a new batch, Lot No. 23A82A300-2, with mean primary and secondary particle size smaller than the specification lower limit (b) (4)

(b) (4)

(b) (4). The Applicant re-used the data from batch 18E85A300-2 (in the original submission) which has mean primary and secondary API particle size larger than the specification upper limit (b) (4)

(b) (4)

(b) (4), and data from batch 19C74A300-4A (b) (4)

(b) (4)

Based on the dissolution results (**Figure 16**) and the f2 values (**Table 10**), the proposed IVR method can discriminate batches with smaller mean primary and secondary API particle sizes and larger mean primary and secondary API particle sizes. To mitigate the risk of dissolution, the Applicant proposed to tighten the dissolution acceptance criteria at the 2 hr time point (b) (4). With the newly proposed dissolution acceptance criteria, the variant batch (b) (4) can be rejected. As part of the mitigation strategy for batch-to-batch consistency, the Applicant also proposed to tighten the primary and secondary API particle size specifications (**Table 11**).

Figure 13 Dissolution profiles of batches with different API primary particle sizes (Aripiprazole 5 mg, pH 5.0 acetate buffer, 1000 mL, flow rate 4 mL/min, n = 12)

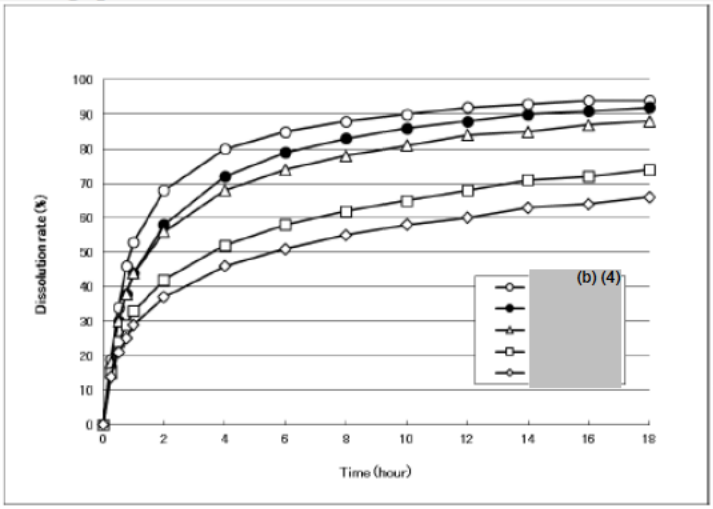

Table 5. Information of batches with different primary API particle sizes

Lot No.	Mean Particle Size (Primary) (µm)	Mean Particle Size (Secondary) (µm)
18E85A300-6	(b) (4)	
18C95A300 (clinical lot)		
18E85A300-3		
18E85A300-2		
18E85A300-1		

Table 6. Dissolution rates of batches with different API primary particle sizes (Aripiprazole 5 mg, pH 5.0 acetate buffer, 1000 mL, flow rate 4 mL/min, n = 12)

Table 3-7	**Dissolution Rate (%) at Tentative Dissolution Specification Time, Mean (Min - Max)**		
Mean Particle Size (Primary)	**0.5 hr**	**2 hr**	(b) (4)
(b) (4)			

dissolution rates in bold: out of specification

Figure 14. Dissolution profiles of batches with different API secondary particle sizes (Aripiprazole 5 mg, pH 5.0 acetate buffer, 1000 mL, flow rate 4 mL/min, n = 12)

