

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209321Orig1s000

PRODUCT QUALITY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 25 April 2019

TO: NDA 209321

FROM: Mariappan Chelliah, OPQ Drug Product primary reviewer for NDA 209321

SUBJECT: Description of the appearance of the suspension preparation.

APPLICATION/DRUG: NDA 209321, RUZURGI (amifampridine), 10 mg Tablets

This memo clarifies the description of the appearance of the amifampridine tablets dissolved in water that was discussed in the compatibility section of [NDA 209321 Drug Product Quality Review](#), dated 03-11-2019. In eCTD seq. 0014, dated 11-13-2018, the Applicant provided in-use stability/compatibility data to support the proposed prescribing information statement that amifampridine tablets may be dissolved in water for immediate administration by feeding/nasogastric (NG) tube. [Protocol Report #RA-102520187-1](#) described the appearance of the aqueous preparation as “clear solution with excipients”. However, in email dated 04-15-2018, addressed to Michelle Mathers, the Sponsor stated the following:

“Secondly, we are requesting guidance on the best description of the solution/suspension formed on the dissolution of Ruzurgi tablets in water. Amifampridine is highly water soluble and fully dissolves in water, however some of the excipients do not fully dissolve in water. [Dissolution of Ruzurgi tablets in water gives a milky suspension in which amifampridine is fully dissolved](#). The mixture was initially described as a suspension, so patients would not expect to form a clear solution on dissolution of Ruzurgi tablets in water. We defer to the expertise of the review team, but this was the rationale for our calling it a suspension.”

Based on this information, the aqueous preparation is deemed as “suspension”. Accordingly, “suspension” will be used to describe the aqueous preparation in the prescribing information.

Section 2.2 of the most recently edited version of PI is shown below:

2.2 Administration Instructions

RUZURGI can be taken without regard to food.

Preparation of 1 mg/1 mL Suspension

When patients require a dosage in less than 5 mg increments, have difficulty swallowing tablets, or require feeding tubes, a 1 mg/1 mL suspension can be prepared (e.g., by placing three 10 mg tablets in a 30 mL container, adding 30 mL of sterile water, and shaking well for 30 seconds). Crushing the tablets prior to making the suspension is not necessary. After preparation of the suspension, an oral syringe can be used to draw up and administer the correct dose by mouth or by feeding tube. Refrigerate the suspension between doses and shake well before drawing up each dose. The suspension can be stored under refrigeration for up to 24 h. Discard any unused portion of the suspension after 24 h.



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Recommendation: **APPROVAL**

**NDA 209321
Review #01**

Drug Name/Dosage Form	Amifampridine Tablets
Strength	10 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Jacobus
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
<i>Resubmission after RTF (SD 5)</i>	15-JUN-2018	<i>Amendment (SD 16)</i>	14-NOV-2018
<i>Amendment (SD 9)</i>	17-OCT-2018	<i>Amendment (SD 17)</i>	14-NOV-2018
<i>Amendment (SD 11)</i>	31-OCT-2018	<i>Amendment (SD 20)</i>	22-JAN-2019
<i>Amendment (SD 14)</i>	13-NOV-2018	<i>Amendment (SD 21)</i>	14-FEB-2019
<i>Amendment (SD 15)</i>	13-NOV-2018		

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Ray Frankewich	Suong Tran	ONDP
Drug Product	Mariappan Chelliah	Wendy Wilson-Lee	
Labeling			
Environmental			
Manufacturing	Tianhong Tim Zhou	Nallaperumal Chidambaram Ruth Moore	OPF
Biopharmaceutics	Mei Ou	Ta-Chen Wu	ONDP
Regulatory Business Process Manager	Dahlia Walters		OPRO
Application Technical Lead	Wendy Wilson-Lee		ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	11-MAR-2019	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	54313	Amifampridine Tablets for Treatment of Lambert-Eaton Syndrome

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 209321 for amifampridine tablets, 10 mg.

II. Summary of Quality Assessments

A. Product Overview

Jacobus is seeking approval of amifampridine for the treatment of Lambert-Eaton Myasthenia Syndrome (LEMS). Lambert-Eaton Myasthenia Syndrome (LEMS) is a rare autoimmune disorder caused by antibodies to the presynaptic voltage-gated calcium. LEMS is frequently associated with lung cancer, small cell carcinoma, and symptoms include weakness of proximal limb muscles and eye muscles, and disruption of the autonomic nerve system. In advanced stages respiratory disorders may occur. LEMS generally occurs in patients older than 40. There are no approved treatments. FDA granted Orphan Designation (December 1990), Fast Track Designation (September 2014), and Rolling Review (March 2017). FDA has also granted numerous single patient INDs for treatment of patients under expanded access as part of a compassionate use program since 1993.

Amifampridine is a well characterized, small molecule new molecular entity, available as an immediate-release tablet formulation in one tablet strength – 10 mg. The tablet is functionally scored. OPQ recommended a refuse to file action of the original submission due to a poorly organized submission and insufficient data to support assessment of the adequacy of the chemistry, manufacturing, and controls strategy to assure the identity, purity, strength, purity, and quality of the drug substance and drug product. The key review issue for the resubmission will be to ensure that sufficient information is provided, particularly as it relates to (b) (4) data demonstrating the drug product is suitable for tablet splitting, control of the tablet manufacturing process, and information related to development of the dissolution method.

Proposed Indication(s) including Intended Patient Population	(b) (4) Lambert-Eaton myasthenia in patients (b) (4)
Duration of Treatment	Chronic
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	Dissolve in water prior to administration

B. Quality Assessment Overview

Amifampridine drug substance exists as anhydrous crystalline form and no other polymorph or amorphous form is known to exist. It has not been assigned a BCS

category. However, amifampridine has excellent aqueous solubility in various buffers and simulated intestinal fluids. Therefore, the polymorphic change or particle size distribution of the API are not expected to affect the dissolution performance of this immediate release product and they are unlikely to pose risk to the product quality. (b) (4)

(b) (4)

(b) (4)

Some of the expected impurities in amifampridine drug substance are potential mutagens. Ames testing was performed (b) (4). Results indicate that (b) (4) are positive and are considered to be mutagens. The Ames tests are ambiguous regarding whether or not (b) (4) is a mutagen. Despite the ambiguity the applicant has chosen to control (b) (4) as a mutagen. All three compounds are specified impurities in the DS release specification with a limit of \leq (b) (4) ppm. (b) (4)

(b) (4) They are controlled using a validated analytical procedure employing LC/MS/MS.

