

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211448Orig1s000

PRODUCT QUALITY REVIEW(S)

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Template Revision: 03

NDA 211448 Executive Summary (Assessment 2)

1. Application/Product Information

NDA Number	211448		
Applicant Name	CMG Pharmaceutical Co., Ltd		
Drug Product Name	MEZOFY (Aripiprazole)		
Dosage Form	Oral Film		
Proposed Strength(s)	Aripiprazole; 5 mg, 10 mg, and 15 mg		
NDA Classification	Type 3 - New Dosage Form		
Route of Administration	Oral		
Maximum Daily Dose	30 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of schizophrenia		
Drug Product Description	The proposed drug product is an immediate-release, oral film containing aripiprazole. The product is formulated in strengths of 5 mg, 10 mg, and 15 mg aripiprazole; the composition of the 3 strengths are equivalent, with the dimensions of the film dependent on the dosage strength.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [USP controlled room temperature].		
Review Team	Discipline	Primary	Secondary
	Drug Substance	Zhixing Shan	Donna Christner

	<i>Drug Product/ Labeling</i>	Renishkumar Delvadia	Valerie Amspacher
	<i>Manufacturing</i>	Tarun Mehta	Sridhar Thumma
	<i>Biopharmaceutics</i>	N/A	
	<i>Microbiology</i>	N/A	
	<i>Environmental</i>	N/A	
	<i>RBPM</i>	Teshara Bouie	
	<i>ATL</i>	Renishkumar Delvadia	
Consults			

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The proposed expiry period of 36 months when stored at 20° to 25°C (68° to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [USP controlled room temperature]..

b. Additional Comments for Action: None

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Applicant has adequately addressed the facility deficiency in the first review cycle. CMC recommends approval for this application based on reviews by drug substance, drug product, biopharmaceutics (previous review cycle), labeling (previous review cycle), and process/facilities.

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

Recommendation by Subdiscipline:

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

Application Technical Lead Name and Date:

Renishkumar Delvadia, 03/07/2025



Renishkumar
Delvadia

Digitally signed by Renishkumar Delvadia
Date: 3/11/2025 09:07:57AM
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RECOMMENDATION:

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 211448 Assessment #1

Drug Product Name	(b) (4) (Aripiprazole oral film)
Dosage Form	Oral film
Strength	5 mg, 10 mg, and 15 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	CMG Pharmaceutical Co. Ltd
US agent, if applicable	Camargo Pharmaceutical Services, LLC

Submission(s) Assessed	Document Date	Discipline(s) Affected
0001 (1) Original submission	10/18/2019	Drug product, Drug substance, Process, Facility, Biopharmaceutics
0004 (4) Quality/IR response	12/13/2019	Facility
0005 (5) Quality/IR response	12/14/2019	Facility
0006 (6) Quality/IR response	01/10/2020	Drug product
0010 (10) Quality/IR response	05/29/2020	Drug substance, Biopharmaceutics, Manufacturing process
0011 (11) Quality/IR response	06/22/2020	Drug product
0012 (12) Original submission	06/29/2020	Drug product, Process, Biopharmaceutics
0014 (14) Quality/IR response	07/20/2020	Manufacturing process, Drug substance

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Ray Frankewich	Su Tran
Drug Product	Renishkumar Delvadia	Julia Pinto
Manufacturing	Tarun Mehta	Ubrani Venkataram

		Jonathan Swoboda
Microbiology	N/A	N/A
Biopharmaceutics	Yang Zhao	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Renishkumar Delvadia	
Laboratory (OTR)	N/A	N/A
Environmental	Renishkumar Delvadia	Julia Pinto

EXECUTIVE SUMMARY

[IQA NDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

This application is NOT recommended for approval by OPMA. Current status for the drug substance manufacturing and testing facility, (b) (4) (FEI: (b) (4), is "Withhold/OAI". Removal of OAI status of (b) (4) is required before this NDA may be approved. All other facilities are deemed adequate for this Application. The Application is also recommended for approval from Drug substance, Drug Product, Manufacturing Process, and Biopharmaceutics perspective.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed drug product is an immediate-release, oral film containing aripiprazole. The product is formulated in strengths of 5 mg, 10 mg, and 15 mg aripiprazole; the composition of the 3 strengths are equivalent, with the dimensions of the film dependent on the dosage strength. The films are imprinted with red edible ink identifying the product and strength. of "CMG ARF5" for 5 mg, "CMG ARF10" for 10 mg, or "CMG ARF15mg" for 15 mg strengths. The primary commercial packaging container closure system is sealed foil pouches.

Proposed Indication(s) including Intended Patient Population	Treatment of schizophrenia
Duration of Treatment	See Label
Maximum Daily Dose	30 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, aripiprazole, is recommended for approval from the perspective of the drug substance reviewer. DMF (b) (4) is referenced in every part of section 3.2.S of this NDA for Drug Substance. In this NDA a LOA for DMF (b) (4) is also provided for Drug Substance. Both DMFs have been found adequate by the Agency.

Drug Product: Adequate

The to-be-marketed (TBM) formulation compositions of the proposed drug product contains excipients of USP or NF grade, except for red ink, which is used in trace amount for printing for identifying the product and strength. The Applicant has provided adequate CMC information within the NDA submission to support the use of red ink. The Applicant has performed adequate product development studies to justify the selection of the excipients and to demonstrate/justify their chemical compatibility with the drug substance.

Different levels of two crystalline forms, a (b) (4) and an (b) (4) were present in various batches. The pivotal PK BE batch contained (b) (4) form when samples were tested 30 to 36 months after batch production for crystallinity; the Applicant did not test for crystallinity at release or at the time of PK BE study. The applicant provided additional information during the course of the NDA review cycle to justify that the two different crystalline forms have comparable solubility and dissolution profiles. The Applicant also proposed manufacturing process changes and controls to further ensure that the crystalline form of aripiprazole in the finished drug product is consistently (b) (4) at release and during stability.

The Applicant has provided 36 months of long-term (25°C/60%RH and 30°C/75% RH) and 6 months of accelerated stability data for three batches of all strengths; 36-month expiry has been proposed for all three strengths. The Applicant has submitted photo-stability and freeze/thaw stability data as well. All the stability data met the proposed specifications, except for few minor out-of-specification (OOS) results for film flexibility and size; all OOS results have been adequately justified by the Applicant. The overall stability data provided by the Applicant support the proposed shelf-life of 36 months for all proposed strengths.

Overall, the information submitted in the IR responses/CMC amendments received during the review cycle adequately addressed all the drug product related issues. There is no outstanding CMC deficiency related to the drug product review.

Labeling: Adequate

Minor labelling comments were discussed with DMEPA reviewer and included in the DMEPA review for sending out to the Applicant, along with the other DMEPA comments.

Manufacturing: Inadequate

The subject application lists four facilities requiring evaluation. One drug product and one drug substance site as well as two external testing and/or stability storage facilities. After review of inspectional documents, the drug product site (Tesa Labtec Company GmbH; FEI: 3010375003) did not have US inspectional history for manufacturing oral films; therefore, a 704(a)(4) request took place, and the firm is deemed adequate. The inspectional histories for the external sites were adequate. However, the API manufacturing site (b) (4) FEI: (b) (4) is currently OAI; therefore, this site cannot be approved for this application until the OAI alert is removed.

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)			
Tesa Labtec Company GmbH Heykenaukamp 10 , Hamburg , Hamburg, Germany , 21147	3010375003	(b) (4)	Other – Approved based on 704(a)(4) request
Tesa Labtec Company GmbH Raiffeisenstrase 4 , Langenfeld, Langenfeld, Germanv. 40764	3010969322		Approve - Based on Previous History
(b) (4)			Approve - Based on Previous History
			No Evaluation Necessary
			No Evaluation Necessary

The proposed product is manufactured in (b) (4)

(b) (4)

(b) (4) Overall, the manufacturing process is adequate.

Biopharmaceutics: Adequate

The Applicant's request for waiver of an in vivo BA/BE study for the proposed Aripiprazole oral film, 5 mg and 15 mg, is granted based on the following information and data: (a) the bioequivalence data on the 10 mg strength, (b) same release mechanism and manufacturing process for all strengths, (c) compositional proportionality among all strengths, (d) evidence on linear pharmacokinetics in the dose range of 5 mg to 30 mg, and (e) comparable dissolution profiles among all strengths in multi-pH media (pH 1.2, 4.0, and 6.8). After the Division of Biopharmaceutics recommendation, the Applicant tighten the dissolution acceptance criterion from the originally proposed "Q = (b) (4) % at (b) (4) min" to "Q = (b) (4) % at 15 minutes". As mentioned before in the summary, both aripiprazole (b) (4) form and (b) (4) form existed in the final drug product [for example, (b) (4) form API is the predominant form in the bio-batch (PV1), while (b) (4) form API is present in PV2 and PV3 batches]. In the response dated 05/29/2020, the Applicant provided comparative aqueous solubility data at 37 °C for API aripiprazole (b) (4) form and (b) (4) form over pH range of 1.2 – 5 and the solubilities of aripiprazole (b) (4) form and (b) (4) form were not different over this pH range tested.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, Stability	Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	M	(b) (4)	Acceptable	None

Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M	(b) (4)	Acceptable	None
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M		Acceptable	None
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	None
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M		Acceptable	None

D. List of Deficiencies for Complete Response

- Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

- Drug Substance Deficiencies

None

- Drug Product Deficiencies

None

- Labeling Deficiencies

None

- Manufacturing Deficiencies

During a recent inspection of the (b) (4) (FEI: (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies (Specify discipline, such as Environmental)

None

Application Technical Lead Name and Date:
Renishkumar Delvadia, 08/13/2020

QUALITY ASSESSMENT DATA SHEET

[IQA NDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	June 18, 2019	Assessment for ANDA 205589 (no significant updates)
	II			Adequate	March 18, 2019	Assessment for ANDA 201519 (no significant updates)
	III				DMF assessment was not necessary	Sufficient information provided in the application
	III				DMF assessment was not necessary	Sufficient information provided in the application
	III				DMF assessment was not necessary	Sufficient information provided in the application
	IV				DMF assessment was not necessary	Sufficient information provided in the application

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
Meetings and communications	IND 119610	Aripiprazole tablet
Reference product	NDA 021436	Abilify Oral Tablets, Otsuka

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	None			
Pharmacology/Toxicology	None			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	None			

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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4)	Changed to (b) (4)
Established name(s)	(aripiprazole) Oral	(aripiprazole) oral film"
Route(s) of administration	(b) (4) Film	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Oral (b) (4) Films: 5 mg, 10 mg, 15 mg	Changed to "Oral Film: 5 mg, 10 mg, 15 mg"
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.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
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)	N/A	

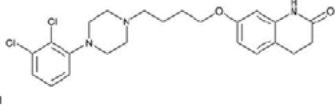
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Oral (b) (4) Films	Changed to "oral film"
Strength(s) in metric system	5 mg, 10 mg, 15 mg	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White rectangular film with red print; Applicant has provided information in a tabular format.	Suggested format in the working draft label • 5 mg white, rectangular-shaped, oral film with "CMG ARF5" printed in red on one side. • 10 mg white, rectangular-shaped, oral film with "CMG ARF10" printed in red on one side. • 15 mg white, rectangular-shaped, oral film with "CMG ARF15" printed in red on one side.
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 labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Aripiprazole is an atypical antipsychotic drug that is available as (b) (4) (aripiprazole) (b) (4) oral film is available in 5 mg, 10 mg, and 15 mg strengths	Changed to (b) (4) contains aripiprazole, an atypical antipsychotic"
Dosage form(s) and route(s) of administration		
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Inactive ingredients include acesulfame potassium, citric acid, FD&C Red No. 40, glycerin, hypromellose, L-menthol, polysorbate 80, polyvinyl alcohol, sucralose, and xylitol.	Acceptable
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.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/therapeutic class	See above	

