CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216655Orig1s000

PRODUCT QUALITY REVIEW(S)

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Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment

NDA Executive Summary

1. Application/Product Information

NDA Number	216655		
Applicant Name	Xiamen LP Pharmaceutical Co., Ltd.		
Drug Product Name	Aripiprazole Oral Soluble Film		
Dosage Form	Film		
Proposed Strength(s)	2 mg, 5 mg and 10 mg		
NDA Classification	Type 3 - New Dosage Form		
Route of Administration	Oral		
Maximum Daily Dose	30 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Schizophrenia		
Drug Product Description	rectangular white film placed in the oral cavity then swallowed and absorbed in the gastrointestinal tract; packaged into individual (b) (4) pouches (b) (4)		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20°–25ºC		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Katharine Duncan
	Drug Product/ Labeling	Andrei Ponta	Valerie Amspacher/Julia Pinto
	Manufacturing	Yeung Chan	Jingbo Xiao

	Biopharmaceutics	Swapna Pamu	Okpo Eradiri
	Microbiology	N/A	N/A
	Other (specify)	N/A	N/A
	RBPM	Teshara Bouie	
	ATL	Valerie Amspacher	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The drug product may be granted a 36-month expiry when stored at 20°–25°C (68°–77° F). [USP controlled room temperature]

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The CMC recommendation is for approval based on reviews by drug substance, drug product, process and facilities and biopharmaceutics.

This NDA was issued a refuse-to-file letter on 21 Oct 2022 due to a lack of imprint on the dosage form as well as clinical issues. It was resubmitted 19 Sep 2023.

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

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate
Biopharmaceutics - Adequate
Microbiology - N/A

Environmental Assessment: Categorical Exclusion - 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:

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 4; eCTD 0004	19 Sep 2023	All, resubmission
Supporting document 11; eCTD 0011	6 Mar 2024	Drug product
Supporting document 14; eCTD 0014	26 Mar 2024	Process and facilities
Supporting document 16; eCTD 0016	2 Apr 2024	Biopharmaceutics

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 (OPQ-ALL-WI-0006)

NDA Number	216655
Assessment Cycle Number	1
Drug Product Name	Aripiprazole Oral Film

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN #
Prescribing Information Labeling	Adequate	**0006**
Patient Information	Adequate	**0006**
Instruction for Use (IFU)	N/A	**NA**
Container Labels	Adequate	**0004**
Carton Labeling	Adequate	**0004**

Brief Description of Outstanding Issues: To be communicated during labeling negotiations.

1. The Applicant will be asked to remove (b) (4) for the drug product name.
2. The required information in Section 3 is present in the dosage form and strengths section; however, it is presented in a table. The Applicant will be asked to provide the information in a sentence format.
3. The Applicant will be asked to include pH and solubility information in the description section.
4. The Applicant does not include information regarding child-resistant packaging.
5. The Applicant will be asked to include the excipients as part of the container labeling.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0004	19 – Sep – 2023	NDA Resubmission
0006	13 – Dec – 2023	Labeling
0012	11 – Mar – 2024	Labeling

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

[redacted]

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

Item	Item 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[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	Aripiprazole Oral Film
Route(s) of administration	Adequate	Oral
Controlled drug substance symbol (if applicable)	N/A	NA
Initial U.S. Approval [§201.57(a)(3)]	Adequate	2002
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)
[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

Item	Item 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 form(s)[4] and strength(s) in metric system[5]	Adequate	Oral Film: 2 mg, 5 mg, 10 mg
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).[6]	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral 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.[8]	N/A	

Assessment: *Adequate*

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>
[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>
[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

(b) (4)

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(b) (4)

Item	Item 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 and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	N/A	

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

Item	Item 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 parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
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	

Assessment: *Adequate*

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition
[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

(b) (4)

Item	Item 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 (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	
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	
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 parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include	N/A	

Item	Item 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)
pharmacy bulk package and imaging bulk package (see USP <659>).		

Assessment: *Adequate*

The required information is present; however, it is presented in a table. The Applicant will be asked to provide the information in a sentence format.