The retest period for amifampridine drug substance

(b) (4)
(b) (4)

The drug product will be marketed as a single, 10 mg strength. All excipients are compendial and present at levels qualified at the maximum daily exposure in this product. (b) (4) The tablets used in the pivotal clinical studies are comparable to the registration and proposed commercial batches.

The proposed tests and criteria for the amifampridine 10 mg tablets are appropriate for controlling the quality of this immediate release solid oral dosage form. All the three primary stability batches met the drug product specification. the batch data demonstrates that the Applicant can manufacture the drug product in very high purity that meet the

acceptance criteria for all the critical quality attributes. Key analytical methods have been validated and are acceptable for quality control and regulatory purposes.

The Applicant confirmed [REDACTED] (b) (4) using single crystal X-ray crystallography. Although the Applicant's (Q)SAR analysis predicted [REDACTED] (b) (4) as non-mutagenic, the Agency's independent (Q)SAR analysis predicted it to be positive for mutagenicity. The negative Ames data supports that this impurity is non-mutagenic.

Because of the sensitivity of the drug product to moisture, the applicant selected [REDACTED] (b) (4) that provide improved protection from moisture. The two-proposed container closure system for the commercial batches are same as those used in the primary stability batches. Based on the available stability data, the two container closure systems are expected to provide adequate protection to the amifampridine tablets under the proposed storage condition. The components of the primary container closure systems meet the USP and 21 CFR requirements. The stability data shows that the [REDACTED] (b) (4) provide adequate stability over the shelf-life. The primary container closure systems are appropriate choice for packaging the amifampridine tablets.

Per labeling, the starting dose is [REDACTED] (b) (4) is increased in 5 to 10 mg. The 10 mg scored tablets can be broken into halves and dosed as 5 mg tablets. The split halves met the following quality attributes at the lower, target, and upper range of the tablet breaking forces: loss of mass, weight, dissolution, content uniformity, and friability. Furthermore, the split halves are stable for 90 days when stored in a pharmacy dispensing container at 25°C/60%RH. Split tablet quality and stability was confirmed for both mechanically and manually split tablets. **The functionally scored tablets comply with current requirements as outlined in guidance.**

Amifampridine tablets are packaged as 100 counts and will require pharmacy dispensing to provide 30/90-day supplies. Although the applicant did not provide stability data for the whole tablets in pharmacy containers, the data for the split tablets (a worst-case condition) can be used to justify dispensing of the tablets in the pharmacy containers. Despite the slightly increased degradant levels observed for the split tablets, the degradant levels remained well below their respective acceptance limits. Therefore, dispensing the whole or split tablets in pharmacy containers without desiccant and storage for up to 90 days at controlled room temperature is acceptable.

The proposed shelf-life of 24 months for Amifampridine tablets is acceptable. However, the Agency recommends the following storage condition:

Prior to dispensing: store in a refrigerator between 2°C to 8°C (36°F to 46°F). Keep container tightly closed with desiccant canister inside. Protect from moisture and light.

After dispensing: store at 20°C to 25°C (68°F to 77°F) for up to 3 months; excursions permitted between 15°C to 30°C (59°F to 86°F).

In general, other than the impurities, no trending was noted for any of the attributes. The only notable trend is the formation of (b) (4)

(b) (4) While these specified impurities were not detected for batches stored in freezer or refrigerator, (b) (4)

Solution stability and the compatibility data support that amifampridine tablets may be dissolved in water and administered using feeding tube without any significant loss of potency. (b) (4)

The manufacturing of 3,4-DAP 10 mg tablets (b) (4)

After the refuse to file, the applicant also addressed previous concern related to sampling size issues (b) (4) in the proposed commercial process. In the current re-submission, (b) (4) individual sampling size has been modified (b) (4). The residual risks of the proposed commercial manufacturing process are related to the need of further control the excipients physical property and the need in addition of an enhance stratified sampling plan (b) (4). The applicant provided the commercial MBR, as requested with updates. All process related deficiencies were adequately addressed.

This Biopharmaceutics review focused on (1) the proposed quality control dissolution method and acceptance criterion for the immediate-release tablet, (2) dissolution data to support functional score of the 10 mg strength, and (3) formulation bridging. The currently proposed in vitro dissolution method is: USP apparatus II (paddle), 50 rpm, 500 mL of pH 4.5 Acetate Buffer, sampling at 5, 10, 15, 20, 30 and 45 minutes. The proposed dissolution method showed acceptable discriminating ability by differentiating drug release profiles of the drug product batches with different concentrations of disintegrant (b) (4). Therefore, **the proposed dissolution method is acceptable for the routine quality control of the finished product for release and stability testing.**

Manual or mechanical splitting of the 10 mg tablet into equal halves did not impact the in vitro dissolution profile of the tablet. Because the only excipient change of the finished drug product was from (b) (4) the finished drug product is considered having the same formulation throughout the pharmaceutical development. Additionally, the pivotal clinical batch has the same formulation as the commercial batch formulation. Therefore, no additional formulation bridging is needed.

All facilities are acceptable for the operations listed in NDA 209321. The claim for categorical exclusion is granted in accordance with 21 CFR 25.31(a) and 25.15(d). All labeling, including carton and container labels, comply with the CMC requirements.