Chemical name, structural formula, molecular weight	Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyrl. The (b) (4) formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38. The (b) (4) structure is: 	Changed to "The chemical name of aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyrl. The molecular formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38. The structural formula is:"
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Not included	Following comment sent to the Applicant in the working draft label "Include information about solubility and physical properties of drug substance"

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
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	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments																				
HOW SUPPLIED/STORAGE AND HANDLING section																						
Available dosage form(s)	Film	Acceptable; minor formatting changes recommended																				
Strength(s) in metric system	5 mg, 10 mg, 10 mg	Acceptable																				
Available units (e.g., bottles of 100 tablets)																						
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Included <table><tr><th>Strength</th><th>Film Color/Shape</th><th>Print</th><th>Pack Size</th><th>NDC Code</th></tr><tr><td>5 mg</td><td>white rectangular</td><td>CMG ARF5</td><td>one strip (film) per pouch, box of 30 pouches</td><td>XXXX-XXXX-XXXX</td></tr><tr><td>10 mg</td><td>white rectangular</td><td>CMG ARF10</td><td>one strip (film) per pouch, box of 30 pouches</td><td>XXXX-XXXX-XXXX</td></tr><tr><td>15 mg</td><td>white rectangular</td><td>CMG ARF15</td><td>one strip (film) per pouch, box of 30 pouches</td><td>XXXX-XXXX-XXXX</td></tr></table>	Strength	Film Color/Shape	Print	Pack Size	NDC Code	5 mg	white rectangular	CMG ARF5	one strip (film) per pouch, box of 30 pouches	XXXX-XXXX-XXXX	10 mg	white rectangular	CMG ARF10	one strip (film) per pouch, box of 30 pouches	XXXX-XXXX-XXXX	15 mg	white rectangular	CMG ARF15	one strip (film) per pouch, box of 30 pouches	XXXX-XXXX-XXXX	Asked to include NDC code
Strength	Film Color/Shape	Print	Pack Size	NDC Code																		
5 mg	white rectangular	CMG ARF5	one strip (film) per pouch, box of 30 pouches	XXXX-XXXX-XXXX																		
10 mg	white rectangular	CMG ARF10	one strip (film) per pouch, box of 30 pouches	XXXX-XXXX-XXXX																		
15 mg	white rectangular	CMG ARF15	one strip (film) per pouch, box of 30 pouches	XXXX-XXXX-XXXX																		
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.	N/A																					

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

Item	Information Provided in the NDA	Assessor's Comments
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.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [USP controlled room temperature].	Asked to change to "Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [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	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	(b) (4) manufactured by Tesa Labtec Company GmbH Heykenaukamp 10 21147 Hamburg Germany Distributed and marketed by CMG Pharmaceutical Co., Ltd, 14 Dosan-daero 66-gil, Gangnam-gu, Seoul, 06064, South Korea (b) (4) is a trademark of CMG Pharmaceutical Co., Ltd.	Acceptable

2.0 PATIENT LABELING

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

In the DMEPA's IR response dated 01/17/2020 the Applicant stated " Two different color schemes were proposed in ^{(b) (4)} packaging for consideration and feedback from the Agency in an effort to reduce medication errors. In the first proposed scheme, the strengths are distinguished by the brightness of the green background and the difference in color of the product strength. In the second proposed scheme, the strengths are distinguished by the variety of background color, with the product strength font corresponding in color. The Sponsor prefers the second proposed scheme that differentiates product strength by background color and font color. Based on the Agency's collaborative feedback, the design of carton labeling will be chosen to minimize patient misuse." The outstanding C/C labeling deficiencies related to quality are conveyed to DMEPA reviewer and will be included in DMEPA review along with their labeling other comments.



Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	(b) (4) (D) (4) (Aripiprazole oral film)	Not acceptable: (b) (4) (aripiprazole oral film)
Dosage strength	5mg, 10 mg, 15 mg	Acceptable
Route of administration	Oral	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not applicable	
Net contents (e.g. tablet count)	30 films	Acceptable
"Rx only" displayed on the principal display	Yes	Acceptable
NDC number	Not listed yet	DMEPA will review this
Lot number and expiration date	Not included	Not acceptable DMEPA will include comment asking the Applicant to revise label with lot number and expiration date for carton label
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [USP controlled room temperature]	Not acceptable Change to Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [USP controlled room temperature]. For both carton and pouch labels
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Not included	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured by : tesa Labtec GmbH Heykenaukamp 10, D-21147 Hamburg, Germany Manufactured for : CMG Pharmaceutical Co., Ltd. 14 Dosandaero 66 Gil, Gangnamgu Seoul, Republic of Korea	Acceptable
Medication Guide (if applicable)	States (b) (4)	Acceptable
No text on Ferrule and Cap over seal	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	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: Adequate

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

None; deficiencies will be addressed through DMEPA's review.

Overall Assessment and Recommendation:

Adequate

*Primary Drug Product Assessor Name and Date: Renishkumar Delvadia,
06/24/2020*

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



Renishkumar
Delvadia

Digitally signed by Renishkumar Delvadia
Date: 7/08/2020 01:40:35PM
GUID: 5388ee7d000671ff7781f1835a3ff7b9



Julia
Pinto

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Date: 7/08/2020 03:25:29PM
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BIOPHARMACEUTICS**NDA:** 211448**Drug Product Name/Strengths:** (b) (4) (Aripiprazole) Oral Soluble Film (OSF)/5 mg, 10 mg, and 15 mg**Route of Administration:** Oral**Applicant Name:** CMG Pharmaceutical Co. Ltd.**List of Reviewed Submissions:**

Original submission dated 10/18/2019

Response dated 05/29/2020 to the Information Request dated 03/20/2020

Response dated 06/29/2020 to the Information Request dated 06/25/2020

Biopharmaceutics Review Team:

Primary Reviewer: Yang Zhao, Ph.D.

Secondary Reviewer: Ta-Chen Wu, Ph.D.

REVIEW SUMMARY:

The Applicant submitted NDA 211448 seeking approval for Aripiprazole Oral Soluble Film (OSF), 5 mg, 10 mg, and 15 mg, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for the treatment of schizophrenia. The Listed Drug is Abilify® Oral Tablets (NDA 021436).

Review Objective: The Biopharmaceutics Review evaluated the adequacy of (1) the proposed dissolution method and acceptance criterion for QC testing of the proposed drug product at batch release and during stability, and (2) biowaiver request for 5 mg and 15 mg strengths of Aripiprazole OSF.

Reviewer's Assessment:**(1) Dissolution Method and Acceptance Criterion:**

The Applicant proposed "USP Apparatus 5 (paddle over disk, disk size 56 mm, 40 mesh) at 50 rpm, in 900 mL of pH 4.0 acetate buffer at 37 °C" as dissolution method for the batch release and stability testing for the proposed Aripiprazole OSF, 5 mg, 10 mg, and 15 mg. Dissolution from Aripiprazole OSF batches containing (b) (4) or (b) (4) API forms were similar and very rapid. Discriminating ability of the dissolution method for Aripiprazole OSF was demonstrated in the changes in film thickness and the levels of HPMC. In view of the demonstrated discriminating ability and obtained dissolution profile data, the proposed dissolution method is deemed acceptable as the quality control method for batch release and stability testing of Aripiprazole OSF, 5 mg, 10 mg, and 15 mg.

Based primarily on the provided dissolution data of clinical batch and registration batches, the Division of Biopharmaceutics recommended the Applicant to tighten the dissolution acceptance criterion from the originally proposed "Q = (b) (4) % at (b) (4) min" to "Q = (b) (4) % at 15 minutes". An agreement was reached between the Applicant and the Agency, dated 06/29/2020.

(2) Biowaiver Request:

The Applicant's request for waiver of an in vivo bioavailability/bioequivalence study for the proposed Aripiprazole OSF, 5 mg and 15 mg, is granted based on the following information and data: (a) the bioequivalence data on the 10 mg strength, (b) same release mechanism and manufacturing process for all strengths, (c) compositional proportionality among all strengths, (d) evidence on linear pharmacokinetics in the dose range of 5 mg to 30 mg, and (e) comparable dissolution profiles among all strengths in multi-pH media (pH 1.2, 4.0, and 6.8).

RECOMMENDATION:

From the Biopharmaceutics perspective, the provided information and data are adequate and NDA 211448 for (b) (4) (Aripiprazole) Oral Soluble Film (OSF), 5 mg, 10 mg, and 15 mg is recommended for **APPROVAL**.

The FDA-approved dissolution method and acceptance criterion for the proposed Aripiprazole Oral Soluble Film, 5 mg, 10 mg, and 15 mg are:

Final Dissolution Method and Acceptance Criterion for Aripiprazole Oral Soluble Film				
USP Apparatus	Speed (rpm)	Medium/Temp	Volume (mL)	Acceptance Criterion
USP 5 (paddle over disk, disk size 56 mm, 40 mesh)	50	pH 4.0 acetate buffer/37 °C	900	Q = (b) (4)% at 15 minutes

BIOPHARMACEUTICS ASSESSMENT

1. BACKGROUND OF THE PROPOSED DRUG PRODUCT:

The proposed Aripiprazole Oral Soluble Film (OSF) is designed as an immediate release oral soluble film formulation in three proposed strengths of 5 mg, 10 mg, and 15 mg. Per Applicant's proposed labeling, the typical aripiprazole dosing regimen for adults is 10 mg–15 mg per day, with a maximum dose of 30 mg aripiprazole per day.

Aripiprazole OSF is a white rectangular film imprinted with red edible ink identifying the product and strength. The white films are rectangular shaped strips with a printed identifier in red edible ink of "CMG ARF5" for 5 mg, "CMG ARF10" for 10 mg, or "CMG ARF15" for 15 mg strengths. Three strengths are compositionally proportional (Table 1).

Table 1. Composition of the proposed Aripiprazole OSF, 15 mg, 10 mg, and 5 mg

Component	Function	Reference to Quality Standard	mg/film unit		
			15mg	10mg	5mg
Aripiprazole	Active Ingredient (b) (4)	USP	15.000	10.000	5.000
Glycerin		NF	(b) (4)		
Polysorbate 80		NF			
Citric acid		NF			
Xylitol		NF			
Sucralose		NF			
Acesulfame potassium		NF			
L-Menthol		NF			
Polyvinyl alcohol		NF			
Hydroxypropyl methylcellulose (b) (4)		NF			
Hydroxypropyl methylcellulose (b) (4)		USP			
Red edible ink ^a			(b) (4)		
Total Film Weight (mg)			60	40	20

(b) (4)
Note: (b) (4) are used in manufacturing and (b) (4)
(b) (4) The (b) (4)
NF = National Formulary; USP = United States Pharmacopeia

2. INFORMATION OF THE DRUG SUBSTANCE:

2.1 Solubility:

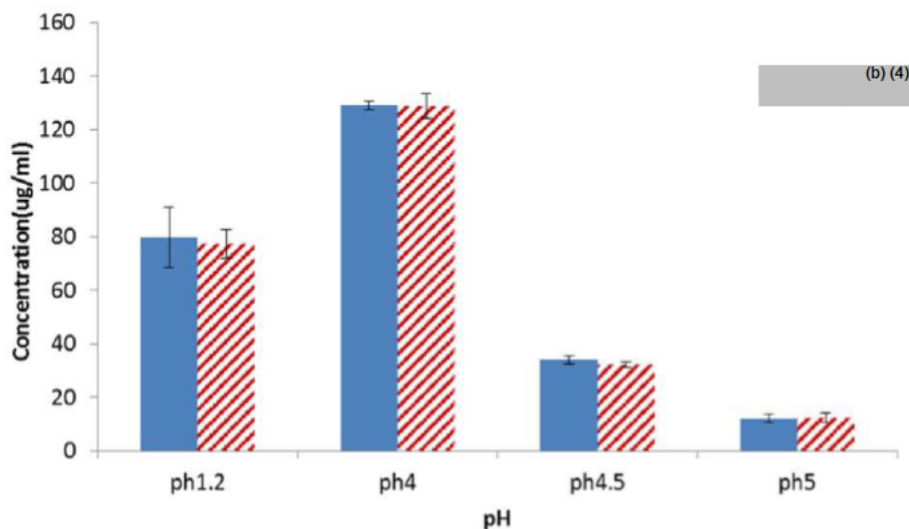
The Applicant reported that aripiprazole has pH-dependent solubility (Table 2).

