CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215446Orig1s000

PRODUCT QUALITY REVIEW(S)

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval with Post-Marketing Commitment

NDA 215446
Review # 1

Drug Product Name	Radicava ORS (edaravone)
Dosage Form	Oral suspension
Strength	105 mg/5 mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Mitsubishi-Tanabe Pharma Corporation
US agent, if applicable	Denzel Ngoma, Associate Director, Regulatory Affairs, Regulatory Affairs & CMC

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Jeffrey Medwid	Gaetan Ladouceur
Drug Product	Jizhou Wang	Martha Heimann
Manufacturing	Ebern Dobbin	Tianhong Tim Zhou
Microbiology	Eric Adeeku	Elizabeth Bearr
Biopharmaceutics	Hansong Chen	Ta-Chen Wu
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	
Environmental	N/A	

Submission(s)	Document Date	Discipline(s) Affected
SD-01, Original NDA	11/12/2021	All
SD-05, Response to IR	1/26/2022	Microbiology
SD-07, Labeling	2/28/2022	Biopharmaceutics
SD-08, Response to IR	3/3/2022	Drug product
SD-10, Response to IR	3/8/2022	Drug product
SD-11, Response to IR	4/8/2022	Manufacturing
SD-12, Labeling	4/14/2022	Drug product

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	III		(b) (4)	N/A [1]		
	III			N/A [1]		
	III			N/A [1]		
	III			N/A [1]		

[1] Adequate information provided in NDA.

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
IND	138145	Development of edaravone oral suspension
NDA	209176	Applicant's approved NDA for Radicava (edaravone) injection

2. CONSULTS

None

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Pharmaceutical Quality Review team has assessed NDA 215446 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this NDA from a quality perspective. The CMC post-marketing commitment (PMC) below should be included in the action letter:

PMC 4266-1 Provide updated extractable/leachable studies to confirm that the container closure system does not adversely impact the drug product.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Edaravone is a free radical scavenger developed as a neuroprotectant by Mitsubishi Tanabe Pharma Corporation (Applicant). Edaravone was first approved in 2001 in Japan, under the tradename of "RADICUT®", for the treatment of acute ischemic stroke. It was subsequently approved in Japan in 2015 for the treatment of amyotrophic lateral sclerosis (ALS) followed by approval in the US as Radicava® (edaravone) injection, for the ALS indication under NDA 209176 in 2017. The recommended dose is 60 mg/day by intravenous infusion. Radicava is administered in intermittent dosing cycles as follows:

- Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period.
- Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.

In the current NDA, the applicant proposes to market edaravone as a 105 mg/5 mL aqueous suspension for oral administration. The proposed product contains typical (b) (4), sorbitol as (b) (4), and sodium bisulfite and L-cysteine as (b) (4). The product will be packaged in 60 mL amber glass bottles containing 35 mL or 50 mL of suspension. The recommended dose for the oral suspension is 105 mg/day following the same schedule as for Radicava injection. Thus, the initial treatment cycle requires two 35 mL bottles. One 50 mL bottle contains sufficient drug for each subsequent treatment cycle.

Proposed indication(s) including intended patient population	Treatment of amyotrophic lateral sclerosis (ALS)
Duration of treatment	Chronic
Maximum daily dose	105 mg
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: **Adequate**

NDA 215446 is recommended for approval from the CMC drug substance perspective. The CMC Information is cross referenced to NDA 209176. The applicant provided the same CMC information as previously disclosed with additional batch data.

The proposed retest period of (b) (4) months while stored at (b) (4) in the proposed container closure system is granted.

Drug Product: **Adequate**

Edaravone Oral Suspension 105 mg/5 mL is provided as 7-day or 10-day multi-dose bottle, containing 35 mL or 50 mL of the suspension. The recommended dose is 105 mg edaravone in 5 mL of suspension.

Edaravone Oral Suspension was developed based on Radicut® Injection 30 mg/20 mL (ampule formulation), which was the commercial presentation of Edaravone Injection originally approved in Japan. All excipients except for the two pH adjusting agents fall within the FDA Inactive Ingredient Database (IID) limits. The sponsor has provided data to support the selection of (b) (4) (b) (4) pH adjusting agents for a stable oral suspension.

The release and stability specifications for the drug product have been adequately justified based on ICH guideline, the referenced NDA, available batch analysis data, and stability study results. The analytical methods have been fully validated and are suitable for their intended use. Data of three (3) registration batches for each presentation fall into the pre-determined release specification.

Three (3) registration and three (3) supportive batches for each presentation were placed on long term stability studies (5°C ± 3ºC) and accelerated stability (25°C ± 2ºC / 60% ±5% RH) with both upright and inverted orientations. Available 6 months

accelerated stability data and 12-month and 18-month long term stability data from registration and supporting batches, respectively, comply with the specifications. The proposed **18-month shelf life** for the drug product when **stored refrigerated** is acceptable based on the data provided. The applicant provided data from 7-day and 15-day in-use stability studies at room temperature. The in-use data show no trend and support storage by the patient/caregiver at room temperature while the product is being used.

