CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216718Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216718		
Applicant Name	Reata Pharmaceuticals		
Drug Product Name	SKYCLARIS (proposed proprietary name) omaveloxolone capsules		
Dosage Form.	Capsule		
Proposed Strength(s)	50 mg		
Route of Administration	Oral		
Maximum Daily Dose	150 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.		
Drug Product Description	Opaque hard HPMC capsules with a light green body and blue cap, printed with "RTA 408" on the body and "50" on the cap in white ink.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Gaetan Ladouceur
	Drug Product/ Labeling	Andrei Ponta	Martha Heimann
	Manufacturing	Pratibha Bhat	Chengjiu Hu
	Biopharmaceutics	Hansong Chen	Ta-Chen Wu

	Microbiology	N/A	N/A
	Other (specify):	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

36 months for product stored at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

b. Additional Comments for Action

No additional comments.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Office of Pharmaceutical Quality (OPQ) The Office of Product Quality (OPQ) review team recommends APPROVAL of NDA 216718 for SKYCLARIS (omaveloxolone capsules). From a quality perspective, the application meets all applicable standards to support the identity, strength, quality, and purity that it purports to possess.

NDA 216718 provides for use of omaveloxolone, a novel neurosteroid, for treatment of Friedreich's ataxia. Friedreich's ataxia is a rare, debilitating, life-shortening, neurodegenerative disorder that affects approximately 5,000 patients in the US. Onset of symptoms for most patients occurs between 5 and 15 years of age. Most patients lose the ability to ambulate and are wheelchair dependent by their mid-20s. The average age of death is 37.5 years. Currently, there no approved treatments for Friedreich's ataxia

During review of the NDA, the review team identified deficiencies related to drug substance and drug product controls, manufacturing process, and biopharmaceutics that were communicated as information requests. The applicant has adequately addressed these deficiencies and the application, as amended, is deemed adequate.

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

Recommendation by Subdiscipline:

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

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments: No

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The PI complies with statutory/regulatory requirements and is consistent with guidance recommendations and CDER labeling policies.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

[redacted]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	SKYCLARYS (omaveloxolone) capsules for oral use
Route(s) of administration	Adequate	Oral
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	50 mg
Assess if the tablet is scored.	Adequate	Not scored

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

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	Not Applicable
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Adequate	Not Applicable

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling	Assessor's Comments

	(choose "Adequate", "Inadequate", or "N/A")	(If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Do not crush or chew
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement	N/A	

"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]*"* with x numerical citation to "OSHA Hazardous Drugs".		

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Capsules
Strength(s) in metric system	Adequate	50 mg
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

(b) (4)

[redacted]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	SKYCLARYS (omaveloxolone) capsules for oral use Applicant will be asked to include the proprietary and established name in the description
Dosage form(s) and route(s) of administration	Adequate	50 mg, oral
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order.	Adequate	Applicant will be asked to include the inactive ingredients alphabetically

Avoid brand names.		
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	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

Section 11 (DESCRIPTION) Continued

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

requirement may be applicable to another section of the PI (e.g., Section 2).		

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

[redacted]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Capsules
Strength(s) in metric system	Adequate	50 mg
Available units (e.g., bottles of 100 tablets)	Adequate	90 capsules
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for 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	
Special handling about the	N/A	

supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."		

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	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	Adequate	

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 review 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)

(b) (4)

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

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling:

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

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels – Not Applicable

3.2 Carton Labeling

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Inadequate	The Applicant will be asked to include the lot number and expiration date.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

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

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *Adequate*

Andrei Ponta

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Martha Heimann

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	NDA 216718
Assessment Cycle Number	01
Drug Product Name/ Strength	SKYCLARYS™ (omaveloxolone) Capsules, 50 mg
Route of Administration	Oral
Applicant Name	Reata Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Uncategorized Neurologic Disorders /DN1
RLD/RS Number	N/A
Proposed Indication	For the treatment of Friedreich's ataxia
Primary Reviewer	Hansong Chen, PharmD, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

Reata Pharmaceuticals, Inc. developed SKYCLARYS™ (omaveloxolone) or RTA 408 capsules, 50 mg and submitted this NDA to seek approval through the 505(b)(1) regulatory pathways on 3/30/2022. The proposed indication is for the treatment of Friedreich's ataxia.

The Biopharmaceutics review focused on the evaluation of the adequacy of the overall information/data pertaining to: 1) the proposed dissolution method and acceptance criterion, 2) BCS characteristics of omaveloxolone, 3) variability, and 4) bridging of clinical batches manufactured at different sites.

Key findings of the Biopharmaceutics assessment:

1) The Applicant's proposed dissolution method [USP apparatus I (Basket) at 100 rpm; 900 mL of 50 mM Sodium Phosphate Buffer, pH 6.8 at 37 °C] is considered acceptable. The proposed dissolution method was demonstrated to be discriminatory toward (b) (4) , but not toward formulation variations intentionally manufactured and particle size distribution (PSD) of omaveloxolone (b) (4)

   The proposed acceptance criterion of Q= (b) (4)% in (b) (4)minutes has been (b) (4) "Q= (b) (4)% in 45 minutes", based on the provided dissolution profiles of biobatch/registration batches and investigation of discriminating ability of the method. The agreement to the recommended acceptance criterion was reached with the Applicant.