Table 2. Aqueous solubility of aripiprazole at different pHs at 37 °C (data provided in dissolution method development report, \\cdsesub1\evsprod\nda211448\0001\m3\32-body-data\32p-drug-prod\aripiprazole-film\32p2-pharm-dev\rpt-disso-devt-new-method.pdf)

Aripiprazole (API) Solubility at 37±0.5°C (µg/mL) (n=3)					
	2h	4h	6h	8h	24h
0.01N HCl	992.1±107.7	1059.7±107	1074.5±88.9	1089.4±124.4	1099.6±70.9
pH1.2	164.3±10.7	134.1±9.3	123±6.9	108±6.7	83.7±2.8
pH4.0	197.1±12.8	137.6±14.1	118±7.5	103.6±3.4	117±61.2
pH4.5	81.6±5.1	57.8±8.3	48.2±5	41.3±3	45.6±21.4
pH5.0	27.5±0.3	15.7±1.1	16.1±1.8	13.1±1.6	13.7±5.1
pH6.0	0±0	0±0	0±0	0±0	0±0
pH6.8	0±0	0±0	0±0	0±0	0±0
purified water	0±0	0±0	0±0	0±0	0±0

For the originally submitted solubility data, the Applicant did not specify that the solubility data were collected from aripiprazole (b) (4) form or (b) (4) form. Both aripiprazole (b) (4) form and (b) (4) form exist in the final drug product [for example, (b) (4) form API is the predominant form in the bio-batch (PV1), while (b) (4) form API is present in PV2 and PV3 batches]. In view of the starting API material used for product manufacturing being aripiprazole (b) (4) form, with an Information Request dated 03/20/2020, the Applicant was requested to provide solubility data for both (b) (4) and (b) (4) forms. In the Response dated 05/29/2020, the Applicant provided comparative aqueous solubility data at 37 °C for API aripiprazole (b) (4) form and (b) (4) form over pH range of 1.2 – 5 and the solubilities of aripiprazole (b) (4) form and (b) (4) form were not different over this pH range tested (Figure 1). Note that aripiprazole has no solubility at pH 6-6.8 tested, thus precipitation of aripiprazole might occur at high pHs.

Figure 1. Solubilities of Aripiprazole (b) (4) form (b) (4) and (b) (4) form (b) (4) (n = 3) over pH 1.2–5 (provided in the Response dated 05/29/2020)



2.2 Permeability:

The Applicant did not provide any permeability data for aripiprazole. However, the Applicant reported (per labeling information), that aripiprazole is well absorbed when administered orally, the T_{max} occurs within 3 to 5 hours, and the absolute oral bioavailability is 87% when administered as a tablet formulation. The available information suggests the highly permeable characteristics of the drug substance.

3. PROPOSED DISSOLUTION METHOD AND ACCEPTANCE CRITERION:

The proposed dissolution method and dissolution acceptance criterion for the batch release and stability testing for Aripiprazole OSF, 5 mg, 10 mg, and 15 mg are as follows:

Proposed dissolution method and acceptance criterion for Aripiprazole OSF				
USP Apparatus	Speed (rpm)	Medium/Temp	Volume (mL)	Proposed acceptance criterion
5 (paddle over disk, disk size 56 mm, 40 mesh)	50	pH 4.0 acetate buffer/37 °C	900	NLT (b) (4) % (Q) dissolved in (b) (4) minutes

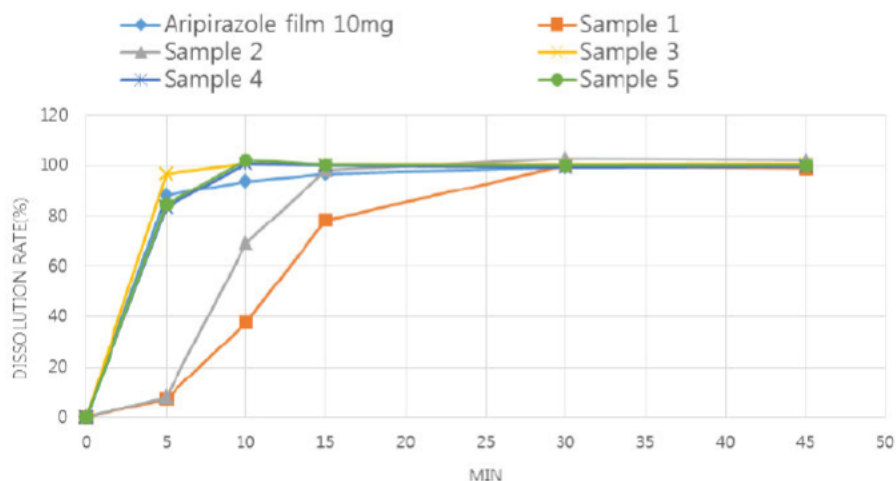
(b) (4)

3.3.2 Formulation compositional variables:

In addition, the Applicant provided dissolution profile data from batches intentionally manufactured with various compositional variables (Figure 4) (Page 22 in Module 3.2.P.2 New dissolution method development report). The Sample 1 in Figure 4 has changes in (b) (4) levels ((b) (4) % vs. the target of (b) (4) for (b) (4) and (b) (4) vs. the target of (b) (4) % for (b) (4), while the Sample (b) (4) has multiple changes in (b) (4) levels, in (b) (4) levels ((b) (4) % vs. (b) (4) %), and in (b) (4) levels. Figure 4 demonstrated that the proposed dissolution method is discriminating towards the changes in the levels of (b) (4). This Reviewer noticed that the Sample (b) (4) and the Sample (b) (4) have significant changes in compositions. Therefore, in the Information Request dated 03/20/2020, the Applicant was asked to provide rationale/explanation for the changes in compositions for the above evaluation of discriminating ability of the dissolution method.

In the Response dated 05/29/2020, the Applicant explained that the substantial changes made in the OSF composition, instead of the recommended variation of (b) (4) % in critical material attributes (CMAs), was intentionally designed to evaluate the discriminating ability of the proposed dissolution method for the proposed drug product which is designed to rapidly disintegrate and dissolve. This explanation is reasonable for a rapidly dissolving drug product.

Figure 4. Dissolution profiles of Aripiprazole OSF batches intentionally manufactured with various compositional variables (data provided in dissolution method development report Page 22). Dissolution similarity factor $f_2=20$ between the target formulation vs. sample 1, $f_2=24$ between the target formulation vs. sample 2, calculated by this Reviewer



The dissolution method's discriminating power for changes in API particle size was not investigated. Considering that the API during manufacturing process is (b) (4) this Reviewer considers that the risk towards the changes in API particle size is low.

3.3.3 Process parameters:

In the Response dated 05/29/2020, the Applicant provided investigational results for the discriminating ability of the proposed dissolution method towards the changes in film thickness (range tested: (b) (4) μm (b) (4) μm), (b) (4) (Table 6), and (b) (4) (Table 7). The dissolution method was shown to be discriminating towards the changes in film thickness (Figure 5).

Figure 5. Effects of film thickness on dissolution for Aripiprazole OSF 10 mg (in the Response dated 05/29/2020). The target OSF thickness is (b) (4) μm , dissolution similarity factor $f_2=34$ between the target of (b) (4) μm film thickness vs. (b) (4) μm , calculated by this Reviewer

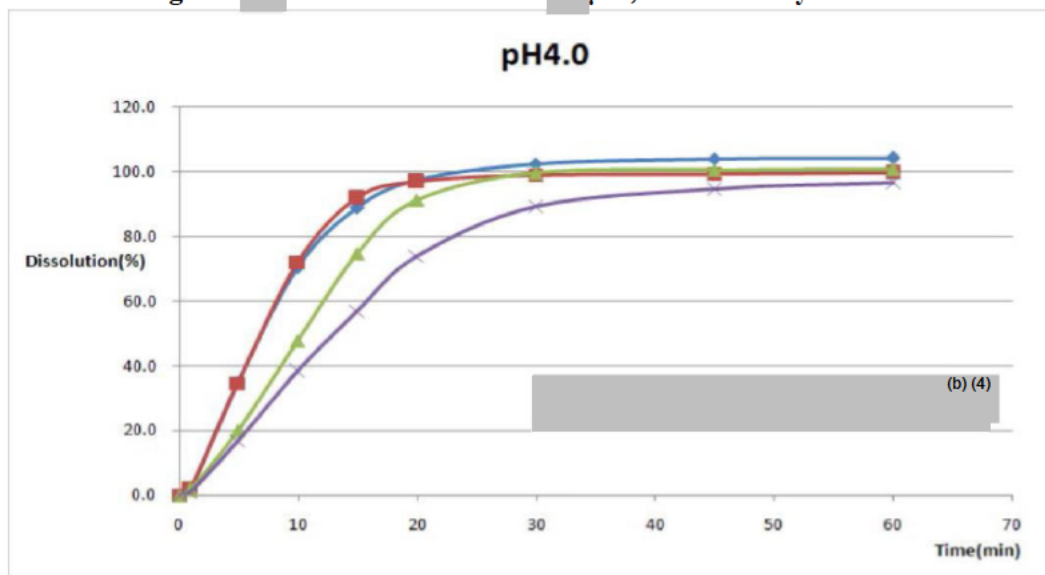


Table 6. Effects of (b) (4) on dissolution for Aripiprazole OSF 10 mg using the proposed dissolution method

Sample	(b) (4)	Results: % Drug Release (% CV)							
		1 min	5 min	10 min	15 min	20 min	30 min	45 min	60 min
Tech#1-1		1.1 (20.9)	21.3 (18.9)	40.4 (18.5)	59.1 (15.2)	71.7 (11.0)	84.3 (3.6)	90.2 (1.0)	92.6 (0.7)
Tech#1-2		1.8 (49.4)	26.6 (49.8)	47.1 (28.9)	61.0 (25.9)	76.2 (11.2)	87.3 (3.0)	92.9 (2.0)	95.3 (1.7)
Tech#1-3		1.6 (13.1)	21.2 (24.5)	42.9 (19.5)	64.4 (12.1)	77.9 (7.8)	87.3 (5.5)	91.1 (4.6)	94.3 (5.5)
Tech#1-4		2.2 (11.8)	24.1 (14.9)	54.4 (8.7)	76.6 (3.8)	89.6 (1.3)	98.8 (1.2)	100.7 (1.0)	100.7 (1.1)

Table 7. Effects of (b) (4) on dissolution for Aripiprazole OSF 10 mg using the proposed dissolution method

Sample	(b) (4)	Results: % Drug Release (%CV)							
		1 min	5 min	10 min	15 min	20 min	30 min	45 min	60 min
ARF1401-1		1.6 (16.3)	38.7 (19.0)	66.2 (7.8)	82.0 (3.6)	92.2 (2.3)	98.5 (1.5)	101.7 (0.2)	103.3 (0.4)
ARF1401-2		5.5 (31.8)	39.2 (20.7)	69.9 (8.4)	84.6 (2.6)	94.1 (1.8)	99.3 (1.1)	102.2 (0.2)	104.0 (0.3)
ARF1401-3		2.2 (14.5)	33.7 (20.1)	62.0 (16.2)	79.9 (10.1)	92.0 (5.4)	98.1 (3.8)	100.9 (1.7)	102.4 (2.0)

3.4 Dissolution profile data for Aripiprazole OSF using the proposed dissolution method:

The dissolution profile data for Aripiprazole OSF using the proposed QC method were provided in the following Tables (data provided in <\\cdsesub1\evsprod\nda211448\0001\m3\32-body-data\32p-drug-prod\aripiprazole-film\32p2-pharm-dev\rpt-disso-devt-new-method.pdf>). The clinical batch of Aripiprazole OSF, ^{(b) (4)}mg (401455) was 12 to 14 months old at the time of relative bioavailability studies (Studies 140051 and 140052). These bio-batches and registration batches (batches #: 401452, 401455 and 401472 for PV1, 401451, 401454 and 401471 for PV2, 401681, 401682 and 401683 for PV3) were manufactured at November 2014 or February 2015. There are more than ^{(b) (4)}% dissolution in 10 minutes for all batches (Tables 8-10).