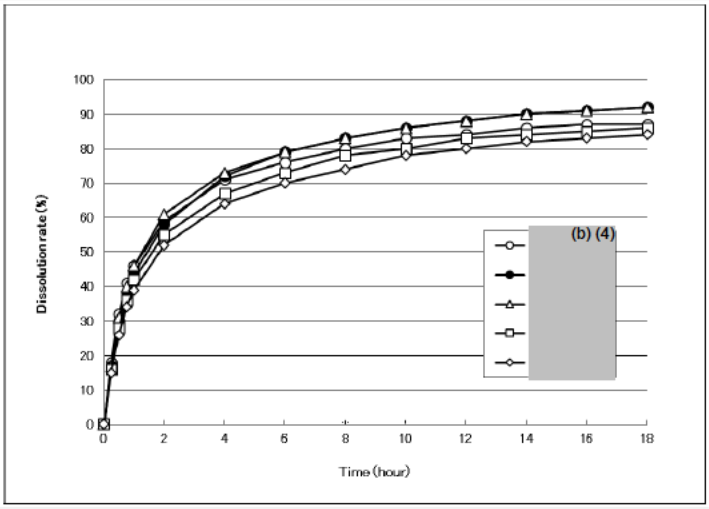

Table 7. Information of batches with different mean secondary API particle sizes

Lot No.	Mean Particle Size (Primary) (µm)	Mean Particle Size (Secondary) (µm)
18C95A300-N	(b) (4)	
18C95A300 (clinical lot)		
18C95A300-50		
18C95A300-70		
18C95A300-90		

Table 8. Dissolution rates of batches with different API secondary particle sizes (Aripiprazole 5 mg, pH 5.0 acetate buffer, 1000 mL, flow rate 4 mL/min, n = 12)

Table 3-8	**Dissolution Rate (%) at Tentative Dissolution Specification Time, Mean (Min - Max)**		
Mean Particle Size (Secondary)	**0.5 hr**	**2 hr**	(b) (4)
(b) (4)			

dissolution rates in bold: out of specification

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Table 10. F2 values for the variant bathes and clinical batch

	23A82A300-2 (smaller primary and secondary particle size)	18E85A300-2 (larger primary and secondary particle size)	19C74A300-4A ((b) (4))
18C95A300 (clinical batch)	(b) (4)	(b) (4)	(b) (4)

Table 11. Mitigation strategy for batch-to-batch consistency

Primary particle size		
Critical process	(b) (4)	
Critical process parameters[a]		
Quality tests	Evaluation item	Acceptance criteria
(b) (4)	Mean particle size	(b) (4)
	10%D	
	90%D	
	Mean particle size	
Product release test	10%D	
	90%D	
	Mean particle size	
Secondary particle size		
Critical process	(b) (4)	
Critical process parameters[e]		
Quality controls	Evaluation item	Acceptance criteria
(b) (4)	**Mean particle size**	(b) (4)
	10%D	
	90%D	
	Mean particle size	
Product release test	10%D	
	90%D	
	Mean particle size	
Dissolution profile		
Quality controls	Evaluation item	Acceptance criteria
Product release test using **the existing IVR method**	0.5-hour time point	(b) (4)
	2-hour time point	
(b) (4)	hour time point	
(b) (4)		

Reviewer's overall comment on the IVR method:
The Applicant provided data to support the selection of flow rate, medium pH, and sample amount. The selection of the IVR parameters is acceptable. The Applicant also demonstrated the discriminating ability of the proposed IVR method against mean primary and secondary particle sizes. Overall, the proposed IVR method is acceptable.

2. Dissolution Acceptance Criteria

The originally proposed dissolution acceptance criteria of "0.5 hr (b) (4), 2 hr (b) (4) (b) (4)" were deemed permissive and the Applicant was requested to tighten the dissolution acceptance criteria in the IR dated 1/19/2023.

As the dissolution profile data for the clinical batch provided in a vial (18C95A300) were obtained without using an injection needle (**Table 12**), in response to the IR, the Applicant additionally provided dissolution data for the clinical batch obtained using an injection needle (**Table 13**) to be in line with the commercial product, which is provided in a pre-filled syringe. The dissolution of the clinical batch at the 2 hr time-point appears to be slightly faster when tested with an injection needle. Based on the dissolution data from the clinical batch tested with and without an injection needle, long-term stability study (LTSS) batches, and the process validation (PV) batches (**Table 14**), the Applicant tightened the dissolution acceptance criterion at the 2 hr time-point but upshifted the mean dissolution value at the 2 hr time-point. The newly proposed dissolution acceptance criteria are "0.5 hr (b) (4) 2 hr (b) (4)".

