

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**214377Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

# NDA 214377: Verquvo (Vericiguat) Tablets

## Integrated Quality Review

### Recommendation: Approval

<b>Product Name</b>	Verquvo (Vericiguat) Tablets
<b>Indication</b>	Treatment of chronic heart failure
<b>Strength</b>	2.5 mg, 5.0 mg and 10 mg
<b>Dosage Form; Route of Administration</b>	Oral Tablets
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Merck Sharp & Dohme Corporation
<b>Submissions (s) Reviewed</b>	NDA 214377 and all the submitted CMC amendments

### Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Zhengfu Wang	OPQ/ONDP/DNDAPI/NDB3
Drug Product, and Environmental Assessment	Dan Berger	OPQ/ONDP/DNDPIII/NDPB5
Process and Facility	Teng (Daisy) Xu	OPQ/OPMA/DPMII/PMB6
Biopharmaceutics	Min Sung Suh	OPQ/ONDP/DB/BB3
Application Technical Lead	Mohan Sapru	OPQ/ONDP/DNDPIII/NDPB5

RBPM: Grafton Adams (OPQ/OPRO/DRBPMI/RBPMB2)

### RELATED/SUPPORTING DOCUMENTS:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

**CONSULTS: None**

## Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 214377 Vericiguat Tablet is recommended for approval. As part of this action, an expiration period of 36 months is granted for the product, when stored at controlled room temperature of 20°C to 25°C (68°F to 77°F) in the purposed commercial packaging, consisting of either HDPE bottles or blister packs.

#### B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

### II. Quality Assessment Summary

**1. Background:** The Applicant, Merck Sharp & Dohme Corp., has sought U.S. marketing approval for Vericiguat Tablets under the provisions of Section 505(b)(1) of the Federal Food and Cosmetic (FDC) Act. The proposed product is indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization, following a worsening HF event, in adults with symptomatic chronic HF and ejection fraction less than 45%, in combination with other HF therapies. Vericiguat is a new compound which belongs to a novel class of direct soluble guanylate cyclase (sGC) stimulators. It directly stimulates sGC, independently of and synergistically with NO, to augment the levels of intracellular cGMP, which is likely to improve both myocardial and vascular function. Vericiguat film-coated tablets have been developed as immediate-release (IR) tablet formulations for oral administration. The recommended starting dose is 2.5 mg once daily, taken with food. The dose can be doubled approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient. From the quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, and stability.

**2. Drug Substance (Vericiguat):** The drug substance is a New Molecular Entity (NME). (b) (4) drug substance is used for product manufacturing. The information provided regarding the characterization of its physicochemical characteristics, structure, and impurity profile is adequate. The drug substance is practically insoluble in most of solvents and aqueous buffers, (b) (4) for optimal dissolution of the drug product. Multiple potential polymorphic forms exist in the screening study; however, the commercial drug substance manufactured by the Applicant is the (b) (4) stable form i.e., (b) (4). Per the information in the NDA, the different polymorphic forms do not differ in their

dissolution behavior. The drug substance manufacturing process is well-controlled. The designation of starting material (b) (4) is adequately supported per ICH Q11. The specification includes testing of all critical qualities (CQAs). For example, (b) (4) the drug substance is controlled by release specification. Content uniformity is tested on release as per USP<905>. (b) (4) is controlled in the drug substance with a limit of (b) (4) ppm. The stability data support a retest period of (b) (4) months for the drug substance when stored (b) (4).