2) The provided low solubility across physiological pH range (pH 1-10) and low permeability data from in vitro Caco-2 and human mass-balance studies indicate that omaveloxolone can be characterized as a BCS Class IV drug.

3) High intra- and inter-batch dissolution variabilities at the early time-points were observed for the clinical and registration batches. The high variability can be attributed to HPMC capsule shell's variability in time to disintegrate/rupture. Due to insufficient data and the lack of an established IVIVC (in vitro in vivo correlation) for this drug product, the potential impact of the observed high dissolution variability on the PK profiles of omaveloxolone cannot be quantitively predicted. Given that all units/batches achieved close to complete release at 45 minutes and Tmax is approximately 11 hours, and the drug substance's BCS classification, it is concluded that high dissolution variability is unlikely to have significant effects on the in vivo pharmacokinetics of omaveloxolone.

4) The calculated similarity factors (f_2) show that dissolution profile data generated with most batches manufactured at two different sites are not similar, likely attributed to variability at the early time-points associated with the HPMC capsules. However, it is also noted that all batches were used in the same efficacy study. The Biopharmaceutics consideration is delineated in (2). The Clinical outcome would provide further support for the bridging.

Recommendation:
From a Biopharmaceutics perspective, NDA 216718 for SKYCLARYS™ (omaveloxolone) capsules, 50 mg, is ADEQUATE.

FDA-approved dissolution method and acceptance criterion:

USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)	Acceptance Criteria
I (Basket)	100	50 mM Sodium Phosphate Buffer, pH 6.8 with 1% SLS/ 37 °C ± 0.5°C	900	Q= (b) (4)% in 45 minutes

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 0001 /Original submission	3/30/2022
Sequence 0010 /Partial response to Biopharmaceutics IR 1	6/10/2022
Sequence 0012 /Response to Biopharmaceutics IR 1	6/20/2022
Sequence 0021 /Response to Biopharmaceutics IR 2	8/1/2022

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

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

B.1 BCS DESIGNATION

Assessment:

No BCS designation was requested. The Applicant reported that omaveloxolone capsules, 50 mg, is a BCS Class IV drug. The solubility data show that omaveloxolone is poorly soluble. The Applicant conducted an in vitro permeability study and a mass balance study, and the results of these two studies indicate that omaveloxolone is poorly permeable.

Solubility:

Table 1. Aqueous Solubility of Omaveloxolone Across Physiological pH Range

Aqueous Environment	Solubility (mg/mL)	Form Change	pH at End of Study
pH 1	0.0009	No	0.5
pH 2	<LOQ[a]	No	2.0
pH 3	<LOQ[a]	No	3.1
pH 4	0.0002	No	4.0
pH 5	0.0009	No	5.0
pH 7	0.0002	No	7.0
pH 8	0.0051	No	8.0
pH 10	0.4468[b]	No	9.9

LOQ = limit of quantitation; PTFE = polytetrafluoroethylene
a Limit of quantitation is 0.00013 mg/mL.
b A suspension was obtained after centrifugation and filtration through (b) (4) µm PTFE membrane.

Reviewer's comment:

The solubility data in Table 1 show that omaveloxolone is poorly soluble per BCS criteria because more than 250 mL of aqueous solution is needed to dissolve 50 mg of omaveloxolone across the physiological pH range. It should be noted that the Applicant did not report the temperature at which the solubility was determined. However, even the solubility testing was conducted at a temperature less than 37 °C, the conclusion that omaveloxolone has low solubility would not change because its solubility is so low across the physiological pH range. Additional information pertaining to solubility is presented in Tables 4 and 5.

Permeability:

Table 2. Permeability coefficient, Papp (Caco-2 cells in the presence of 0.5% bovine serum albumin (BSA), absorption)

Concentration of omaveloxolone tested	Papp
1 µM	1.43×10^{-6} cm/sec
2.5 µM	2.19×10^{-6} cm/sec
10 µM	3.22×10^{-6} cm/sec

The Applicant conducted an in vitro study to determine the bidirectional permeability of omaveloxolone across Caco-2 cell monolayers. The results show that the apparent permeability (Papp) values for omaveloxolone (1, 2.5, and 10 µM) in Caco-2 cells in the apical to basal (i.e., absorption) direction were 1.43×10^{-6}, 2.19×10^{-6}, and 3.22×10^{-6} cm/sec, respectively. The efflux ratios for omaveloxolone (1, 2.5, and 10 µM) on Caco-2 cells were 2.8, 2.6, and 1.8, respectively. The data indicate that omaveloxolone had low absorptive permeability in Caco-2 cell monolayers and may be a weak P-gp substrate in vitro.

Reviewer's comment:
The Caco-2 transport study was conducted without standard model drugs, thus a definitive conclusion cannot be drawn with respect to the classification of permeability.

The Applicant also conducted a mass balance study to evaluate the in vivo omaveloxolone metabolism. The data from the pooled samples of 6 subjects show that fecal excretion was the predominant route of elimination, with a mean recovery of 92.4%. Unchanged omaveloxolone was present in feces and accounted for 40.3% of the dose. In addition, the absorption of omaveloxolone is slow and variable with a median Tmax of 9 hours. This study results indicate that omaveloxolone has low permeability, per BCS.

Dissolution: The dissolution data show that the proposed omaveloxolone capsules, 50 mg, achieve a complete dissolution by 45 minutes in the proposed dissolution medium (i.e., 50 mM Sodium Phosphate Buffer, pH 6.8 with 1% SLS).

