CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219016Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	219016
Applicant Name	Janssen Products LP
Drug Product Name	EDURANT PED (rilpivirine) tablets, for oral suspension
Dosage Form.	Tablet, for suspension
Proposed Strength(s)	2.5 mg
Route of Administration	Oral
Maximum Daily Dose	15 mg
Rx/OTC Dispensed	Rx
Proposed Indication	In combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in treatment-naïve patients 2 years of age and older and weighing at least 14 kg with HIV-1 RNA less than or equal to 100,000 copies/mL. The EDURANT PED tablets for oral suspension should only be given to pediatric patients weighing at least 14 kg to less than 25 kg.
Drug Product Description	The tablets are white to almost white, round 6.5 mm, and debossed with “TMC” on one side and “PED” on the other side. The formulation is an immediate release tablet for oral suspension, containing 2.75 mg rilpivirine hydrochloride, equivalent to 2.5 mg of rilpivirine free base. The tablets need to be dispersed in water prior to oral administration and should not be chewed or swallowed whole. Following dispersion, the oral suspension can be further diluted in water, milk, orange juice or applesauce to aid in administration. The drug product is packaged in a cold form film blister with integrated desiccant and an aluminum peelable lidding foil. Each blister contains 10 tablets with 9 blisters per carton.
Co-packaged product information	N/A
Device information:	N/A

Storage Temperature/ Conditions	20º to 25ºC (68º to 77ºC) with excursions permitted to 15º to 30ºC (59º to 86ºC)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Daniel Chan	Katherine Windsor
	Drug Product/ Labeling	Akshata Nevrekar	David Claffey/Molly Lee
	Manufacturing	Naveen Kanthamneni	Hang Guo
	Biopharmaceutics	Hardikkumar Patel	Elsbeth Chikhale
	Microbiology	N/A	
	Other (specify):	N/A	
	RBPM	Omolara Oyinlola-Adeyemi	
	ATL	Molly Lee	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 24 months at 20° to 25°C (68° to 77°F)

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The NDA was submitted in accordance with the required pediatric study requirements for rilpivirine tablets (NDA 202022) to introduce an age-appropriate formulation (tablet for oral suspension) for the treatment of pediatric patients with HIV.

The Applicant cross-referenced the CMC information for rilpivirine hydrochloride drug substance to DMF (b) (4) which was previously found adequate to support NDA 202022. Adequate drug substance information was provided in either the NDA 219016 or Rilpivirine hydrochloride DMF # (b) (4)

The drug product is an immediate release tablet for oral suspension that needs to be dispersed in water prior to oral administration. The Applicant provided adequate drug product and biopharmaceutics information to ensure the identity, purity, and strength of the registration batches and support the proposed commercial drug product and 24-month shelf-life. The proposed labeling and container labels include adequate information to meet the regulatory requirements and include detailed instructions in the PI and IFU on the administration instructions for the tablet dispersion and further dilution.

The method of manufacture proposed is a [redacted] (b) (4) This product uses the same [redacted] (b) (4) as the approved EDURANT 25 mg film-coated tablets. The overall manufacturing process was found to be adequate. The drug substance manufacturing facility has manufacturing experience with proposed drug substance, and the drug product facility has experience with manufacturing solid dosage forms. The manufacturing inspection recommendation is approval for all facilities associated with this application.

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

Recommendation by Subdiscipline:

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

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments: N/A

Molly Lee

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CHAPTER III: ENVIRONMENTAL

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

R REGIONAL INFORMATION

Environmental

Assessment: *{Adequate}*

Edurant (Rilpivirine) is currently approved in the US for use in combination with other antiretroviral agents (ARVs) in the treatment of human immunodeficiency virus type 1 (HIV-1) in adults.

In the current application, the applicant is requesting a lowers strength formulation of rilpivirine for use in pediatric HIV patients (≥2 to <12 years).

Under 21CFR 25.31(b) a categorical exclusion exists for: "Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion."

A conservative calculation of the expected introduction concentration (EIC) of the active moiety rilpivirine in the United States using estimated peak use of the active substance to support all uses in the United States is (b) (4) µg/L. The EIC based on the highest quantity of active substance is < 1 ppb, therefore the sNDA meets the criterion for a categorical exclusion pursuant to 21 CFR 25.31(b).

Janssen Research & Development further submits a statement of no knowledge of extraordinary circumstances that might significantly affect the quality of the human environment, per 21 CFR 25.15(a).

Categorical exclusion as per 21CFR 25.31 has been granted based on the justification (above) provided by the applicant.

Primary Environmental Assessor Name and Date: Akshata Nevrekar; 12/11/2023

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

Akshata Nevrekar

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Molly Lee

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CHAPTER IV: LABELING[1]

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The information submitted in the PI, carton label and container label are adequate from quality perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	EDURANT® PED	Adequate
Established name(s)	(rilpivirine) tablets, for oral suspension	Adequate
Route(s) of administration	oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	2.5 mg tablets for oral suspension	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not Scored tablet
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	Not for injectable/Parenteral use

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		

APPEARS THIS WAY ON ORIGINAL

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)	EDURANT PED must be **dispersed in water** and taken immediately with a meal. The patient should not chew or swallow EDURANT PED whole. To aid with administration, the dispersed mixture can be further diluted with the following beverages or soft food: water, milk, orange juice or applesauce. Place the tablets in a cup, add 5 mL (1 teaspoon) of water at room temperature. Do not crush the tablets. Swirl the cup carefully to disperse the tablets. The oral suspension will start to look cloudy. Take all the prepared oral suspension immediately to aid in administration, the oral suspension can be further diluted with 5 mL (1 teaspoon) of water, milk, orange juice or applesauce. Swirl and take all the medicine immediately. A spoon can be used if needed. Make sure the entire dose is taken and no medicine is left in the cup, if required add another 5 mL (1 teaspoon) of water or	Note: EDURANT PED 2.5 mg tablets for oral suspension should only be given to pediatric patients weighing at least (b) (4) kg and less than 25 kg.: Dosage of EDURANT PED, is based on body weight. Maximal daily dose for Edurant PED: 15 mg q.d. (six 2.5 mg tablets for oral suspension) The applicant has submitted compatibility data and in-use stability data (2h) for the drug product dispersed in water + apple sauce, orange juice, milk and sparkling water. Refer drug product review for further information. As per dosing directions, no in-use time is proposed. The dispersed tablet needs to be consumed immediately upon preparation. The carton includes directions such as **1. Disperse in liquid** 2. Do not chew 3. Do not swallow whole As a part of DMEPA comments sent to the applicant, The applicant was asked to revise the cautionary warning statement box on the carton label as follows: 1. DISPERSE IN WATER 2. Do not crush, chew, or swallow whole. This is adequate and in line with instructions in the PI.