### 3. Drug Product (Vericiguat Tablets)

**3.1. Product Design, and Release Specification:** Vericiguat Tablets are to be made available at three strengths – 2.5 mg, 5 mg and 10 mg. All excipients are compendial, present in quantities within FDA Inactive Ingredients Database levels and are BSE/TSE free. Although the drug substance can be isolated in several polymorphic forms (b) (4) stability studies have confirmed that commercially manufactured (b) (4). Additionally, dissolution studies show no differences in release profiles for all isolated polymorphs (b) (4). The commercial formulation includes color, size and markings differences that adequately distinguish the tablet strengths. The product release specification, involves testing of all the product critical quality attributes (CQAs), is adequate to ensure the identity, strength, quality, purity, and potency of the drug product. The specification includes two orthogonal methods for identity, thereby establishing adequate identity testing as per ICH Q6A. Specified degradation products have not been detected at release or on stability under tested conditions. The drug product is to be presented in HDPE bottle, enclosed with a (b) (4) closure and aluminum seal, or blister packs. The Applicant has performed a risk assessment screening for elemental impurities taking into account any potential contributions from the drug substance, excipients, manufacturing equipment and process, and leachables from the container closure system per ICH Q3D. Based on this assessment, the product as a whole does not exceed the control threshold of 30% for elemental impurities, and hence no additional testing for elemental impurities is required.

### 3.2. Manufacturing:

(b) (4)

(b) (4)

(b) (4)

he in-process controls performed during different manufacturing steps are adequate. Overall, the product manufacturing is well-controlled.

**3.3. Microbiological Aspects:** The drug product batches are tested on release for microbial purity, which involves testing for total aerobic microbial count, combined yeast/mold count and Escherichia coli. Because of the (b) (4) content of the formulation, and lack of any unprocessed material of natural origin in the formulation, no additional testing for other objectionable micro-organisms is necessary.

**3.4. Biopharmaceutics Aspects:** Vericiguat is administered as an immediate release tablet with a non-functional film coating and rapid dissolution characteristics under the proposed dissolution conditions. Vericiguat is a weak base, and is identified a BCS class 2 compound, based on the *in vitro* solubility and permeability studies. Pharmacokinetics (C<sub>max</sub> and AUC) of Vericiguat Tablet administered orally as a crushed tablet in water is comparable to that of a whole tablet. The Biopharmaceutics review focused on the evaluation and acceptability of the dissolution method and acceptance criterion for quality control of the proposed product. In the current submission, the Applicant has provided dissolution method development/validation reports, dissolution data of the batches used during clinical development as well as the registration batches for each dose strength. The Applicant also provided comparative dissolution data from development batches with different particle size of the drug substance, hardness, and excipient variables to demonstrate discriminatory power and robustness of the proposed dissolution method. The dissolution profiles of the product, from development batches, demonstrate that the proposed method has adequate discriminating ability towards critical attributes. Biowaiver is not necessary and applicable since all the proposed product strengths have been tested in dose proportionality studies and phase 3 clinical trial.

**3.5. Container Closure System:** The commercial packages for the product consist of 75 cc high density polyethylene (HDPE) bottles, and the (b) (4) blister. The bottle and the blisters comply with the CFR Title 21 Part 177.1520 and CFR Title 21 Part 175.300, respectively. Based on the information provided, the proposed container closure system (HDPE bottles or blister packs) is adequate for the intended use. The stability data lends additional support to the suitability of the container closure system for providing adequate protection to the drug product over the proposed shelf-life.

**3.6. Stability, Storage Conditions and Expiration Date:** Based on stability studies, the Applicant has demonstrated stability for the proposed product for a period of 18



**B. Comparability Protocol for**

(b) (4)

(b) (4)

In response to Agency's recommendations, the Applicant, per revised CP, has appropriately agreed that:

•

(b) (4)

•

Thus, the revised CP is considered acceptable.

**V. Product Quality Labeling Recommendations:**

The product quality recommendations are included in the latest version of labeling, including the Prescription Information.

**VI. Life Cycle Knowledge Information**

*See Final Risk Assessment on the next page.*

### Final Risk Assessment

#### NDA 214377: Verquvo (Vericiguat) Tablets

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Assay, Stability	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Impurity exceeding specification</li> <li>• Process parameters</li> <li>• Scale/equipment/site</li> </ul>	Low (L)	(b) (4)	Acceptable	.
Solid state Polymorphic form)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment/site</li> </ul>	Moderate (M)		Acceptable	N/A
Content Uniformity	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Particle size</li> <li>• (b) (4)</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment/site</li> </ul>	Moderate (M)		Acceptable	Any proposed changes to formulation, manufacturing, or the control strategy will need to be evaluated for possible impact on content uniformity.

