

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209176Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

**NDA 209176
Review #1**

Drug Name/Dosage Form	Radicava (edaravone) Injection
Strength	30 mg/100 mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Mitsubishi Tanabe Pharma Corporation
US agent, if applicable	Mitsubishi Tanabe Parma Development America, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	June 16, 2016	All
Amendment	June 22, 2016	All
Amendment	September 13, 2016	DP
Amendment	October 3, 2016	DS, DP
Amendment	October 4, 2016	Micro
Amendment	October 12, 2016	DP
Amendment	October 20, 2016	DP
Amendment	October 27, 2016	DP, Process, Facilities
Amendment	November 2, 2016	DP, Process
Amendment	November 8, 2016	DP
Amendment	November 10, 2016	DP
Amendment	November 16, 2016	Micro
Amendment	November 30, 2016	DP, Process
Amendment	December 7, 2016	DP, Process
Amendment	December 8, 2016	DP
Amendment	December 15, 2016	DP, Process
Amendment	December 16, 2016	DP
Amendment	January 13, 2017	DS

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY	BRANCH/DIVISION
Drug Substance	Sithmalli Chandramouli	Kasturi Srinivasachar	Branch 1/DNDAPI
Drug Product	Dan Berger	Wendy Wilson-Lee	Branch 1/ DNDPI
Process	Kumar Janoria	Maotang Zhou	Branch VII/DP AIII
Microbiology	Eric Adeeku	Erika Pheiler	Branch I/DMA
Facilities	Aditi Thakur	Christina Capacci-Daniel	Branch II/DIA
Biopharmaceutics	Banu Zolnik	Okpo Eradiri	Branch 1/DB
Regulatory Business Process Manager	Dahlia Woody	-	Branch 1/DRBPM
Application Technical Lead	Wendy Wilson-Lee	-	Branch 1/DNDPI
Environmental Analysis	Dan Berger	Wendy Wilson-Lee	Branch 1/DNDPI

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Date	Comments
(b) (4)	Type III		(b) (4)	Adequate	18-NOV-2016	(b) (4)
	Type III			Adequate	14-OCT-2016	
	Type III			Adequate	14-OCT-2016	
	Type III			Adequate	14-OCT-2016	
	Type III			Adequate	14-OCT-2016	
	Type III			Adequate	14-OCT-2016	
	Type III			Adequate	17-JAN-2017	
	Type III			Adequate	17-JAN-2017	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	126396	Edaravone (MCI-186)
Designation Request	15-4782	Orphan designation for treatment of amyotrophic lateral sclerosis

2. CONSULTS: None

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of Radicava (edaravone) Injection, 30 mg/100 mL when packaged in the commercial packaged and stored as recommended.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	<i>Treatment of amyotrophic lateral sclerosis</i>
Duration of Treatment	<i>Chronic</i> - 60 mg administered intravenously over 60 minutes daily for 14 consecutive days followed by a 2-week drug free period (Cycle 1), and then 60 mg administered intravenously over 60 minutes daily for 10 days within a 14 day period followed by a 2-week drug free period (Cycle 2 and thereafter).
Maximum Daily Dose	<i>60 mg</i>
Alternative Methods of Administration	<i>None</i>

Edaravone is a free radical scavenger indicated for the treatment of ALS. Edaravone was approved in Japan in 2001 as an IV infusion (30 mg over 30 minutes for up to 14 days) for the treatment of acute ischemic stroke and in 2015 for the treatment of amyotrophic lateral sclerosis (ALS) (60 mg over 60 minutes, once daily). It was also approved in South Korea for ALS in 2015. Rilutek (riluzole) Tablets are currently the only FDA-approved treatment for ALS. FDA granted edaravone orphan designation on May 12, 2015. The proposed drug product is a 30 mg/100 mL sterile solution of edaravone formulated in commonly used excipients. The drug product packaging includes both an oxygen ^{(b) (4)} and an oxygen ^{(b) (4)} elements not normally found in packaging. ^{(b) (4)}

^{(u) (4)} Critical product quality review issues included:

1. the adequacy of the proposed control strategy for ^{(b) (4)}, ^{(b) (4)} in both the drug substance and drug product;
2. the adequacy of the proposed control strategy to limit exposure of the ^{(b) (4)} drug product to oxygen which may lead to reduced efficacy of the product;
3. the compatibility of the drug substance, excipients, manufacturing process, and packaging;
4. the adequacy of the proposed drug packaging to protect the drug product from exposure to light and oxygen.