For LAI or modified-release drug products, the Agency's current guideline recommends the last time-point of the specifications be selected based on where > (b) (4) (mean value) drug release occurs. Based primarily on the clinical batches, the provided dissolution profile data support the setting of "NLT (b) (4) at 8 hours" as the acceptance criterion for the last time-point. In the IR dated 3/13/2023, the Applicant was requested to tighten the dissolution acceptance criterion for the last time point from (b) (4) to 8 hr NLT (b) (4). The Applicant accepted the recommendation. The agreed dissolution acceptance criteria are "0.5 hr (b) (4) 2 hr (b) (4) 8 hr NLT (b) (4)". The Applicant also provided full IVR profiles for the 6 stability batches at the initial time point and the current 18-month time point to support the new dissolution acceptance criteria. The IVR data of the stability batches conform to the agreed-upon dissolution acceptance criteria.

Table 12. Dissolution profiles data for the clinical batch (18C95A300) tested without using an injection needle

Table 1.1-7	Dissolution Rate (%) at Each Time Point (n = 12) of Lot No.18C95A300 (Existing IVR Methods)					
Time (hr)	n = 1	n = 2	Max	Min (b) (4)	Mean	RSD
0					0	0
0.25					17	6
0.5					30	5
0.75					38	4
1					44	4
2					58	3
4					72	4
6					79	4
8					83	3
10					86	4
12					88	4
14					90	3
16					91	3
18					92	3

The data were obtained without using a needle.

Table 13. Dissolution data at the specification time points for the clinical batch (18C95A300) tested with an injection needle

Time (hr)	n = 1						n = 2						Max	Min	Mean	RSD
	1	2	3	4	5	6	1	2	3	4	5	6				
0														(b) (4)	0	0
0.25															17	4
0.5															32	4
0.75															42	5
1															49	6
2															64	4
4															76	3
6															81	2
8															85	2
10															87	3
12															88	2
14															89	2
16															90	2
18															91	2

Table 14. Summary of the dissolution rate the 2 hr time point

Injection Needle	Batch	Lot No.	Dissolution rate (%)
Tested Without Needle	Clinical	18C95A300	58 (b) (4)
Tested With Needle	Clinical	18C95A300	64
	LTSS 600mg	21B80A600	62
		21B86A600	61
		21B91A600	63
	LTSS 960mg	21B80A960	63
		21B86A960	63
		21B91A960	65
	PV 720mg	22E93YRB	66
		22I87YRB	64
		22I92YRB	61
	PV 960mg	22E87YRA	63
		22I76YRA	64
		22I81YRA	63

3. Effect of External Factors on Drug Release

No in vitro investigation was performed. Instead, the Applicant evaluated the effect of external stress factors on drug release in rats. The external factors evaluated are physical stimulation (approximately (b) (4) pressure), exercise stimulation (treadmill), whole body heat stimulation (b) (4) and local heat stimulation (b) (4). According to Nonclinical review team, single IM administration of aripiprazole 2M RTU LAI at 50 mg/kg to rats along with stress factors in 6 conditions (control, anesthesia control, physical stimulation, exercise stimulation, whole body heat stimulation, and local heat stimulation) resulted in less than 2-fold changes in Cmax or AUC after stress challenge, while Tmax values and mean residence time were similar across all groups. These challenges, representing the worst-case scenario, are not likely to cause clinically significant changes in aripiprazole exposure after IM administration of aripiprazole 2M RTU LAI. Examining the individual profiles any potential dose dumping was performed by the Clinical Pharmacology review team.

B.12 BRIDGING OF FORMULATIONS

Assessment: *{Adequate}*

To support this NDA, the Applicant conducted three clinical trials: one pivotal trial (031-201-00181) and two supportive trials (031-201-00104 and 031-201-00279). The batch used in the pivotal clinical trial 031-201-00181 and the supportive clinical trial 031-201-

00279 is 18C95A300. The batch used in the supportive clinical trial 031-201-00104 is 14C93A400. According to the Applicant, the composition of batch 18C95A300 is the same as the proposed commercial products, although the dose strength and container closure system were different (**Table 15**). For batch 18C95A300, a glass vial product filled with 5.4 mL of drug suspension (1620 mg/vial as anhydrous aripiprazole) was manufactured as clinical product. Each vial was tapped and shaken before administration following the established procedures. The composition of batch 14C93A400 and batch 18C95A300 is identical, except the filling volume (1.41 mL versus 5.4 mL) and container closure system (syringe versus vial) are different (**Table 16**).