C. Final Risk Assessment

From Initial Risk Identification		Review Assessment		
Critical Quality Attributes	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
<i>Assay</i>	Low		Acceptable	
<i>Solid State</i>	Low		Acceptable	
<i>Content Uniformity</i>	Medium	Adequate process controls such as multiple screenings steps and geometric mixing coupled with adequate sampling plan	Acceptable	
<i>Dissolution</i>	Low		Acceptable	
<i>Microbial Limits</i>	Low		Acceptable	
<i>Scored Tablet: Content Uniformity</i>	Medium	Data provided demonstrates that content uniformity of split tablets not a concern	Acceptable	
<i>Scored Tablet: Friability</i>	Low		Acceptable	
<i>Scored Tablet: Dissolution</i>	Medium	Data provided demonstrates that dissolution of split tablets not a concern	Acceptable	



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LABELING

I. Package Insert

1. Highlights of Prescribing Information

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	RUZURGI (amifampridine)
Dosage form, route of administration	Tablets for oral use
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 10 mg, functionally scored

2. Section 2 Dosage and Administration

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	For patients having difficulty swallowing, 1 mg/mL (b) (4) in water can be administered through feeding tube. For patients requiring <5mg strength, appropriate volume of 1mg/mL (b) (4) in water can be administered.

3. Section 3 Dosage Forms and Strengths

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablet
Strengths: in metric system	10 mg
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	RUZURGI 10 mg functionally scored tablets are oval, white to off-white, and debossed "10 110" on one side and "JACOBUS" on the other side.

4. Section 11 Description

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Proprietary and established names are provided
Dosage form and route of administration	Tablet for oral administration
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Excipients are listed alphabetically
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Potassium channel blocker
Chemical name, structural formula, molecular weight	adequate
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	adequate

5. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	10 mg
Available units (e.g., bottles of 100 tablets)	NDC 49938-110-01 (bottles of 100 tablets).
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	RUZURGI (amifampridine) 10 mg functionally scored tablets are oval, white to off-white, and debossed “10 110” on one side, and “JACOBUS” on the other side.
Special handling (e.g., protect from light)	Keep container tightly closed with desiccant canister inside. Protect from moisture and light.
Storage conditions	Prior to dispensing: store in a refrigerator between 2°C to 8°C (36°F to 46°F). After dispensing: store at 20°C to 25°C (68°F to 77°F) for up to 3 months; excursions permitted between 15°C to 30°C (59°F to 86°F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Adequate

Reviewer’s Assessment of Package Insert: *Adequate*

The labeling meets the appropriate regulations.

II. Labels:



(b) (4)

None

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Ruzurgi (amifampridine)	n/a
Dosage strength	10 mg	n/a
Net contents		n/a
“Rx only” displayed prominently on the main panel	Yes	n/a
NDC number (21 CFR 207.35(b)(3)(i))	49938-110-01	n/a
Lot number and expiration date (21 CFR 201.17)	Control # is used instead of lot#	n/a
Storage conditions	The Agency will recommend editing the storage condition as: Store between 2°C to 8°C (36°F to 46°F).	n/a
Bar code (21CFR 201.25)	Adequate	n/a
Name of manufacturer/distributor	Adequate	n/a
And others, if space is available	n/a	n/a

Reviewer’s Assessment of Labels: *Adequate*

The container label complies with all regulatory requirements from a CMC perspective.

- 1) Please note that the Sponsor is using control # instead of lot#. Per the Applicant’s [response](#) in eCTD seq. 0016, a 5-digit control number is assigned in a master log book and printed on the production record. The control # can be used to track back to the lot#. This meets the requirement of 21 CFR 203.38.
- 2) The Agency will recommend editing the storage condition as: Store between 2°C to 8°C (36°F to 46°F).

Note: The storage statements (but not the storage conditions) differ slightly between the PI and the container.

Prescribing Information:

Prior to dispensing: store in a refrigerator between 2°C to 8°C (36°F to 46°F).

Keep container tightly closed with desiccant canister inside. Protect from moisture and light.

After dispensing: store at 20°C to 25°C (68°F to 77°F) for up to 3 months; excursions permitted between 15°C to 30°C (59°F to 86°F).

Container Label:

Store in the refrigerator between 2°C to 8°C (36°F to 46°F).

List of Deficiencies: None

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer Name: Mariappan Chelliah

Secondary Reviewer Name: Wendy Wilson-Lee



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BIOPHARMACEUTICS

NDA: 209321 [505(b)(1)], Resubmission
Drug Product Name / Strength: Ruzurgi™ [Amifampridine (3,4-diaminopyridine)]
Tablets, 10 mg
Route of Administration: Oral
Applicant Name: Jacobus Pharmaceutical Company, Inc.
Proposed Indication: (b) (4) Lambert-Eaton Myasthenia (LEM) in patients (b) (4)
Submission Dates: 06/15/2018, 10/17/2018
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

REVIEW SUMMARY

The Applicant is seeking approval for the proposed immediate-release (IR) oral tablet, Ruzurgi™ (Amifampridine, 3,4-diaminopyridine) Tablets, 10 mg, for (b) (4) (b) (4) Lambert-Eaton Myasthenia (LEM) in patients (b) (4) (b) (4). The current submission, NDA 209321, is a resubmission of an original application submitted on 12/05/2017 which received a Refuse-to-File (RTF) letter on 01/31/2018 due to the drug product quality and nonclinical deficiencies. In both the RTF letter and the subsequent Type A meeting on 03/29/2018, the Division of Biopharmaceutics requested the Applicant to submit the complete *in vitro* dissolution method development report and the dissolution profile data of the proposed drug product.

This Biopharmaceutics review focused on (1) the proposed QC dissolution method and acceptance criterion for the IR tablet, Ruzurgi™, (2) dissolution data to support functional score of the 10 mg strength, and (3) formulation bridging, as summarized below.

In Vitro Dissolution Testing of the Finished Product:

The currently proposed *in vitro* dissolution method is: *USP apparatus II (paddle), 50 rpm, 500 mL of pH 4.5 Acetate Buffer, sampling at 5, 10, 15, 20, 30 and 45 minutes.* The proposed dissolution method showed acceptable discriminating ability by differentiating drug release profiles of the drug product batches with different concentrations of disintegrant (b) (4). Therefore, the proposed dissolution method is acceptable for the routine QC test of the finished drug product for batch release and stability testing.