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *{Adequate}*

1. Dissolution Method

The Applicant proposed the following dissolution method and acceptance criterion for the prosed product:

Table 3. The proposed dissolution method and acceptance criterion

USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)	Acceptance Criteria
I (Basket)	100	50 mM Sodium Phosphate Buffer, pH 6.8 with 1% SLS / 37 °C ± 0.5°C	900	Q= (b)(4)% in (b)(4)min

1) Dissolution method development

(b) (4)

[redacted]

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2) Discriminating power of the dissolution method

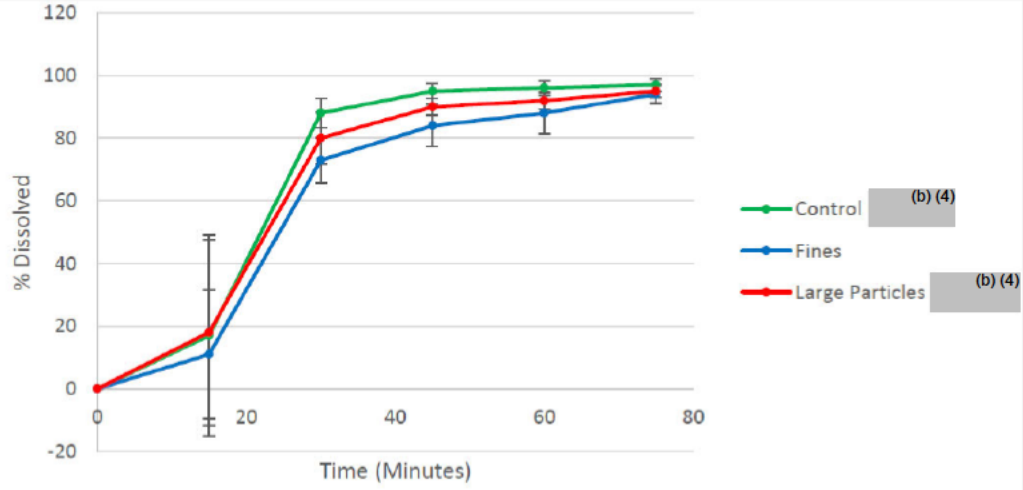
a) Changes in particle size distribution (PSD) of drug substance

The Applicant explored the discriminating power of the dissolution method towards the change in PSD of drug substance by intentionally manufacturing different batches of drug product with different PSD of drug substance, as shown in Table 6. The dissolution results are presented in Figure 4, which demonstrates that the proposed dissolution method is not able to differentiate the change in PSD.

Table 6. Particle Size Distribution of Amorphous Drug Substance Variants in Dissolution Discriminating Study

	Small	Control	Large
Particle Size Attribute	**17BT07SD.2F.NJ00010**	**17BT07SD.NJ00006**	**17BT07SD.NJ00006**
Dv10		(b) (4)	
Dv50			
Dv90			

Figure 4. Mean Dissolution Profiles (N=18) for Omaveloxolone Capsules, 50 mg with Amorphous Drug Substance Particle Size Variants in 1% SLS in Phosphate Buffer pH 6.8 at 100 RPM Rotation Speed



Reviewer's comment:

Omaveloxolone is a BCS Class IV drug, which has a medium/high biopharmaceutics risk. We expect that the proposed dissolution method has some meaningful discriminating power against CMAs and CPPs. Especially, we expect that the method is able to differentiate the change in PSD. However, in the above study, the proposed dissolution method is not discriminating for changes in particle size distribution (PSD) of the drug substance. The reason might be that the differences in PSD among the three batches are not significant. In the Biopharmaceutics IR (see Appendix for details), this Reviewer requested the Applicant to further explore whether the proposed dissolution method is discriminating for greater differences in PSD.

In the response to the IR, the Applicant stated that the drug substance (b) (4) *Given that, it is not feasible to obtain different batches of drug substances with greater differences in particle size distribution. However, the Applicant proposed changing the D90 specification from NMT* (b) (4) *µm to NMT* (b) (4) *µm.*

(b) (4)

(b) (4)