	same beverage (milk, orange juice) or applesauce, swirl and drink immediately. **The patient must take the dose of medicine immediately. If not taken immediately, then the mixture should be discarded, and a new dose of medicine should be prepared**	

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)	Tablets for Oral Suspension	Adequate
Strength(s) in metric system	2.5 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Each tablet for oral suspension contains 2.75 mg rilpivirine hydrochloride equivalent to 2.5 mg rilpivirine.	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	2.5 mg white to almost white, round 6.5 mm tablet, debossed with "TMC" on one side and "PED" on the other side.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	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)	EDURANT PED	Adequate
Dosage form(s) and route(s) of administration	tablets for oral suspension	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Each tablet for oral suspension contains rilpivirine hydrochloride equivalent to 2.5 mg rilpivirine.	**Adequate** **As per internal discussion, 2.75 mg rilpivirine hydrochloride does not need to be specified.**
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	inactive ingredients croscarmellose sodium, lactose monohydrate, mannitol, microcrystalline cellulose, polysorbate 20, povidone K30, sodium lauryl sulfate and sodium stearyl fumarate.	All names are as per USP/NF
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	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1)	Adequate

Chemical name, structural formula, molecular weight	The chemical name for rilpivirine hydrochloride is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride. Its molecular formula is C22H18N6 • HCl and its molecular weight is 402.88.	Adequate in line with information submitted in section 3.2.S.1
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	Rilpivirine hydrochloride is practically insoluble in water over a wide pH range.	Adequate in line with information submitted in section 3.2.S.1

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	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	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)	tablets for oral suspension	Adequate
Strength(s) in metric system	2.5 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Packaged in aluminum cold form film blister with integrated desiccant and an aluminum peelable lidding foil. Each blister contains 10 tablets with 9 blisters per carton.	Adequate in line with information submitted in section 3.2.P.7
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to almost white, round 6.5 mm tablets, debossed with "TMC" on one side and "PED" on the other side. (NDC 59676-280-90)	Adequate in line with information submitted in section 3.2.P.1
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	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.)	Store EDURANT PED tablets for oral suspension in original package in order to protect from moisture.	Adequate
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.”	integrated desiccant in packaging	Adequate in line with information submitted in section 3.2.P.7.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°-25°C (68°-77°F); with excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature]	Adequate in line with information submitted in section 3.2.P.8
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	N/A
Include information about child-resistant packaging	-	As per information printed on Carton. This package is child resistant. Carton label states keep out of reach of children.

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	Janssen Products, LP Horsham, PA 19044, USA	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):
Information submitted in the PI is adequate for the drug product Edurant® PED, 2.5 mg, tablets for oral suspension.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."
None

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Edurant® PED Rilpivirine tablets for oral suspension	Adequate
Dosage strength	2.5 mg	Adequate
Route of administration	Tablets for oral suspension	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each tablet contains 2.75 mg of rilpivirine hydrochloride which is equivalent to 2.5 mg of rilpivirine	Adequate
Net contents (e.g. tablet count)	90 Tablets 9 blister cards, 10 tablets each	Adequate
"Rx only" displayed on the principal display	yes	Adequate
NDC number	NDC 59676-280-90	Adequate
Lot number and expiration date	yes	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature 20°-25°C (68°-77°F); with excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature. Store in original package in order to protect from moisture	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	Disperse in Liquid Do not chew Do not swallow whole	Adequate **Comment:** **Disperse in liquid** **Do not crush** As a part of DMEPA comments sent to the applicant, The applicant was asked to revise the cautionary warning statement box on the carton label as follows: 1. DISPERSE IN WATER 2. Do not crush, chew, or swallow whole. This is adequate and in line with instructions in the PI.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	yes	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for Janssen Products, LP Horsham, PA 19044, USA (b) (4)	Adequate
Medication Guide (if applicable)		
No text on Ferrule and Cap overseal	N/A	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	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: ***Adequate***

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

None

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Akshata Nevrekar; 01/19/2024

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

Akshata Nevrekar

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David Claffey

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CHAPTER VI: BIOPHARMACEUTICS

Application type	505(b)(1)
NDA Number	219016
Assessment Cycle Number	1
Drug Product Name/ Strength	Rilpivirine hydrochloride tablets for oral suspension, 2.5 mg
Route of Administration	Oral
Applicant Name	Janssen Products LP
Therapeutic Classification/ OND Division	OND/OID/DAV
Cross reference	NDA 202022
Proposed Indication	HIV-1 in pediatric patients

Assessment Recommendation: **Adequate**

Background: Janssen Products LP is seeking approval for Rilpivirine hydrochloride tablets for oral suspension, 2.5 mg under section 505(b)(1) for the treatment of HIV-1 in pediatric patients. The Applicant originally submitted the application as a supplement to their already approved NDA for Rilpivirine tablets, 25 mg (EDURANT®, NDA 202022) for adult patients. However, they were advised to submit a standalone NDA to support the new dosage form (tablet for oral suspension). Therefore, the Applicant submitted this NDA 219016 for Rilpivirine hydrochloride tablets for oral suspension, 2.5 mg.

Assessment Summary:
The drug substance, Rilpivirine hydrochloride has low aqueous solubility. The highest solubility (0.003 g/100 mL) for the drug substance is obtained in 0.01M HCl where sink conditions (0.001 g/100 mL) are met for the 2.5 mg tablet strength.
The Applicant provided a dissolution method development report to justify the proposed dissolution parameters and acceptance criterion for the drug product.

Proposed and acceptable dissolution method and acceptance criterion

USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion
II (Paddle)	60 rpm	0.025% polysorbate in 0.01 N HCl	900 mL/ 37.0 ± 0.5 °C	Q=(b) (4)% in 30 minutes

The dissolution method has been demonstrated to have discriminating ability towards changes in critical bioavailability attributes (CBAs) like particle size of the drug substance, particle size of (b) (4) used to manufacture the tablet, change in (b) (4) and (b) (4) levels. The Applicant proposed a dissolution specification of NLT %(Q) in 30 minutes. Based on individual dissolution data from the clinical batches and considering the drug product risk and PK information, the proposed dissolution acceptance criterion is acceptable.