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
(b) (4)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Process parameters</li> <li>• Scale/equipment/site</li> </ul>	Low (L)	(b) (4)	Acceptable	
Dissolution	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment/site</li> <li>• API sources</li> </ul>	Moderate (M)		Acceptable	
Microbial limits	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>Scale/equipment/site</li> </ul>	Low (L)		Acceptable	

**OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY**

From the Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 214377 Vericiguat Tablet is recommended for approval. As part of this action, an expiration period of 36 months is granted for the product, when stored at controlled room temperature of 20°C to 25°C (68°F to 77°F) in the purposed commercial packaging, consisting of either HDPE bottles or blister packs.

Mohan Sapru, M.S., Ph.D.  
 Application Technical Lead (ATL)  
 CMC Lead; Division of Cardiology and Nephrology  
 CDER/OPQ/ONDP/DNDPIII/NDPB5

# CHAPTER IV: LABELING

## 1.0 PRESCRIBING INFORMATION

### Assessment of Product Quality Related Aspects of the Prescribing Information:

The prescribing information meets all regulatory requirements from a CMC perspective, following edits made to alphabetize the inactive ingredients in Section 11.

### 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
<b>Product Title in Highlights</b>		
Proprietary name	Tradename (Verquvo)	Adequate (listed as Tradename)
Established name(s)	Vericiguat	Adequate
Route(s) of administration	Oral	Adequate
<b>Dosage Forms and Strengths Heading in Highlights</b>		
Summary of the dosage form(s) and strength(s) in metric system.	2.5 mg, 5 mg and 10 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

### 1.2 FULL PRESCRIBING INFORMATION

### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
<b>DOSAGE AND ADMINISTRATION section</b>		
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)	Tablets may be crushed and mixed with water for patients who have difficulty swallowing.	Adequate

### 1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
<b>DOSAGE FORMS AND STRENGTHS section</b>		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	2.5 mg, 5 mg and 10 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Dosage strength, shape, color, coating and imprinting for 2.5 mg, 5 mg and 10 mg strengths.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

### 1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
<b>DESCRIPTION section</b>		
Proprietary and established name(s)	Trademark, vericiguat	Adequate
Dosage form(s) and route(s) of administration	2.5 mg, 5 mg and 10 mg tablets, oral administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	NA
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. Coating: hypromellose, talc, titanium dioxide, ferric oxide red (5 mg), ferric oxide yellow (10 mg)	Adequate, after edits made.
For parenteral injectable dosage forms, include name and quantities of all inactive ingredients.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ Therapeutic class	Soluble guanylate cyclase stimulator	Adequate
Chemical name, structural formula, molecular weight	Methyl {4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b] pyridin-3-yl] pyrimidin-5-yl} carbamate, C <sub>19</sub> H <sub>16</sub> F <sub>2</sub> N <sub>8</sub> O <sub>2</sub> , 426.39.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Solubility profile in various organic solvents listed.	Adequate

**Section 11 (DESCRIPTION) Continued**

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	NA	NA

**1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)**

Item	Information Provided in the NDA	Assessor's Comments
<b>HOW SUPPLIED/STORAGE AND HANDLING section</b>		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	2.5 mg, 5 mg and 10 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 14, 30 and 90, Blister packages of 100 (10 strips of 10 tablets)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Shape, size, color, imprinting, NDC numbers present for all strengths & packaging.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

**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.)	NA	NA
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."	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)	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."	NA	NA
Include information about child-resistant packaging	Not present	NA

### 1.2.5 Other Sections of Labeling

No other sections of the labeling contain product quality information.