The container closure system (CCS) for Edaravone Oral Suspension is a 60-cc amber glass bottle with child resistant, (b) (4) screw cap. The product is co-packaged with an adapter and two oral dispensers. All plastic packaging components comply with USP <661> or <661.1>: some materials also comply with USP<87>, <88>. The sponsor has performed extractables and leachables (E&L) studies for the CCS. However, the E&L studies were not deemed adequate due to use of less vigorous extraction than recommended unvalidated analytical methods with low sensitivity. Additionally, only one batch (of three) was stored in an inverted orientation (worst case condition). Based on the generally acceptable quality of the drug product and the relatively low risk of leachables for an oral dosage, the applicant's PMC to repeat the E&L studies under more rigorous conditions is acceptable.

Labeling: **Adequate**

Recommended revisions have been incorporated into the product labeling.

Manufacturing: **Adequate**

The proposed drug product, Edaravone Oral Suspension,105 mg/5 mL, is filled into 60 mL amber glass bottle market presentations in two fill volumes, 35 mL and 50 mL. Due to (b) (4), the proposed drug product needs to be stored under refrigeration. Therefore, the (b) (4) (b) (4) will be the focus for the proposed manufacturing process.

The bulk drug product compounding unit operation is (b) (4)

(b) (4)

(b) (4)

All facilities proposed for manufacture and testing of edaravone and Edaravone Oral suspension have been evaluated and found acceptable. Facility status should be verified prior to final action.

Biopharmaceutics: **Adequate**

The Biopharmaceutics review focused on the evaluation of the adequacy of the overall information/data supporting: 1) the proposed dissolution method and acceptance criterion, and 2) the bridging of two clinical batches manufactured at different sites and scales. Based on the review of the provided information/data, Biopharmaceutics has the following assessments:

1) The Applicant's proposed dissolution method [USP apparatus II (Paddle) at 75 rpm; 900 mL of pH 4.0 acetate buffer at 37 °C] is considered acceptable. The proposed acceptance criterion of Q=(b)(4)% in (b)(4) minutes has been tightened to Q=(b)(4)% in 15 minutes. The following dissolution method and acceptance criterion can be approved:

Method Source	USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)	Acceptance Criterion
In-house	II (Paddle)	75	pH 4.0 acetate buffer / 37 °C ± 0.5°C	900	Q=(b)(4)% in 15 minutes

2) The Applicant provided similar and very rapid comparative dissolution profile data to bridge drug products manufactured at different sites with different batch scales.

Microbiology: **Adequate**

Edaravone Oral Suspension is a multi-dose product; however, (b) (4) (b) (4) because several components, including edaravone have antimicrobial properties. The final formulation, (b) (4) (b) (4), showed both bactericidal and fungicidal effects in glass bottles.

Adequate release microbial limit specification, test methods and acceptance criteria to demonstrate that the product is free from *E. coli* and *B. cepacia* are provided. The microbial limit release specification also includes test methods and acceptance criteria to demonstrate that the product is free of the objectionable microorganism *B. cepacia* and *E. coli.* Suitability of the test methods has been verified.

Environmental: **Adequate**

The Applicant's claim for categorical exclusion under 21 CFR § 25.31(b) is acceptable. The expected introduction concentration (EIC) of edaravone into the aquatic environment is substantially lower than 1 ppb.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay/stability		**Low**	(b) (4)	**Adequate**	
Physical stability (phase separation)		**Low**		**Adequate**	
Physical stability (solid state)		**Low**		**Adequate**	
Dose accuracy		**Low**		**Adequate**	
Dissolution		**Low**		**Adequate**	
Palatability		**Moderate**		**Adequate**	
Microbial limits		**Low**		**Adequate**	
Leachables		**Moderate**		**Adequate**	

D. List of Deficiencies for Complete Response

Not applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
Senior Product Quality Assessor for Neurology Products
Office of New Drug Products

4/22/2022

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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	RADICAVA ORS®	Adequate
Established name(s)	edaravone	Adequate
Route(s) of administration	Oral	Adequate
Summary of the dosage form(s) and strength(s) in metric system.	Oral, 105 mg (5 mL) once daily	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 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

1.2 FULL PRESCRIBING INFORMATION

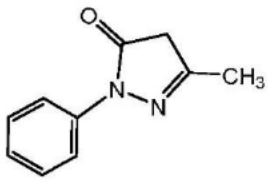
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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	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 suspension	Adequate
Strength(s) in metric system	105 mg/5 mL	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	yes	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)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	RADICAVA ORS	Adequate
Dosage form(s) and route(s) of administration	oral suspension	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	sorbitol, xanthan gum, polyvinyl alcohol, sodium bisulfite, L-cysteine hydrochloride hydrate and simethicone emulsion. Phosphoric acid and sodium hydroxide are added to adjust to pH 4.	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Adequate
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	Adequate
Pharmacological/therapeutic class	No (listed as unknown in Section 12)	Adequate
Chemical name, structural formula, molecular weight	 3-methyl-1-phenyl-2-pyrazolin-5-one molecular formula: $C_{10}H_{10}N_2O$ molecular weight = 174.20.	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	pH 4	Adequate

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)