The proposed commercial drug product is qualitatively and quantitatively identical to the drug product used for clinical studies but are differentiated through use of debossing; clinical tablets are plain, while the commercial tablets are debossed. In addition, drug product manufacturing site for clinical batches (b) (4)) and commercial batches ((b) (4) are different as per the batch analysis reports. The dissolution profiles for the clinical and commercial drug product batches using the proposed dissolution method are comparable. Comparative dissolution data between clinical and commercial drug product is sufficient to support the bridging.

Risk Assessment for dissolution:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking	Comments
Particle size of API	Medium	Rilpivirine HCl is a low solubility API, particle size is considered a CQA for the dissolution	Low	The proposed dissolution method shows sensitivity to changes in particle size of API in the drug product

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
New NDA	09/15/23
CMC IR response	11/08/23
Biopharm IR response	11/29/23
CMC IR response	12/01/23
Biopharm IR response	12/15/23

Highlight Key Issues from Last Cycle and Their Resolution: Not applicable, this is the first review cycle.

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*: Not applicable.

B.1 BCS DESIGNATION

Assessment: There is no official BCS designation request for the proposed drug product.

Solubility: Rilpivirine hydrochloride has low aqueous solubility as shown in Table 1 (Pg 8 of 43).

Table 1: Drug Substance Solubility in Aqueous Media of Different pH at 37 °C

Medium	Solubility (g/100 mL)	pH of Solution
Water	0.001	2.2
0.1M HCl	<0.001	1.1
0.01M HCl	0.003	2.0
Citrate-HCl buffer pH 2	<0.001	2.0
Citrate-NaOH buffer pH 5	<0.001	5.0
Phosphate buffer pH 7	<0.001	6.9
Borate-KCl-NaOH buffer pH 9	<0.001	8.9
Phosphate-NaOH buffer pH 12	<0.001	11.9
0.1M NaOH	<0.001	12.9

Permeability: The drug substance permeability data is not provided.

Dissolution: See Section B.2.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

The proposed dissolution method uses USP 2 apparatus at 60 rpm in 900 mL of 0.025% Polysorbate 20 (Tween 20) in 0.01N HCl at 37 °C.

(b) (4)

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(b) (4)

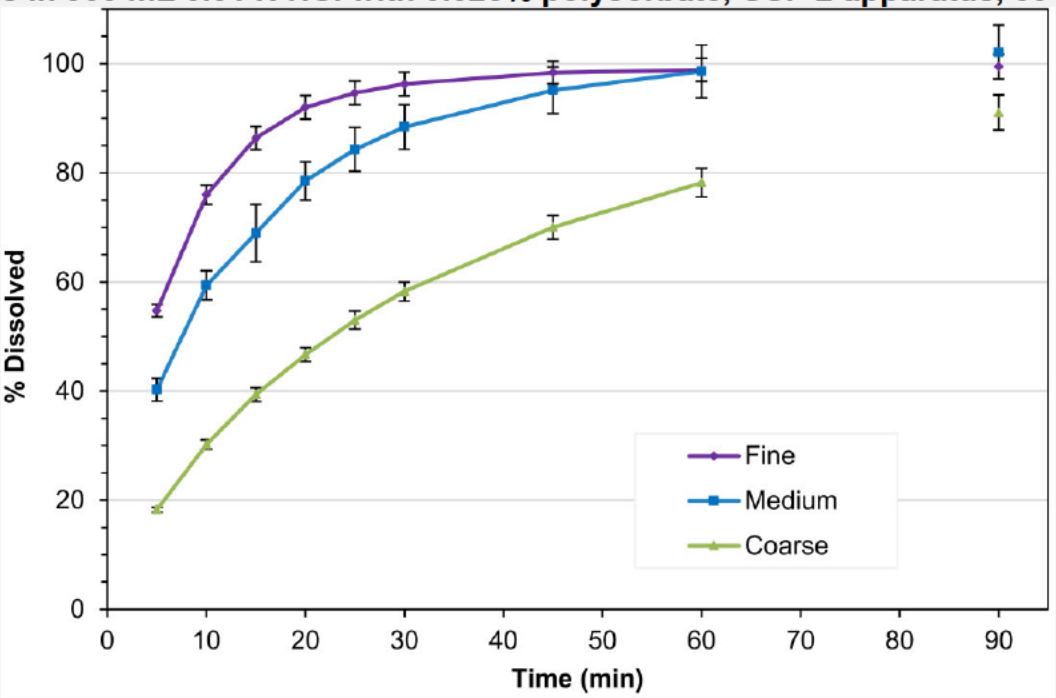
Discriminating ability: The Applicant has identified various Critical Bioavailability Attributes (CBAs: particle size, (b) (4) composition change, and process parameters) to evaluate dissolution method sensitivity towards them.

1) **Particle size:** The drug product batches with different drug substance particle size distributions were tested using the proposed dissolution method.

Batches Used to Demonstrate Discriminating Capability for Drug Substance Particle Size

DP Batch	DS Batch	Label	Particle Size (µm)	
			d_v50	d_v90
4437846	A20EC1399	Fine	(b) (4)	
4384766	A20IC2495	Medium		
4384801	I20IC3080	Coarse		

Figure 4: Dissolution profiles of batches with different drug substance particle sizes in 900 mL 0.01 N HCl with 0.025% polysorbate, USP 2 apparatus, 60 rpm