### 1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
<b>Manufacturing Information After Section 17</b>		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Merck & Co., Inc., Whitehouse Station, NJ 08889, USA	Adequate.

## 2.0 PATIENT LABELING

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

The Medication Guide has been edited to alphabetize excipients consistent with the PI. With these edits, all regulatory requirements are met from a CMC perspective.

## 3.0 CARTON AND CONTAINER LABELING

### 3.1 Container Label

Blister Pack (10 mg strength):



Item	Information Provided in the NDA	Assessor's Comments about Blister, Carton and Bottle Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Trademark, vericiguat	Adequate
Dosage strength	2.5 mg, 5 mg and 10 mg	Adequate
Route of administration	oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	NA
Net contents (e.g. tablet count)	Bottles of 14, 30 and 90. Blisters of 100 tablets	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	Present	Adequate
Lot number and expiration date	Present	Adequate, following response to IR.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Present	Adequate





Dan  
Berger

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## CHAPTER VI: BIOPHARMACEUTICS

### [IQA NDA Assessment Guide Reference](#)

<b>NDA Number</b>	214377
<b>Drug Product Name/ Strength</b>	Vericiguat, Immediate Release (IR) Tablets, 2.5 mg, 5 mg, and 10 mg
<b>Route of Administration</b>	Oral
<b>Applicant Name</b>	Merck Sharp & Dohme Corp.
<b>Therapeutic Classification/ OND Division</b>	CDER/OCHEN/DCN
<b>IND Number</b>	116743
<b>Proposed Indication</b>	Treatment of chronic heart failure
<b>Primary Reviewer</b>	Min Sung Suh, Ph.D.
<b>Secondary Reviewer</b>	Poonam Delvadia, Ph.D.
<b>Recommendation</b>	Adequate

#### **Assessment Recommendation: Adequate**

##### **Assessment Summary:**

The Applicant submitted a 505 (b)(1) for approval of Vericiguat Immediate Release Tablets, 2.5 mg, 5 mg, and 10 mg, indicating chronic heart failure treatment in accordance with the Federal Food, Drug and Cosmetic Act and part 314.50 of Title 21 of the Code of Federal Regulations. A Fast Track designation was granted on 06/23/2014 during the IND stage.

Vericiguat is administered as an IR tablet with a non-functional film coating and rapid dissolution characteristics under the proposed dissolution conditions. The recommended starting dose is 2.5 mg once daily, taken with food. The dose can be doubled approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient. Under fasted conditions, Vericiguat is rapidly absorbed with median time to reach maximum drug concentration ( $T_{max}$ ) of 1 to 1.5 h. The absolute oral bioavailability of Vericiguat administered as a 10 mg IR tablet with food is 93%, and the  $C_{max}$  was increased by 9% at 5 mg and by 41% at 10 mg. Thus, Vericiguat is recommended to be taken with food. Vericiguat tablets may be crushed and mixed with water for patients who have difficulty swallowing. Pharmacokinetics ( $C_{max}$  and AUC) of Vericiguat administered orally as a crushed tablet in water is comparable to that of a whole tablet.

The Biopharmaceutics review focused on the evaluation and acceptability of the dissolution method and acceptance criterion for quality control of the proposed product.

##### **Dissolution Method and Acceptance Criterion:**

The Applicant provided dissolution method development/validation reports, dissolution data of the batches used during clinical development as well as the registration batches for each dose strength in this submission. The Applicant also provided comparative dissolution data from development batches with different particle size of the API, hardness, and excipient variables to demonstrate discriminatory power and robustness of the proposed dissolution method.

The provided dissolution profiles of the development batches demonstrated that the proposed method has adequate discriminating ability towards critical attributes. The Applicant proposed dissolution acceptance criterion of NLT<sup>(b) (4)</sup>% in <sup>(b) (4)</sup> minutes for all strengths. However, based on the dissolution data of clinical and registration batches, the proposed dissolution acceptance criterion was <sup>(b) (4)</sup>. The data driven acceptance criterion of NLT<sup>(b) (4)</sup>% (Q) in 15 minutes for all strengths was recommended via the Information Request (IR) dated 09/01/2020. In the response to the IR, the Applicant accepted the recommendation and revised the dissolution specification tables and relevant sections, accordingly. The approved dissolution method and acceptance criterion for all strengths of Vericiguat IR tablets is shown in Table 1.