In the original submission, the Applicant provided dissolution comparison for the clinical batch 18C95A300 and the commercial product in multi-pH medium (pH 1.2, 4.5, 6.8, and 5) using USP Apparatus 4 (**Figure 17 – 20**). In response to Biopharmaceutics IR dated 1/19/2023, the Applicant provided dissolution comparison using the proposed IVR method and particle size (primary and secondary) comparison for both clinical batches and the commercial product, including long-term stability study (LTSS) batches and the process validation (PV) batches (**Figure 21 - 23**). Based on the provided data, the clinical batches and the commercial product is deemed adequately bridged.

Table 15. Composition comparison of the clinical batch 18C95A300 and the commercial product

Component	Reference Standard	Suspension Quantity (mg/mL)	Proposed commercial product Quantity (mg/syringe)		Clinical Product Quantity (mg/vial)
			720-mg	960-mg	
Sterile Aripiprazole Monohydrate	In-house	300[a]	(b) (4)		
Carboxymethylcellulose Sodium	USP/Ph Eur	5.0			
Povidone[b]	USP/Ph Eur	4.0			
Polyethylene Glycol 400	NF/Ph Eur	1.0			
Sodium Phosphate, Monobasic, Monohydrate	USP/In-house	0.74			
Sodium Chloride	USP/Ph Eur	6.1			
Sodium Hydroxide	NF/Ph Eur	q.s. to pH (b) (4)			
Water for Injection	USP/Ph Eur	q.s. to 1.0mL			
Container Closure System	--	--	Single chamber syringe[d]	Single chamber syringe[d]	Glass vial[e]

Abbreviations: NF = National Formulary; USP = United States Pharmacopeia; Ph Eur = European Pharmacopoeia; q.s. = quantum sufficit (as much as suffices).

(b) (4)

Table 16. Composition comparison of the clinical batch 18C95A300 and the clinical batch 14C93A400

Table 1.5-1		Batch Information for the Test Product Used in Two Supporting Clinical Trials 031-201-00104 and 031-201-00279		
Component	**Reference Standard**	**Suspension Quantity (mg/mL)**	**Clinical Product Quantity (mg/syringe) for Clinical Trials 031-201-00104**	**Clinical Product Quantity (mg/vial) for Clinical Trials 031-201-00279**
Sterile Aripiprazole Monohydrate	In-house	300[a]	(b) (4)	
Carboxymethylcellulose Sodium	USP	5.0		
Povidone[b]	USP	4.0		
Polyethylene Glycol 400	NF	1.0		
Sodium Phosphate, Monobasic, Monohydrate	USP	0.74		
Sodium Chloride	USP	6.1		
Sodium Hydroxide	NF	q.s. to pH (b) (4)		
Water for Injection	USP	q.s. to 1.0mL		
Batch Number	--	--	14C93A400	18C95A300[f]
Manufacturing Date	--	--	24 March 2014	26 March 2018
Container Closure System	--	--	Single chamber syringe[d]	Glass vial[e]

Abbreviations: NF = National Formulary; USP = United States Pharmacopeia; q.s. = quantum sufficit (as much as suffices).

(b) (4)

Figure 17. Dissolution comparison of the pivotal clinical batch and the commercial product in pH 1.2 medium

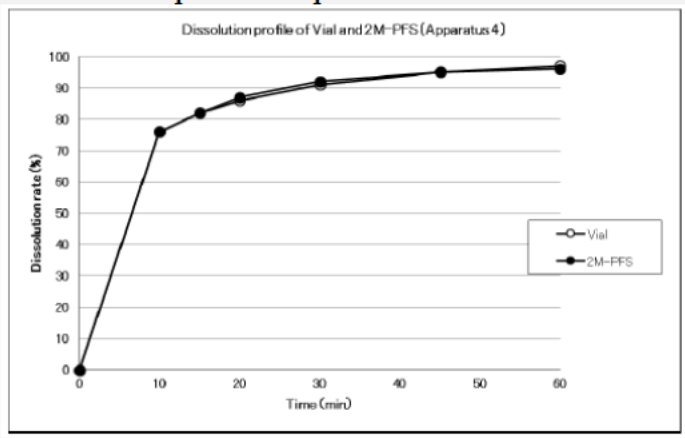


Figure 18. Dissolution comparison of the pivotal clinical batch and the commercial product in pH 4.5 medium