Table 8. Dissolution profile data (n=12) for Aripiprazole OSF, PV1 batch (batches 401452, 401455, 401472 for 5 mg, 10 mg, and 15 mg strengths, respectively. PV1 batch contains predominantly ^{(b) (4)} API form) using the proposed dissolution method

Media		pH4.0		Test method		Apparatus 5		Rpm		50 rpm	
Volume		900mL		Temp		37±0.5℃		N		12	
Lot		401452									
Time		5 Min	10 Min	15 Min	30 Min	45 Min	60 Min	90 Min	120 Min		
	Ave	77.9	94.3	97.6	100.3	100.9	100.7	100.9	100.9		
	SD	7.0	2.9	2.2	1.5	1.6	1.5	1.7	1.8		
	RSD	9.0	3.1	2.2	1.5	1.6	1.5	1.7	1.8		
Lot		401455									
Time		5 Min	10 Min	15 Min	30 Min	45 Min	60 Min	90 Min	120 Min		
	Ave	65.7	87.7	93.9	98.5	99.4	100.1	100.8	100.7		
	SD	4.2	2.8	1.9	1.3	1.3	1.3	1.3	1.1		
	RSD	6.4	3.2	2.0	1.3	1.3	1.3	1.3	1.1		
Lot		401472									
Time		5 Min	10 Min	15 Min	30 Min	45 Min	60 Min	90 Min	120 Min		
	Ave	65.5	87.1	93.1	97.6	98.6	98.9	99.6	100.1		
	SD	2.9	2.0	1.4	1.1	1.2	1.1	1.0	1.0		
	RSD	4.4	2.3	1.5	1.1	1.2	1.1	1.0	1.0		

Table 9. Dissolution profile data (n=12) for Aripiprazole OSF, PV2, PV3 batches (PV2 and PV3 batches mainly contain (b) (4) API form) using the proposed dissolution method

Lot No.	5 Min	10 Min	15 Min	30 Min	45 Min	60 Min	90 Min	120 Min
PV2	401451 5mg	(b) (4)						
	401454 10mg							
	401471 15mg							
	401681 5mg							
PV3	401682 10mg							
	401683 15mg							

Table 10. Dissolution profile data (n=12) for Aripiprazole OSF, PV1, PV2, PV3 batches before and after stress test (70 °C, 85% RH, 4 weeks) using the proposed dissolution method

PH 4.0	5 min	10 min	15min	30 min	45 min	60 min	f ₂ value
PV1 10mg (401455), n=3	89.2	94.5	98.1	102.6	104.4	105.5	
PV1 10mg (401455)_ stress 70°C, 85%RH, 4 W. n=3	85.8	92.5	95.8	99.9	101.7	102.4	76.8
PH 4.0	5 min	10 min	15min	30 min	45 min	60 min	f ₂ value
PV2 10mg (401454), n=3	88.6	98.7	102.6	104.3	105.6	108.3	
PV2 10mg (401454)_ stress 70°C, 85%RH, 4 W. n=3	63.3	90.7	98.8	107.4	106.7	108.7	47.8
PH 4.0	5 min	10 min	15min	30 min	45 min	60 min	
PV3 10mg (401682), n=3	92.2	100.2	95.3	94.7	95.1	95.0	
PV3 10mg (401682)_ stress 70°C, 85%RH, 4 W. n=3	64.3	94.5	93.0	96.0	95.3	95.2	46.6

Reviewer's Conclusion: The discriminating ability of the dissolution method for Aripiprazole OSF was demonstrated in the changes in film thickness and the levels of (b) (4). The dissolution profile data obtained from Aripiprazole OSF batches containing (b) (4) or (b) (4) API forms were rapid and similar with more than (b) (4) % dissolution in 10 minutes. In view of the demonstrated discriminating ability and obtained dissolution profile data, the proposed dissolution method [USP apparatus 5 (paddle over disk, disk size 56 mm, 40 mesh) at 50 rpm, in 900 mL of pH 4.0 acetate buffer at 37 °C] is acceptable as a quality control method for batch release and stability testing of Aripiprazole OSF, 5 mg, 10 mg, and 15 mg.

3.5 Dissolution Acceptance Criterion:

Based primarily on the provided dissolution data of biobatch and registration batches, this Reviewer considered that the Applicant's originally proposed dissolution acceptance criterion of "Q = (b) (4) % at (b) (4) minutes" was permissive and not acceptable. In the Information Request dated 06/25/2020, the Applicant was recommended to revise the dissolution acceptance criterion. In the Response dated 06/30/2020, the Applicant revised the dissolution acceptance criterion to "Q = (b) (4) % at 15 minutes".

3.6 Dissolution Stability Data:

The Applicant provided dissolution data at (b) (4) minutes (n=6) for stability samples of the clinical batches and registration batches (batches: 401452, 401451, and 401681 for 5 mg strength, 401455, 401454, and 401682 for 10 mg strength, 401472, 401471, and 401683 for 15 mg strength) stored under two long-term conditions (25 °C/60% RH and 30 °C/75% RH) for 36 months and accelerated conditions (40 °C/75% RH) for 6 months. The stability data show that all registration batches passed the proposed dissolution acceptance criterion of "Q = (b) (4) at (b) (4) minutes" at S1 and no decrease were observed for dissolution data on stability. No dissolution stability data at 15 minutes were provided. In the Response dated 06/29/2020, the Applicant reported that the tested long-term stability samples complied with the agreed-upon dissolution acceptance criterion of "Q = (b) (4) at 15 minutes" over the proposed shelf-life. The Applicant proposed a shelf-life of 36 months for the proposed Aripiprazole OSF, 5 mg, 10 mg, and 15 mg. The assigned Drug Product Reviewer will determine the shelf life for the proposed drug product.

4. DISINTEGRATION TIME:

The Applicant also proposed a disintegration time (NMT (b) (4)) for the quality control of Aripiprazole OSF. The assigned Drug Product Reviewer will determine the adequacy of the proposal.

5. BIOWAIVER REQUEST FOR 5 MG AND 15 MG STRENGTHS:

The Applicant requested a waiver of an in vivo bioavailability study for Aripiprazole OSF, 5 mg and 15 mg, per CFR 320.22(d)(2).

This Reviewer considered the biowaiver request for 5 mg and 15 mg strengths acceptable and supported by the following information:

- (1) Data of an acceptable bioequivalence study on Aripiprazole OSF, 10 mg (Study 140052);
- (2) All the strengths are of the same immediate-release dosage form and have the same release mechanism and manufacturing process;
- (3) All the strengths are compositionally proportional in the active and inactive ingredients;
- (4) Aripiprazole linear pharmacokinetics across the dose range of 5 mg to 30 mg (refer to product labeling);
- (5) Similar comparative in vitro dissolution profiles across Aripiprazole OSF different strengths in pH 1.2 (more than (b) (4)% aripiprazole dissolution in 5 minutes for all strengths), pH 4 (more than (b) (4)% aripiprazole dissolution in 15 minutes for all strengths), and pH 6.8 (less than (b) (4)% aripiprazole dissolution in 120 minutes for all strengths) (all data provided in <\\cdsesub1\evsprod\nda211448\0001\m2\27-clin-sum\rpt-disso-profiles-biowaiver.pdf>) (Tables b, c, and d in Appendix 1).

Reviewer's Assessment: As per 21 CFR 320.22(d)(2), FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of the drug product, if the drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product. The overall information/data supporting the biowaiver for Aripiprazole OSF, 5 mg and 15 mg is adequate and acceptable. Therefore, the Applicant's biowaiver request for Aripiprazole OSF, 5 mg and 15 mg is granted.

Appendix 1 Additional dissolution data

Table a. Dissolution conditions tested (submitted in the Response dated 05/29/2020)

Method Number	Temperature	pH	RPM	Test Method	Volume	Vessels	Time Points (min)		
1	37 °C	(b) (4) 4.0	50	(b) (4)	900 mL	N=6	(b) (4)		
2	(b) (4)	4.0	50				15, (b) (4)		
3		4.0	50				(b) (4)		
4	37 °C	(b) (4)	50	(b) (4)					
5	37 °C	(b) (4)	50						
6	37 °C		50						
7	37 °C	(b) (4) 4.0	(b) (4)						
8	37 °C	4.0	50						
9	37 °C	4.0	(b) (4)						
10	37 °C	(b) (4)	50						
11	37 °C	(b) (4) 4.0	50		(b) (4)				
(b) (4)									
(b) (4)									

Table b. Comparative dissolution profile data (n=12) for Aripiprazole OSF, 5 mg, 10 mg, and 15 mg in pH (b) (4) medium (dissolution method: USP 5 (paddle over disk) at 50 rpm, in 900 mL pH (b) (4) medium)

5 mg								
Time		10min	15min	30min	45min	60min	90min	120min
Mean	95.6	96.1	96.5	97.0	96.2	96.2	96.8	96.4
SD	8.2	4.1	4.1	1.5	1.0	0.8	0.9	0.8
RSD	8.5	4.3	2.3	1.5	1.0	0.9	1.0	0.8
10 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	90.8	94.4	97.1	99.4	99.4	99.3	99.3	99.6
SD	9.3	6.6	3.4	0.8	0.9	0.6	0.4	0.7
RSD	10.2	7.0	3.5	0.8	0.9	0.6	0.4	0.7
15 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	95.0	97.7	98.8	99.5	99.3	99.2	99.5	99.4
SD	6.3	3.5	2.0	0.6	0.4	0.5	0.6	0.5
RSD	6.6	3.6	2.0	0.6	0.4	0.5	0.6	0.5

Table c. Comparative dissolution profile data (n=12) for Aripiprazole OSF, 5 mg, 10 mg, and 15 mg in pH 4.0 medium (dissolution method: USP 5 (paddle over disk) at 50 rpm, in 900 mL pH 4.0 medium)

5 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	78.0	94.3	97.6	100.4	100.9	100.8	101.0	100.9
SD	7.0	2.9	2.2	1.5	1.6	1.5	1.7	1.8
RSD	9.0	3.1	2.2	1.5	1.6	1.5	1.7	1.8
10 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	65.7	87.7	93.9	98.5	99.4	99.6	100.7	100.7
SD	4.2	2.8	1.9	1.3	1.3	2.5	1.3	1.1
RSD	6.4	3.2	2.0	1.3	1.3	2.5	1.3	1.1
15 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	65.5	87.1	93.1	97.6	98.6	98.9	99.6	100.1
SD	2.9	2.0	1.4	1.1	1.2	1.1	1.0	1.0
RSD	4.4	2.3	1.5	1.1	1.2	1.1	1.0	1.0

Table d. Comparative dissolution profile data (n=12) for Aripiprazole OSF, 5 mg, 10 mg, and 15 mg in pH (b) (4) medium (dissolution method: USP 5 (paddle over disk) at 50 rpm, in 900 mL pH (b) (4) medium)

5 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	4.8	3.5	3.8	3.5	4.4	4.3	4.5	2.7
SD	3.4	0.6	0.6	1.0	1.7	1.3	1.5	0.4
RSD	69.9	15.9	15.1	28.3	37.5	30.8	33.2	14.9
10 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	4.3	3.4	4.1	3.4	2.3	2.3	4.0	2.7
SD	2.7	0.5	2.2	0.2	0.2	0.3	0.3	0.3
RSD	63.2	15.9	52.0	7.0	11.0	12.4	8.0	11.6
15 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	2.4	2.6	2.9	2.6	2.7	2.1	2.1	2.3
SD	0.5	0.2	0.2	0.1	0.3	0.1	0.1	0.2
RSD	21.4	7.5	7.5	5.1	10.3	6.0	6.8	8.3



Yang
Zhao

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Ta-Chen
Wu

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/s/

RENISHKUMAR R DELVADIA
08/13/2020 09:42:51 AM

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Biopharmaceutics.....	134

RECOMMENDATION: Facility assessment is pending; all other quality disciplines have recommended an approval. Once the facility review is complete, an addendum or a revision of this executive ATL summary with the final approvability recommendation will be added in Panorama and DARRTS.