<table>
<tr><th>Item</th><th>Information Provided in the NDA</th><th>Assessor's Comments</th></tr>
<tr><td colspan="3">HOW SUPPLIED/STORAGE AND HANDLING section</td></tr>
<tr><td>Available dosage form(s)</td><td>Oral suspension</td><td>Adequate</td></tr>
<tr><td>Strength(s) in metric system</td><td>105 mg/5 mL dose</td><td>Adequate</td></tr>
<tr><td>Available units (e.g., bottles of 100 tablets)</td><td>Two configurations: (1) bottle of 735 mg/35mL (105 mg/5 mL dose), one (1) bottle of 1050 mg/50 mL (105 mg/5 ml dose)</td><td>Adequate</td></tr>
<tr><td>Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number</td><td>
<table>
<tr><th>Unit of sale</th><th>NDC number</th><th>Package configuration</th></tr>
<tr><td rowspan="2">RADICAVA ORS Starter Kit</td><td>NDC 70510-2321-1</td><td>Carton of One (1) bottle of 35mL (105 mg/5 mL dose)</td></tr>
<tr><td>NDC 70510-2321-2</td><td>Carton of two (2) NDC 70510-2321-1</td></tr>
<tr><td>RADICAVA ORS Kit</td><td>NDC 70510-2322-1</td><td>Carton of One (1) bottle of 50 mL (105 mg/5 ml dose)</td></tr>
</table>
</td><td>Adequate</td></tr>
<tr><td>Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"</td><td>N/A</td><td>N/A</td></tr>
<tr><td>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.</td><td>N/A</td><td>N/A</td></tr>
</table>

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	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	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	<u>Pharmacy</u> Store RADICAVA ORS refrigerated between 2ºC–8 ºC (36°F–46°F) and protect from light. Do not freeze. Store upright. <u>Patient</u> Store RADICAVA ORS upright at room temperature between 20°C–25°C (68°F–77°F). Protect from light. Discard 15 days after opening bottle or if unopened 30 days from date of shipment indicated on the carton pharmacy label.	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A
Include information about child-resistant packaging	Provided (the cap is CRC, see P.7)	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 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		
Distributed by	Mitsubishi Tanabe Pharma America, Inc., a US subsidiary of Mitsubishi Tanabe Pharma Corporation 525 Washington Blvd., Suite 400, Jersey City, NJ 07310	Adequate

2.0 PATIENT LABELING

N/A

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

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

3.0 CARTON AND CONTAINER LABELING

3.1 & 3.2. Container and Carton Label

(b) (4)

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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	yes	Adequate
Dosage strength	Yes	Adequate
Route of administration	Yes	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Yes	
Net contents (e.g. tablet count)	Yes	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	Yes	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.	Yes	Adequate
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	N/A
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor’s Comments about Carton Labeling
Name of manufacturer/distributor	Yes	Adequate
Medication Guide (if applicable)	Yes	N/A
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	Yes	Adequate

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

Overall Assessment and Recommendation:

Primary Labeling Assessor Name and Date:
Secondary Assessor Name and Date (and Secondary S

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Jizhou Wang

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Martha Heimann

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CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	NDA 215446
Assessment Cycle Number	01
Drug Product Name/ Strength	RADICAVAORS™ (edaravone) oral suspension, 105mg/5mL
Route of Administration	Oral
Applicant Name	Mitsubishi Tanabe Pharma Corporation
Therapeutic Classification/ OND Division	Motor Neuron Disease /DN1
RLD/RS Number	N/A
Proposed Indication	For the treatment of Amyotrophic Lateral Sclerosis (ALS)
Primary Reviewer	Hansong Chen, PharmD, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Low	This is a highly soluble drug	Low	Biopharmaceutics risk is further mitigated with the tightened dissolution acceptance criterion.

Background

Mitsubishi Tanabe Pharma Corporation developed edaravone oral suspension, 105mg (5mL) and seek approval through the 505(b)(1) regulatory pathways on 11/12/2021. The proposed indication is for the treatment of Amyotrophic Lateral Sclerosis (ALS).

RADICAVA (edaravone) for IV infusion with the same indication, held by the same Applicant, was approved under NDA 209176 on 5/5/2017. In NDA 215446, the Applicant conducted a PK study to bridge the approved IV formulation of edaravone to

the proposed oral edaravone suspension. The Applicant also conducted a Phase 3 Study MT-1186 -A01 to support the safety of the oral suspension.

Review Summary

The Biopharmaceutics review focused on the evaluation of the adequacy of the overall information/data supporting: 1) the proposed dissolution method and acceptance criterion, and 2) the bridging of two clinical batches manufactured at different sites and scales.

Based on the review of the provided information/data, Biopharmaceutics has the following assessments:
1) The Applicant's proposed dissolution method [USP apparatus II (Paddle) at 75 rpm; 900 mL of pH 4.0 acetate buffer at 37 °C] is considered acceptable. The proposed acceptance criterion of Q= (b)(4)% in (b)(4) minutes has been tightened to Q= (b)(4)% in 15 minutes. The following dissolution method and acceptance criterion can be approved:

Method Source	USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)	Acceptance Criteria
In-house	II (Paddle)	75	pH 4.0 acetate buffer / 37 °C ± 0.5°C	900	Q= (b)(4)% in 15 minutes

2) The Applicant provided similar and very rapid comparative dissolution profile data to bridge drug products manufactured at different sites with different batch scales.