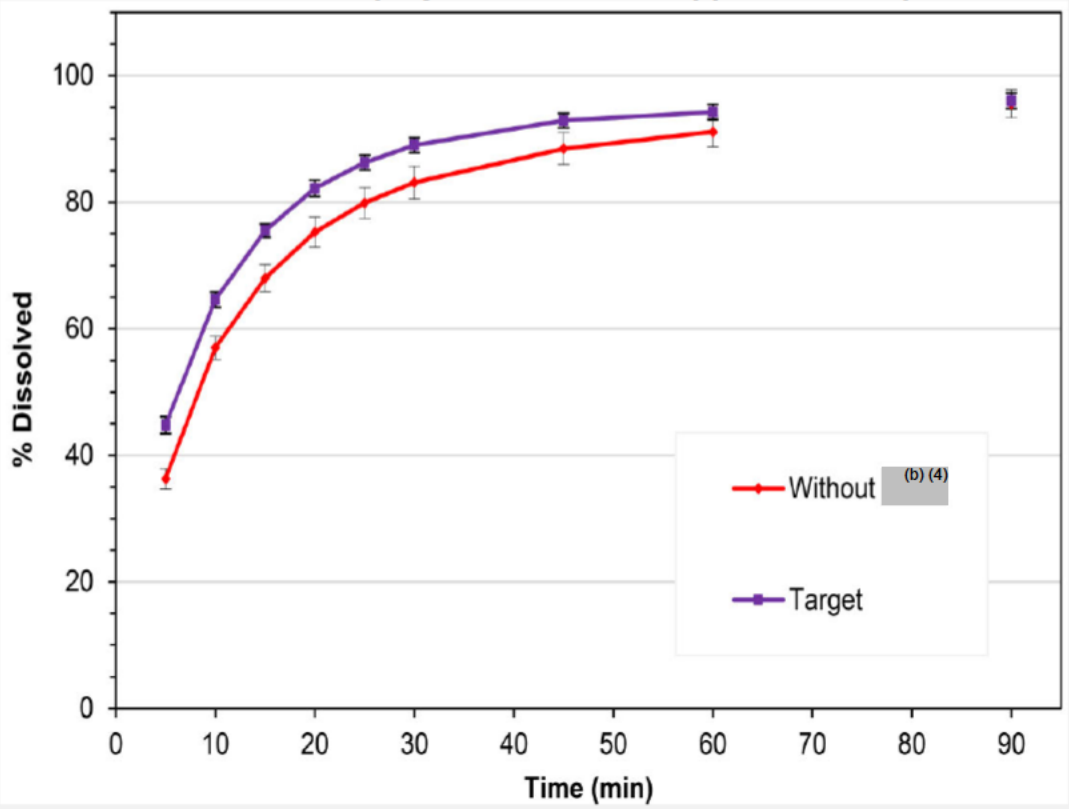


The dissolution profiles of the drug product batches produced with a medium and coarser drug substance particle size distribution are slower than the dissolution profile of the drug product batch produced with fine drug substance. Particle size for fine drug substance complies with the proposed PSD for the API (d50: NMT (b) (4) µ and d90: NMT (b) (4) µ, 3.2.S.4.1). Whereas particle size for medium drug substance is slightly above the acceptance criterion for d90. The proposed dissolution method demonstrates sensitivity against changes in API particle size, however, the proposed dissolution acceptance criterion will not reject the drug product batch containing medium size drug substance.

2) **Formulation change:**

A) **(b) (4) levels:** The drug product contains (b) (4)% w/w (b) (4)mg) (b) (4) in the proposed formulation as a (b) (4) The dissolution of drug product batches with and without (b) (4) in the formulation was tested using the proposed dissolution method.

Figure 5: Dissolution profiles of batches with and without (b) (4) in 900 mL 0.01 N HCl with 0.025% polysorbate, USP 2 apparatus, 60 rpm



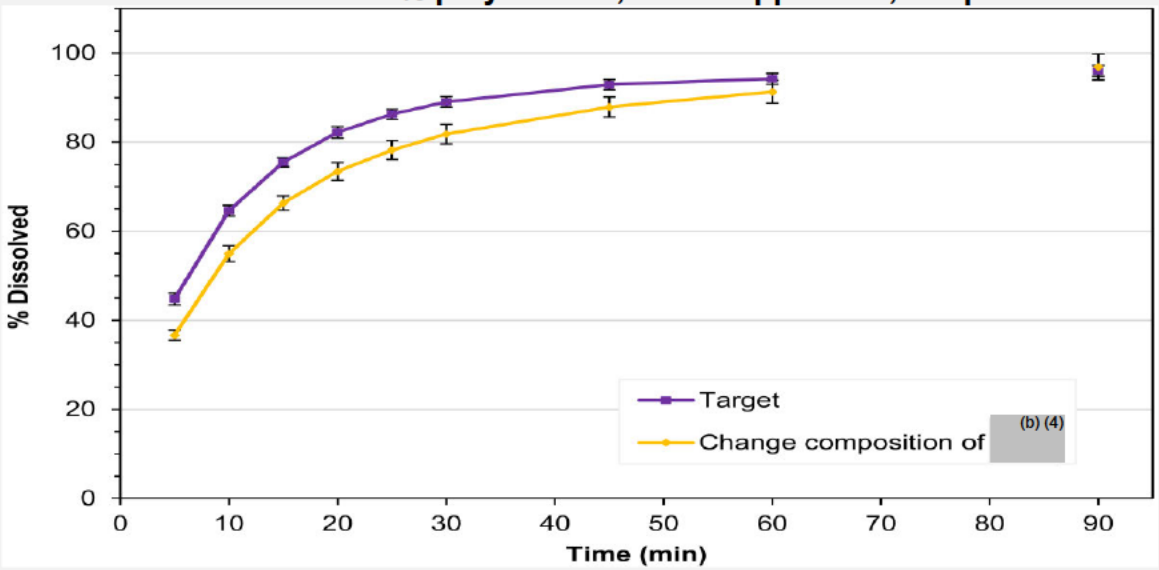
The dissolution profile of the drug product batch without (b) (4) showed a slightly slower dissolution profile compared to the target drug product.

B) **(b) (4) levels:** Two drug product batches with different ratios of (b) (4) were tested using the proposed dissolution method.