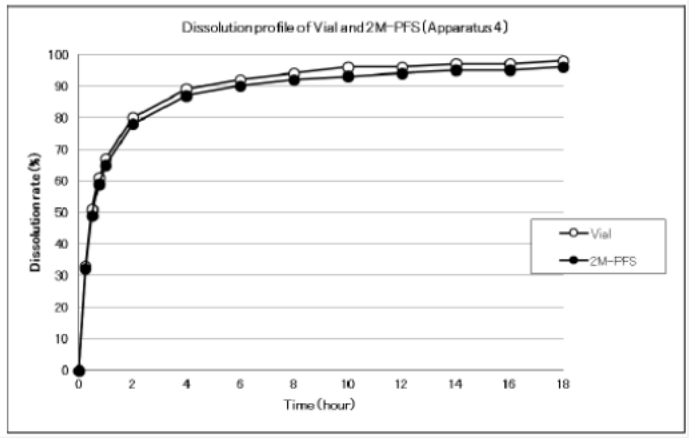


Figure 19. Dissolution comparison of the pivotal clinical batch and the commercial product in pH 6.8 medium

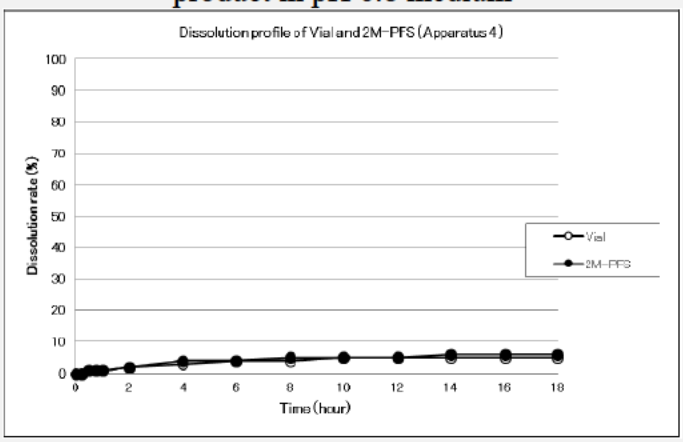


Figure 20. Dissolution comparison of the pivotal clinical batch and the commercial product in pH 5 medium

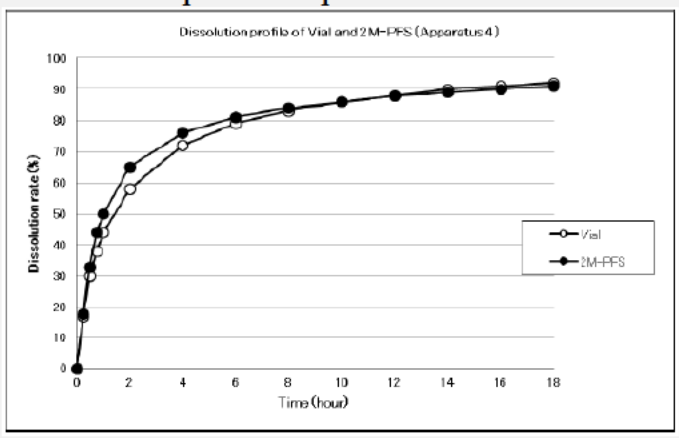


Figure 21. Dissolution comparison of the clinical batches and the commercial product in pH 5 medium (proposed IVR method)

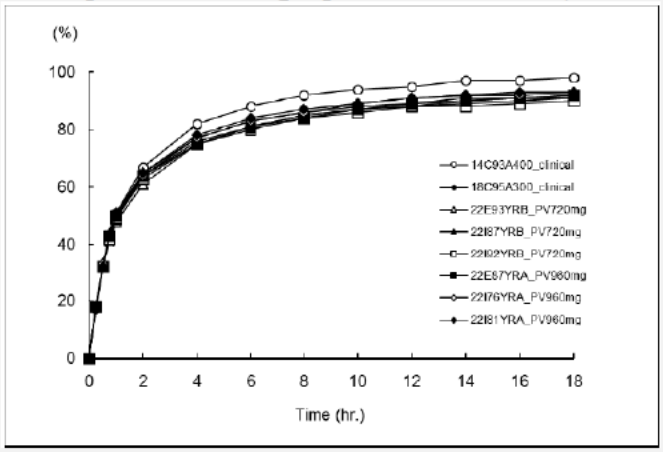


Figure 22. Primary particle size comparison of the clinical batches and the commercial product