Recommendation:
From a Biopharmaceutics perspective, NDA 215446 for RADICAVAORS™ (edaravone) oral suspension, 105mg/5ml, is ADEQUATE.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 0001 /Original submission	11/12/2021
Sequence 0006 /Response to Biopharmaceutics IR 1	1/26/2022
Sequence 0008 /Response to Biopharmaceutics IR 2	3/3/2022

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.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ***{Adequate}***

1. Dissolution method

The Applicant proposed the following dissolution method:

Table 1. The proposed dissolution method

Method Source	USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)	Acceptance Criteria
In-house	II (Paddle)	75	pH 4.0 acetate buffer / 37 °C ± 0.5°C	900	Q= (b)(4)% in (b)(4) minutes

1) Dissolution method development

(b) (4)

[redacted]

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2) Discriminating power of the dissolution method

In order to investigate the discriminating power of the dissolution method, the Applicant intentionally manufactured two aberrant batches, [redacted] Table 3 is a side-by-side comparison of these two batches and the target batch. As shown in Table 3, the aberrant batch with [redacted] was manufactured with [redacted].

Table 3. A side-by-side comparison of two aberrant batches and the target batch

Products		Target batch (Normal)	Aberrant batch	Aberrant batch	Aberrant batch
Batch No.		019874	1186-2010-API-18006	1186-2010-API-18004	MT-1186-2201-API-18006
Drug Substance Lot No. used		240020	1186AP18006	1186AP18004	1186AP18006
Component	Edaravon				
	Polyvinyl alcohol				
	Xanthan gum				
	Sodium bisulfite				
	L-Cysteine [redacted] hydrochloride hydrate				
	Sodium hydroxide				
	Phosphoric acid				
	[redacted] Sorbitol				
	Simethicone emulsion [redacted]				
Manufacturing process					
Viscosity					
Particle size distribution of drug substance	D_{10} D_{50} D_{90}				

Figure 5. Discrimination Power with Aberrant Formulation Batches at pH 4.0 acetate buffer, 900 mL, 75 rpm (N=12)

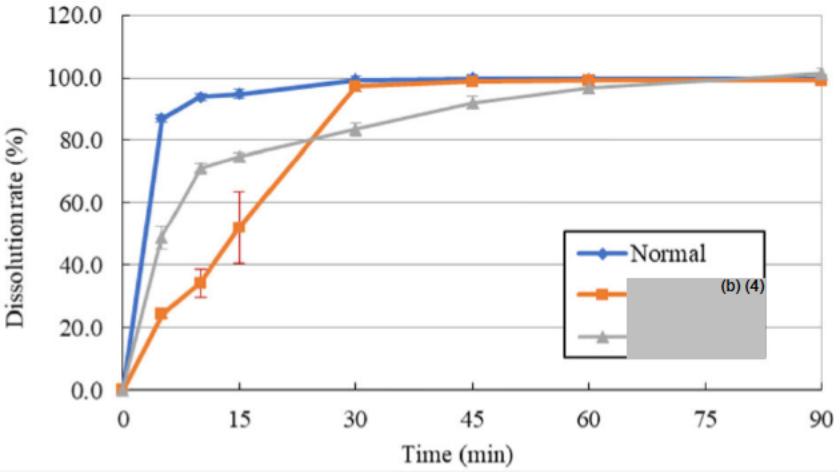


Table 4. Dissolution data of Aberrant Formulation Batches at pH 4.0 acetate buffer, 900 mL, 75 rpm (N=12)

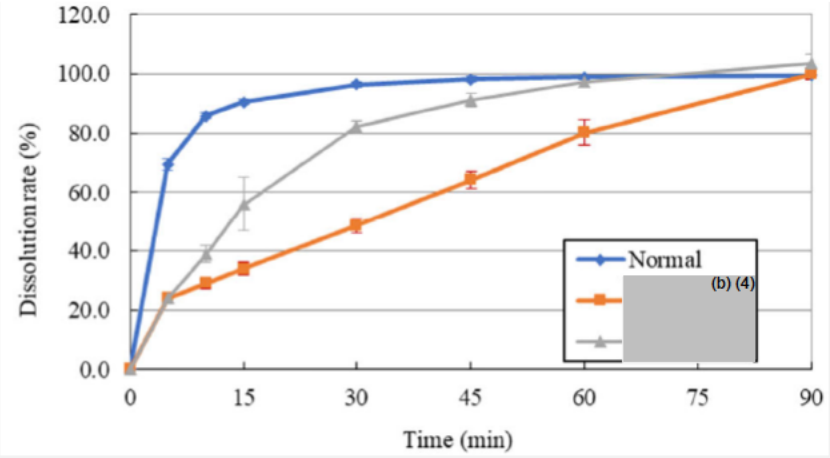
Time (min)	pH4.0 Acetate Buffer, 900 mL, 75 rpm					
	Normal		(b) (4)		(b) (4)	
	Average (%)	SD (%)	Average (%)	SD (%)	Average (%)	SD (%)
0	0.0	0.0	0.0	0.0	0.0	0.0
5	86.9	1.2	24.1	1.1	48.7	3.5
10	93.9	1.1	34.2	4.6	71.2	1.4
15	94.9	1.5	52.0	11.6	74.7	1.3
30	99.3	1.4	97.2	1.6	83.4	2.1
45	99.7	1.4	98.7	1.6	92.0	2.0
60	99.6	1.4	99.1	1.6	96.8	1.7
90	99.6	1.5	99.2	1.7	101.2	1.7
F2 value			15.8 (5~30min)		31.7 (5~45min)	