Batches Used to Evaluate Discriminating Capability for Drug Product with Change in (b) (4) Ratio

DP Batch	Label	Concentration (%)
C23142-9	Change in (b) (4) ratio (b) (4) (b) (4)	(b) (4)
LC57184760	Target	(b) (4)

Figure 6: Dissolution profiles of batches with different (b) (4) ratios in 900 mL 0.01 N HCl with 0.025% polysorbate, USP 2 apparatus, 60 rpm



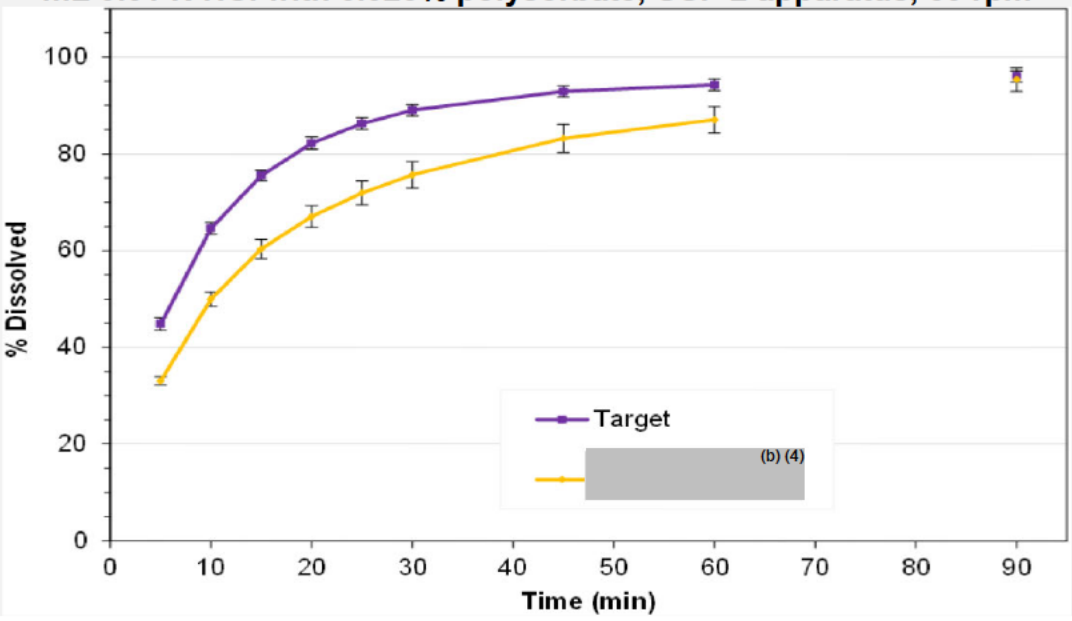
The dissolution profile of the drug product batch with a change in the (b) (4) ratio is slower as compared to the dissolution profiles of the target drug product batch.

C) (b) (4) levels: Two drug product batches with different levels of (b) (4) were tested using the proposed dissolution method.

Batches Used to Evaluate Discriminating Capability for Drug Product Change in amount of (b) (4)

DP Batch	Label	Concentration (%)
C23142-7	(b) (4)	(b) (4)
LC57184760	Target	

Figure 7: Dissolution profiles of batches with different (b) (4) levels in 900 mL 0.01 N HCl with 0.025% polysorbate, USP 2 apparatus, 60 rpm



The dissolution profile of the drug product batch with (b) (4) level is slower than the target drug product. The proposed dissolution method demonstrates sensitivity against changes in (b) (4) levels in the formulation.

3) **Process para** (b) (4) ee drug product batches with different (b) (4) (Figure 8) and (b) (4) (Figure 9) were tested using the proposed dissolution method.

Figure 8: Dissolution profiles of batches with different (b) (4) (b) (4) and (b) (4) (b) (4) in 900 mL 0.01 N HCl with 0.025% polysorbate, USP 2 apparatus, 60 rpm

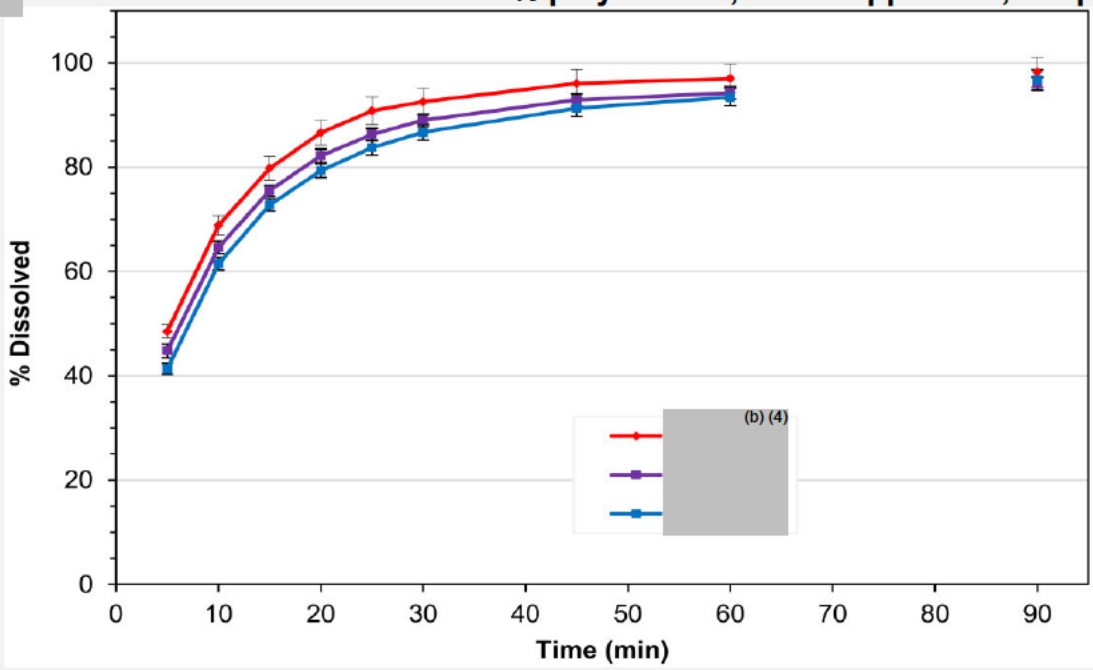
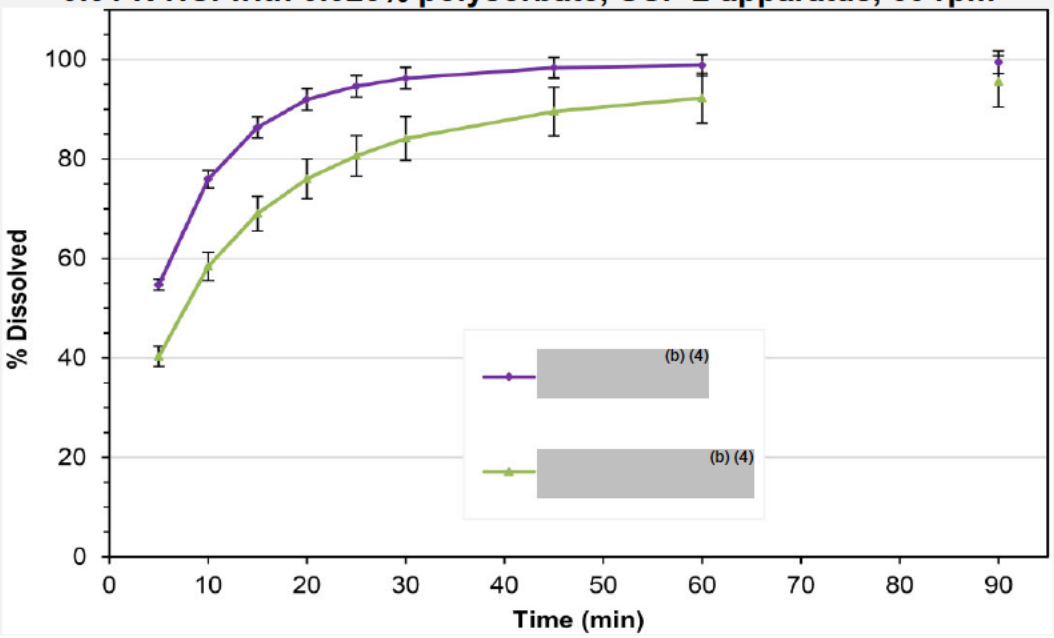