**Table 1. Approved Dissolution Specification for Vericiguat IR Tablets (2.5mg, 5mg, and 10mg)**

<b>Apparatus</b>	USP II (Paddle)
<b>Speed</b>	75 rpm
<b>Medium</b>	900 mL, 0.01 M HCl, pH 2.0
<b>Temperature</b>	37 °C
<b>Acceptance criterion</b>	Q = <sup>(b) (4)</sup> % in 15 minutes

**List Submissions being assessed (table):**

<b>Document(s) Assessed</b>	<b>Date Received</b>
<b>Original review (Seq. 0001)</b>	<b>05/20/2020</b>
<b>IR response (Seq. 0020)</b>	<b>09/15/2020</b>

**Highlight Key Issues from Last Cycle and Their Resolution:** None

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

**B.1 BCS DESIGNATION**

Vericiguat is a weak base. The Applicant identified that the API belongs to BCS class 2 based on the in vitro solubility and permeability studies.

**Solubility:**

The solubility of the API in aqueous media is shown in Table 2.

**Table 2. Solubility of Vericiguat in different solvents**

Solvent	Solubility at 37°C (mg/mL)	Dose/Solubility ratio for 10 mg vericiguat (mL)
Buffer (phosphate) pH 6.8	0.0009	<b>11111</b>
Buffer (phosphate) pH 6.0	0.001	<b>10000</b>
Buffer (phosphate) pH 5.0	0.0012	<b>8333</b>
Buffer (acetate) pH 4.5	0.002	<b>5000</b>
Buffer (citric acid/ phosphate) pH 4.0	0.0035	<b>2857</b>
Buffer (glycol / HCl) pH 3.0	0.026	<b>385</b>
0.01 M HCl pH 2	0.247	40
0.1 M HCl pH 1	0.133	75
Buffer (acetate) pH 4.5 + 0.1% SDS <sup>c</sup>	0.157	64
Buffer (phosphate) pH 6.74 + 0.1% SDS	0.018	<b>556</b>
Buffer (phosphate) pH 6.74 + 0.2% SDS	0.035	<b>286</b>
Buffer (phosphate) pH 6.74 + 0.3% SDS	0.042	238

Note: bold indicates that the ratio of dose (mg) to solubility (mg/ml) is 250 ml or higher, indicating the aqueous solubility is considered to be high [Ref. 5.4: 05DB59, 05DB6K, 04GWZ5].

SDS = Sodium dodecyl sulfate (SDS)

### Permeability:

The efflux ratio in in vitro permeability indicated that the API is highly permeable. The absolute oral bioavailability of Vericiguat administered as a 10 mg dose with food is 93% and the relative bioavailability with respect to the overall exposure and maximum plasma concentration was comparable when given as intact tablets or as crushed tablets (fed state).

## B.2 FORMULATION

(b) (4) All strengths were evaluated in phase 3 clinical trials. The composition of the proposed drug product strengths is shown in Table 3. It is noted that (b) (4)

(b) (4) during manufacturing. The proposed API PSD for Vericiguat is  $X_{90} \leq (b) (4) \mu\text{m}$ .