Functional Score of the 10-mg Strength:

Manual or mechanical splitting of the 10 mg tablet into equal halves did not impact the *in vitro* dissolution profile of the tablet.

Formulation Bridging:

Because the only excipient change of the finished drug product was (b) (4) (b) (4) the finished

drug product is considered having the same formulation throughout the pharmaceutical development. Additionally, the pivotal clinical batch has the same formulation as the commercial batch formulation. Therefore, no additional bridging study is needed.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 209321 for Ruzurgi™ [Amifampridine (3,4-diaminopyridine)] Tablets, 10 mg, is recommended for **APPROVAL**.

The final approved *in vitro* dissolution method and acceptance criterion for the routine QC test of the finished drug product for batch release and stability testing are presented below:

USP Apparatus	II (Paddle)
Rotation Speed	50 rpm
Dissolution Medium and Volume	pH 4.5 Acetate Buffer, 500 mL
Temperature	37°C±0.5°C
Acceptance Criterion	Q (b) (4) % in 15 minutes

BIOPHARMACEUTICS REVIEW

1. BCS Classification

The drug substance, Amifampridine (pKa = 9.02), has high solubility in water and aqueous buffer in pH range from 1.2 to 10 (solubility >10 mg/250 mL = 0.04 mg/mL) per FDA’s BCS Guidance (2017). The solubility data are presented in Table 1 below. No BCS classification request or permeability data was submitted.

Table 1: Solubility of the drug substance, Amifampridine

Solvent	Solubility (mg/mL)	Initial pH	Final pH
Water ^a	18.5	11.19	11.19
Ethanol ^a	26.1	Not determined	Not determined
FaSSIF ^a	22.9	10.20	10.20
FeSSIF ^a	27.6	9.90	9.95
FaSSGF ^a	23.0	10.06	10.06
pH 9 glycine buffer ^a	46.5	9.20	9.24
pH 10 glycine buffer ^a	22.5	10.00	10.03
pH 2.6 citrate phosphate buffer ^b	≥103	NA	NA
pH 3 citrate phosphate buffer ^b	≥103	NA	NA

pH 4 citrate phosphate buffer ^b	68	NA	NA
pH 5 citrate phosphate buffer ^b	68	NA	NA
pH 6 citrate phosphate buffer ^b	51	NA	NA
pH 7 citrate phosphate buffer ^b	34	NA	NA
pH 8 citrate phosphate buffer ^b	29	NA	NA

NA = not applicable; FaSSIF = Fasting simulated intestinal fluid; FeSSIF = Fed simulated intestinal fluid;
 FaSSGF = Fasting simulated gastric.

- ^a Solubility was determined by adding excess solute, agitating for ~ 24 hours at ambient temperature, filtration, dilution of the filtrate with acetate buffer (3600 times), and analysis of absorbance at 284 nm.
- ^b Solubility was estimated at ambient temperature by addition of solute until the solid dissolved. Solubility is reported to the nearest mg/mL. If complete dissolution was achieved by only 1 aliquot addition, the value is reported as “≥.”

2. In Vitro Dissolution Method

The proposed dissolution method and acceptance criterion for routine QC test are “USP apparatus II (paddle), 50 rpm, pH 4.5 Acetate Buffer, 500 mL, Q ^{(b) (4)}% in 15 minutes”.

The following dissolution parameters were evaluated by the Applicant during the dissolution method development:



(b) (4)

- 5) Discriminating ability: To evaluate the discriminating capabilities of the proposed dissolution method, the Applicant manufactured drug product batches using different process parameters or composition, as detailed below.
- a) Particle size: Per the Applicant, the particle size of a crystalline drug substance may not affect the in vitro dissolution due to the high solubility of drug substance. Therefore, there is a low probability that dissolution profiles will be influenced by particle size.

During the OPQ mid-cycle meeting on 09/18/2018, both Drug Product and Process Reviewers had no concerns for the crystallization, polymorphisms, and particle size of drug substance because of its high solubility. This Reviewer also assessed that the proposed dissolution method is not necessary to discriminate in particle size of drug substance because of the drug substance high solubility and drug product very rapid dissolution.

- b) Disintegrant: Three deliberately manufactured batches [batch 17569 (control), 17570, and 17571; presented in Table 2 below] with different levels of disintegrant in formulation were used to evaluate the discriminating ability of the proposed dissolution method. (b) (4)

In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) drug product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes, critical formulation variables, and critical process parameters (e.g., \pm (b) (4)% change to the specified values or ranges for these variables).

For the tested batches 17569 and 17571, the overall disintegrant changes (e.g., (b) (4)) also, both batches showed very rapid and similar dissolution profiles (e.g. (b) (4)% in 15 min; see Figure 2). Therefore, the proposed dissolution method cannot discriminate the batches with different levels of (b) (4)

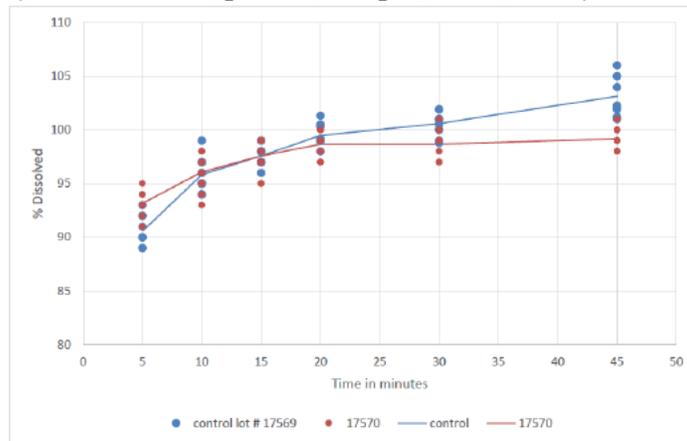
However, batch 17571 showed relatively slower dissolution at early time points (e.g., 5 and 10 min) and continued through the entire duration compared to that of the control batch 17569 (with (b) (4)% w/w of (b) (4) in tablet

composition) (Figure 3). Therefore, this Reviewer considers that the proposed dissolution method showed acceptable discriminating ability by showing different drug release profiles of the drug product batches with different concentrations of disintegrant (b) (4)