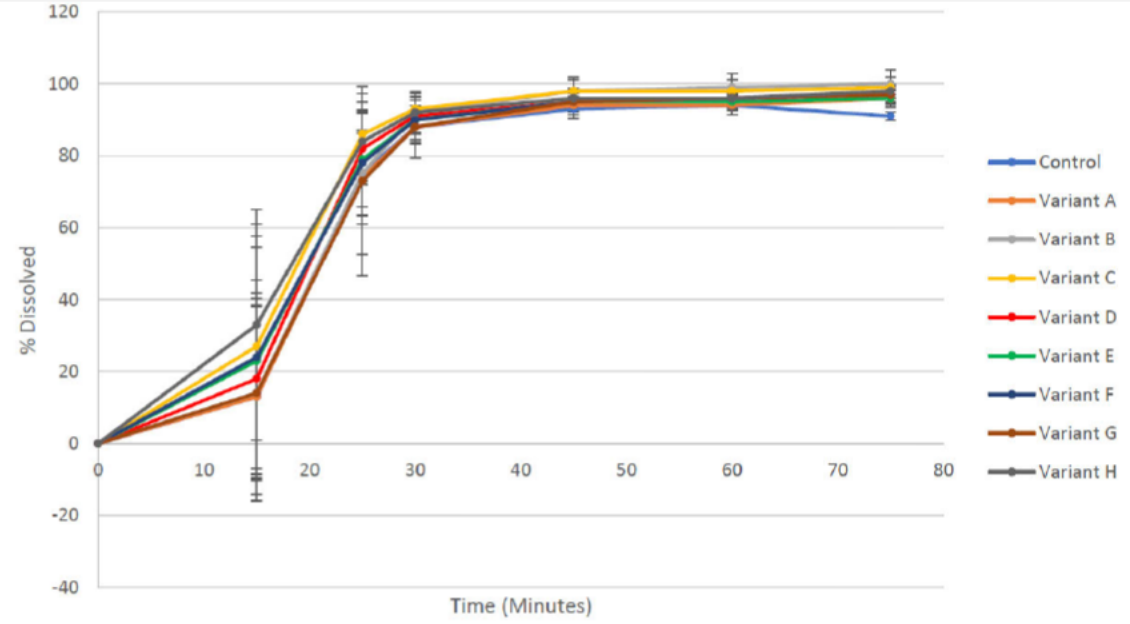
c) Formulation variation

The Applicant intentionally manufactured the following batches by varying the concentration of excipients in the formulation as shown in Table 7. As shown in Figure 5, the proposed dissolution method does not discriminate for the formulation variants.

Table 7. Formulation Variant Compositions

Excipient/ Function		Variant (% w/w)							
	Control	A	B	C	D	E	F	G	H
(b) (4) RTA408/Drug Substance	(b) (4)								(b) (4)
Starch	(b) (4) (b) (4)								
Magnesium Stearate	(b) (4)								

Figure 5. Mean Dissolution Profiles (N=12) for Omaveloxolone Capsules, 50 mg with Formulation Variations in 1% SLS in Phosphate Buffer pH 6.8 at 100 rpm Rotation Speed



Reviewer's overall comment on the dissolution method:
Because of the manufacturing process limitation of the API, the Applicant could not generate different batches of drug product with greater differences in PSD to further investigate whether the method is able to discriminate for them. However, the proposed dissolution method is discriminatory (b) (4) *When the dissolution acceptance criterion is* (b) (4) *"Q=* (b) (4)*% in* (b) (4)*min" to "Q=* (b) (4)*% in 45 min, the batches with* (b) (4) *will be rejected, which would further mitigate the biopharmaceutics risk. Overall, the proposed dissolution method is considered acceptable.*

2. Dissolution Data and Acceptance Criterion

a) Dissolution data

The Applicant provided detailed information and complete dissolution profile data of 10 clinical and 3 registration batches (Tables 8 and 9).

It was noted that almost all dissolution data were generated with 6 units/batch, instead of 12 units/batch as the Division typically requires. In addition, different batches have different sampling timepoints (e.g., Batch 170114 has time points: 10, 15, 20, 30, 45, and 60 min; and Batch 318136R has time points: 15, 30, 45, and 60 min), which made it difficult to meaningfully compare the dissolution profiles among batches. In response to Biopharmaceutics IR 1 (Appendix), the Applicant provided all requested data (Table 10).

Table 8. List of all clinical and registration batches

Batch number	Manufacturing Site	Manufacturing Date	Use of batch
3187136R	(b) (4)	22 Jun 2020	Phase 3 in FA, open label extension (408-C-1402, Part 3)
3173957R		23 Oct 2018	Phase 3 in FA, efficacy (408-C-1402, Part 2); Phase 3 in FA, open label extension (408-C-1402, Part 3)
3169638R		28 Jun 2018	Phase 3 in FA, open label extension (408-C-1402); Phase 1, PK (408-C-1703); Phase 1, Hepatic impairment (408-C-1804); Phase 1, Drug-drug interactions (408-C-1806)
3165601R		01 Mar 2018	Phase 3 in FA, open label extension (408-C-1402, Part 3)
3164723R		17 Jan 2018	Phase 3 in FA, open label extension (408-C-1402, Part 3)
170114		11 Jul 2017	Phase 3 in FA, efficacy (408-C-1402, Part 2)
170103		21 Jun 2017	Phase 3 in FA, efficacy (408-C-1402, Part 2)
170031		03 Mar 2017	Phase 1b/2 in melanoma (408-C-1401)
160033		11 Mar 2016	Phase 1b/2 in melanoma (408-C-1401) Phase 2 in FA (408-C-1402, Part 1) Phase 3 in FA, efficacy (408-C-1402, Part 2) Phase 2 in mitochondrial myopathy (408-C-1403)
150174		05 Dec 2015	Phase 2 in FA (408-C-1402, Part 2) Phase 2 in mitochondrial myopathy (408-C-1403)

*This batch was reinspected for appearance and the material post-inspection was assigned the batch number 3169638RS.
FA = Friedrich's ataxia

Table 9. List of all registration batches

Batch number	Manufacturing Site	Manufacturing Date	Use of batch
3173381R	(b) (4)	14 Jan 2019	Registration, Primary Stability
3173382R		16 Jan 2019	Registration, Primary Stability
3173383R		17 Jan 2019	Registration, Primary Stability

Table 10. Mean dissolution profile data of pivotal clinical and registration batches (n=12)