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

Item	Item 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)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item 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 form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	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)" [§ 201.57(c)(12)(i)(C)].	N/A	
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	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. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item 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)
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	
For oral prescription drug products, include gluten statement[19] (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	

Assessment: *Adequate*

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

Item	Item 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) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] 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. No equivalency statement.	Adequate	
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item 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)
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 parenteral 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 (see USP <659>).	N/A	
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." [§ 201.57(c)(17)(iv)]	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	
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.*	N/A	

Item	Item 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)
Avoid statements such as "latex-free."[21]		
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Adequate	

Assessment: *Adequate*

1.2.5 Other Sections of Labeling

Not Applicable

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	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	

Assessment: *Adequate*

2.0 PATIENT LABELING

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

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	
Special preparation instructions (if applicable).	N/A	
Storage and handling information (if applicable).	Adequate	
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 differ from the dosage form.	N/A	
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

3.0 CONTAINER AND CARTON LABELING[25]

[24] Established name = [Drug] [Route of Administration] [Dosage Form]
[25] Carton and Container Labeling Resources

3.1 Container Labels[26]

3.2 Carton Labeling

Not Applicable.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	

[26] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.
[27] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	Yes	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms	N/A	Yes	

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).			
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Adequate	Yes	
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx,	Adequate	Yes	

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
required for OTC [§ 201.66(c)(5)(x)].			
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Yes	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	
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.[31]	N/A	Yes	
And others if space is available.	Adequate	Yes	

Assessment of Carton Labels and Container Labeling: *Adequate*

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Not Applicable

Primary Labeling Assessor Name: Andrei Ponta

[31] USP General Notices 3.20 Indicating Conformance

Julia Pinto

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Andrei Ponta

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-216655-ORIG-1-RESUB-4
Assessment Cycle Number	1
Drug Product Name/ Strength	Aripiprazole Oral Soluble Film/ 2 mg, 5 mg and 10 mg
Route of Administration	Oral
Applicant Name	Xiamen LP Pharmaceutical Co., Ltd.
Therapeutic Classification/ OND Division	Division of Psychology (DP)
RLD/RS Number	Abilify® (Aripiprazole), NDA-021436
Proposed Indication	For Schizophrenia, adjunctive Treatment of major depressive disorder, irritability associated with autistic disorder and treatment of tourette's disorder.
Submission Date	08/24/2022 (Original); 09/19/2023 (Resubmission after RTF)
Primary Reviewer	Swapna Pamu, M.S.
Secondary Reviewer	Okponanabofa Eradiri, Ph.D.
Recommendation	**Adequate**

EXECUTIVE SUMMARY

BACKGROUND:

The original submission (NDA-216655-ORIG-1) resulted in refused to file[1] and the Applicant submits this NDA-216655-ORIG-1-RESUB-4. The Applicant is seeking approval for the proposed Aripiprazole Oral Soluble Film, 2 mg, 5 mg and 10 mg via the 505(b)(2) regulatory pathway. It is indicated for the treatment of schizophrenia, adjunctive treatment of major depressive disorder, irritability associated with autistic disorder and treatment of tourette's disorder. The Listed Drug (LD) is Abilify (Aripiprazole) tablets approved on November 15, 2002 under NDA-021436[2].

The proposed product (oral soluble film) is a new dosage form which is helpful for the elderly and other patients with difficulty swallowing. The oral soluble film will also be a helpful dosage form to increase compliance for schizophrenic patients where the patient may be unwilling to swallow a pill.

REVIEW SUMMARY:

The Biopharmaceutics review is focused on evaluation of (1) the adequacy of the proposed dissolution method and acceptance criterion, (2) formulation bridging throughout product development, (3) biowaiver, and (4) biopharmaceutics risk assessment.

1) Dissolution Method and Acceptance Criterion:

The Applicant proposed an in-house dissolution method for Aripiprazole Oral Soluble Film as shown in the table below.

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
II (Paddle)	75	pH 4.0 sodium acetate buffer	1000 mL/37°C	Q= (b) (4) % in 30 minutes

[1] https://panorama.fda.gov/project/view?ID=63079e65006662b92d00f7dd9821b5f3

[2] https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021436#22489

However, the selection of USP apparatus (II), agitation speed (75 rpm), and media volume (1000 mL) are not adequately justified for the proposed drug product. In addition, the proposed dissolution method was found not to be discriminating for the studied parameters. In response to the information request on above comments, the Applicant justified the selection of above parameters using (b) (4) (b) (4). Applicant also provided additional discriminatory data using critical formulation variable. Based on the submitted data, the proposed dissolution method is found to be acceptable.

2) Biopharmaceutics Risk Assessment:

Based on the risk assessment, dissolution is considered a low risk critical quality attribute (CQA).

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 216655-ORIG-1-RESUB-4 for Aripiprazole Oral Soluble Film/ 2 mg, 5 mg and 10 mg, is adequate.

BIOPHARAMCEUTICS ASSESSMENT

B.1 BCS DESIGNATION *Not requested*

According to the Applicant, Aripiprazole belongs to BCS class 2 with low solubility and high permeability[3].