Table 2: Drug Product Batches with Different Levels of Disintegrant

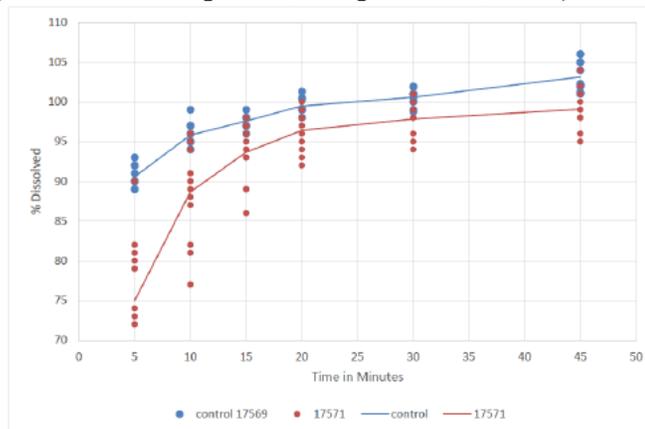
Batch	Description
17569	(b) (4)
17570	(b) (4)
17571	(b) (4)
DP = drug product	(b) (4)

Figure 2: Dissolution Profiles of Drug Product Manufactured with Reduced Concentration of the Disintegrant (b) (4) (Acetate Buffer, pH 4.5, 50 rpm, 37°C, n=12) Batch 17570



DP = drug product, (b) (4) = number of test samples.

Figure 3: Dissolution Profiles of Drug Product Manufactured without the Disintegrant (b) (4) (Acetate Buffer, pH 4.5, 50 rpm, 37°C, n=12) Batch 17571



DP = drug product, rpm = revolutions per minute.

c) Excipients: The impact of multiple excipients (b) (4) on the formulation was investigated. The batch information is presented in Table 3. The dissolution profiles are presented in Figures 4 to 6.

Table 3: Batch Information

Study Number	Batch Number	Description	Batch Size (Tablets)
2	17570	(b) (4)	(b) (4)
3	17571		
4	17572		
5	17573		
6	17574		

DP = drug product; DS = drug substance; NA = not applicable.

Figure 4: Dissolution Profiles for Drug Product Manufactured with Reduced Concentration of (b) (4) (Acetate Buffer, pH 4.5, 50 rpm, 37°C, n=12) – Batch 17572 and Control Batch 17569

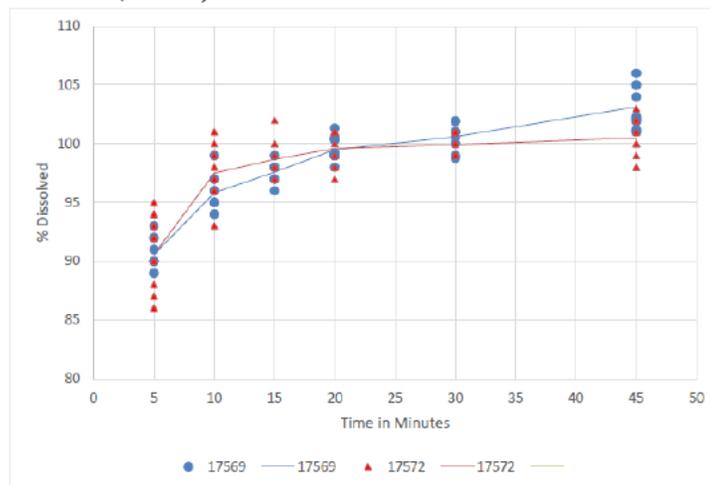


Figure 5: Dissolution Profiles for Drug Product Manufactured with Reduced Concentration of (b) (4) (Acetate Buffer, pH 4.5, 50 rpm, 37°C, n=12) – Batch 17573 and Control Batch 17569

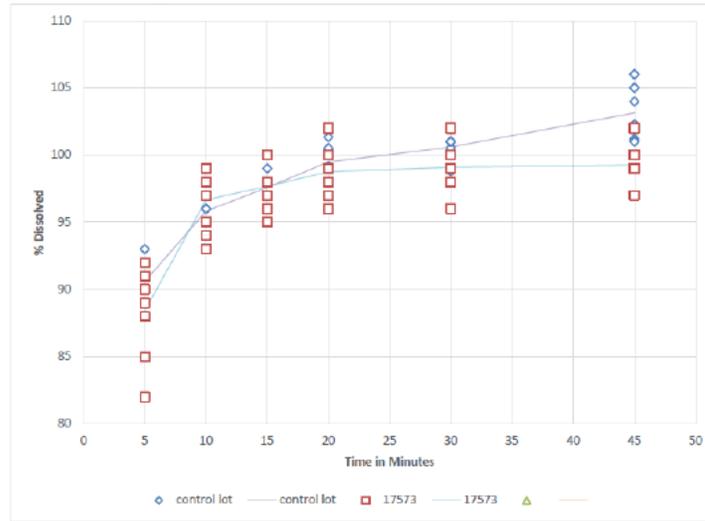
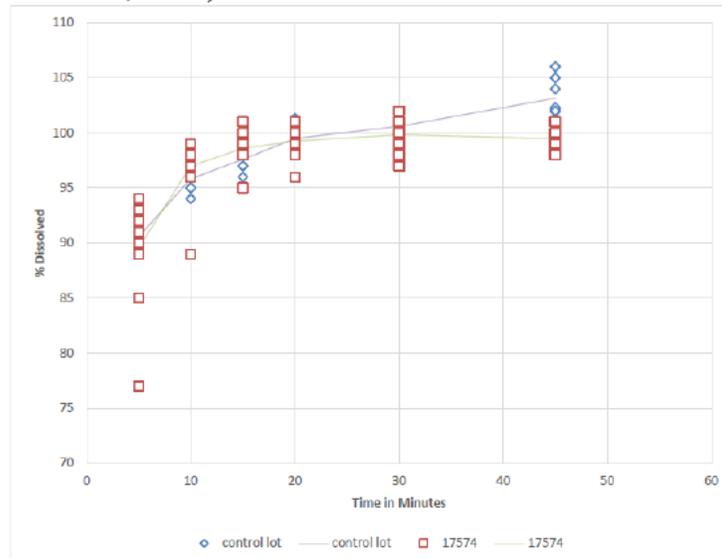