Figure 9: Dissolution profiles of batches with different (b) (4) in 900 mL 0.01 N HCl with 0.025% polysorbate, USP 2 apparatus, 60 rpm

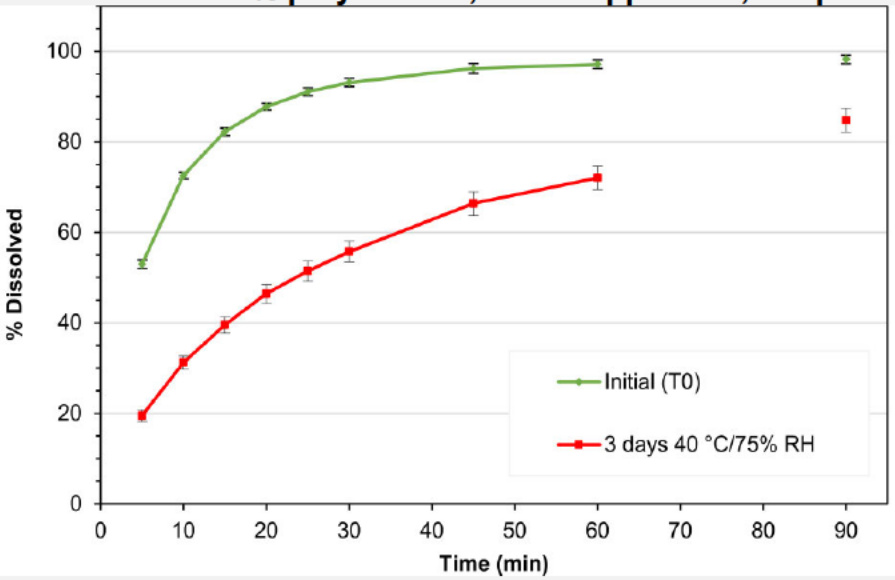


The dissolution profiles of the drug product batches with different (b) (4) were similar (Figure 8).

The dissolution profile of the drug product batch with (b) (4) is slower than the drug product with (b) (4) (Figure 9). The proposed dissolution method demonstrates sensitivity against changes in (b) (4).

4) **Drug product stability:** The drug product exposed to stability stress conditions for 3 days at 40°C/75% RH in open dish was tested using the proposed dissolution method.

Figure 10: Dissolution profiles of drug product stability samples in 900 mL 0.01 N HCl with 0.025% polysorbate, USP 2 apparatus, 60 rpm



The dissolution profile of the drug product batch stored at stress conditions is slower than the target drug product. The proposed dissolution method demonstrates sensitivity against product changes due to storage at high temperature and humidity.

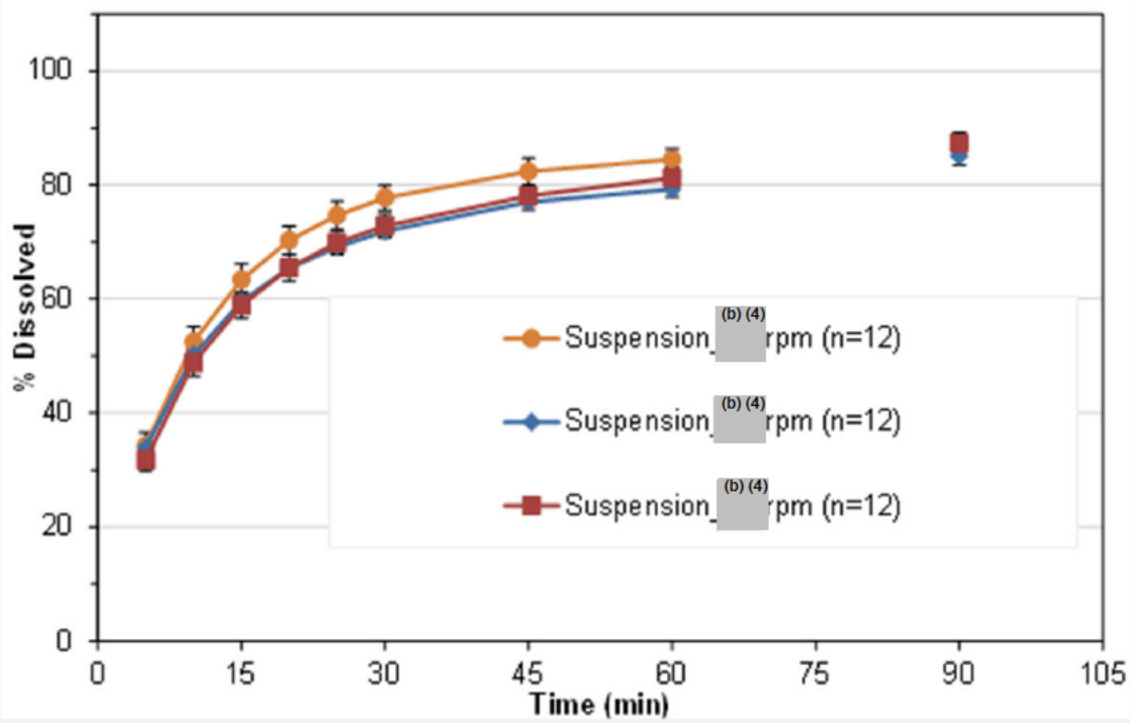
Based on the data provided, the proposed dissolution s found sensitive to the drug product CBAs like API particle size, (b) (4) levels, (b) (4) levels, and (b) (4) (b) (4)