Based on the information provided in the submission and in response to information requests, OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. The control strategy provides adequate assurance of sterility, (b) (4) during manufacturing, and control of (b) (4) formation. In addition, the primary and secondary packaging components were deemed suitable to protect the drug product from photolytic and oxidative degradation, as evidenced by the stability data.

Therefore, OPQ recommends **APPROVAL** of NDA 209176 and grants a (b) (4) month retest period for the drug substance and a 36 month drug product expiration period when stored at controlled room temperature in the intended commercial packaging.

B. Quality Assessment Overview

Drug Substance

(b) (4)

Approximately (b) (4) commercial batches of edaravone have been manufactured on a (b) (4) scale since 1999. The drug substance has been adequately characterized. The analytical methods to control the quality of the drug substance are adequately described and validated to ensure quality control. Edaravone has a monograph in the Japanese Pharmacopeia. The stability data supports a (b) (4) month retest period. The retest period should be confirmed for drug substance manufactured at the (b) (4) site post-approval. This NDA is recommended for approval from the Drug Substance perspective.

Drug Product

All excipients used in edaravone injection are compendial, with none being of human or animal origin. The excipient selection is appropriate and overall compatible. A critical

(b) (4)

The secondary packaging is of key importance in maintaining the integrity of the primary packaging, (b) (4). An oxygen absorber is contained in the secondary packaging to capture oxygen that permeates into the container closure, while an oxygen indicator provides an alert to the presence of oxygen within the packaging closure system. (b) (4)

(b) (4)

(b) (4) The container closure is adequate, providing a robust packaging system

(b) (4)

(b) (4) The packaging is additionally adequate to protect against degradation on exposure to (b) (4) light. The categorical exclusion is acceptable as it complies with 21 CFR 25.15(d) and 25.31(b).

Process

(b) (4)

Facilities

Following a review of the application, inspectional documents, and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 209176 are found to be acceptable

Biopharmaceutics

A review was not conducted for this product as the supporting pharmacokinetic studies were reviewed by Office of Clinical Pharmacology. There were no significant formulation or manufacturing changes that required bridging. As the product is a solution, there are no proposed tests for in vitro dissolution or disintegration.

Microbiology

The submission is recommended for approval on the basis of sterility assurance. No outstanding microbiology deficiencies remain. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process. Container closure integrity is assured via 100% testing of product.

C. Special Product Quality Labeling Recommendations (NDA only)

The following statements are recommended:

- a. Protect from light. Store in overwrapped package until time of use.
- b. Once the overwrap package is opened, use within 24 h.
- c. A special warning statement will be required in the labeling due to the potential for allergic reactions to the sodium bisulfite.

D. Final Risk Assessment (see Attachment)



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LABELING*{For NDA only}***R Regional Information****1.14 Labeling***Immediate Container Label*

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Route of administration 21.CFR 201.100(b)(3))	Delete the statement (b) (4) and change to "Injection" to correctly display the dosage form	Needs revision
Net contents* (21 CFR 201.51(a))		Adequate
Name of all inactive ingredients (Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Quantitative inactive ingredient information has not been provided	Needs revision
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)		Adequate
Storage (not required)	States: "Store at up to 25 °C (77 °F); excursions permitted between 15 and 30 °C (59 to 86 °F)"	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)***		Adequate
Name of manufacturer/distributor (21 CFR 201.1)		Adequate
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

Conclusion:

There are 2 revisions required for the container label: 1) The route of administration must be revised to “injection,” 2) Quantitative inactive ingredient information be provided to comply with 21 CFR 201.100(b)(5) for injectables. An email was sent to the Sponsor regarding the revision to the route of administration on December 16, 2016, and regarding the inactive ingredient information on January 5, 2017. Apart from these issues, the container label is adequate. The storage statement: “Store at up to 25 °C (77 °F)...” is acceptable as long term stability studies are underway at 1 °C, with no increase in degradants or trends observed at the 3 month timepoint. The Sponsor sent a courtesy email on January 19, 2017, enclosing revised container labels that address the route of administration issue, but does not list quantitative inactive ingredient information. This is acceptable if an agreement is made to incorporate the required changes in future product batches. Pending deficiencies will be worked on during labeling negotiations via the clinical division. A follow-up memorandum will be provided once final draft labels are received and reviewed.