The dissolution profiles of the above three batches were compared under proposed dissolution conditions. As shown in Figure 5 and Table 4, two aberrant batches have significantly faster drug release than the target one.

Therefore, the Applicant concluded that the proposed dissolution method is able to discriminate changes in (b) (4) of the drug product.

Comparation with FDA Standard Dissolution Testing Method for High Solubility Drug Substances

Figure 6. Discrimination Power of the standard dissolution method with Aberrant Formulation Batches at (b) (4) (N=12), (b) (4) (b) (4)



FDA 2018 guidance recommends a standard dissolution testing for a drug product containing a highly soluble drug substance. The Applicant used a standard dissolution condition ((b) (4)) to compare the dissolution profiles of these two aberrant batches and the target one (Figure 6).

As shown in Figure 6, the standard method is also discriminating changes in (b) (4) (b) (4) of the drug product.

Reviewer's comment on the discriminatory power of the dissolution method

The Applicant altered one variable at a time to investigate the discriminatory power of the dissolution method. The change in (b) (4) from the target to the aberrant one is reasonable. However, the change in (b) (4) (i.e., (b) (4) (b) (4)) is beyond our expected 20% range. Considering that the drug substance is highly soluble and the proposed drug product is for immediate release, which would suggest a low biopharmaceutics risk, this Reviewer did not request the Applicant to reinvestigate the discriminating power of the method with the meaningful change in the (b) (4) (b) (4) in the formulation. Because the proposed drug product has very rapidly dissolving, the demonstrated discriminatory power might not have any clinical relevance other than keeping batch-to-batch consistency.

Reviewer's overall comment on the dissolution method

The proposed dissolution method is considered acceptable. (b) (4) (b) (4) (b) (4). *Additionally, this Reviewer recommends the tightening of the dissolution acceptance criterion from "Q=(b) (4)% in (b) (4) min" to "Q=(b) (4)% in 15 min", which would further mitigate any biopharmaceutics risks.*

2. Dissolution profile data and acceptance criterion

There are 13 batches used in clinical studies and, among them, 6 of them are also primary stability batches. The Applicant provided detailed information of those batches shown in Table 5. The complete dissolution profile data were provided and summarized in Table 6 by this Reviewer.

Table 5. List of all clinical and registration batches

Drug Product Batch number	Drug Substance Batch number	Batch Size	Date of Manufacture	Manufacturing site	Purpose of DP Batch/Usage
18P083	240020	(b) (4)L	January 2019	MTPF, Onoda Plant	Clinical studies (MT-1186-J03, J04, J05 and J06)
018811	240030	(b) (4)L	September 2019	(b) (4)	Clinical studies (MT-1186-A01 and Z-101)
018812	240030	(b) (4)L	September 2019		Clinical studies (MT-1186-A01 and Z-101)
018813	240020	(b) (4)L	September 2019		Clinical studies (MT-1186-A01 and Z-101)
018814	240020	(b) (4)L	September 2019		Clinical studies (MT-1186-A01 and Z-101)
018816	240010, 240030	(b) (4)L	September 2019		Clinical studies (MT-1186-A01 and Z-101)
018817	240010, 240030	(b) (4)L	September 2019		Clinical studies (MT-1186-A01 and Z-101)
019873	240020	(b) (4)L	March 2020		Clinical studies (MT-1186-A01 and Z-101) and primary stability studies
019874	240020	(b) (4)L	March 2020		Clinical studies (MT-1186-A01 and Z-101) and primary stability studies
019919	240030	(b) (4)L	March 2020		Clinical studies (MT-1186-A01 and Z-101) and primary stability studies
019920	240030	(b) (4)L	March 2020		Clinical studies (MT-1186-A01 and Z-101) and primary stability studies
019984	1073870010	(b) (4)L	March 2020		Clinical studies (MT-1186-A01 and Z-101) and primary stability studies
019985	1073870010	(b) (4)L	March 2020		Clinical studies (MT-1186-A01 and Z-101) and primary stability studies

Table 6. Mean dissolution profile data of pivotal clinical batches.