Batch number/time(min)	10	15	20	30	45	60
3187136R	12	38	77	90	93	95
3173957R	34	60	89	95	97	97
3169638R*#	N.D.	69	N.D.	91	94	94
3165601R*	N.D.	55	N.D.	63	81	84
3164723R*	N.D.	0	N.D.	76	87	90
170114	50	83	94	97	98	98
170103	41	73	91	95	95	96
170031*	N.D.	73	N.D.	92	94	95
160033	53	79	93	98	99	100
150174*	N.D.	37	N.D.	87	90	91
3173381R	4	31	73	90	94	96
3173382R	0	28	67	93	97	98
3173383R	9	28	71	94	97	98

N.D.-not determined
*The batches do not have data at 10 min and 20 min.
Batch 3169638R was used for PK in Friedreich's ataxia.

b) Dissolution variability

Intra-batch variability
High variability is observed at early timepoints (up to 20 minutes) for all batches, as shown in Table 11. Among all batches whose data were generated on 12 capsules/batch, the %RSD at the 10 minute timepoint ranges from 54.4 to 255.9, at the 15 minute timepoint ranges from 22.9 to 102.8, and at 20 minutes, the %RSD ranges from 3.4 to 43.4 (including capsules with very low drug release).

Table 11. Variability Comparison Between Phase 3 Efficacy and Registration Batches of Omaveloxolone Capsules, 50 mg

Batch Type	**% RSD Range**		
	10 minutes	**15 minutes**	**20 minutes**
Phase 3 Efficacy Batches	54.4 – 107.6	22.9 – 65.6	3.4 – 7.9
Registration Batches	81.8 – 255.9	34.0 – 102.8	19.4 – 43.4
Sister Batches	79.2 – 104.6	43.4 – 88.7	7.2 – 33.8

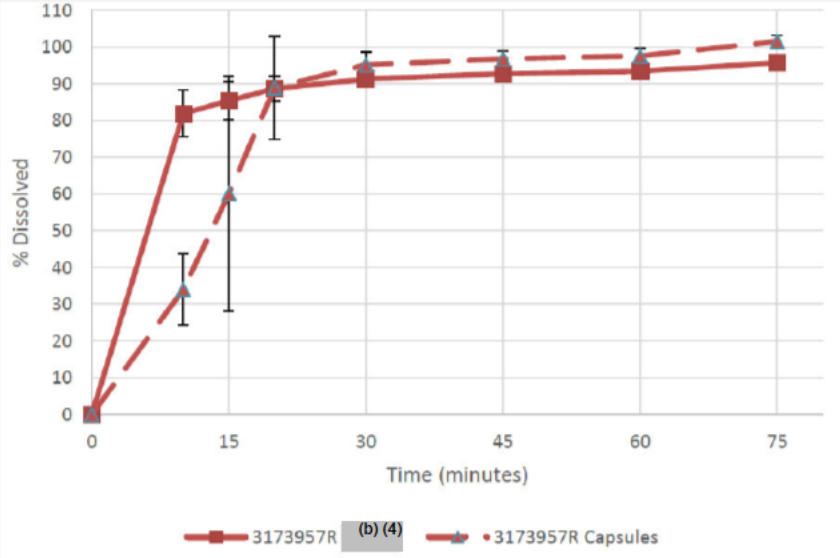
It should be noted that sister batches (b) (4)

(b) (4)

Because of the high intra-batch variability, the Applicant was requested to provide justification, with sufficient supporting data, that the proposed dissolution method is appropriate for the drug product. In the response to the IR (Appendix), the Applicant reported that they investigated the root cause of variability and concluded that higher variability in early time points is due to HPMC capsule shell variability in time to disintegrate/rupture. The Applicant compared the rupture times of HPMC and gelatin capsules and found that the drug product filled in HPMC capsule generally has delayed rupture.

To further support that the variability and delay in dissolution in omaveloxolone capsules is attributed to the variability related to the opening of the HPMC capsule shells, the Applicant compared the dissolution profiles of three batches with and without the capsule shell. As shown in Figure 6, in the absence of the capsule shell, dissolution of omaveloxolone from the capsule contents (b) (4) is rapid, with much lower variability compared to the intact capsules, which indicates that the capsule shell is the cause of the variability in individual capsule results at the early time points as evidenced by the wide variability marks, particularly at 10 minutes and 15 minutes.

Figure 6. Omaveloxolone Capsules, 50 mg, Batch 3173957R*: Whole Capsule vs. Capsule Contents (b) (4)



Although high intra-batch variability was observed, the Applicant does not believe that this variability is likely to have any effect on in vivo pharmacokinetics of omaveloxolone because it is a BCS Class IV compound for which absorption is not significantly affected by gastric emptying.

Reviewer's assessment:
This Reviewer agrees with the Applicant that the observed high variability came from the variable rupture time of the HPMC capsules. This Reviewer also acknowledges that HPMC capsules tend to have delayed rupture compared to gelatin capsules. However, the

Applicant's justification for HPMC capsules having such high dissolution variability was not deemed satisfactory to this Reviewer. It is possible that the HPMC capsules were not manufactured consistently so that it caused high variability in rapture time. It could be a quality issue from a Biopharmaceutics perspective. This Reviewer communicated this concern with the Drug Product reviewer team during the review cycle.

As shown in Table 12, the variability of PK parameters is more than 35%. Food has a significant effect on Cmax and Tmax shifted to the left (from 11 hours to 5 hours) under fed conditions, indicating food significantly promotes the absorption of omaveloxolone by increasing its permeability. The results of the food effect study confirm that omaveloxolone has low permeability.