Carton Labeling



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Revise the strength statement to display the strength per total followed by strength per mL enclosed by parentheses	Needs revision
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate

Expiration date per 21 CFR 201.17		Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables) 201.10(a), 21CFR201.100(d)(2)]	Quantitative inactive ingredient information has not been provided	Needs revision
Sterility Information (if applicable)	Sterility of product is noted in the USAGE statement: "If leaks are found, discard bag as sterility may be impaired."	Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		Adequate
Storage Conditions	States: "Store at up to 25 °C (77 °F); excursions permitted between 15 and 30 °C	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
"See package insert for dosage information" (21 CFR 201.55)	Equivalent statement included	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)		Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Delete the statement (b) (4) and change to "Injection" to correctly display the dosage form	Needs revision

Conclusion:

There are 2 revisions required for the carton label: 1) The route of administration must be revised to "injection," 2) Quantitative inactive ingredient information be provided to comply with 21 CFR 201.100(b)(5) for injectables. As noted above for the container label, an email was

sent to the Sponsor regarding the revision to the route of administration on December 16, 2016, and regarding the inactive ingredient information on January 5, 2017. While the drug product is not specifically described as a sterile solution, the sterility of the drug product is discussed in the usage statement. This statement is considered to adequately describe the sterility of the drug product. As discussed above for the container label, the storage statement: "Store at up to 25 °C (77 °F)..." is acceptable as long term stability studies are underway at 1 °C. In the courtesy email sent by the Sponsor on January 19, 2017, the enclosed carton labels were revised to address the route of administration issue, but quantitative inactive ingredient information was not listed. This is acceptable if an agreement is made to incorporate the required changes in future product batches. We will follow up with the Sponsor to confirm that the required changes are made to the container and carton labels. As noted for the container label, pending deficiencies will be worked on during labeling negotiations via the clinical division. A follow-up memorandum will be provided once final draft labels are received and reviewed.

List of Deficiencies:

1. The container label and carton label route of administration must be revised to "injection."
2. The container label and carton label must be revised to include quantitative inactive ingredient information to comply with 21 CFR 201.100(b)(5) for injectables.

Primary Labeling Reviewer Name and Date: Dan Berger

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Wendy Wilson



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Dan
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MICROBIOLOGY**Product Background:**

NDA: 209176

Drug Product Name / Strength: Edaravone Injection / 30 mg/100 mL**Route of Administration:** Intravenous**Applicant Name:** Mitsubishi Tanabe Pharma Corporation**Manufacturing Site:**

(b) (4)

Method of Sterilization:

(b) (4)

Review Summary:

The submission is **recommended** for approval on the basis of sterility assurance. No outstanding microbiology deficiencies remain. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

List Submissions being reviewed:

Submit	Received	Review Request	Assigned to Reviewer
06/16/2016	06/16/2016	N/A	06/28/2016
10/04/2016	10/04/2016	N/A	10/14/2016
11/16/2016	11/16/2016	N/A	11/21/2016

Highlight Key Outstanding Issues from Last Cycle:

None

Concise Description Outstanding Issues Remaining:

Please see 'List of deficiencies'.

Supporting/Related Documents:

N200677R1.doc – Sterility assurance review of the CCIT using high voltage leak test detector that was found adequate by B. Riley on 06/29/2012.

202496a1.doc – Sterility assurance review of the CCIT using high voltage leak test method that was found adequate by J. Arigo on 09/28/2012.

077259s10.doc – Sterility assurance review of the CCIT using high voltage leak test that was found adequate by H. Ngai on 11/15/2013.

Remarks Section:

No CP was included in the application.

The PDUFA date is 02/16/2017.

The deficiencies issued in the 09/19/2016 and 11/09/2016 microbiology information request were responded to in the 10/04/2016 and 11/16/2016 submissions respectively.

P.1 Description of the Composition of the Drug Product

Reviewer’s Assessment:

(section 3.2.P.1.1).

MCI-186 (edaravone) Injection 30 mg/100 mL is provided as 100 mL of sterile intravenous aqueous solution for infusion contained in a printed polypropylene infusion bag which is sealed inside a polyvinyl alcohol (b) (4)

(section 3.2.P.1.2).

Components ^a	Function	Quantity
Edaravone	Active ingredient	30 mg
Sodium bisulfite	(b) (4)	20 mg
L-Cysteine hydrochloride hydrate	(b) (4)	10 mg
Sodium chloride	Isotonic agent	(b) (4)
Sodium hydroxide	pH adjusting agent	(b) (4)
Phosphoric acid	pH adjusting agent	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Description of container closure system –

(section 3.2.P.7).

Package configuration	Description	Component suppliers	DMF No.
Polypropylene bag	(b) (4)	(b) (4)	(b) (4)

Reviewer’s Assessment: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

Acceptable

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

No data provided in the initial submission regarding the container closure integrity.