Solubility and permeability:

Table 1: Solubility of Aripiprazole in Various Aqueous Media[4]

S.No.	Media Name	Saturation solubility (µg/mL)
1	0.01N Hydrochloric Acid	102.63
2	pH 4.0 Acetate Buffer	62.11
3	pH 4.5 Acetate Buffer	41.3
4	pH 5.0 Acetate Buffer	11.8
5	pH 5.5 Acetate Buffer	6.0
6	pH 6.0 Phosphate Buffer	0.8
7	pH 6.8 Phosphate Buffer	0.6
8	Water	0.1
9	pH 6.8 Phosphate Buffer with 0.5% SDS	1282.6
10	Water with 0.5% SDS	670.7

(b) (4)

(b) (4)

[3] \\CDSESUB1\EVSPROD\nda216655\0004\m3\32-body-data\32p-drug-prod\aripiprazole-oral-film-xiamen-lp-pharmaceutical\32p2-pharm-dev\pharmaceutical-development.pdf, page 16

[4] \\CDSESUB1\EVSPROD\nda216655\0004\m1\us\in-vivo-bioavail-stud-waiver-req.pdf

Dissolution:
The proposed drug product has rapid dissolution profiles with at least 85% of the drug dissolved in 15 to 30 minutes.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION
Assessment: Based on the submitted method development and discriminating ability data, suitability of the proposed dissolution method for this test product was not justified. Applicant was sent an information request (IR) for additional information. See appendix 2 for details of the deficiencies.

Dissolution method development[5].
Dissolution method development has been conducted by testing various parameters as shown below.

(b) (4)

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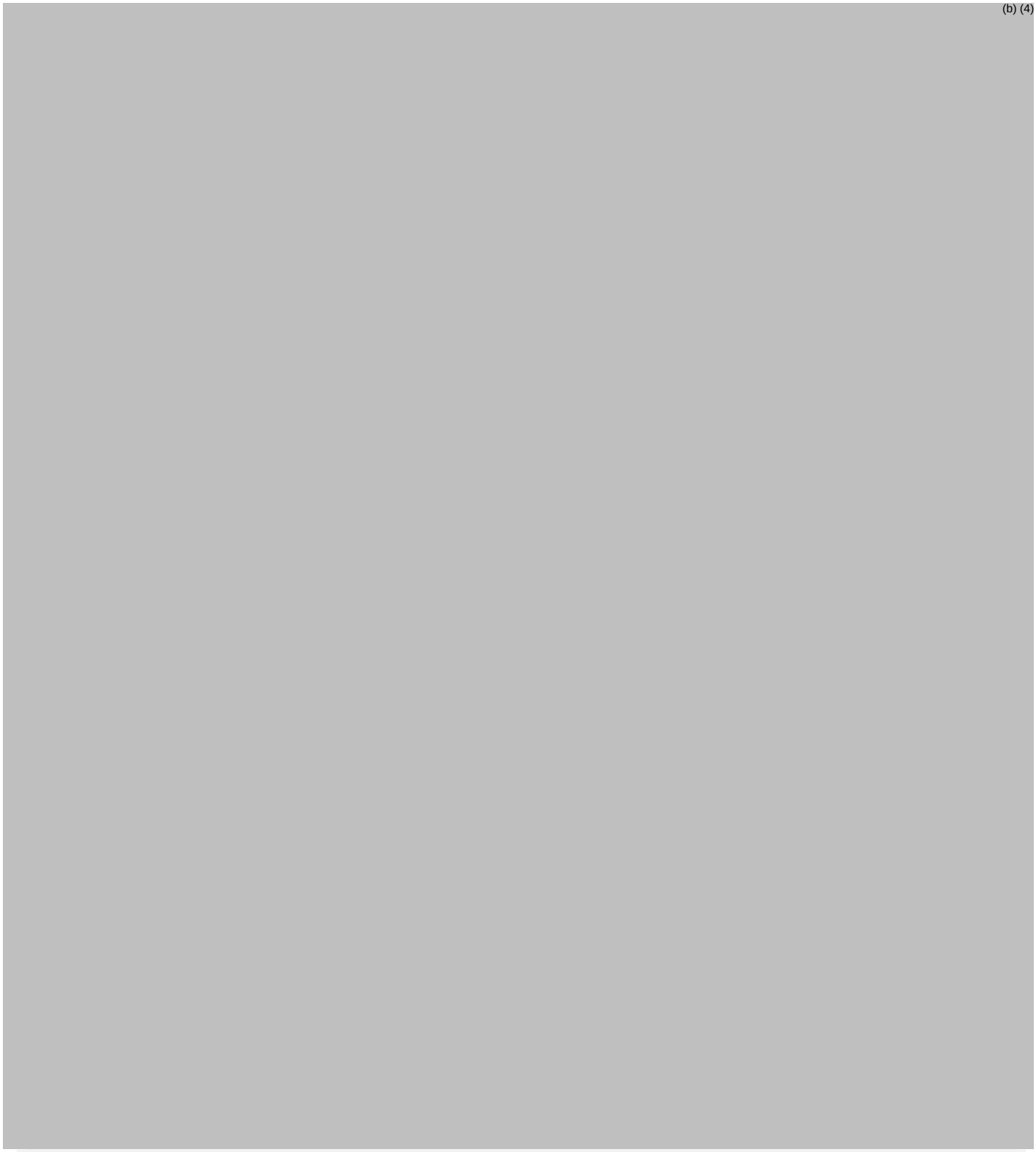