**Table 3. Composition of proposed commercial formulation of Vericiguat coated tablet [mg/tablet]**

Dose in (mg)	2.5	5.0	10.0
<b>Tablet core</b>			
Vericiguat (b) (4)	2.50	5.00	10.00
Cellulose microcrystalline	(b) (4)		
Croscarmellose sodium			
Hypromellose (b) (4)			
Lactose monohydrate			
Magnesium stearate			
Sodium laurilsulfate			
(b) (4)			
<b>Weight (tablet core)</b>			
<b>Film coating</b>			
(b) (4)			
Hypromellose (b) (4)	(b) (4)		
Ferric oxide red			
Ferric oxide yellow			
Talc			
Titanium dioxide			
(b) (4)			
<b>Weight (film coating)</b>	(b) (4)		
<b>Total tablet weight (coated tablet)</b>			
	(b) (4)		

### B.3 DISSOLUTION METHOD

The Applicant provided dissolution method development and validation reports for all strengths. The proposed dissolution method is shown in Table 4.

**Table 4. Proposed Dissolution Method for Finished Product Batch Release and Stability Testing of Vericiguat Tablets**

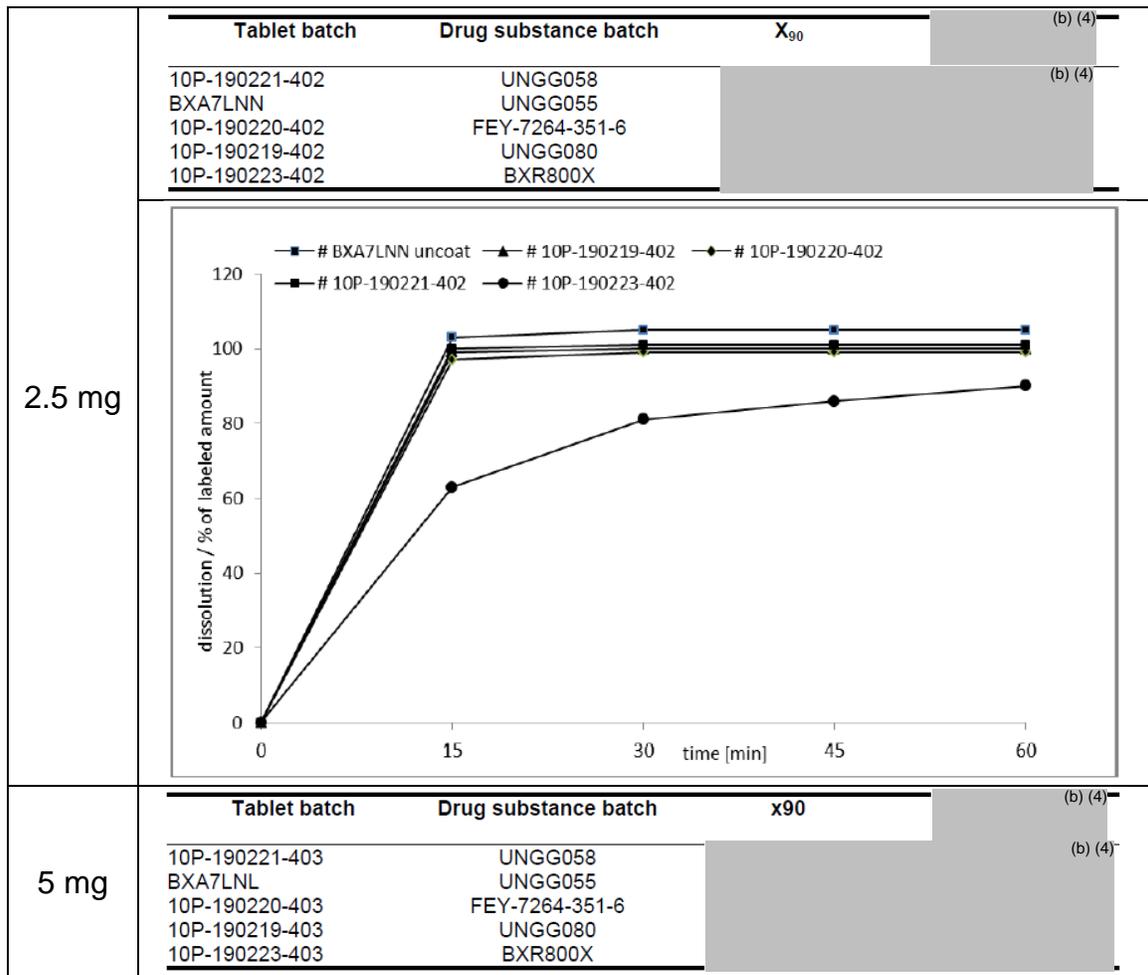
Apparatus	Speed	Medium	Temperature
II (Paddle)	75 rpm	900 mL, 0.01 M HCl, pH 2.0	37 °C