Batch number/time(min)	5	10	15	30	45	60
Batch 18P083	80.6	90.0	91.1	95.3	96.9	97.1
Batch 018811	N.D.	N.D.	96	97	97	97
Batch 018813	N.D.	N.D.	96	98	98	97
Batch 018816	N.D.	N.D.	97	99	99	99
Batch 018812	N.D.	N.D.	95	97	97	97
Batch 018814	N.D.	N.D.	97	100	100	100

Batch 018817	N.D.	N.D.	98	99	99	98
Batch 019873	N.D.	N.D.	99	99	100	100
Batch 019919	N.D.	N.D.	97	99	99	99
Batch 019984	N.D.	N.D.	98	99	99	99
Batch 019874	N.D.	N.D.	103	103	103	104
Batch 019920	N.D.	N.D.	102	103	103	103
Batch 019985	N.D.	N.D.	101	102	103	102

N.D.-not determined

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

Reviewer's comment
Since the proposed dissolution method is not a recommended method by the 2018 FDA guidance, the setting of the dissolution acceptance criterion should be data-driven.

Table 6 shows that all clinical/registration batches have a mean dissolution of at least 95% at 15 minutes, i.e., very rapid dissolution, indicating that the proposed dissolution acceptance criterion is liberal and can be tightened as follows:
Q= (b)(4)% in 15 minutes. The study of the discriminating power of the proposed dissolution method further supports the regulatory decision. When the acceptance criterion is set as Q= (b)(4)% in 15 minutes, it can reject aberrant batches (see Figure 5 and Figure 6). Note that the reported median Tmax of edaravone is 0.5 hours (range, 0.25 to 0.75 hours).

*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 update to the relevant documents.*

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: *N/A*

BB.12 BRIDGING OF FORMULATIONS

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

Batch 18P083 employed in clinical studies MT-1186-J03, J04, J05, and J06 was manufactured at Mitsubishi Tanabe Pharma Factory, Onoda Site, Japan at the scale of (b)(4)L. All other batches used in clinical studies MT-1186-A01 and Z-101 were manufactured at (b)(4) at the scale of (b)(4) L (Table 7). The Applicant provided comparative dissolution data to bridge the differences in manufacturing site and scale.

Table 7. Comparison of Manufacturing Site and Manufacturing Batch Scale

Batch number	Clinical use	Manufacturing size	Manufacturing scale
18P083	MT-1186-J03, J04, J05, and J06	Mitsubishi Tanabe Pharma Factory, Onoda Site, Japan	(b) (4) L
019874	MT-1186-A01 and Z-101	(b) (4)	(b) (4) L

Table 8. Mean dissolution data comparison of Batches 18P083 and 019874

Batch number/time(min)	5	10	15	30	45	60
Batch 18P083	80.6	90.0	91.1	95.3	96.9	97.1
Batch 019874	86.4	92.7	93.9	98.1	98.7	98.3

Figure 7. Dissolution profile comparison of Batches 18P083 and 019874

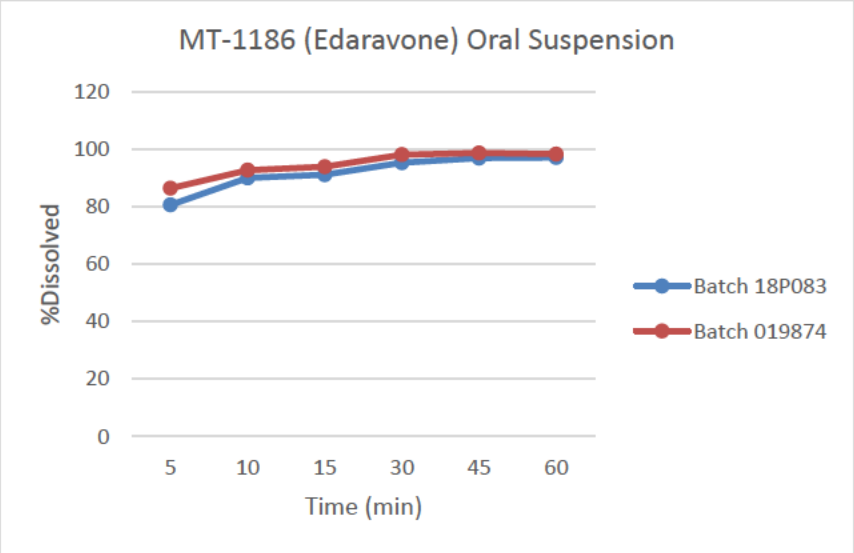


Table 8 and Figure 7 show that Batches 18P083 and 019874 have similar dissolution profiles and achieving very rapid dissolution (i.e., greater than (b) (4)% at 15 minutes).

Reviewer's comment

The Applicant did not submit multimedia comparative dissolution data for the bridging. This Reviewer considers it acceptable because edaravone is a highly soluble drug across physiologic pH range. It is expected that both batches would be very rapidly dissolving in other dissolution media.