(2) Discriminating ability of the selected dissolution method:

Dissolution studies with different film thickness:

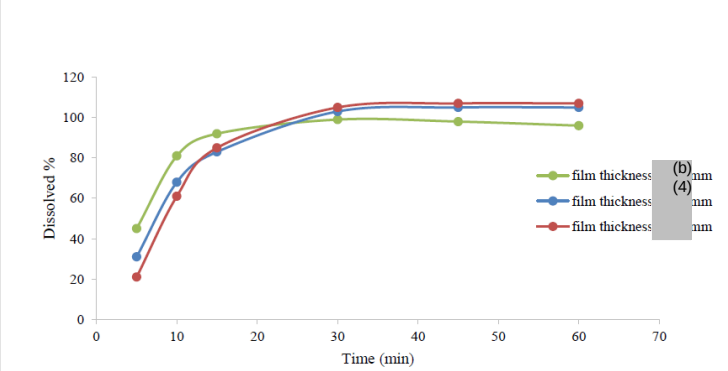
The dissolution studies were conducted with three different film thicknesses ((b) (4) mm, (b) (4) mm, (b) (4) mm) using the proposed dissolution method (Apparatus 2/ paddle with 1000 mL of pH 4.0 acetate buffer @ 75 rpm). Results demonstrated that the proposed dissolution method shows slight difference in dissolution at early time points (see table 6 & figure 4 below). Hence the proposed method is not

considered to have the discriminating ability towards aberrant formulations. f2 could not be calculated.

Table 6: Dissolution Results with Different Film Thickness:

	Time (min)	5	10	15	30	45	60
Film thickness: (b) (4) mm	Average (%)	45	81	92	99	98	96
	Range (%)	(b) (4)					
	RSD (%)	19.75	15.18	6.52	3.61	3.18	2.45
Film thickness: (b) (4) mm	Average (%)	31	68	83	103	105	105
	Range (%)	(b) (4)					
	RSD (%)	21.59	12.64	6.91	2.88	2.58	2.64
Film thickness: (b) (4) mm	Average (%)	21	61	85	105	107	107
	Range (%)	(b) (4)					
	RSD (%)	9.99	4.39	2.74	2.72	2.83	3.24

Figure 4: Dissolution Profiles of Different Film Thickness:



Dissolution studies using films with different drug substance particle size:
Dissolution studies were conducted using two batches of samples which were prepared from two different particle sizes of drug substance (d90: (b) (4) µm, and d90: (b) (4) µm).

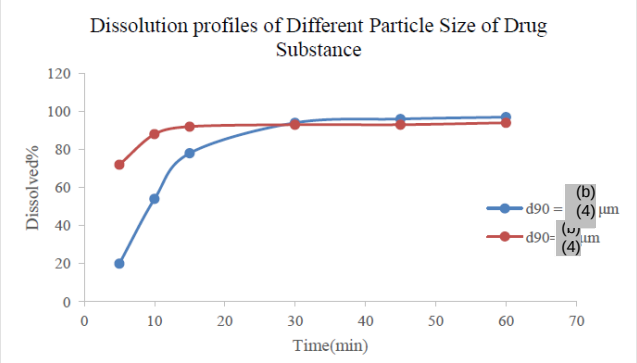
As shown in Table 7 and figure 5 below, results demonstrated that the dissolution method is able discriminate the aberrant formulation (b) (4) It is confirmed with an f2 value of less than 50 (21.72). The acceptable particle size distribution is established at D90 ≤ (b) (4) µm[6].

Table 7: Dissolution Results of Different Particle Size of Drug Substance:

	Time (min)	5	10	15	30	45	60
d90 = (b) (4) µm (Lot: XYF088079)	Average (%)	20	54	78	94	96	97
	Range (%)	(b) (4)					
	RSD (%)	8.15	4.70	2.55	1.95	2.75	2.39
d90 = (b) (4) µm (Lot: s201201-2)	Average (%)	72	88	92	93	93	94
	Range (%)	(b) (4)					
	RSD (%)	5.37	1.65	0.16	0.58	1.22	0.57

[6] \\CDSESUB1\EVSPROD\nda216655\0004\m3\32-body-data\32p-drug-prod\aripiprazole-oral-film-xiamen-lp-pharmaceutical\32p2-pharm-dev\pharmaceutical-development.pdf pg 17