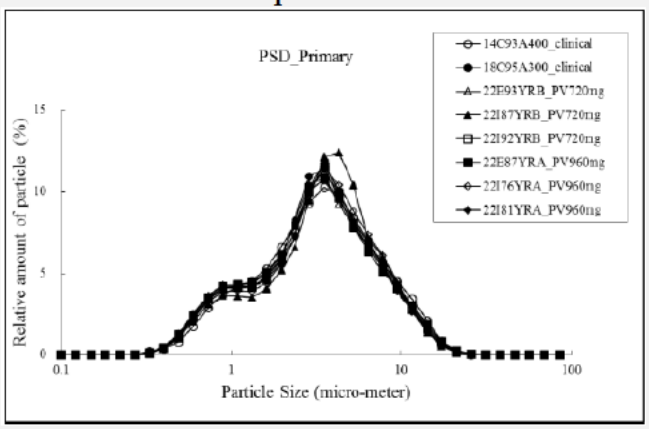
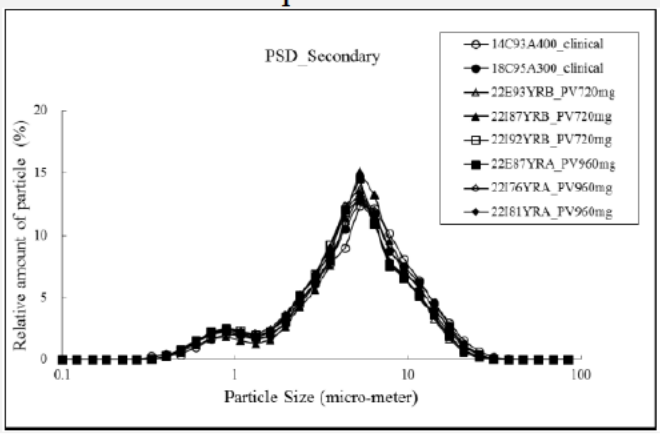


Figure 23. Seconary particle size comparison of the clinical batches and the commercial product



BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

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Ta-Chen Wu

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CHAPTER VII: MICROBIOLOGY

Product Information	505(b)(1) - Type 3 new dosage form, combination product type 2
NDA Number	217006
Assessment Cycle Number	1
Drug Product Name/ Strength	Proprietary (proposed): Abilify Asimtufii; Non-proprietary: Aripiprazole 2-month RTU long acting injectable/300 mg/mL, as 720 mg/2.4 mL and 960 mg/3.2 mL, in a 5 mL prefilled syringe, single dose
Route of Administration	Intramuscular
Applicant Name	Otsuka Pharmaceutical Co. Ltd.
Therapeutic Classification/ OND Division	ON/DP
Manufacturing Site	Otsuka Pharmaceutical Co. Ltd. – Tokushima Mima Factory 1-3 Azasatohirano, Mima-cho, Mima-shi, Tokushima, Japan 771-2106
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: (b) (4) solution containing excipients and Water for Injection (b) (4)

(b) (4)

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
0001 (1)	6/27/22
0002 (2), 0003 (3), 0004 (4)	8/12/22[a], 8/16/22[b], 9/22/22[c]
0005 (5), 0006 (6), 0007 (8)	10/7/22[a], 10/11/22[a], 11/9/22[b]
0010 (7), 0008 (9), 0009 (10)	11/7/22[d], 11/10/22, 11/14/22[e]
0011 (11), 0012 (12), 0013 (13)	11/14/22[e], 11/18/22, 11/23/22[e]
0014 (14), 0016 (15), 0018 (16)	12/21/22[c], 2/2/23, 2/15/23
0020 (17), 0019 (19), 0021 (18)	2/16/23[a], 2/17/23[f], 2/17/23[h],
0015 (20), 0017 (21), 0023 (22)	2/21/23[a,g], 2/23/23[a], 2/23/23[d],
0024 (23), 0022 (24)	2/24/23[h], 2/28/23