The following deficiency was issued in the 09/19/2016 microbiology information request and responded to in the 10/04/2016 submission:

Reviewer's Assessment:

Comments: Please provide container closure validation testing data to demonstrate that the ability of the container closure system to serve as a microbiological barrier is maintained. Describe the method used and provide acceptable positive and negative controls and describe how the controls were prepared. Note that prior to testing, units should be processed using minimally, production parameters. Provide the sensitivity of the test. Ensure that the entire fluid path of the bag is tested for integrity. For more information, please see FDA's Guidance to Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>).

Response:

(b) (4)

(b) (4)

(b) (4)

Based on previous review practices in DMA of CCIT where the high voltage leak test method was used and the fact that high voltage leak testing was performed on 100 % of the products, the response to deficiency is deemed adequate.

Acceptable

Antimicrobial Effectiveness Testing

Reviewer's Assessment:

The subject drug product is filled in a single-use bags; antimicrobial effectiveness testing is not required.

P.3 Manufacture

P.3.1 Manufacturers

(b) (4)

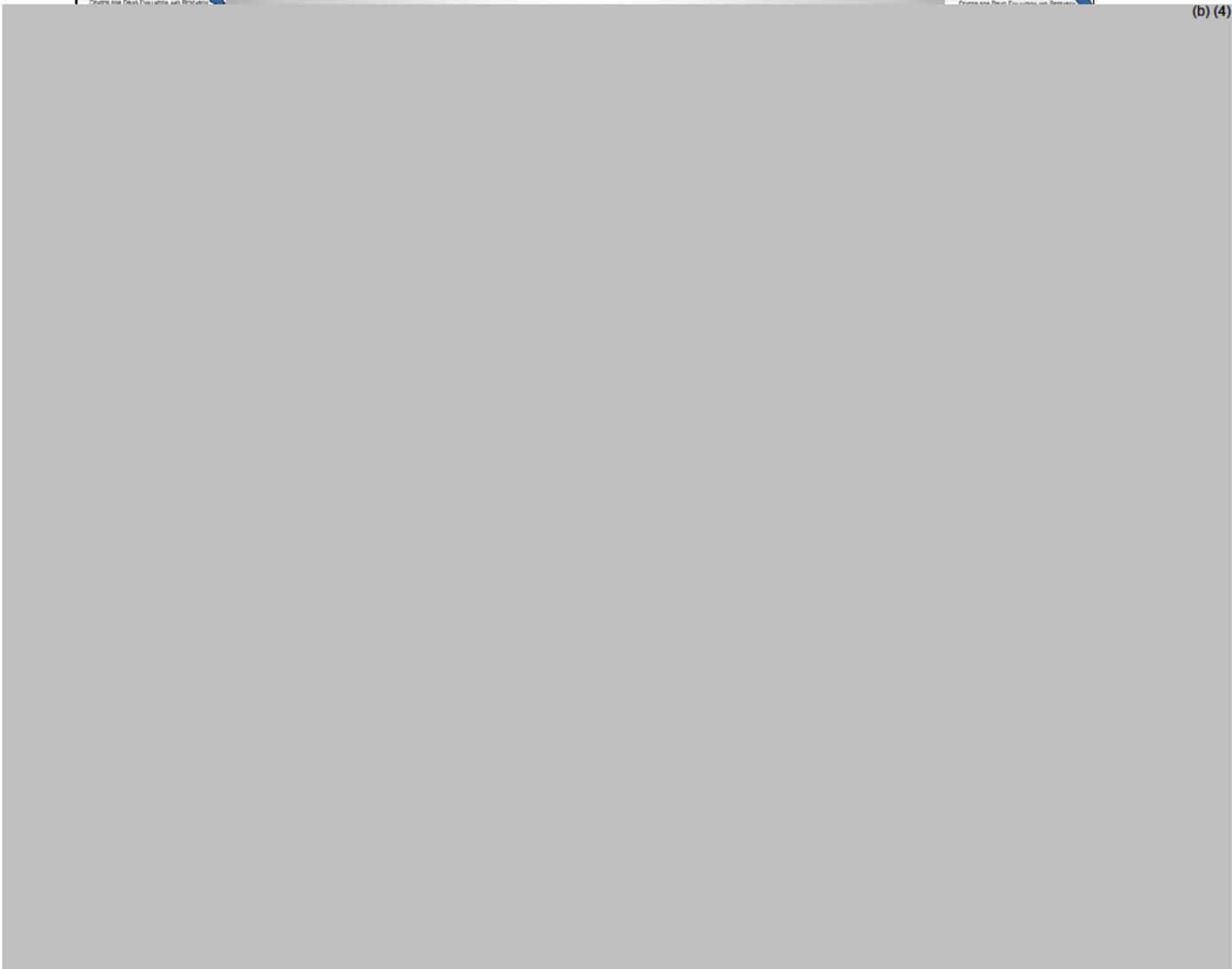
Drug product

P. 3.3 Description of the Manufacturing Process and Process Controls

Overall Manufacturing Operation

(section 3.2.P.3.3.1).