Figure 5: Dissolution Profiles of Different Particle Size of Drug Substance:



Applicant stated that the studied API particle sizes (PSD) were d90: (b) (4) µm, and d90: (b) (4) µm. However, this reviewer noted that there is discrapency where the data provided in Table 7 and graphical presentation in Figure 5 above, the studied PSDs were listed as d90: (b) (4) µm, and d90: (b) (4) µm. Applicant was sent an IR to clarify. In response to the IR comment, Applicant clarified that API with particle size distributions (PSD) of d90: (b) (4) µm and d90: (b) (4) µm were used in the early formulation screening studies. The noted discrepancy in the API particle size distributions was due to a transcription error from these PSDs. The API with particle size distributions of d90: (b) (4) µm (batch XYF088079), and d90: (b) (4) µm (Lot: S201201-2) were used for the discriminating ability studies. The discrepancy is corrected in the dissolution development report (DisDev-FP088, page 18). Please see appendix 2 for details.

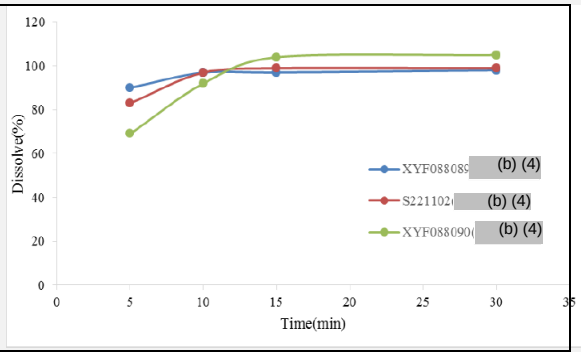
Based on the investigation of discriminating ability studies together with the proposed dissolution acceptance criterion at 30 minutes does not appear to have any discriminating ability toward any critical bioavailability attributes (CBA's) or rule out the non-BE batches. The Applicant was asked to submit data to demonstrate the discriminatory ability of the newly proposed dissolution method (if one is developed) for the proposed drug product.

In response to above deficiency, the Applicant provided additional discriminatory data and demonstrated dissolution comparison of BE batch/registration batch with films that were intentionally manufactured with meaningful variations in the formulation.

Critical formulation variables:

The %Wt of (b) (4) is considered to be a critical formulation variable, the target %Wt. of (b) (4) is (b) (4)%. Two batches of films were made with (b) (4)% of (b) (4) (Lot: XYF088089) and (b) (4)% of (b) (4) (Lot: XYF088090) respectively, the dissolution between the two batches and the BE batch (Lot: S221102) was performed. Results shows that higher the % (b) (4), slower the dissolution and also with lower % (b) (4) faster dissolution observed at 5 min.

%Wt. of (b) (4)	Time (min)	5	10	15	30
(b) (4) (Lot: XYF088089)	Average (%)	90	97	97	98
	Range (%)	(b) (4)			
	RSD (%)	0.76	0.66	0.38	1.02
(b) (4) (Lot: S221102, BE batch)	Average (%)	83	97	99	100
	Range (%)	(b) (4)			
	RSD (%)	2.02	5.10	3.07	3.01
(b) (4) (Lot: XYF088090)	Average (%)	69	92	104	105
	Range (%)	(b) (4)			
	RSD (%)	6.78	1.46	2.65	1.89



The Applicant provided revised dissolution method development report including above additional data ((b) (4) discriminatory study with critical formulation variable)[7]. Based on the applicant's response, the proposed dissolution method is found to be suitable for the proposed drug product.

Dissolution Acceptance Criterion[8]:
The Applicant proposed acceptance criterion of "Q =(b) (4)% in 30 minutes". Based on the submitted dissolution data in QC media, the test product has rapid dissolution profiles where at least 85% of the drug is dissolved in 15 - 30 minutes. Hence, the proposed acceptance criterion is acceptable.

For the stability samples, Applicant provided dissolution data for 3 registration batches of each strength at the proposed acceptance criterion (Q= (b) (4)% in 30 minutes) and it conform to the proposed criterion. Applicant was sent an IR recommending submitting complete dissolution data at all time points for these stability samples.

In response to the above comment, The Applicant provided dissolution data from stability samples of 6 imprinted batches (including individual data, mean and %RSD at each time point). One imprinted batch of 2 mg, 5 mg and 10 mg strength and 3 imprinted registration batches of 2 mg strength. Dissolution profile data provided for above batches under long term stability condition at 15-month period.