B. 13 BIOWAIVER REQUEST

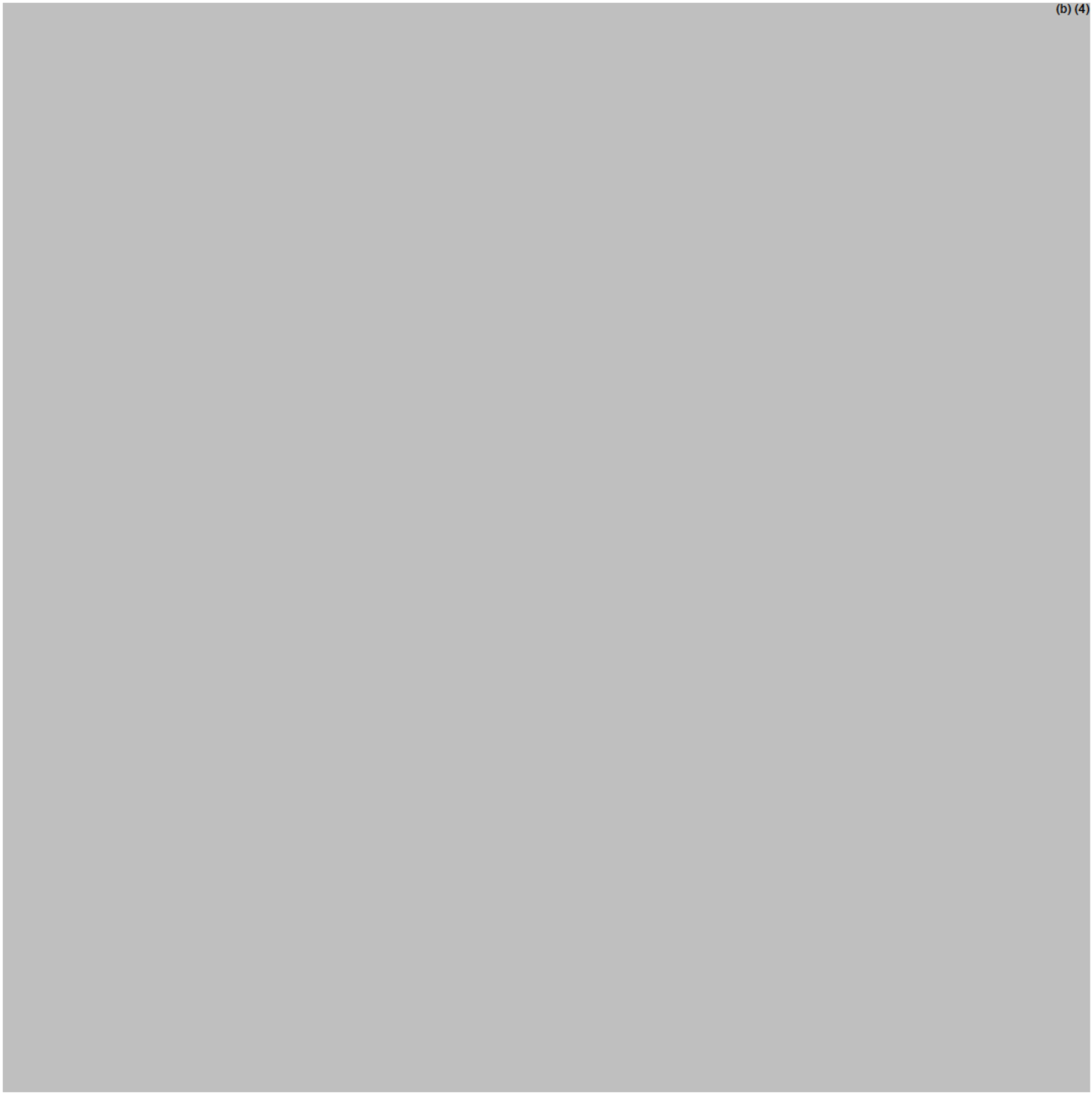
Assessment: *N/A*

The proposed drug product has only one strength.

Appendix

Biopharmaceutics IRs (dated 01/18/2022 and 02/25/2022) and Applicant's response (dated 01/26/2022 and 03/03/2022)

(b) (4)



R. REGIONAL INFORMATION

Comparability Protocols

Assessment:

Post-Approval Commitments

Assessment:

Lifecycle Management Considerations

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

APPEARS THIS WAY ON ORIGINAL

Hansong Chen

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Ta-Chen Wu

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	215446
Assessment Cycle Number	01
Drug Product Name/ Strength	Edaravone (Radicava ORS) / 105 mg/5 mL
Route of Administration	
Applicant Name	Mitsubishi Tanabe Pharma Corporation
Therapeutic Classification/ OND Division	N/A
Manufacturing Site	(b) (4)
Method of Sterilization	Non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary: The submission is **recommended** for approval.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
1 (eCTD seq. #0001)	11/12/2021
5 (eCTD seq. #0005)	01/26/2022

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
11/12/2021	11/12/2021	N/A	11/22/2021
01/26/2022	01/26/2022	N/A	01/26/2022

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks:

This is an electronic submission.
Goal date is 05/12/2022.

Priority review status granted.

Response to the Agency's information request letter was provided in the 01/26/2022 submission.

Concise Description of Outstanding Issues: No outstanding issues remain.

Select Number of Approved Comparability Protocols: 0

This review contains original information as well as response to microbiology deficiency conveyed to the sponsor in the Agency's information request letter dated 01/20/2022. The deficiency are italicized.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product –

(section 3.2.P.1: Description and composition of the drug product).