☐ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 211448 Assessment #1

Drug Product Name	(b) (4) (Aripiprazole oral film)
Dosage Form	Oral film
Strength	5 mg, 10 mg, and 15 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	CMG Pharmaceutical Co. Ltd
US agent, if applicable	Camargo Pharmaceutical Services, LLC

Submission(s) Assessed	Document Date	Discipline(s) Affected
0001 (1) Original submission	10/18/2019	Drug product, Drug substance, Process, Facility, Biopharmaceutics
0004 (4) Quality/IR response	12/13/2019	Facility
0005 (5) Quality/IR response	12/14/2019	Facility
0006 (6) Quality/IR response	01/10/2020	Drug product
0010 (10) Quality/IR response	05/29/2020	Drug substance, Biopharmaceutics, Manufacturing process
0011 (11) Quality/IR response	06/22/2020	Drug product
0012 (12) Original submission	06/29/2020	Drug product, Process, Biopharmaceutics

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Ray Frankewich	Su Tran

Drug Product	Renishkumar Delvadia	Julia Pinto
Manufacturing	Tarun Mehta	Ubrani Venkataram Jonathan Swoboda
Microbiology	N/A	N/A
Biopharmaceutics	Yang Zhao	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Renishkumar Delvadia	
Laboratory (OTR)	N/A	N/A
Environmental	Renishkumar Delvadia	Julia Pinto

EXECUTIVE SUMMARY

[IQA NDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Facility assessment is currently pending for two facilities. Current status for the drug substance manufacturing and testing facility, (b) (4) is "Withhold/OAI" due to cGMP compliance issues. Current status for the drug product manufacturing facility, Tesa Labtec Company GmbH, is "PAI under review (704a4 initiated)". Removal of OAI status of (b) (4) and satisfactory inspection of Tesa Labtec Company GmbH are required before this NDA may be approved. The Application is recommended for approval from Drug substance, Drug Product, Manufacturing Process, and Biopharmaceutics perspective. Once the facility review is complete, an addendum to this executive ATL summary will be added with the final approvability recommendation.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed drug product is an immediate-release, oral film containing aripiprazole. The product is formulated in strengths of 5 mg, 10 mg, and 15 mg aripiprazole; the (b) (4). The films are imprinted with red edible ink identifying the product and strength. of "CMG ARF5" for 5 mg, "CMG ARF10" for 10 mg, or "CMG ARF15mg" for 15 mg strengths. The primary commercial packaging container closure system is sealed foil pouches.

Proposed Indication(s) including Intended Patient Population	Treatment of schizophrenia
Duration of Treatment	See Label
Maximum Daily Dose	30 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Choose an item.

Drug Product: Adequate

The to-be-marketed (TBM) formulation compositions of the proposed drug product contains excipients of USP or NF grade, except for red ink, which is used in trace amount for printing for identifying the product and strength. The Applicant has provided adequate CMC information within the NDA submission to support the use of red ink. The Applicant has performed adequate product development studies to justify the selection of the excipients and to demonstrate/justify their chemical compatibility with the drug substance.

Different levels of two crystalline forms, a (b) (4) and an (b) (4) were present in various batches. The pivotal PK BE batch contained (b) (4) form when samples were tested 30 to 36 months after batch production for crystallinity; the Applicant did not test for crystallinity at release or at the time of PK BE study. The applicant provided additional information during the course of the NDA review cycle to justify that the two different crystalline forms have comparable solubility and dissolution profiles. The Applicant also proposed manufacturing process changes and controls to further ensure that the crystalline form of aripiprazole in the finished drug product is consistently (b) (4) at release and during stability.

The Applicant has provided 36 months of long-term (25°C/60%RH and 30°C/75% RH) and 6 months of accelerated stability data for three batches of all strengths; 36-month expiry has been proposed for all three strengths. The Applicant has submitted photo-stability and freeze/thaw stability data as well. All the stability data met the proposed specifications, except for few minor out-of-specification (OOS) results for film flexibility and size; all OOS results have been adequately justified by the Applicant. The overall stability data provided by the Applicant support the proposed shelf-life of 36 months for all proposed strengths.

Overall, the information submitted in the IR responses/CMC amendments received during the review cycle adequately addressed all the drug product related issues. There is no outstanding CMC deficiency related to the drug product review.

Labeling: Adequate

Minor labelling comments were discussed with DMEPA reviewer and included in the DMEPA review for sending out to the Applicant, along with the other DMEPA comments.

Manufacturing: Inadequate

As of today, 07/09/2020, the facility status for (b) (4) the drug substance facility, is OAI. Also, Drug product manufacturing facility

(Tesa Labtec Company GmbH) review is on-going (704a4 initiated). Satisfactory inspection is necessary for both these facilities before the Application are recommended for approval or required no evaluation (see table below). All other facilities are adequate.

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)			Withhold - Based on CGMP
Tesa Labtec Company GmbH Heykenaukamp 10 , Hamburg , Hamburg, Germany , 21147	3010375003	(b) (4)	Pending PAI
Tesa Labtec Company GmbH Raiffeisenstrase 4 , Langenfeld, Langenfeld, Germanv. 40764	3010969322		Approve - Based on Previous History
(u) (4)			Approve - Based on Previous History
			No Evaluation Necessary
			No Evaluation Necessary

The proposed product is manufactured in (b) (4)

(b) (4)

(b) (4)

Overall, the manufacturing process is adequate. Note that the ATL document contains the current

version of the process and facility review, which will be replaced with the final version in the ATL review addendum/revision.

Biopharmaceutics: Adequate

The Applicant's request for waiver of an in vivo BA/BE study for the proposed Aripiprazole oral film, 5 mg and 15 mg, is granted based on the following information and data: (a) the bioequivalence data on the 10 mg strength, (b) same release mechanism and manufacturing process for all strengths, (c) compositional proportionality among all strengths, (d) evidence on linear pharmacokinetics in the dose range of 5 mg to 30 mg, and (e) comparable dissolution profiles among all strengths in multi-pH media (pH 1.2, 4.0, and 6.8). After the Division of Biopharmaceutics recommendation, the Applicant tighten the dissolution acceptance criterion from the originally proposed "Q = (b) (4) % at (b) (4) min" to "Q = (b) (4) at 15 minutes". As mentioned before in the summary, both aripiprazole (b) (4) form and (b) (4) form existed in the final drug product [for example, (b) (4) form API is the predominant form in the bio-batch (PV1), while (b) (4) form API is present in PV2 and PV3 batches]. In the response dated 05/29/2020, the Applicant provided comparative aqueous solubility data at 37 °C for API aripiprazole (b) (4) form and (b) (4) form over pH range of 1.2 – 5 and the solubilities of aripiprazole (b) (4) form and (b) (4) form were not different over this pH range tested.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, Stability	- Formulation - Container closure - Raw materials - Process parameters - Scale/equipment - Site	M	(b) (4)	Acceptable	None
Physical stability (solid state)	- Formulation - Raw materials - Process parameters - Scale/equipment - Site	M		Acceptable	None

			(b) (4)		
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M		Acceptable	None
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	None
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M		Acceptable	None

D. List of Deficiencies for Complete Response

- Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

- Drug Substance Deficiencies

None

- Drug Product Deficiencies

None

- Labeling Deficiencies

None

- Manufacturing Deficiencies

Pending review;

- Biopharmaceutics Deficiencies

None

- Microbiology Deficiencies

None

- Other Deficiencies (Specify discipline, such as Environmental)

None

Application Technical Lead Name and Date:
Renishkumar Delvadia, 07/09/2020

QUALITY ASSESSMENT DATA SHEET

[IQA NDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	June 18, 2019	Assessment for ANDA 205589 (no significant updates)
	II			Adequate	March 18, 2019	Assessment for ANDA 201519 (no significant updates)
	III				DMF assessment was not necessary	Sufficient information provided in the application
	III				DMF assessment was not necessary	Sufficient information provided in the application
	III				DMF assessment was not necessary	Sufficient information provided in the application
	IV				DMF assessment was not necessary	Sufficient information provided in the application

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
Meetings and communications	IND 119610	Aripiprazole tablet
Reference product	NDA 021436	Abilify Oral Tablets, Otsuka

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	None			
Pharmacology/Toxicology	None			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	None			

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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4)	Changed to (b) (4)
Established name(s)	(aripiprazole) Oral	(aripiprazole) oral film"
Route(s) of administration	(b) (4) Film	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Oral (b) (4) Films: 5 mg, 10 mg, 15 mg	Changed to "Oral Film: 5 mg, 10 mg, 15 mg"
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.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

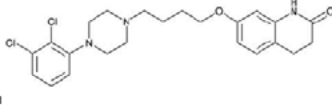
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Oral (b) (4) Films	Changed to "oral film"
Strength(s) in metric system	5 mg, 10 mg, 15 mg	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White rectangular film with red print; Applicant has provided information in a tabular format.	Suggested format in the working draft label • 5 mg white, rectangular-shaped, oral film with "CMG ARF5" printed in red on one side. • 10 mg white, rectangular-shaped, oral film with "CMG ARF10" printed in red on one side. • 15 mg white, rectangular-shaped, oral film with "CMG ARF15" printed in red on one side.
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 labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Aripiprazole is an atypical antipsychotic drug that is available as (b) (4) (aripiprazole) (b) (4) oral film is available in 5 mg, 10 mg, and 15 mg strengths	Changed to (b) (4) contains aripiprazole, an atypical antipsychotic"
Dosage form(s) and route(s) of administration		
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Inactive ingredients include acesulfame potassium, citric acid, FD&C Red No. 40, glycerin, hypromellose, L-menthol, polysorbate 80, polyvinyl alcohol, sucralose, and xylitol.	Acceptable
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.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	See above	

Chemical name, structural formula, molecular weight	Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyrl. The ^{(b) (4)} formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38. The ^{(b) (4)} structure is: 	Changed to "The chemical name of aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyrl. The molecular formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38. The structural formula is:"
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Not included	Following comment sent to the Applicant in the working draft label "Include information about solubility and physical properties of drug substance"