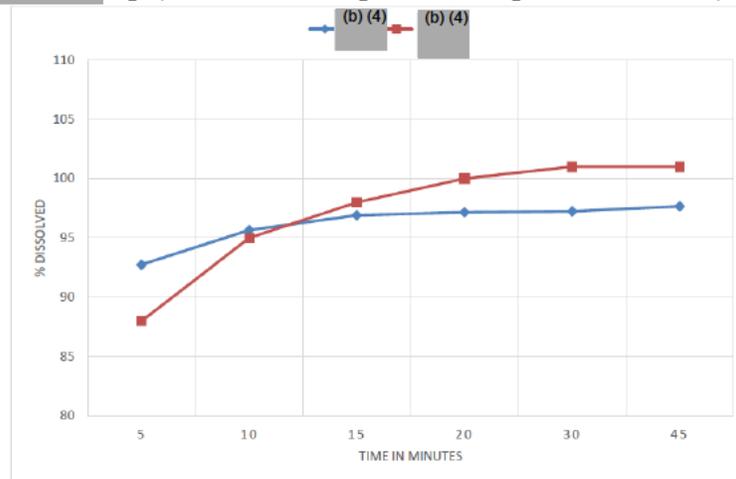
Figure 6: Dissolution Profiles for Drug Product Manufactured with Change in the Order of Addition of Components - Batch 17574 (Acetate Buffer, pH 4.5, 50 rpm, 37°C, n=12) – Batch 17574 and Control Batch 17569



Overall, tested Batches 17572, 17573 and 17574 showed very rapid and similar dissolution profiles compared to the control batch 17569. It appears that the changes of the excipients' concentrations did not impact the dissolution behavior of the drug product. The order of introducing drug substance to the formulation did not impact the dissolution behavior of the final drug product. The removal of (b) (4) did alter the dissolution rate, indicating the effect of (b) (4) on the disintegration of the product. Judging from the totality of the data, this Reviewer determined that the proposed dissolution method has acceptable discriminating ability.

- d) Tablet hardness: As indicated by the Applicant, Batch 17575 was produced from a (b) (4) using different parameters to produce tablets with hardness values at the low and high ends of the hardness specification range (b) (4) kp), as presented in Figure 7.

Figure 7: Dissolution Profiles for Drug Product Produced with Hardness Values of (b) (4) kp (Acetate Buffer pH 4.5, 50 rpm, 37°C, n=12) Batch 17575



DP = drug product, kp = kilopond, rpm = revolutions per minute.

As confirmed by the CMC Reviewer (Dr. Mariappan Chelliah), batch 17575 was considered to have the same formulation as the three registration/commercial batches (16908, 16913, and 16914), considering that the only formulation change occurred in March 2010 was the (b) (4)

As presented in the Figure 7, tablets with either high or low end of hardness showed very rapid dissolution profiles (b) (4) % dissolution in 15 min); therefore, tablets in the proposed hardness range (b) (4) kp) are considered to have similar dissolution behavior. In view of the high solubility of the drug substance and the very rapid dissolution of the drug product, the proposed dissolution method is not expected to be discriminating toward the tablet hardness (e.g., \pm (b) (4) % change of the proposed hardness range).

Overall, the proposed dissolution method is acceptable for the drug product for routine QC test of the finished drug product for batch release and stability testing.

3. In Vitro Dissolution Data and Acceptance Criterion

The complete dissolution profile data of whole tablets of three registration batches (batch 16908, 16913, and 16914) are provided, as presented in Table 4 and Figure 8 below. The three batches have same formulation, manufacturing process and manufacturing site. The dissolution profile data of six batches/strengths used in DAPPER clinical study (as presented in Table 5 below) and the supportive dissolution data of eighty-five batches

were also provided. In the 10/17/2018 responses to the information request conveyed on 09/26/2018, the Applicant confirmed that the 10 mg tablet (batch 13817) used in DAPPER study has identical formulation with the above three registration batches with commercial formulations.

The dissolution conditions (b) (4) were provided. Note that the originally proposed dissolution acceptance criterion was “Q (b) (4)% in (b) (4) minutes” in the original submission (which received RTF status), the dissolution data were then collected at single time point at (b) (4) minutes under different stability storage conditions. The dissolution data under long-term stability condition (n=6 units/batch, (b) (4)) showed that more than (b) (4)% dissolution was obtained at (b) (4) minutes for (b) (4) months. Overall, no dissolution trend was observed under long-term, intermediate, and accelerated stability conditions.