(b) (4)

**Acceptable****P.7 Container Closure**

Please see P.1 for this information.

P.8 Stability**P. 8.1 Stability Summary and Conclusion****Reviewer's Assessment:**

(section 3.2.P.8.1).

Three lots of the drug product were placed on stability testing under the following conditions:

- ❖ Accelerated stability: 40 °C/75 % RH
- ❖ Long term stability: 25 °C/60 % RH

Proposed Expiry: 36 months

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

Reviewer's Assessment:

(section 3.2.P.8.2).
 The product stability specification includes the following microbiological tests:
 (section 3.2.P.5.1).

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	USP <85>	NMT (b) (4)
Sterility	USP <71>	Meet requirement for USP <71>

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

Stability storage conditions: 25 °C/40 % RH

Test	Time (Months)									
	0	3	6	9	12	15	18	24	36	
Bacterial Endotoxins	X				X			X	X	
Sterility	X				X			X	X	

Post Approval Stability Commitment

(section 3.2.P.3.8.2).

[Redacted content] (b) (4)

Acceptable

P.8.3 Stability Data

Reviewer's Assessment:

(section 3.2.P.8.3).
 Exhibit batch #s R002V, R003V and R004V met specifications for the USP <71> sterility and USP <85> endotoxins at the 36 month time points.

Acceptable

A Appendices

A.2 Adventitious Agents Safety Evaluation

Not applicable

R Regional Information

Executed Batch Records

(section 3.2.R.1).
 Executed lot #R002V

The batch records confirm that validated [REDACTED] (b) (4) manufacturing processes were used for the manufacture of the exhibit batch.

The drug product was [REDACTED] (b) (4)

Acceptable

Comparability Protocols

No CP was included in the application.

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

2.A. Package Insert

(section 1.14.1.3).

Storage temperature: Store at 25 °C (77 °F); excursions permitted to 15 – 30 °C (59 – 86 °F)

Route of administration: IV infusion

Container: single use bags

Protect from light. Store in overwrapped package until time of use. Once the overwrap package is opened, use within 24 h.

Acceptable

Lifecycle Management Considerations

None

List of Deficiencies: No outstanding deficiencies remain.

Primary Microbiology Reviewer Name and Date:

Eric Adeeku, 11/22/2016

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



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Pfeiler

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ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment – *NDA 209176 Edaravone Injection 30 mg/100 mL*

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Sterility	Raw materials Formulation Container closure Process Scale/equipment/site	High	The product is manufactured (b) (4)	Low	
Endotoxin	Raw materials Formulation Container closure Process Scale/equipment/site	Moderate		Low	
Assay	Raw materials Formulation Container closure Process Scale/equipment/site	Low	Secondary packaging includes (b) (4), oxygen absorber and oxygen sensor to prevent oxidative degradation of drug substance.	Low	Continue to monitor effectiveness and performance of the oxygen sensor and oxygen absorber. (b) (4) (b) (4)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Uniformity of Dose	Formulation Container closure Process Scale/equipment/site	Low	The product is a solution packaged in a single-use, ready to use container. (b) (4)	Low	
(b) (4)	Raw materials Formulation Container closure Process Scale/equipment/site	Low	(b) (4)	Low	(b) (4)
pH	Raw materials Formulation Container closure Process Scale/equipment/site	Low	A phosphate buffer is utilized to maintain pH (b) (4)	Low	Confirm that pH remains within specified (b) (4) over extended time periods and/or after excursions from room temperature.
Particulate matter	Raw materials Formulation Container closure Process Scale/equipment/site	Moderate	(b) (4)	Low	

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Leachables/ Extractables	Raw materials Formulation Container closure Process Scale/equipment/site	Low	All potential leachables/ extractables from the primary packaging components have been identified and are being monitored under long term storage and accelerated conditions.	Low	
(b) (4) content	Raw materials Formulation Container closure Process Scale/equipment/site	Moderate	(b) (4)	Low	As (b) (4) is genotoxic, confirm all commercial batches meet specified limit.
Oxygen content	Formulation Container closure Process Scale/equipment/site	Moderate	(b) (4) The secondary packaging of the drug product contains an oxygen absorber and oxygen sensor to minimize exposure to oxygen.	Low	Continue to monitor effectiveness and performance of the oxygen sensor and oxygen absorber.



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