Due to insufficient data and the lack of an established IVIVC (in vitro in vivo correlation) for this drug product, the potential impact of the observed high inter-batch dissolution variability on the PK parameters of omaveloxolone cannot be quantitatively predicted. However, omaveloxolone is a BCS Class IV drug, which has low solubility and low permeability. Dissolution is not a rate-limiting step for oral absorption. Considering that all units achieved a close-to complete drug release at 45 minutes and Tmax is approximately 11 hours, and the drug substance's BCS classification, this Reviewer concludes that high intra-batch dissolution variability is unlikely to have any significant effect on the in vivo pharmacokinetics of omaveloxolone; consequently, he does not believe that high dissolution variability is an approvability issue from a Biopharmaceutics perspective. The acceptable clinical outcome of the proposed drug product would support the approvability of the application.

Table 12. Summary of Plasma Omaveloxolone Pharmacokinetic Parameters Pharmacokinetic Population (Study 408-C-170

PK Parameter Statistic	Omaveloxolone			
	50 mg Fasted (N=10)	100 mg Fasted (N=8)	150 mg Fasted (N=16)	150 mg Fed (N=15)
C_{max} (ng/mL)				
n	10 55.45%	8 35.09%	16 46.10%	15 36.06%
Mean (SD)	21.1 (11.7)	27.7 (9.72)	28.2 (13.0)	129 (51.1)
GM (CV%)	18.8 (52.9)	26.1 (38.5)	25.4 (51.3)	119 (45.6)
T_{max} (h)				
n	10	8	16	15
Median (min, max)	5.5 (1.0, 8.0)	10.0 (8.0, 12.0)	11.0 (3.0, 24.0)	5.0 (2.0, 8.0)
AUC_{0-t} (h*ng/mL)				
n	10	8	16	15
Mean (SD)	483 (188)	1110 (498)	1140 (526)	1340 (557)
GM (CV%)	456 (35.1)	1030 (43.3)	1030 (47.0)	1220 (48.1)
$AUC_{0-\infty}$ (h*ng/mL)				
n	9 39.45%	8 49.92%	16 47.40%	15 49.96%
Mean (SD)	545 (215)	1230 (614)	1230 (583)	1440 (633)
GM (CV%)	513 (36.4)	1120 (46.4)	1120 (48.4)	1310 (49.8)

Inter-batch variability

High variability at earlier timepoints is also observed between batches. Especially, the dissolution profiles of the three registration batches (Batch 3173381R, 3173382R, 3173383R) are significantly different from those of four Phase 3 efficacy batches (Batches 160033, 170103, 170114, and 3173957R) as shown in Figure 7 (i.e., originally Figure 1 of Module 3.2.P.5. 6 Justification of Specifications).

Figure 7. Omaveloxolone Capsules, 50 mg, Dissolution Results (Release) for Registration and Phase 3 Efficacy Batches (n=6 capsules)

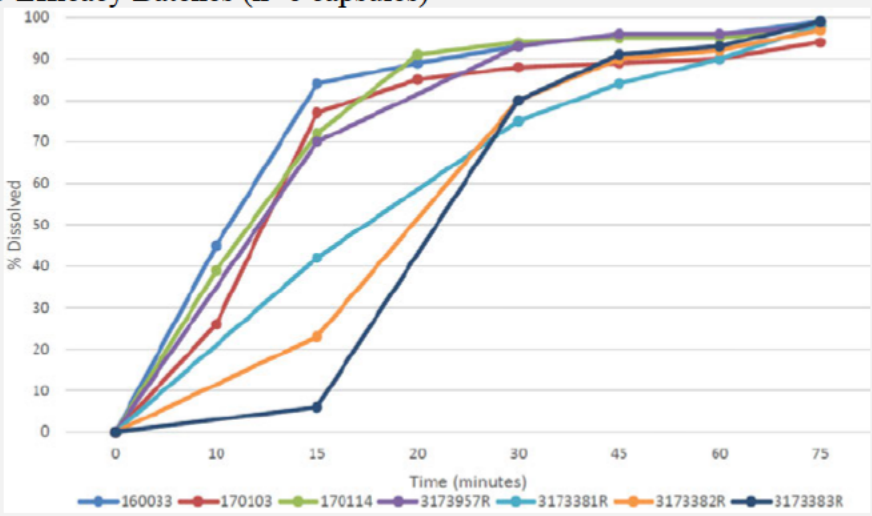
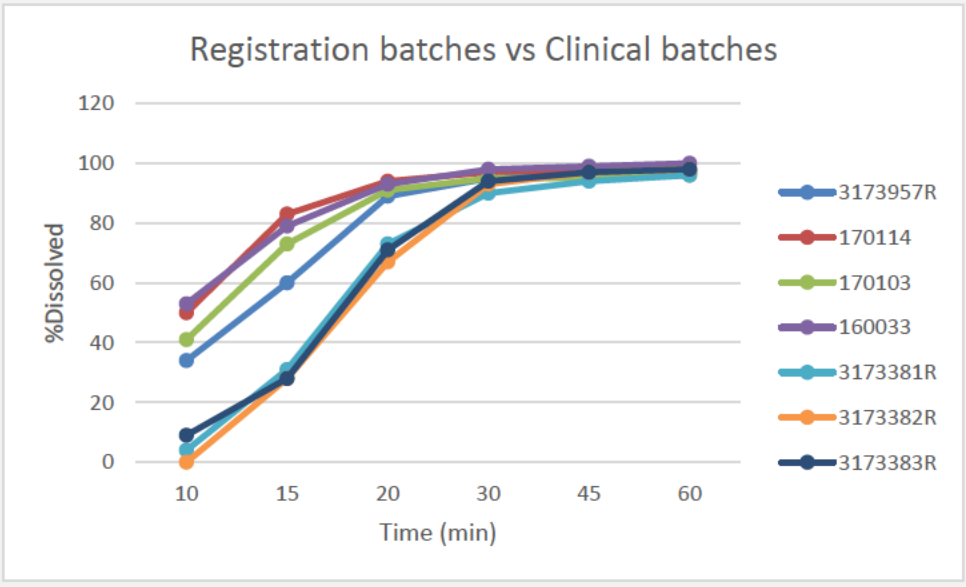