Dissolution Profile Results of 2 mg (Batch S221103) and 5 mg (Batch S221101) Imprinted Batch (T=0, 15 month)

%Dissolved Aripiprazole at Specified Time Points (Time Unit: minute)								
Batch No.	Test product: S221103, mfg., LP Pharma							
Time point	T0				15 Month			
T (min)	5	10	15	30	5	10	15	30
V1	(b) (4)							
V2								
V3								
V4								
V5								
V6								
Mean	91%	98%	103%	104%	91%	96%	100%	102%
%RSD	1.73%	4.73%	0.68%	0.57%	1.78%	1.94%	1.63%	2.13%
Min	(b) (4)							
Max								

%Dissolved Aripiprazole at Specified Time Points (Time Unit: minute)								
Batch No.	Test product: S221101, mfg., LP Pharma							
Time point	T0				15 Month			
T (min)	5	10	15	30	5	10	15	30
V1	(b) (4)							
V2								
V3								
V4								
V5								
V6								
Mean	89%	93%	99%	100%	89%	95%	100%	100%
%RSD	3.68%	2.21%	0.50%	0.90%	2.20%	1.17%	1.80%	1.86%
Min	(b) (4)							
Max								

Dissolution Profile Results of 10 mg (Batch S221102) and 2 mg (Batch S221201) Imprinted Batch (T=0, 15 month)

%Dissolved Aripiprazole at Specified Time Points (Time Unit: minute)								
Batch No.	Test product: S221102, mfg., LP Pharma							
Time point	T0				15 Month			
T (min)	5	10	15	30	5	10	15	30
V1	(b) (4)							
V2								
V3								
V4								
V5								
V6								
Mean	83%	97%	99%	100%	82%	95%	98%	99%
%RSD	2.02%	5.10%	3.07%	3.01%	3.67%	1.62%	1.04%	1.08%
Min	(b) (4)							
Max								

%Dissolved Aripiprazole at Specified Time Points (Time Unit: minute)								
Batch No.	Test product: S221201, mfg., LP Pharma							
Time point	T0				15 Month			
T (min)	5	10	15	30	5	10	15	30
V1	(b) (4)							
V2								
V3								
V4								
V5								
V6								
Mean	90%	95%	99%	99%	88%	95%	99%	100%
%RSD	1.09%	5.21%	2.63%	1.67%	3.17%	2.04%	2.66%	0.86%
Min	(b) (4)							
Max								

[7] \\CDSESUB1\EVSPROD\nda216655\0016\m3\32-body-data\32p-drug-prod\aripiprazole-oral-film-xiamen-lp-pharmaceutical\32p2-pharm-dev\p2-disdev-fp088.pdf
[8] \\CDSESUB1\EVSPROD\nda216655\0004\m3\32-body-data\32p-drug-prod\aripiprazole-oral-film-xiamen-lp-pharmaceutical\32p5-contr-drug-prod\32p51-spec\specifications.pdf

Dissolution Profile Results of 10 mg (Batch S221202) and 2 mg (Batch S221203) Imprinted Batch (T=0, 15 month)

%Dissolved Aripiprazole at Specified Time Points (Time Unit: minute)								
Batch No.	Test product: S221202, mfg., LP Pharma							
Time point	T0				15 Month			
T (min)	5	10	15	30	5	10	15	30
V1	(b) (4)							
V2								
V3								
V4								
V5								
V6								
Mean	95%	99%	104%	104%	93%	99%	102%	102%
%RSD	1.28%	3.38%	2.17%	0.78%	1.50%	0.96%	0.94%	0.84%
Min	(b) (4)							
Max								

%Dissolved Aripiprazole at Specified Time Points (Time Unit: minute)								
Batch No.	Test product: S221203, mfg., LP Pharma							
Time point	T0				15 Month			
T (min)	5	10	15	30	5	10	15	30
V1	(b) (4)							
V2								
V3								
V4								
V5								
V6								
Mean	90%	97%	100%	100%	90%	97%	100%	100%
%RSD	1.64%	3.86%	1.47%	1.03%	2.63%	2.81%	0.95%	1.36%
Min	(b) (4)							
Max								

The Applicant stated that full time point data at t = 0 and 15 months is also included in updated stability tables in 3.2.P.8.3. To ensure that the requested dissolution study data continue to be obtained and reported, the dissolution test method (FP088DS) has been updated to require all sampling time points (5 min, 10 min, 15 min and 30 min) for full dissolution profile test until completion of stability study of registration batches. All the stability batches meet the proposed dissolution acceptance criteria of Q = (b) (4)% in 30 minutes. The Applicant's response to above deficiency is adequate.

Based on the method development and discriminating ability studies, Applicant finalized the proposed dissolution method for Aripiprazole Oral Soluble Film as below.

Proposed dissolution method for Aripiprazole oral soluble film, 2 mg, 5 mg and 10 mg:

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
II (Paddle)	75	pH 4.0 sodium acetate buffer	1000 mL/37°C	Q= (b) (4)% in 30 minutes

Dissolution profiles[9]:

Applicant provided multi-media dissolution profiles. Biopharmaceutics review focused on the assessment of dissolution data generated in QC media shown below.