The overall dissolution profile data demonstrated that the whole tablets of drug product dissolved very rapidly (b) (4)% dissolution in 15 minutes). Three registration batches have comparable dissolution profiles. The six batches in DAPPER study also showed similar, very rapid dissolution profiles to the three registration batches. [The overall data support the currently proposed dissolution acceptance criterion of “Q \(b\) \(4\)% in 15 minutes”.](#)

Table 4: Dissolution Results for Registration Batches
(Acetate Buffer pH 4.5, 50 rpm, 37°C, n=12)

Vessel	% Dissolved																	
	16908 (10 mg)						16913 (10 mg)						16914 (10 mg)					
Batch	5	10	15	20	30	45	5	10	15	20	30	45	5	10	15	20	30	45
Minutes																		
1	(b) (4)																	
2	(b) (4)																	
3	(b) (4)																	
4	(b) (4)																	
5	(b) (4)																	
6	(b) (4)																	
7	(b) (4)																	
8	(b) (4)																	
9	(b) (4)																	
10	(b) (4)																	
11	(b) (4)																	
12	(b) (4)																	
Mean	93	98	99	101	102	103	94	97	99	101	102	103	93	98	99	101	102	103
% RSD	0.8	1.1	0.7	0.5	0.5	0.6	1.0	1.1	0.8	0.7	0.6	0.4	1.3	0.8	0.8	0.4	0.5	0.4

DP = drug product; rpm = revolutions per minute; RSD = relative standard deviation.

Figure 8: Dissolution Profiles for Registration Batches
(Acetate Buffer pH 4.5, 50 rpm, 37°C, n=12)

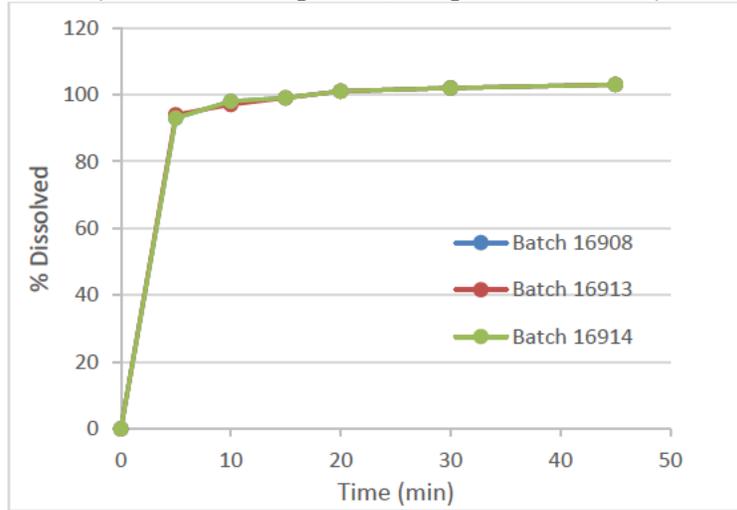


Table 5: Dissolution Results of DAPPER Clinical Batches
(Acetate Buffer pH 4.5, 50 rpm, 37°C, n=12)

Vessel	% Dissolved																	
	13812 (0.5 mg)						13813 (2 mg)						13814 (3 mg)					
Batch	5	10	15	20	30	45	5	10	15	20	30	45	5	10	15	20	30	45
Minutes	5	10	15	20	30	45	5	10	15	20	30	45	5	10	15	20	30	45
1	(b) (4)																	
2																		
3																		
4																		
5																		
6																		
7																		
8																		
9																		
10																		
11																		
12																		
Mean	90	96	94	97	97	97	88	93	97	98	98	98	86	98	102	104	106	105
% RSD	4.3	5	4.6	2.3	4.6	3.5	5.3	4.8	2.4	2.0	1.8	1.7	1.8	2.3	2.0	1.6	1.3	1.6

Max = maximum; Min = minimum; rpm = revolutions per minute; RSD = relative standard deviation.

Vessel	% Dissolved																	
	13815 (4 mg)						13816 (5 mg)						13817 (10 mg)					
Batch	5	10	15	20	30	45	5	10	15	20	30	45	5	10	15	20	30	45
Minutes	5	10	15	20	30	45	5	10	15	20	30	45	5	10	15	20	30	45
1	(b) (4)																	
2																		
3																		
4																		
5																		
6																		
7																		
8																		
9																		
10																		
11																		
12																		
Mean	94	99	100	101	102	104	92	95	97	98	99	99	93	99	101	103	104	105
% RSD	1.6	1.8	1.7	1.8	1.5	0.9	2.3	2.5	1.7	2.5	2.3	2.0	1.4	0.5	0.7	0.8	0.9	0.8

Max = maximum; Min = minimum; rpm = revolutions per minute; RSD = relative standard deviation.

4. In Vitro Dissolution of Functionally Scored Tablet (10 mg): Whole vs. Halved:

The dissolution profile data of manual and mechanical split tablets (at low hardness target hardness (b) (4) kp and high hardness (b) (4) kp hardness) are provided. The results (as presented in Figures 9-11 below) indicated that the mechanically and manually split tablets have very rapid drug release (b) (4) % dissolution in 15 minutes), comparable to that of the whole tablets.

Overall, the dissolution data of split vs. whole tablets met the proposed dissolution acceptance criterion of Q (b) (4) % in 15 minutes, supporting the functional scoring of the proposed finished oral tablets.

Figure 9: Dissolution Profiles for Drug Product Tablets Mechanically and Manually Split - Low Hardness (b) (4) kp (Acetate Buffer pH 4.5, 50 rpm, 37°C, n=12)

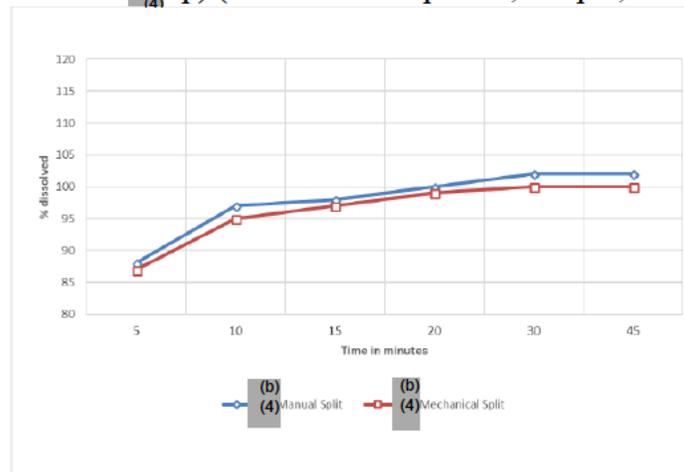


Figure 10: Dissolution Profiles for Drug Product Tablets Mechanically and Manually Split - Target Hardness (b) (4) kp (Acetate Buffer pH 4.5, 50 rpm, 37°C, n=12)