Dosage form for the dissolution test sample

Note: The proposed drug product Rilpivirine Hydrochloride tablet for oral suspension, 2.5 mg is administered as an oral suspension. However, the Applicant is using intact tablets for the dissolution test. In general, dissolution testing should be conducted on the administered dosage form (i.e., oral suspension). Therefore, the Applicant was requested to assess the suitability of the dissolution method using oral suspension (one 2.5 mg tablet dispersed in 5 mL water, per labeling instructions) through IR sent on 10/27/23.

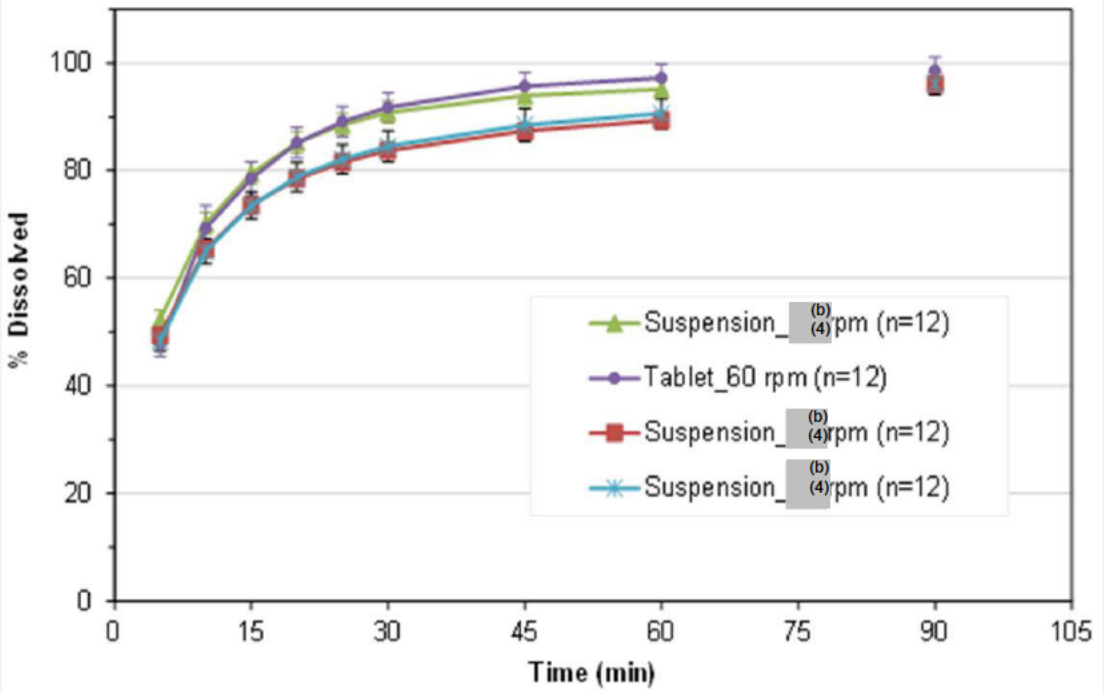
The Applicant provided the requested dissolution data using the oral suspen n in 900 mL 0.01 N HCl with and without 0.025% polysorbate at (b) (4) rpm (b) (4) rpm, and (b) (4) rpm paddle speeds.

Figure 12: Dissolution profiles of drug product samples in suspension dosage form in 900 mL 0.01 N HCl, USP 2 apparatus at different rotation speeds



Incomplete dissolution profiles were obtained for the oral suspension when the dissolution was performed in 900 mL of 0.01 N HCl without polysorbate at (b) (4) and (b) (4) rpm.

Figure 13: Dissolution profiles of drug product samples in tablet and suspension dosage forms in 900 mL 0.01 N HCl with 0.025% polysorbate, USP 2 apparatus



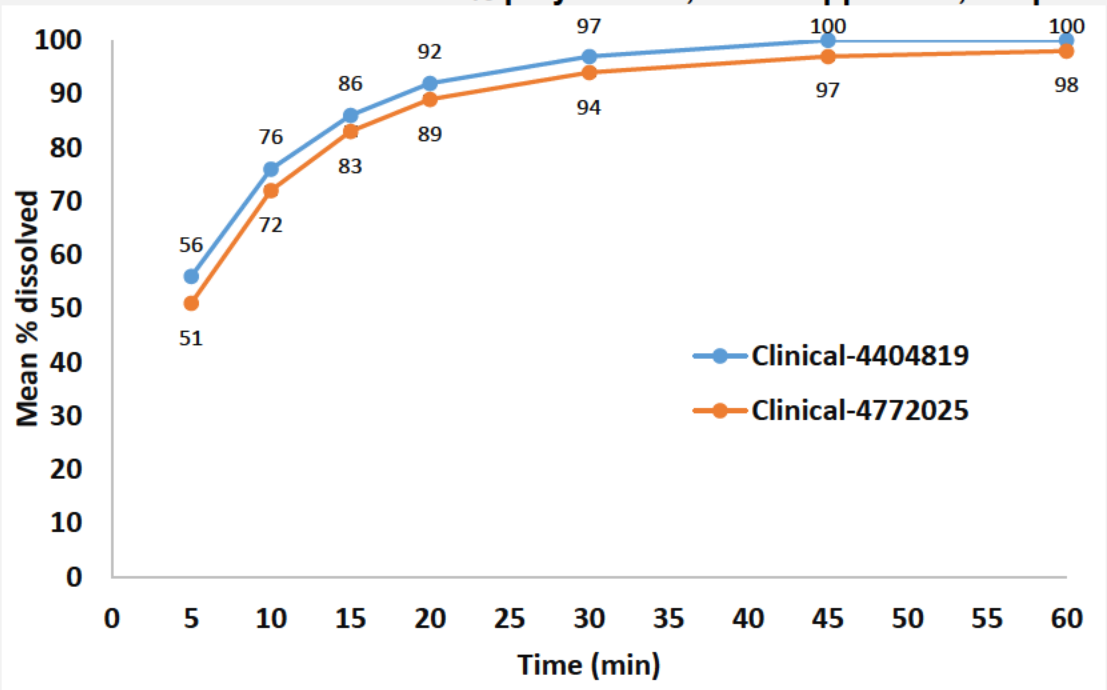
Similar dissolution profiles were obtained in 0.01N HCl containing 0.025% (w/v) polysorbate when comparing the dissolution of the oral suspension at (b) (4) pm with the dissolution of the intact tablet at 60 rpm. Coning and incomplete dissolution was observed for the oral suspension tested at (b) (4) rpm and (b) (4) rpm.