Figure 8. Omaveloxolone Capsules, 50 mg, Dissolution Results (Release) for Registration and Phase 3 Efficacy Batches (n=12 capsules)



Because of different timepoint implemented for registration batches and clinical batches in the original submission, it is not appropriate to compare their dissolution profile similarity.

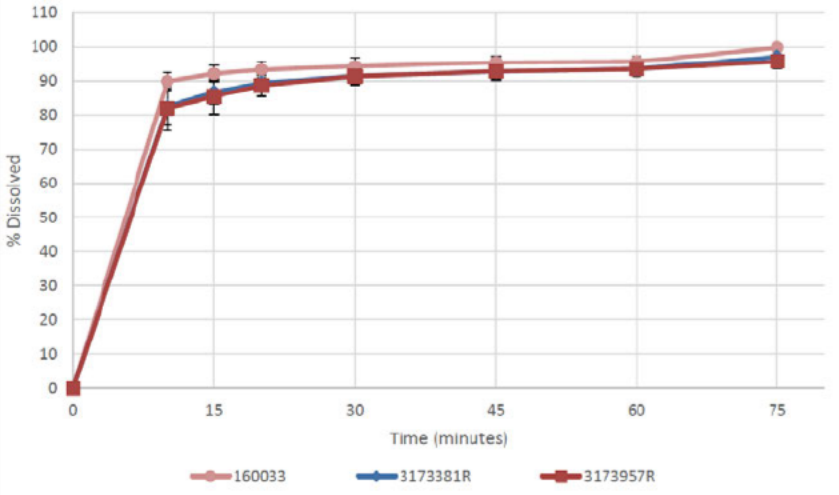
Upon request, the Applicant repeated dissolution testing on the above batches and generated data with same points, which are shown in Figure 8. The calculated similarity factors (f2s <50) show that registration batches have significantly slower dissolution rate than clinical batches.

Because of the above significant difference in dissolution profiles between the registration and clinical batches, the Applicant was requested to provide justification (Biopharm IR 1 in Appendix) including any information pertaining to PBBM modeling and/or other in vivo data, whether significant differences in dissolution profiles would cause different in vivo performance.

In the response to the IR, the Applicant stated that even these batches have different dissolution profiles, dissolution profiles of the capsule contents from three batches are similar, which demonstrates that omaveloxolone is typically 80-90% released within the first 10 minutes (Figure 9). In order to evaluate the impact of dissolution variability on in vivo performance, the Applicant evaluated the omaveloxolone pharmacokinetic profiles. Because that the rate of drug absorption is slow and reaches maximum concentration (Tmax) at 11 hours (ranging 3 to 24 hours), the Applicant concluded that the variability in the earlier time points of the dissolution profile is not expected to have an effect on the Tmax of omaveloxolone. Consequently, the Applicant concluded that the variability in early time points (10-20 minutes) of the dissolution profile will have minimal to no impact on the total bioavailability of omaveloxolone.

Additionally, the Applicant reported that they are in the process to establish a collaboration with (b) (4) to develop an In Vitro/In Vivo relationship (IVIVR) under fasted conditions, and to establish a safe space via conventional and/or modeling approaches (PBBM). Of note, no subsequent information was provided.

Figure 9. Comparison of Drug Product Capsule Contents Dissolution Profiles from Batches 160033, 3173381R, and 3173857R



Reviewer's comment:

This Reviewer looked at the data further and found that the batches with capsules manufactured in (b) (4) *tend to have faster drug release, and the baches with capsules manufactured in* (b) (4) *have slower drug release (Table 10). This finding further confirms that, in view of the similar dissolution profiles and small variability of capsule contents in Figure 9, dissolution variability comes from variability in capsule rupture time because these HPMC capsules are not uniform across different manufacturing sites.*

Table 13. (b) (4) *Capsule Shells used in Clinical and Registration Batches of Drug Product*

Drug Product Manufacturer		(b) (4)						
Drug Product Batch Number	160033	170103	170114	3165638R	3173957R	3173381R	3173382R	3173383R
Capsule Shell Batch Number	9030175	9030370	9032232	7156389	9038443	7159463	7159463	7159463
Capsule Shell Manufacturer	(b) (4)							
Capsule Shell Site of Manufacture								
Disintegration Time* (minutes)								
Average Weight (mg)								

It should be noted that there is limited information/data to evaluate how in vitro dissolution affects the in vivo PK of omaveloxolone. Only one batch (i.e., Batch 3169638R) was used for PK study. Additionally, an IVIVC was not established for this drug product, we could not ensure that registration batches with slower dissolution will lead to lower bioavailability than clinical batches. Although the capsule contents from three different batches exhibit similar dissolution profiles (Figure 9), one cannot rule out the possibility that different dissolution profiles caused by HPMC capsules have an impact on the in vivo performance of omaveloxolone. In the response to Biopharmaceutics IR 1, the Applicant reported at the time that they are in the process of using PBBM modeling and simulation to address this issue.