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
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	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments																				
HOW SUPPLIED/STORAGE AND HANDLING section																						
Available dosage form(s)	Film	Acceptable; minor formatting changes recommended																				
Strength(s) in metric system	5 mg, 10 mg, 10 mg	Acceptable																				
Available units (e.g., bottles of 100 tablets)																						
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Included <table><tr><th>Strength</th><th>Film Color/Shape</th><th>Print</th><th>Pack Size</th><th>NDC Code</th></tr><tr><td>5 mg</td><td>white rectangular</td><td>CMG ARF5</td><td>one strip (film) per pouch, box of 30 pouches</td><td>XXXX-XXXX-XXXX</td></tr><tr><td>10 mg</td><td>white rectangular</td><td>CMG ARF10</td><td>one strip (film) per pouch, box of 30 pouches</td><td>XXXX-XXXX-XXXX</td></tr><tr><td>15 mg</td><td>white rectangular</td><td>CMG ARF15</td><td>one strip (film) per pouch, box of 30 pouches</td><td>XXXX-XXXX-XXXX</td></tr></table>	Strength	Film Color/Shape	Print	Pack Size	NDC Code	5 mg	white rectangular	CMG ARF5	one strip (film) per pouch, box of 30 pouches	XXXX-XXXX-XXXX	10 mg	white rectangular	CMG ARF10	one strip (film) per pouch, box of 30 pouches	XXXX-XXXX-XXXX	15 mg	white rectangular	CMG ARF15	one strip (film) per pouch, box of 30 pouches	XXXX-XXXX-XXXX	Asked to include NDC code
Strength	Film Color/Shape	Print	Pack Size	NDC Code																		
5 mg	white rectangular	CMG ARF5	one strip (film) per pouch, box of 30 pouches	XXXX-XXXX-XXXX																		
10 mg	white rectangular	CMG ARF10	one strip (film) per pouch, box of 30 pouches	XXXX-XXXX-XXXX																		
15 mg	white rectangular	CMG ARF15	one strip (film) per pouch, box of 30 pouches	XXXX-XXXX-XXXX																		
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.	N/A																					

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

Item	Information Provided in the NDA	Assessor's Comments
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.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [USP controlled room temperature].	Asked to change to "Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [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	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	(b) (4) manufactured by Tesa Labtec Company GmbH Heykenaukamp 10 21147 Hamburg Germany Distributed and marketed by CMG Pharmaceutical Co., Ltd, 14 Dosan-daero 66-gil, Gangnam-gu, Seoul, 06064, South Korea (b) (4) is a trademark of CMG Pharmaceutical Co., Ltd.	Acceptable

2.0 PATIENT LABELING

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

In the DMEPA's IR response dated 01/17/2020 the Applicant stated " Two different color schemes were proposed in ^{(b) (4)} packaging for consideration and feedback from the Agency in an effort to reduce medication errors. In the first proposed scheme, the strengths are distinguished by the brightness of the green background and the difference in color of the product strength. In the second proposed scheme, the strengths are distinguished by the variety of background color, with the product strength font corresponding in color. The Sponsor prefers the second proposed scheme that differentiates product strength by background color and font color. Based on the Agency's collaborative feedback, the design of carton labeling will be chosen to minimize patient misuse." The outstanding C/C labeling deficiencies related to quality are conveyed to DMEPA reviewer and will be included in DMEPA review along with their labeling other comments.



Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	(b) (4) (Aripiprazole oral (b) (4) film)	Not acceptable: (b) (4) (aripiprazole oral film)
Dosage strength	5mg, 10 mg, 15 mg	Acceptable
Route of administration	Oral	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not applicable	
Net contents (e.g. tablet count)	30 films	Acceptable
"Rx only" displayed on the principal display	Yes	Acceptable
NDC number	Not listed yet	DMEPA will review this
Lot number and expiration date	Not included	Not acceptable DMEPA will include comment asking the Applicant to revise label with lot number and expiration date for carton label
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [USP controlled room temperature]	Not acceptable Change to Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [USP controlled room temperature]. For both carton and pouch labels
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Not included	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured by : tesa Labtec GmbH Heykenaukamp 10, D-21147 Hamburg, Germany Manufactured for : CMG Pharmaceutical Co., Ltd. 14 Dosandaero 66 Gil, Gangnamgu Seoul, Republic of Korea	Acceptable
Medication Guide (if applicable)	States (b) (4) (b) (4)	Acceptable
No text on Ferrule and Cap over seal	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	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: Adequate

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

None; deficiencies will be addressed through DMEPA's review.

Overall Assessment and Recommendation:

Adequate

*Primary Drug Product Assessor Name and Date: Renishkumar Delvadia,
06/24/2020*

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



Renishkumar
Delvadia

Digitally signed by Renishkumar Delvadia
Date: 7/08/2020 01:40:35PM
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Julia
Pinto

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BIOPHARMACEUTICS**NDA:** 211448**Drug Product Name/Strengths:** (b) (4) (Aripiprazole) Oral Soluble Film (OSF)/5 mg, 10 mg, and 15 mg**Route of Administration:** Oral**Applicant Name:** CMG Pharmaceutical Co. Ltd.**List of Reviewed Submissions:**

Original submission dated 10/18/2019

Response dated 05/29/2020 to the Information Request dated 03/20/2020

Response dated 06/29/2020 to the Information Request dated 06/25/2020

Biopharmaceutics Review Team:

Primary Reviewer: Yang Zhao, Ph.D.

Secondary Reviewer: Ta-Chen Wu, Ph.D.

REVIEW SUMMARY:

The Applicant submitted NDA 211448 seeking approval for Aripiprazole Oral Soluble Film (OSF), 5 mg, 10 mg, and 15 mg, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for the treatment of schizophrenia. The Listed Drug is Abilify® Oral Tablets (NDA 021436).

Review Objective: The Biopharmaceutics Review evaluated the adequacy of (1) the proposed dissolution method and acceptance criterion for QC testing of the proposed drug product at batch release and during stability, and (2) biowaiver request for 5 mg and 15 mg strengths of Aripiprazole OSF.

Reviewer's Assessment:**(1) Dissolution Method and Acceptance Criterion:**

The Applicant proposed "USP Apparatus 5 (paddle over disk, disk size 56 mm, 40 mesh) at 50 rpm, in 900 mL of pH 4.0 acetate buffer at 37 °C" as dissolution method for the batch release and stability testing for the proposed Aripiprazole OSF, 5 mg, 10 mg, and 15 mg. Dissolution from Aripiprazole OSF batches containing (b) (4) or (b) (4) API forms were similar and very rapid. Discriminating ability of the dissolution method for Aripiprazole OSF was demonstrated in the changes in film thickness and the levels of HPMC. In view of the demonstrated discriminating ability and obtained dissolution profile data, the proposed dissolution method is deemed acceptable as the quality control method for batch release and stability testing of Aripiprazole OSF, 5 mg, 10 mg, and 15 mg.

Based primarily on the provided dissolution data of clinical batch and registration batches, the Division of Biopharmaceutics recommended the Applicant to tighten the dissolution acceptance criterion from the originally proposed "Q = (b) (4) % at (b) (4) min" to "Q = (b) (4) % at 15 minutes". An agreement was reached between the Applicant and the Agency, dated 06/29/2020.

(2) Biowaiver Request:

The Applicant's request for waiver of an in vivo bioavailability/bioequivalence study for the proposed Aripiprazole OSF, 5 mg and 15 mg, is granted based on the following information and data: (a) the bioequivalence data on the 10 mg strength, (b) same release mechanism and manufacturing process for all strengths, (c) compositional proportionality among all strengths, (d) evidence on linear pharmacokinetics in the dose range of 5 mg to 30 mg, and (e) comparable dissolution profiles among all strengths in multi-pH media (pH 1.2, 4.0, and 6.8).

RECOMMENDATION:

From the Biopharmaceutics perspective, the provided information and data are adequate and NDA 211448 for (b) (4) (Aripiprazole) Oral Soluble Film (OSF), 5 mg, 10 mg, and 15 mg is recommended for **APPROVAL**.

The FDA-approved dissolution method and acceptance criterion for the proposed Aripiprazole Oral Soluble Film, 5 mg, 10 mg, and 15 mg are:

Final Dissolution Method and Acceptance Criterion for Aripiprazole Oral Soluble Film				
USP Apparatus	Speed (rpm)	Medium/Temp	Volume (mL)	Acceptance Criterion
USP 5 (paddle over disk, disk size 56 mm, 40 mesh)	50	pH 4.0 acetate buffer/37 °C	900	Q = (b) (4)% at 15 minutes

BIOPHARMACEUTICS ASSESSMENT

1. BACKGROUND OF THE PROPOSED DRUG PRODUCT:

The proposed Aripiprazole Oral Soluble Film (OSF) is designed as an immediate release oral soluble film formulation in three proposed strengths of 5 mg, 10 mg, and 15 mg. Per Applicant's proposed labeling, the typical aripiprazole dosing regimen for adults is 10 mg–15 mg per day, with a maximum dose of 30 mg aripiprazole per day.

Aripiprazole OSF is a white rectangular film imprinted with red edible ink identifying the product and strength. The white films are rectangular shaped strips with a printed identifier in red edible ink of "CMG ARF5" for 5 mg, "CMG ARF10" for 10 mg, or "CMG ARF15" for 15 mg strengths. Three strengths are compositionally proportional (Table 1).

Table 1. Composition of the proposed Aripiprazole OSF, 15 mg, 10 mg, and 5 mg

Component	Function	Reference to Quality Standard	mg/film unit		
			15mg	10mg	5mg
Aripiprazole	Active Ingredient (b) (4)	USP	15.000	10.000	5.000
Glycerin		NF	(b) (4)		
Polysorbate 80		NF			
Citric acid		NF			
Xylitol		NF			
Sucralose		NF			
Acesulfame potassium		NF			
L-Menthol		NF			
Polyvinyl alcohol		NF			
Hydroxypropyl methylcellulose (b) (4)		NF			
Hydroxypropyl methylcellulose (b) (4)		USP			
Red edible ink ^a			(b) (4)		
Total Film Weight (mg)			60	40	20
(b) (4)					

Note: (b) (4) are used in manufacturing and (b) (4)
(b) (4) The (b) (4)
NF = National Formulary; USP = United States Pharmacopeia

2. INFORMATION OF THE DRUG SUBSTANCE:

2.1 Solubility:

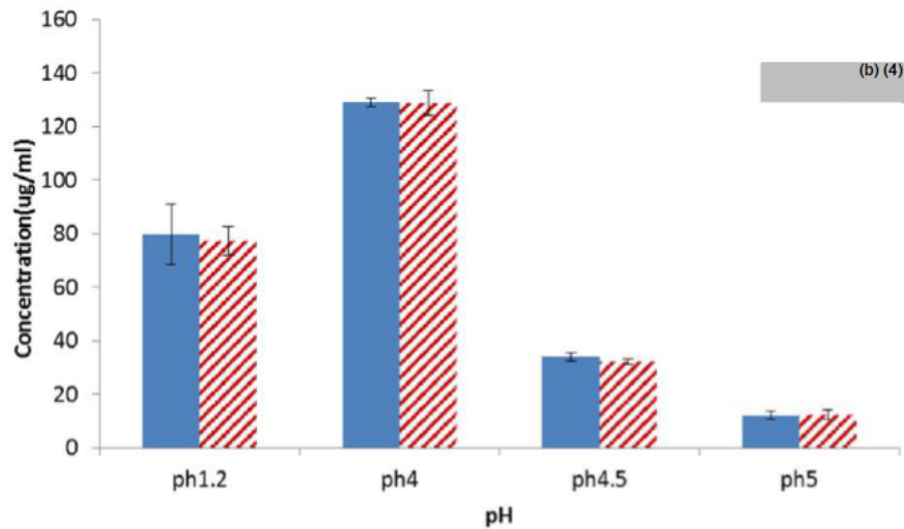
The Applicant reported that aripiprazole has pH-dependent solubility (Table 2).