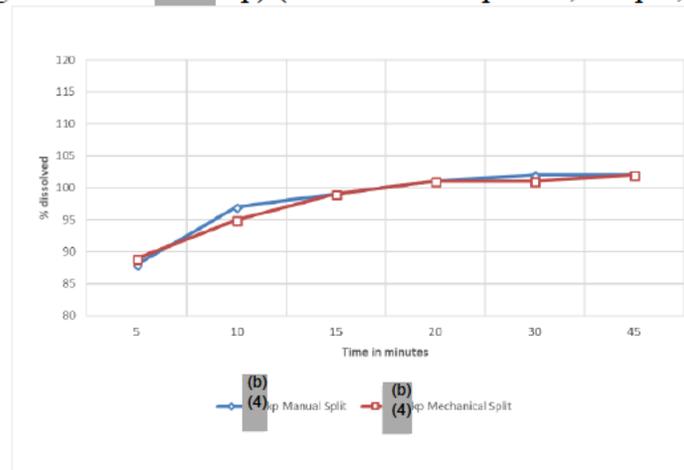
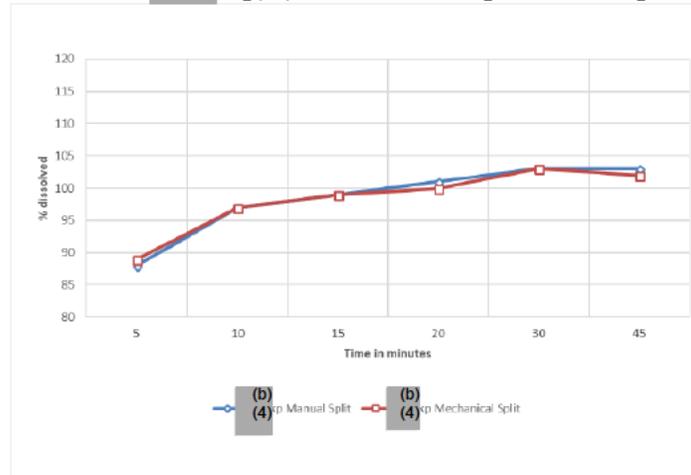


Figure 11: Dissolution Profiles for Drug Product Tablets Mechanically and Manually Split - High Hardness (b) (4) kp) (Acetate Buffer pH 4.5, 50 rpm, 37°C, n=12)



5. Bridging of Formulations:

Since (a) (b) (4) is considered the same excipient being studied throughout the formulation development, as confirmed by CMC Reviewer (Dr. Mariappan Chelliah), and (b) the 10 mg tablet used in DAPPER pivotal clinical study has identical formulation with the commercial batches, no additional in vitro bridging study is deemed necessary.

6. Biowaiver:

N/A since only one strength is proposed.

7. Administration of Dissolved Drug Product as Oral Solution:

In Responses to Question 6 of FDA Pediatric Information Request dated 10/17/2018, the Applicant mentioned that “*Note that for precision in dosing in younger children, 10 mg tablets can be dissolved in 10 cc sterile water. This will result in a 1 mg/mL (b) (4) The appropriate dose can be drawn up into an oral syringe and administered directly into the mouth or feeding tube.* (b) (4)

This Reviewer considered two possible dosing scenarios based on the Applicant’s responses:

- (i) The drug product (10 mg tablet) is first dissolved in 10 mL of sterile water, then the 1 mg/mL (b) (4) can be administered into mouth or feeding tube. (b) (4) Additional dissolution testing is not needed for this scenario, considering the drug substance having high aqueous solubility and drug product having very rapid dissolution.

(b) (4)

After communication with Medical Officer (Dr. Teresa Buracchio) and Drug Product Reviewer (Dr. Mariappan Chelliah), the following IRs were conveyed to the Applicant on 11/21/2018 and 11/30/2018 to clarify the administration options for the proposed drug product, as presented below:

CMC IR (Question 8, conveyed on 11/21/2018):

In the response to Question 6 in the October 17, 2018, submission, you state that

(b) (4)

You have not currently proposed to include such instructions in the draft prescribing information. Please clarify if you intend to propose this method of administration in product labeling.

Applicant's response (submitted on 12/06/2018):

(b) (4)

Jacobus does not plan to propose this method of administration in product labeling.

CMC IR (conveyed on 11/30/2018, in Late-Cycle Meeting Background Package):

As previously noted in our information request dated November 21, 2018, you will need to clarify if you intend to include

(b) (4)

Applicant's response (in Late Cycle Face-to-Face Meeting on 12/11/2018):

The Applicant confirmed that they do not intend to

(b) (4)

The tablets will be dissolved in water first, and then be administered to patients. The Applicant will provide the updated labeling accordingly.

On 12/18/2018, the Applicant responded to the CMC IRs listed in late-cycle meeting package and provided a Homogeneity Protocol. For Pediatric Patients, the Applicant indicated “Where individual doses of less than 5 mg are required, a 1 mg/1 mL suspension can be prepared by placing a 10 mg tablet in a (b) (4) bottle, adding 10 mL of sterile water and shaking for 30 seconds; an oral syringe can be used to draw up and administer the correct dose by mouth or feeding tube.” (b) (4)

(b) (4)

The homogeneity testing showed that the assay results of the three portioned drug solutions were all within (b) (4)% limit, meeting the proposed criterion of (b) (4)% and demonstrating the homogeneity of the solution. Results provide assurance that a proportional fractional dose can be obtained for oral administration.

Based on the Applicant’s responses, it was determined that the proposed tablet will be dissolved in water first to create 1 mg/mL (b) (4) which will then be administered to patients.

When taking into the totality of the data/information, this Reviewer determined that no additional dissolution assessment is needed.



Mei
Ou

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Wendy
Wilson- Lee

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Date: 3/13/2019 10:33:25AM

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