The Applicant selected to maintain the dissolution method using the intact tablets as samples because the dissolution of the intact tablets is theoretically more sensitive and discriminating than the dissolution on the oral suspension because for the oral suspension in water, the (b) (4) of the tablets takes place prior to the dissolution test. This could limit the detection of key formulation attributes which consequently may impact the discriminating capabilities of the dissolution method.

Considering the similar dissolution profiles for the tablet and the oral suspension, the proposal to use the intact tablets as samples for the dissolution testing was found acceptable.

Acceptance criterion: The Applicant has proposed a dissolution acceptance criterion of Q= (b) (4)% in 30 minutes for the drug product. Based on the dissolution data for the clinical batches and variant batches (to evaluate discriminating ability) using the proposed dissolution method (Figure 11), the reviewer considered to recommend a dissolution acceptance criterion of Q= (b) (4)% in (b) (4) minutes for the proposed drug product. However, considering that the proposed drug product has a Tmax of (b) (4) hours (Pg. 10 of formulation development overview) for the proposed drug product and considering the risk, a change in the dissolution acceptance criterion from Q (b) (4)% in 30 minutes to Q= (b) (4)% in (b) (4) minutes is not warranted. Therefore, the proposed dissolution acceptance criterion of Q= (b) (4)% in 30 minutes is found adequate.

Figure 11: Dissolution profiles of drug product batches used for clinical studies in 900 mL 0.01 N HCl with 0.025% polysorbate, USP 2 apparatus, 60 rpm

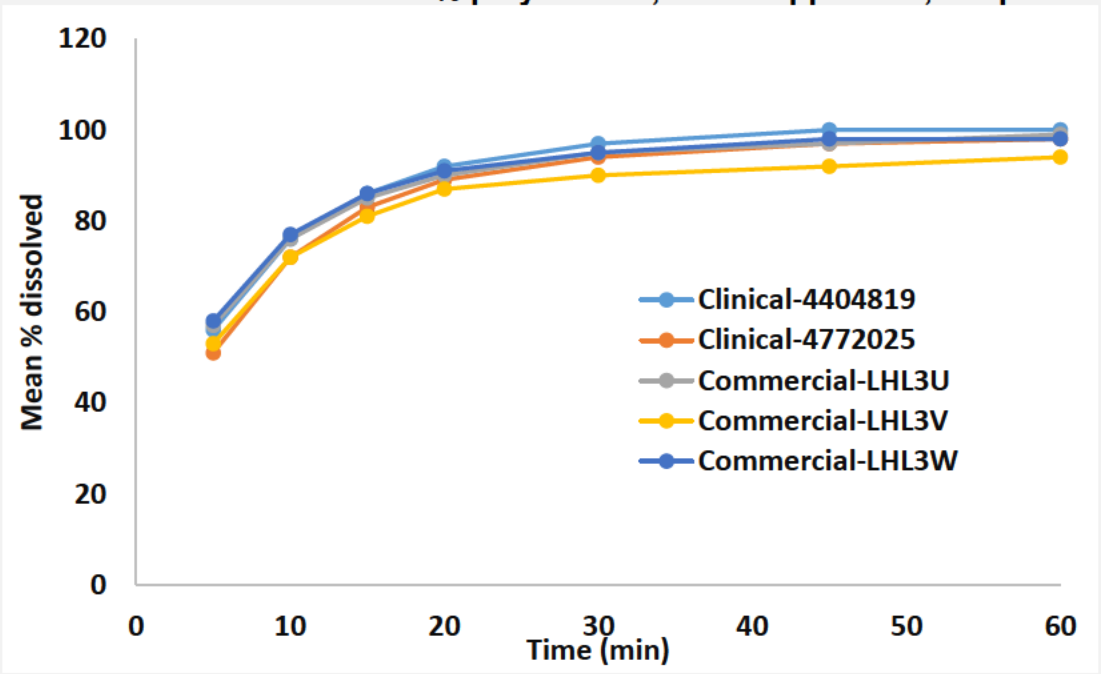


B.12 BRIDGING

Assessment: Adequate

The proposed commercial drug product, Rilpivirine hydrochloride tablets for oral suspension, 2.5 mg is qualitatively and quantitatively identical to the drug product used for clinical studies but are differentiated through use of debossing; the clinical tablets are plain, while the commercial tablets are debossed. In addition, the drug product manufacturing sites for clinical batches (b) (4) and commercial batches (b) (4) are different as per the batch analysis reports (3.2.P.5.4). The Applicant has provided dissolution data for the clinical and the commercial/registration batches using the proposed dissolution method.

Figure 14: Dissolution profiles of clinical and registration batches in 900 mL 0.01 N HCl with 0.025% polysorbate, USP 2 apparatus, 60 rpm



The dissolution profiles for the clinical and commercial/registration drug product batches are comparable (f2>50, calculated by the reviewer). Comparative dissolution data between clinical and commercial drug product is sufficient to support the bridging.

B. 13 BIOWAIVER REQUEST

Assessment: Not Applicable

Biowaiver request is not requested nor needed.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: Not Applicable

Post-Approval Commitments

Assessment: Not Applicable

Lifecycle Management Considerations

BIOPHARMACEUTICS LIST OF DEFICIENCIES

Not Applicable

Primary Biopharmaceutics Assessor's Name and Date: Hardikkumar H Patel, 12/29/23

Secondary Assessor Name and Date: Elsbeth Chikhale, 01/08/2024

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Elsbeth Chikhale

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Date: 1/08/2024 05:41:18PM
GUID: 50743ccc000031928b54eba1769a5df9

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

/s/

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02/15/2024 01:33:49 PM