Table 2. Aqueous solubility of aripiprazole at different pHs at 37 °C (data provided in dissolution method development report, \\cdsesub1\evsprod\nda211448\0001\m3\32-body-data\32p-drug-prod\aripiprazole-film\32p2-pharm-dev\rpt-disso-devt-new-method.pdf)

Aripiprazole (API) Solubility at 37±0.5°C (µg/mL) (n=3)					
	2h	4h	6h	8h	24h
0.01N HCl	992.1±107.7	1059.7±107	1074.5±88.9	1089.4±124.4	1099.6±70.9
pH1.2	164.3±10.7	134.1±9.3	123±6.9	108±6.7	83.7±2.8
pH4.0	197.1±12.8	137.6±14.1	118±7.5	103.6±3.4	117±61.2
pH4.5	81.6±5.1	57.8±8.3	48.2±5	41.3±3	45.6±21.4
pH5.0	27.5±0.3	15.7±1.1	16.1±1.8	13.1±1.6	13.7±5.1
pH6.0	0±0	0±0	0±0	0±0	0±0
pH6.8	0±0	0±0	0±0	0±0	0±0
purified water	0±0	0±0	0±0	0±0	0±0

For the originally submitted solubility data, the Applicant did not specify that the solubility data were collected from aripiprazole (b) (4) form or (b) (4) form. Both aripiprazole (b) (4) form and (b) (4) form exist in the final drug product [for example, (b) (4) form API is the predominant form in the bio-batch (PV1), while (b) (4) form API is present in PV2 and PV3 batches]. In view of the starting API material used for product manufacturing being aripiprazole (b) (4) form, with an Information Request dated 03/20/2020, the Applicant was requested to provide solubility data for both (b) (4) and (b) (4) forms. In the Response dated 05/29/2020, the Applicant provided comparative aqueous solubility data at 37 °C for API aripiprazole (b) (4) form and (b) (4) form over pH range of 1.2 – 5 and the solubilities of aripiprazole (b) (4) form and (b) (4) form were not different over this pH range tested (Figure 1). Note that aripiprazole has no solubility at pH 6-6.8 tested, thus precipitation of aripiprazole might occur at high pHs.

Figure 1. Solubilities of Aripiprazole (b) (4) form (b) (4) and (b) (4) form (b) (4) (n = 3) over pH 1.2–5 (provided in the Response dated 05/29/2020)



2.2 Permeability:

The Applicant did not provide any permeability data for aripiprazole. However, the Applicant reported (per labeling information), that aripiprazole is well absorbed when administered orally, the T_{max} occurs within 3 to 5 hours, and the absolute oral bioavailability is 87% when administered as a tablet formulation. The available information suggests the highly permeable characteristics of the drug substance.

3. PROPOSED DISSOLUTION METHOD AND ACCEPTANCE CRITERION:

The proposed dissolution method and dissolution acceptance criterion for the batch release and stability testing for Aripiprazole OSF, 5 mg, 10 mg, and 15 mg are as follows:

Proposed dissolution method and acceptance criterion for Aripiprazole OSF				
USP Apparatus	Speed (rpm)	Medium/Temp	Volume (mL)	Proposed acceptance criterion
5 (paddle over disk, disk size 56 mm, 40 mesh)	50	pH 4.0 acetate buffer/37 °C	900	NLT (b) (4)% (Q) dissolved in (b) (4) minutes

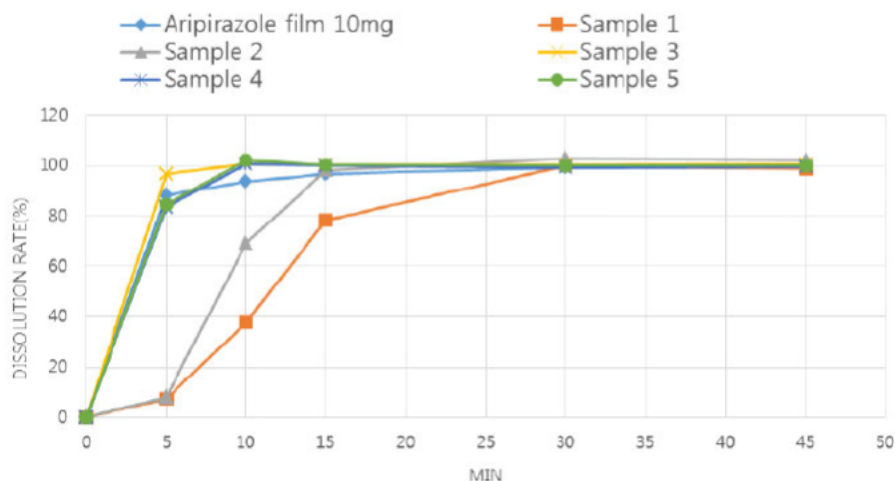
(b) (4)

3.3.2 Formulation compositional variables:

In addition, the Applicant provided dissolution profile data from batches intentionally manufactured with various compositional variables (Figure 4) (Page 22 in Module 3.2.P.2 New dissolution method development report). The Sample 1 in Figure 4 has changes in HPMC levels (b) (4) % vs. the target of (b) (4) % for (b) (4) and (b) (4) vs. the target of (b) (4) % for (b) (4), while the Sample (b) (4) has multiple changes in HPMC levels, in PVA levels (b) (4) % vs. (b) (4) %, and in glycerin levels. Figure 4 demonstrated that the proposed dissolution method is discriminating towards the changes in the levels of HPMC. This Reviewer noticed that the Sample (b) (4) and the Sample (b) (4) have significant changes in compositions. Therefore, in the Information Request dated 03/20/2020, the Applicant was asked to provide rationale/explanation for the changes in compositions for the above evaluation of discriminating ability of the dissolution method.

In the Response dated 05/29/2020, the Applicant explained that the substantial changes made in the OSF composition, instead of the recommended variation of (b) (4) % in critical material attributes (CMAs), was intentionally designed to evaluate the discriminating ability of the proposed dissolution method for the proposed drug product which is designed to rapidly disintegrate and dissolve. This explanation is reasonable for a rapidly dissolving drug product.

Figure 4. Dissolution profiles of Aripiprazole OSF batches intentionally manufactured with various compositional variables (data provided in dissolution method development report Page 22). Dissolution similarity factor $f_2=20$ between the target formulation vs. sample 1, $f_2=24$ between the target formulation vs. sample 2, calculated by this Reviewer



The dissolution method's discriminating power for changes in API particle size was not investigated. Considering that the API during manufacturing process is (b) (4) this Reviewer considers that the risk towards the changes in API particle size is low.

3.3.3 Process parameters:

In the Response dated 05/29/2020, the Applicant provided investigational results for the discriminating ability of the proposed dissolution method towards the changes in film thickness (range tested: (b) (4) μm (b) (4) μm), (b) (4) (Table 6), and (b) (4) (Table 7). The dissolution method was shown to be discriminating towards the changes in film thickness (Figure 5).

Figure 5. Effects of film thickness on dissolution for Aripiprazole OSF 10 mg (in the Response dated 05/29/2020). The target OSF thickness is (b) (4) μm , dissolution similarity factor $f_2=34$ between the target of (b) (4) μm film thickness vs. (b) (4) μm , calculated by this Reviewer

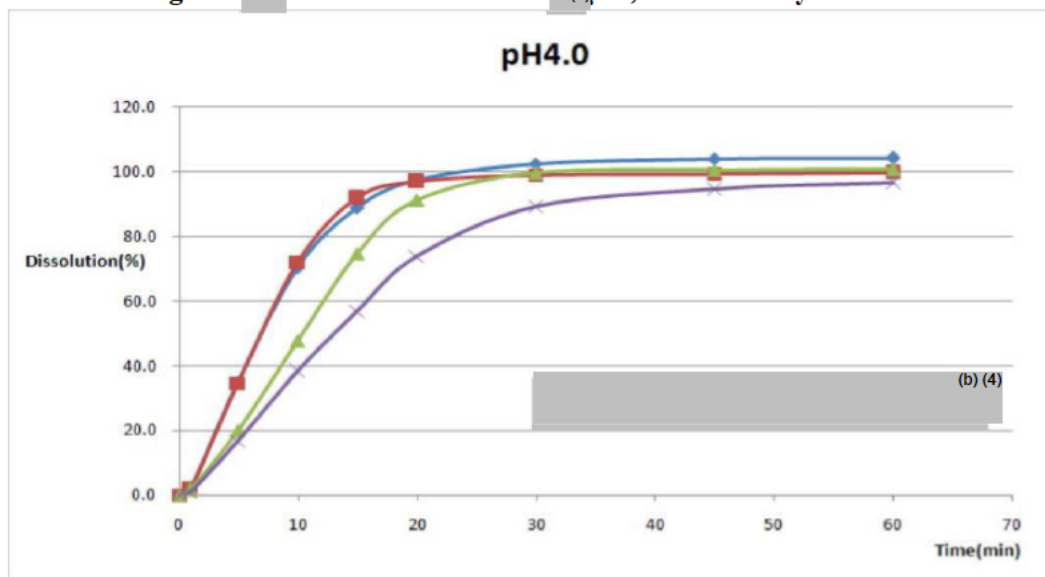


Table 6. Effects of (b) (4) on dissolution for Aripiprazole OSF 10 mg using the proposed dissolution method

Sample	(b) (4)	Results: % Drug Release (% CV)							
		1 min	5 min	10 min	15 min	20 min	30 min	45 min	60 min
Tech#1-1		1.1 (20.9)	21.3 (18.9)	40.4 (18.5)	59.1 (15.2)	71.7 (11.0)	84.3 (3.6)	90.2 (1.0)	92.6 (0.7)
Tech#1-2		1.8 (49.4)	26.6 (49.8)	47.1 (28.9)	61.0 (25.9)	76.2 (11.2)	87.3 (3.0)	92.9 (2.0)	95.3 (1.7)
Tech#1-3		1.6 (13.1)	21.2 (24.5)	42.9 (19.5)	64.4 (12.1)	77.9 (7.8)	87.3 (5.5)	91.1 (4.6)	94.3 (5.5)
Tech#1-4		2.2 (11.8)	24.1 (14.9)	54.4 (8.7)	76.6 (3.8)	89.6 (1.3)	98.8 (1.2)	100.7 (1.0)	100.7 (1.1)

Table 7. Effects of (b) (4) on dissolution for Aripiprazole OSF 10 mg using the proposed dissolution method

Sample	(b) (4)	Results: % Drug Release (%CV)							
		1 min	5 min	10 min	15 min	20 min	30 min	45 min	60 min
ARF1401-1		1.6 (16.3)	38.7 (19.0)	66.2 (7.8)	82.0 (3.6)	92.2 (2.3)	98.5 (1.5)	101.7 (0.2)	103.3 (0.4)
ARF1401-2		5.5 (31.8)	39.2 (20.7)	69.9 (8.4)	84.6 (2.6)	94.1 (1.8)	99.3 (1.1)	102.2 (0.2)	104.0 (0.3)
ARF1401-3		2.2 (14.5)	33.7 (20.1)	62.0 (16.2)	79.9 (10.1)	92.0 (5.4)	98.1 (3.8)	100.9 (1.7)	102.4 (2.0)

3.4 Dissolution profile data for Aripiprazole OSF using the proposed dissolution method:

The dissolution profile data for Aripiprazole OSF using the proposed QC method were provided in the following Tables (data provided in <\\cdsesub1\evsprod\nda211448\0001\m3\32-body-data\32p-drug-prod\aripiprazole-film\32p2-pharm-dev\rpt-disso-devt-new-method.pdf>). The clinical batch of Aripiprazole OSF, ^{(b) (4)} mg (401455) was 12 to 14 months old at the time of relative bioavailability studies (Studies 140051 and 140052). These bio-batches and registration batches (batches #: 401452, 401455 and 401472 for PV1, 401451, 401454 and 401471 for PV2, 401681, 401682 and 401683 for PV3) were manufactured at November 2014 or February 2015. There are more than ^{(b) (4)}% dissolution in 10 minutes for all batches (Tables 8-10).