More than 4 batches employed in the pivotal efficacy study exhibited different dissolution profiles, with a few of them differing significantly. This Reviewer conveyed the high dissolution variability issues to the Medical Officer (Dr. Veneeta Tandon) and inquired whether significantly different efficacy and safety profiles were observed as a result of high intra-batch and inter-batch variability, and whether any sub-group analysis based on batches can be performed.

Per Dr. Tandon, the variable efficacy endpoint (mFARS) was observed. However, one cannot conclude whether the variability in efficacy or safely endpoint can be attributed to the variability of in vitro dissolution. An internal meeting within the Division of

Biopharmaceutics was held on July 22, 2022 with Branch Chief (Dr. Okpo Eradiri) and SPQA (Dr. Ta-Chen Wu). It was concluded that it is difficult to predict how the observed high intra-batch and inter-batch variability affects the PK of the proposed drug based on the currently, limited available in vivo data/information. Although this remains a concern to this Reviewer, the clinical outcome of this proposed drug should determine its approvability.

c) Dissolution acceptance criteria

The Applicant proposed the following dissolution acceptance criterion:
Q= (b)(4)% in (b)(4)minutes

Reviewer's comment
*Table 10 shows that all clinical/registration batches have a mean dissolution of at least 87% at 45 minutes except Batch 3165601R, indicating that the proposed dissolution acceptance criterion is (b)(4) as follows: Q= (b)(4)% in 45 minutes. The study of the discriminating power of the proposed dissolution method further supports this regulatory decision. Setting an acceptance criterion of "Q= (b)(4)% in 45 minutes" can reject the batches (b)(4) (see Figure 5). An IR was sent to the Applicant conveying the recommended dissolution acceptance criterion, as presented in **Appendix**. In response to the IR, the Applicant accepted this Reviewer's recommendation and provided updates to the relevant documents.*

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: *N/A*

BB.12 BRIDGING OF FORMULATIONS

Assessment: ***{****Adequate****}***

As shown in Table 8, Clinical Batches 3187136R, 3173957R, 3169638R, 3165601R , and 3164723R were manufactured in (b)(4). All other batches were manufactured in (b)(4).

Table 14. Mean dissolution data comparison of Batches manufactured at different sites

Batch number/time(min)	10	15	20	30	45	60
3187136R	12	38	77	90	93	95
3173957R	34	60	89	95	97	97
170114	50	83	94	97	98	98
170103	41	73	91	95	95	96
160033	53	79	93	98	99	100

Figure 10. Dissolution profile comparison of Batches manufactured at different sites

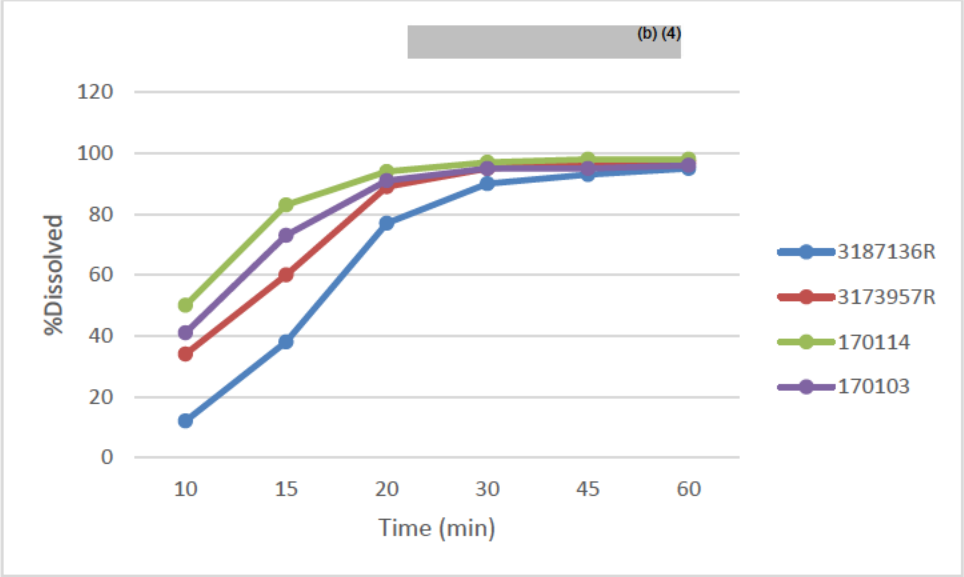


Table 15. Similarity factors between batches manufactured at different sites

Comparison	F2
3187136R vs 170114	22.55
3173957R vs 170114	39.18
3187136R vs 170103	28.05
3173957R vs 170103	53.12
3187136R vs 160033	22.96
3173957R vs 160033	40.05

Reviewer's comment:
The calculated similarity factors in Table 15 show that the batches manufactured at different sites are not similar except Batch 3173957R vs Batch 170103. Note that all of the above batches were used in the efficacy study. The clinical outcome would provide further support for the bridging.

B. 13 BIOWAIVER REQUEST

Assessment: *N/A*

There is only one proposed strength so no biowaiver request was submitted.

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Hansong Chen

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