[a] Clin. Pharm. IR response (R), [b] Administrative, [c] Process/Facilities IR R, [d] HF IR R, [e] Clin. IR R, [f] DP IR R, [g] Biopharm. IR R, [h] Labeling

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The submission was assigned to the reviewer 6/29/22 and is in the eCTD format. The 11/10/22 and 11/18/22 amendments are the responses to a Microbiology Information Request (IR) sent to the Applicant on 10/27/22. The 2/2/23, 2/15/23 and 2/28/23 amendments are the responses to Microbiology IRs sent to the Applicant on 1/20/23 and 2/8/23. Some tables were copied from the submission.

Concise Description of Outstanding Issues: N/A

Supporting Documents:

NDA 202971 is cross-referenced by the applicant. This review notes that submission for information related to the sterile drug substance, drug product suspension (b) (4), environmental monitoring, (b) (4) . Relevant information was reviewed (b) (4) (b) (4)

DMF (b) (4) is referenced for sterile drug substance manufactured at (b) (4) An LOA, dated June 2, 2022, is provided. Relevant information was reviewed (b) (4) (b) (4)

DMF (b) (4) is referenced for depyrogenation and sterilization of the drug product container closure components. An LOA, dated May 5, 2022, is provided. Relevant information regarding the depyrogenation and sterilization processes for the 5 mL (b) (4) syringe system manufactured at the (b) (4) was reviewed (b) (4) Relevant information regarding the depyrogenation and sterilization processes for the 5 mL (b) (4) syringe system manufactured at the (b) (4) was reviewed (b) (4) (b) (4)

S DRUG SUBSTANCE

The drug substance is sterile aripiprazole monohydrate. The sterile aripiprazole monohydrate drug substance is manufactured by two sites as noted below.

The same sterile drug substance is used for Abilify Maintena under NDA 202971 (referenced by the applicant).

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(b) (4)

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Sterile, white to off-white aqueous extended release suspension, pH (b) (4), in a single dose prefilled single chamber syringe.
- **Drug product composition –**

Ingredient	Quantity	Content per syringe (mg)*		Function
	mg/mL	720	960	
Sterile Aripiprazole monohydrate	300	(b) (4)		Active
Carboxymethylcellulose sodium	5.0			(b) (4)
Povidone	4.0			
Polyethylene glycol 400	1.0			
Sodium phosphate, monobasic, monohydrate	0.74			
Sodium chloride	6.1			
Sodium hydroxide	q.s.	q.s. to pH (b) (4)	q.s. to pH (b) (4)	pH adjustment
Water for Injection	q.s.	q.s. to (b) (4) mL	q.s. to (b) (4) mL	(b) (4)

* (b) (4)