Table 8. Dissolution profile data (n=12) for Aripiprazole OSF, PV1 batch (batches 401452, 401455, 401472 for 5 mg, 10 mg, and 15 mg strengths, respectively. PV1 batch contains predominantly ^{(b) (4)} API form) using the proposed dissolution method

Media		pH4.0		Test method		Apparatus 5		Rpm		50 rpm	
Volume		900mL		Temp		37±0.5℃		N		12	
Lot		401452									
Time		5 Min	10 Min	15 Min	30 Min	45 Min	60 Min	90 Min	120 Min		
	Ave	77.9	94.3	97.6	100.3	100.9	100.7	100.9	100.9		
	SD	7.0	2.9	2.2	1.5	1.6	1.5	1.7	1.8		
	RSD	9.0	3.1	2.2	1.5	1.6	1.5	1.7	1.8		
Lot		401455									
Time		5 Min	10 Min	15 Min	30 Min	45 Min	60 Min	90 Min	120 Min		
	Ave	65.7	87.7	93.9	98.5	99.4	100.1	100.8	100.7		
	SD	4.2	2.8	1.9	1.3	1.3	1.3	1.3	1.1		
	RSD	6.4	3.2	2.0	1.3	1.3	1.3	1.3	1.1		
Lot		401472									
Time		5 Min	10 Min	15 Min	30 Min	45 Min	60 Min	90 Min	120 Min		
	Ave	65.5	87.1	93.1	97.6	98.6	98.9	99.6	100.1		
	SD	2.9	2.0	1.4	1.1	1.2	1.1	1.0	1.0		
	RSD	4.4	2.3	1.5	1.1	1.2	1.1	1.0	1.0		

Table 9. Dissolution profile data (n=12) for Aripiprazole OSF, PV2, PV3 batches (PV2 and PV3 batches mainly contain (b) (4) API form) using the proposed dissolution method

Lot No.	5 Min	10 Min	15 Min	30 Min	45 Min	60 Min	90 Min	120 Min
PV2	401451 5mg	(b) (4)						
	401454 10mg							
	401471 15mg							
	401681 5mg							
PV3	401682 10mg							
	401683 15mg							

Table 10. Dissolution profile data (n=12) for Aripiprazole OSF, PV1, PV2, PV3 batches before and after stress test (70 °C, 85% RH, 4 weeks) using the proposed dissolution method

PH 4.0	5 min	10 min	15min	30 min	45 min	60 min	f ₂ value
PV1 10mg (401455), n=3	89.2	94.5	98.1	102.6	104.4	105.5	
PV1 10mg (401455)_ stress 70°C, 85%RH, 4 W. n=3	85.8	92.5	95.8	99.9	101.7	102.4	76.8
PH 4.0	5 min	10 min	15min	30 min	45 min	60 min	f ₂ value
PV2 10mg (401454), n=3	88.6	98.7	102.6	104.3	105.6	108.3	
PV2 10mg (401454)_ stress 70°C, 85%RH, 4 W. n=3	63.3	90.7	98.8	107.4	106.7	108.7	47.8
PH 4.0	5 min	10 min	15min	30 min	45 min	60 min	
PV3 10mg (401682), n=3	92.2	100.2	95.3	94.7	95.1	95.0	
PV3 10mg (401682)_ stress 70°C, 85%RH, 4 W. n=3	64.3	94.5	93.0	96.0	95.3	95.2	46.6

Reviewer's Conclusion: The discriminating ability of the dissolution method for Aripiprazole OSF was demonstrated in the changes in film thickness and the levels of HPMC. The dissolution profile data obtained from Aripiprazole OSF batches containing (b) (4) or (b) (4) API forms were rapid and similar with more than (b) (4) % dissolution in (b) (4) minutes. In view of the demonstrated discriminating ability and obtained dissolution profile data, the proposed dissolution method [USP apparatus 5 (paddle over disk, disk size 56 mm, 40 mesh) at 50 rpm, in 900 mL of pH 4.0 acetate buffer at 37 °C] is acceptable as a quality control method for batch release and stability testing of Aripiprazole OSF, 5 mg, 10 mg, and 15 mg.

3.5 Dissolution Acceptance Criterion:

Based primarily on the provided dissolution data of biobatch and registration batches, this Reviewer considered that the Applicant's originally proposed dissolution acceptance criterion of "Q = (b) (4) % at (b) (4) minutes" was permissive and not acceptable. In the Information Request dated 06/25/2020, the Applicant was recommended to revise the dissolution acceptance criterion. In the Response dated 06/30/2020, the Applicant revised the dissolution acceptance criterion to "Q = (b) (4) at 15 minutes".

3.6 Dissolution Stability Data:

The Applicant provided dissolution data at (b) (4) minutes (n=6) for stability samples of the clinical batches and registration batches (batches: 401452, 401451, and 401681 for (b) (4) mg strength, 401455, 401454, and 401682 for (b) (4) mg strength, 401472, 401471, and 401683 for (b) (4) mg strength) stored under two long-term conditions (25 °C/60% RH and 30 °C/75% RH) for 36 months and accelerated conditions (40 °C/75% RH) for 6 months. The stability data show that all registration batches passed the proposed dissolution acceptance criterion of "Q = (b) (4) % at (b) (4) minutes" at S1 and no decrease were observed for dissolution data on stability. No dissolution stability data at 15 minutes were provided. In the Response dated 06/29/2020, the Applicant reported that the tested long-term stability samples complied with the agreed-upon dissolution acceptance criterion of "Q = (b) (4) % at 15 minutes" over the proposed shelf-life. The Applicant proposed a shelf-life of 36 months for the proposed Aripiprazole OSF, 5 mg, 10 mg, and 15 mg. The assigned Drug Product Reviewer will determine the shelf life for the proposed drug product.

4. DISINTEGRATION TIME:

The Applicant also proposed a disintegration time (NMT (b) (4)) for the quality control of Aripiprazole OSF. The assigned Drug Product Reviewer will determine the adequacy of the proposal.

5. BIOWAIVER REQUEST FOR 5 MG AND 15 MG STRENGTHS:

The Applicant requested a waiver of an in vivo bioavailability study for Aripiprazole OSF, 5 mg and 15 mg, per CFR 320.22(d)(2).

This Reviewer considered the biowaiver request for 5 mg and 15 mg strengths acceptable and supported by the following information:

- (1) Data of an acceptable bioequivalence study on Aripiprazole OSF, 10 mg (Study 140052);
- (2) All the strengths are of the same immediate-release dosage form and have the same release mechanism and manufacturing process;
- (3) All the strengths are compositionally proportional in the active and inactive ingredients;
- (4) Aripiprazole linear pharmacokinetics across the dose range of 5 mg to 30 mg (refer to product labeling);
- (5) Similar comparative in vitro dissolution profiles across Aripiprazole OSF different strengths in pH 1.2 (more than (b) (4) % aripiprazole dissolution in 5 minutes for all strengths), pH 4 (more than (b) (4) aripiprazole dissolution in 15 minutes for all strengths), and pH 6.8 (less than (b) (4) aripiprazole dissolution in 120 minutes for all strengths) (all data provided in <\\cdsesub1\evsprod\nda211448\0001\m2\27-clin-sum\rpt-disso-profiles-biowaiver.pdf>) (Tables b, c, and d in Appendix 1).

Reviewer's Assessment: As per 21 CFR 320.22(d)(2), FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of the drug product, if the drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product. The overall information/data supporting the biowaiver for Aripiprazole OSF, 5 mg and 15 mg is adequate and acceptable. Therefore, the Applicant's biowaiver request for Aripiprazole OSF, 5 mg and 15 mg is granted.

Appendix 1 Additional dissolution data

Table a. Dissolution conditions tested (submitted in the Response dated 05/29/2020)

Method Number	Temperature	pH	RPM	Test Method	Volume	Vessels	Time Points (min)
1	37 °C	(b) (4) 4.0	50	(b) (4)	900 mL	N=6	(b) (4)
2	(b) (4)	4.0	50				15, (b) (4)
3		4.0	50				(b) (4)
4	37 °C	(b) (4)	50				
5	37 °C	(b) (4)	50				
6	37 °C		50				
7	37 °C	(b) (4) 4.0					
8	37 °C	4.0	50	(b) (4)			
9	37 °C	4.0		(b) (4)			
10	37 °C	(b) (4)	50				
11	37 °C	(b) (4) 4.0	50		(b) (4)		
(b) (4)							
(b) (4)							

Table b. Comparative dissolution profile data (n=12) for Aripiprazole OSF, 5 mg, 10 mg, and 15 mg in pH (b) (4) medium (dissolution method: USP 5 (paddle over disk) at 50 rpm, in 900 mL pH (b) (4) medium)

5 mg								
Time		10min	15min	30min	45min	60min	90min	120min
Mean	95.6	96.1	96.5	97.0	96.2	96.2	96.8	96.4
SD	8.2	4.1	4.1	1.5	1.0	0.8	0.9	0.8
RSD	8.5	4.3	2.3	1.5	1.0	0.9	1.0	0.8
10 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	90.8	94.4	97.1	99.4	99.4	99.3	99.3	99.6
SD	9.3	6.6	3.4	0.8	0.9	0.6	0.4	0.7
RSD	10.2	7.0	3.5	0.8	0.9	0.6	0.4	0.7
15 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	95.0	97.7	98.8	99.5	99.3	99.2	99.5	99.4
SD	6.3	3.5	2.0	0.6	0.4	0.5	0.6	0.5
RSD	6.6	3.6	2.0	0.6	0.4	0.5	0.6	0.5

Table c. Comparative dissolution profile data (n=12) for Aripiprazole OSF, 5 mg, 10 mg, and 15 mg in pH 4.0 medium (dissolution method: USP 5 (paddle over disk) at 50 rpm, in 900 mL pH 4.0 medium)

5 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	78.0	94.3	97.6	100.4	100.9	100.8	101.0	100.9
SD	7.0	2.9	2.2	1.5	1.6	1.5	1.7	1.8
RSD	9.0	3.1	2.2	1.5	1.6	1.5	1.7	1.8
10 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	65.7	87.7	93.9	98.5	99.4	99.6	100.7	100.7
SD	4.2	2.8	1.9	1.3	1.3	2.5	1.3	1.1
RSD	6.4	3.2	2.0	1.3	1.3	2.5	1.3	1.1
15 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	65.5	87.1	93.1	97.6	98.6	98.9	99.6	100.1
SD	2.9	2.0	1.4	1.1	1.2	1.1	1.0	1.0
RSD	4.4	2.3	1.5	1.1	1.2	1.1	1.0	1.0

Table d. Comparative dissolution profile data (n=12) for Aripiprazole OSF, 5 mg, 10 mg, and 15 mg in pH ^{(b) (4)} medium (dissolution method: USP 5 (paddle over disk) at 50 rpm, in 900 mL pH ^{(b) (4)} medium)

5 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	4.8	3.5	3.8	3.5	4.4	4.3	4.5	2.7
SD	3.4	0.6	0.6	1.0	1.7	1.3	1.5	0.4
RSD	69.9	15.9	15.1	28.3	37.5	30.8	33.2	14.9
10 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	4.3	3.4	4.1	3.4	2.3	2.3	4.0	2.7
SD	2.7	0.5	2.2	0.2	0.2	0.3	0.3	0.3
RSD	63.2	15.9	52.0	7.0	11.0	12.4	8.0	11.6
15 mg								
Time	5min	10min	15min	30min	45min	60min	90min	120min
Mean	2.4	2.6	2.9	2.6	2.7	2.1	2.1	2.3
SD	0.5	0.2	0.2	0.1	0.3	0.1	0.1	0.2
RSD	21.4	7.5	7.5	5.1	10.3	6.0	6.8	8.3



Yang
Zhao

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