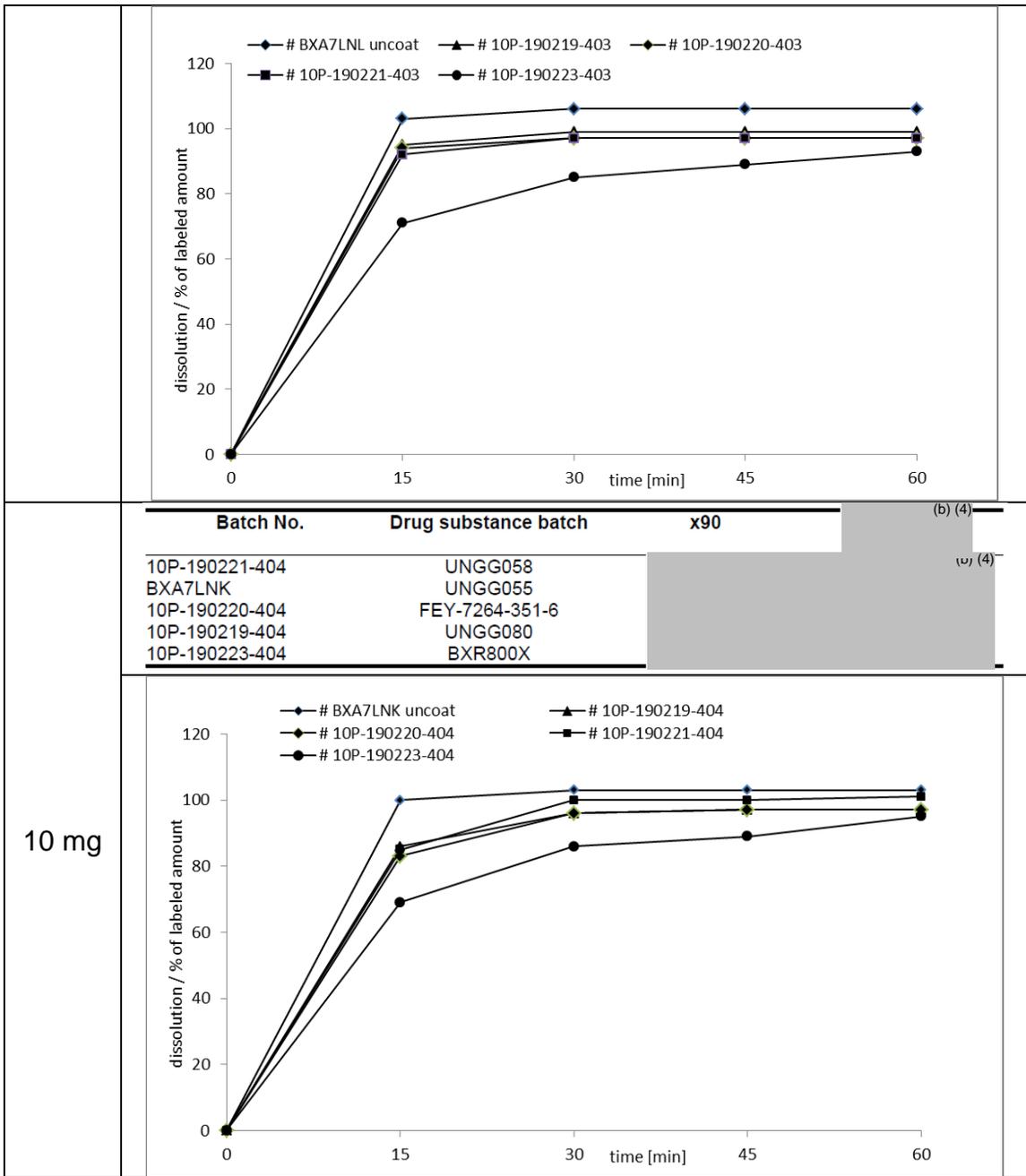
The Applicant also provided comparative dissolution profiles of development batches with variables, such as different particle size (PSD) of the API, hardness, and excipient variables as well as coating, which are associated with Critical