- **Description of container closure system –**

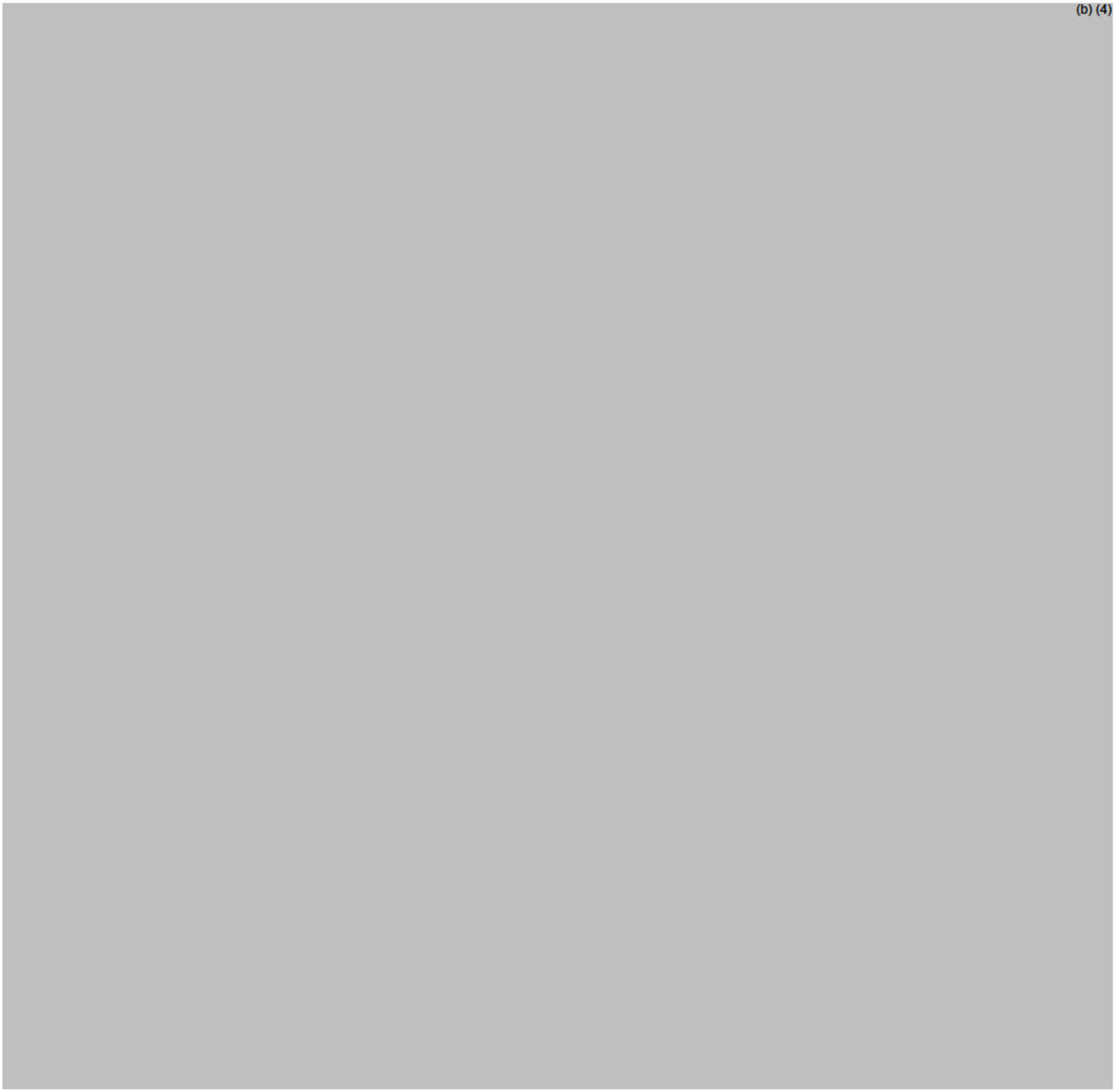
Configuration	Component	Description	Manufacturer
300 mg/mL filled as 720 mg/2.4 mL and 960 mg/3.2 mL	(b) (4) 5 mL syringe , (b) (4) (consisting of the following):	(b) (4)	
	Syringe barrel		(b) (4)
	Tip-cap		
	Plunger stopper		

Each prefilled syringe (PFS) container closure system is supplied Ready to Use (RTU). The drug product kit contains sterile needles. See section P.7 for additional information.

Assessment: ***Adequate***

P.2 PHARMACEUTICAL DEVELOPMENT
P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)



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

MICROBIOLOGY LIST OF DEFICIENCIES – *N/A*

No deficiencies were identified.

Primary Microbiology Assessor: Peggy Kriger, Ph.D., 3/1/23
Senior Pharmaceutical Quality Assessor: Elizabeth Bearr, Ph.D., 3/1/23

Elizabeth Bearr

Digitally signed by Elizabeth Bearr
Date: 3/02/2023 08:59:16AM
GUID: 55370d1e00cfd67fc04d8bfbedbf3096

Peggy Kriger

Digitally signed by Peggy Kriger
Date: 3/01/2023 06:21:59PM
GUID: 534c169d00067f29cedbaa415df21ba2

Valerie Amspacher

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Date: 4/25/2023 12:47:17PM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

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/s/

VALERIE R AMSPACHER
04/25/2023 12:57:40 PM