Dissolution Conditions	**Apparatus:**	USP Apparatus 2 (Paddle)
	Speed of Rotation:	75 rpm
	Medium:	pH 4.0 Sodium acetate buffer
	Volume:	1,000 mL
	Temperature:	37°C
Dissolution Testing Site (Name, Address)	Xiamen LP Pharmaceutical Co., Ltd. 2010 Wengjiao West Road, Xiamen, Fujian 361027, China	

[9] \\CDSESUB1\EVSPROD\nda216655\0004\m2\27-clin-sum\summary-biopharm.pdf

All Test and RLD Batches Used in In Vitro Dissolution Studies[10]

Sample	Name	Batch No.	Manufacturer	Mfg. date of Test Product
Test Product	**Aripiprazole Oral Soluble Film, 2 mg**	**S221201** **S221202** **S221203**	Xiamen LP Pharmaceutical Co., Ltd.	**12/20/22** **12/24/22** **12/28/22**
	Aripiprazole Oral Soluble Film, 5 mg	S201201-1 S201202-1 S201203-1		12/03/20 12/05/20 12/07/20
	Aripiprazole Oral Soluble Film, 10 mg	S201001 S201201-2 S201202-2 S201203-2		10/04/20 12/10/20 12/11/20 12/12/20
Reference Product	**ABILIFY® (Aripiprazole) Tablets, 2 mg**	**AIS00622A**	Otsuka Pharmaceutical Co., Ltd	N/A
	ABILIFY® (Aripiprazole) Tablets, 5 mg	**AKS00621A**		
	ABILIFY® (Aripiprazole) Tablets, 10 mg	ALS00219A		

Summary dissolution data for 2 mg in QC media (pH 4.0 Sodium Acetate Buffer):

2 mg, in QC media						Collection Times (min)				
Study Ref No.	Testing Date	Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		5	10	15	30	Study report location
Study Report #: ComRep-FP088DS.01	Jan. 09, 2023	Test Product Batch No.: S221201 Manufacture Date: Dec. 20, 2022	2 mg Film	12	Mean	90%	96%	99%	99%	Section 5.3.1.3
					Range	(b) (4)				
					% CV	1.74%	4.01%	1.78%	1.64%	
Study Report #: ComRep-FP088DS.01	Jan. 09, 2023	Test Product Batch No.: S221202 Manufacture Date: Dec. 24, 2022	2 mg Film	12	Mean	95%	100%	104%	103%	Section 5.3.1.3
					Range	(b) (4)				
					% CV	1.35%	3.39%	2.34%	2.21%	
Study Report #: ComRep-FP088DS.01	Jan. 10, 2023	Test Product Batch No.: S221203 Manufacture Date: Dec. 28, 2022	2 mg Film	12	Mean	90%	97%	100%	100%	Section 5.3.1.3
					Range	(b) (4)				
					% CV	1.89%	3.27%	1.47%	1.49%	
Study Report #: ComRep-FP088DS.01	May. 24, 2023	Reference Product Batch No.: AIS00622A Expiration Date: Jun. 2024	2 mg Film	12	Mean	85%	97%	99%	100%	Section 5.3.1.3
					Range	(b) (4)				
					% CV	3.18%	1.25%	1.23%	1.09%	

Summary dissolution data for 5 mg in QC media (pH 4.0 Sodium Acetate Buffer):

5 mg, in QC media						Collection Times (min)				
Study Ref No.	Testing Date	Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		5	10	15	30	Study report location
Study Report #: ComRep-FP088DS.01	Dec. 28, 2020	Test Product Batch No.: S201201-1 Manufacture Date: Dec.	5 mg Film	12	Mean	87%	96%	103%	103%	Section 5.3.1.3
					Range	(b) (4)				
					% CV	6.16%	8.62%	1.82%	0.92%	
Study Report #: ComRep-FP088DS.01	Oct. 11, 2021	Test Product Batch No.: S201202-1 Manufacture Date: Dec. 05, 2020	5 mg Film	12	Mean	89%	103%	103%	103%	Section 5.3.1.3
					Range	(b) (4)				
					% CV	1.72%	1.53%	0.86%	0.92%	
Study Report #: ComRep-FP088DS.01	Jan.19, 2021	Test Product Batch No.: S201203-1 Manufacture Date: Dec. 07, 2020	5 mg Film	12	Mean	83%	102%	102%	102%	Section 5.3.1.3
					Range	(b) (4)				
					% CV	2.72%	1.38%	1.81%	1.34%	
Study Report #: ComRep-FP088DS.01	May. 23, 2023	Reference Product Batch No.: AKS00621A Expiration Date: Mar. 2024	5 mg Film	12	Mean	85%	95%	98%	100%	Section 5.3.1.3
					Range	(b) (4)				
					% CV	4.44%	0.97%	0.90%	0.93%	