MT-1186 Oral Suspension 735 mg/35 mL and MT-1186 Oral Suspension 1050 mg/50 mL are provided as 35 mL and 50 mL of suspension respectively, contained in an amber glass bottle. The non-sterile product is provided as 7 days- or 10 days-multi-dose product, each dose comprising 105 mg edaravone in 5 mL of suspension. The drug product is also known in application as Edaravone or Radicava ORS.

Drug product composition –

(section 3.2.P.1.2: Drug product composition).

Component	Function	Quantity (1 bottle contains)		Quantity (each dose contains)
		For 7 days multi-dosing	For 10 days multi-dosing	
Edaravone, In-house	Active ingredient	735 mg	1050 mg	105 mg
Polyvinyl alcohol, USP / NF[1]				(b) (4)
Xanthan gum, USP / NF				
Sodium bisulfite, JP[2]				
Cysteine hydrochloride, USP / NF				
Sodium hydroxide, USP / NF				
Phosphoric acid, USP / NF				
(b) (4) Sorbitol, USP / NF				
Simethicone emulsion, USP / NF				
(b) (4), USP / NF				

[1]USP / NF: The United States Pharmacopeia / National Formulary

[2]JP: The Japanese Pharmacopoeia

Description of container closure system –

(section 3.2.P.7.1).

The MT-1186 Oral Suspension is packaged in 60 mL amber glass bottle. The bottles are closed with a child resistant, (b) (4), screw caps. The primary packaging and dosing device are described below.

The primary packaging is described below.

Component	Description	Component suppliers
Glass Bottle	(b) (4) (b) (4) 60 mL Amber (b) (4)	(b) (4)
Screw Cap	(b) (4) Child-Proof Cap (b) (4)	

The dosing device is described below.

Component		Description	Component suppliers
Adaptor		(b) (4) (b) mm (b) (4) Bottle Adapter	(b) (4)
Oral dispense	Barrel	5 mL Oral Dispenser	
	Plunger	(b) (4) (b) (4)	

(b) (4)

(b) (4)

Adequate

(b) (4)

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(b) (4)

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P.7 CONTAINER CLOSURE

See P.1.

P.8 STABILITY

P.8.1 STABILITY SUMMARY AND CONCLUSION

(section 3.2.P.8.1).

The long-term testing and the accelerated testing of MT-1186 Oral Suspension 735 mg/35 mL and 1050 mg/50 mL configurations were performed with the proposed container and closure. Both of these tests were performed for each configuration using 3 lots in an upright state and 1 lot in an inverted state all performed under the following storage conditions:

- Accelerated condition: 25 ± 2 °C/60 ± 5 % RH
- Long-term condition: 5 ± 3 °C/60 ± 5 % RH

Proposed Expiry: 18 months (section 3.2.P.8.1).

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P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

(section 3.2.P.).

The product stability specification includes the following microbiological tests:

Test	Analytical method	Acceptance criteria
Microbial limit	USP <61>, <62>	TAMC: ≤ (b) (4) CFU/g TYMC: ≤ (b) (4) CFU/g

	Harmonized USP <60>	*Escherichia coli*: (b) (4) (b) g) *Burkholderia cepacia*: (b) (4) (b) g)

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 5 ± 3 °C/60 ± 5 % RH

Test	Time (Months)								
	0	3	6	9	12	15	18	24	36
Microbial Limit	X		X		X			X	X
[1]Preservative effectiveness testing	X		X		X			X	X

[1]Preservative effectiveness testing is not included in the specification, but it is conducted to demonstrate the effectiveness of antibacterial preservatives throughout the shelf life.

Post Approval Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Adequate

P.8.3 STABILITY DATA

(section 3.2.P.8.3).

Batches 019873 (735 mg/35 mL) and 019874 (1050 mg/50 mL) met specification for microbial limit and preservative effectiveness testing the 12-month time point; all these lots met specification for microbial limit, demonstrated (b) (4) of *E. coli* and *B. cepacia*.

Adequate

R REGIONAL INFORMATION

Executed Batch Records

(Section 3.2.R)

Executed lot #(s):

- 019826
- 019862
- 019873
- 019874
- 019919
- 019920

The batch records consist of manufacturing information including formulation, bottle filling and capping.

Adequate

Comparability Protocols

No CP was included in the application.

Adequate

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

Post-dilution/constitution hold time – N/A
(section 1.14.1.3).
Route of administration: oral
Container: Multi-dose

Pharmacy
Store RADICAVA ORS refrigerated between 2 – 8 ºC (36 – 46 °F) and protect from light. Do not freeze. Store upright.

Patient
Store RADICAVA ORS upright at room temperature between 20 – 25 °C (68 – 77 °F). Protect from light.

Discard 15 days after opening bottle or if unopened 30 days from date of shipment indicated on the carton pharmacy label.

Adequate

Post-Approval Commitments
None provided.

MICROBIOLOGY LIST OF DEFICIENCY: None

Primary Microbiology Assessor Name and Date:
Eric Adeeku, Ph.D., 01/27/2022

Secondary Assessor Name and Date
Elizabeth Bearr, Ph.D., 01/27/2022

Eric Adeeku

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Elizabeth Bearr

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/s/

MARTHA R HEIMANN
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