[10] \\CDSESUB1\EVSPROD\nda216655\0004\m2\27-clin-sum\summary-biopharm.pdf

Summary dissolution data for 10 mg in QC media (pH 4.0 Sodium Acetate Buffer):

10 mg, in QC media						Collection Times (min)				
Study Ref No.	Testing Date	Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		5	10	15	30	Study report location
Study Report #: ComRep-FP088DS.01	Oct. 16, 2021	Test Product Batch No.: S201001 Manufacture Date: Oct. 4, 2020	10 mg Film	12	Mean	82%	92%	99%	99%	Section 5.3.1.3
					Range	(b) (4)				
					% CV	6.81%	2.94%	2.33%	2.28%	
Study Report #: ComRep-FP088DS.01	Dec. 29, 2020	Test Product Batch No.: S201201-2 Manufacture Date: Dec. 10, 2020	10 mg Film	12	Mean	79%	96%	97%	97%	Section 5.3.1.3
					Range	(b) (4)				
					% CV	2.31%	3.07%	1.76%	1.86%	
Study Report #: ComRep-FP088DS.01	Oct .15, 2021	Test Product Batch No.: S201202-2 Manufacture Date: Dec. 11, 2020	10 mg Film	12	Mean	83%	98%	101%	102%	Section 5.3.1.3
					Range	(b) (4)				
					% CV	7.76%	4.36%	2.13%	1.88%	
Study Report #: ComRep-FP088DS.01	Jan. 20, 2021	Test Product Batch No.: S201203-2 Manufacture Date: Dec.12, 2020	10 mg Film	12	Mean	85%	92%	99%	99%	Section 5.3.1.3
					Range	(b) (4)				
					% CV	4.03%	7.97%	1.92%	2.89%	
Study Report #: ComRep-FP088DS.01	Sep. 24, 2020	Reference Product Batch No.: ALS00219A Expiration Date: Jan. 2022	10 mg Film	12	Mean	90%	100%	102%	105%	Section 5.3.1.3
					Range	(b) (4)				
					% CV	3.87%	2.02%	1.99%	1.90%	

S201001 is the bio-batch used in fasting and fed BE studies.

An information request (IR) was sent to the Applicant by Office of clinical pharmacology (OCP)[11] and the IR response was received on 6/7/24 where the Applicant provided dissolution data in multi-media using 3 films of the bio-strength (10 mg)[12]. Review of this data confirms that the drug release is similar in multi-media between 1 film vs. 3 films.

(5) Risk Assessment:

A risk assessment of the formulation variables was conducted for the test product. The CQAs include appearance, assay, dissolution, content uniformity, (b) (4) and related substances. (b) (4), (b) (4) and (b) (4) are considered as intermediate CQAs.

B.12 BRIDGING OF FORMULATIONS

[11] https://panorama.fda.gov/project/view?ID=65148c2100f3ef3e45c13969059928be

[12] \\CDSESUB1\EVSPROD\nda216655\0018\m1\us\coverletter.pdf

Assessment: Formulation bridging is not needed as the final formulation of the 10 mg was used in BE studies (Batch # S201001)[13].

Formulation Composition

Components	Function	Composition (w/w %)	Amount per Film (mg)		
			Strength: 2 mg	Strength: 5 mg	Strength: 10 mg
Aripiprazole	Active Ingredient	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Hydroxypropyl Cellulose					
Sodium Lauryl Sulfate					
Sucralose					
(b) (4)					
Total[2]		(b) (4)			

B. 13 BIOWAIVER REQUEST

Assessment: According to the Applicant, BE study results under fasting and fed conditions using the highest strength (10 mg) demonstrated that the test product is bioequivalent to LD.

Applicant is requesting Biowaiver for the two lower strengths (2 mg and 5 mg) based on,

(i) acceptable bioequivalence studies with the 10 mg strength,
(ii) acceptable in vitro dissolution testing of all strengths, and
(iii) proportional similarity of the formulations.

Formulation of the 2 mg and 5 mg strengths of the proposed test product are composition proportional to the bio-strength. In addition, dissolution of the lower strengths 2 mg and 5 mg demonstrated similarity (more than 85% dissolved in 15 minutes) to bio-strength. Applicant also provided dissolution data in additional media (b) (4) and found to be similar between lower strengths and bio-strength[14].

Based on the submitted data, the Applicant's biowaiver request for Aripiprazole (b) (4), 2 mg and 5 mg is granted.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:
Swapna Pamu, MS

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Okponanabofa Eradiri, Ph.D.

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Swapna Pamu

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Okponanabofa Eradiri

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Valerie Amspacher

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