Material Attributes (CMAs) and Critical Process Parameters (CPPs) to demonstrate discriminatory power and robustness of the proposed method.

**Particle size:** Dissolution studies using uncoated tablets with different particle size were investigated. The proposed PSD specification is  $X_{90} \leq (b) (4) \mu\text{m}$ , and the dissolution of the batches for all strengths with  $(b) (4)$  API ( $X_{90} = (b) (4) \mu\text{m}$ ) were significantly slower than ones with lower  $X_{90}$  values shown in Figure 4.

**Figure 4. Dissolution profiles of different Vericiguat tablets (all uncoated), influence of particle size distribution of API on dissolution, 0.01 M HCl pH 2, 75 rpm, 37 °C, mean of n=12, except for batch BXA7LNN uncoat mean of n=6**





**Hardness:** The effect of hardness was investigated using three batches (b) (4). The target hardness for each strength is shown in Table 5.

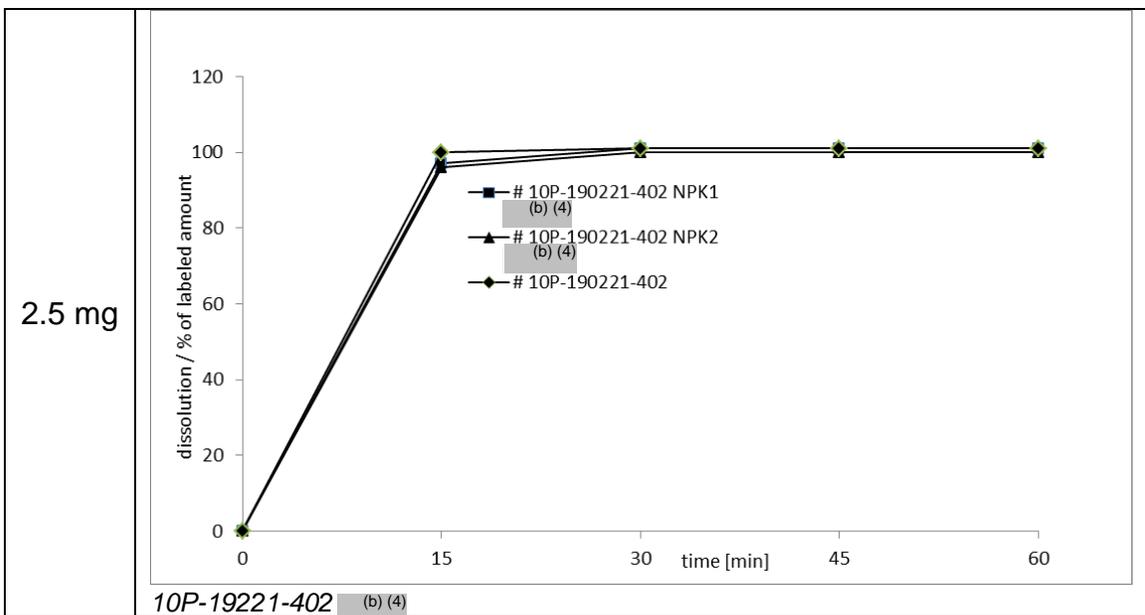
**Table 5.** (b) (4) and tablet hardness of Vericiguat

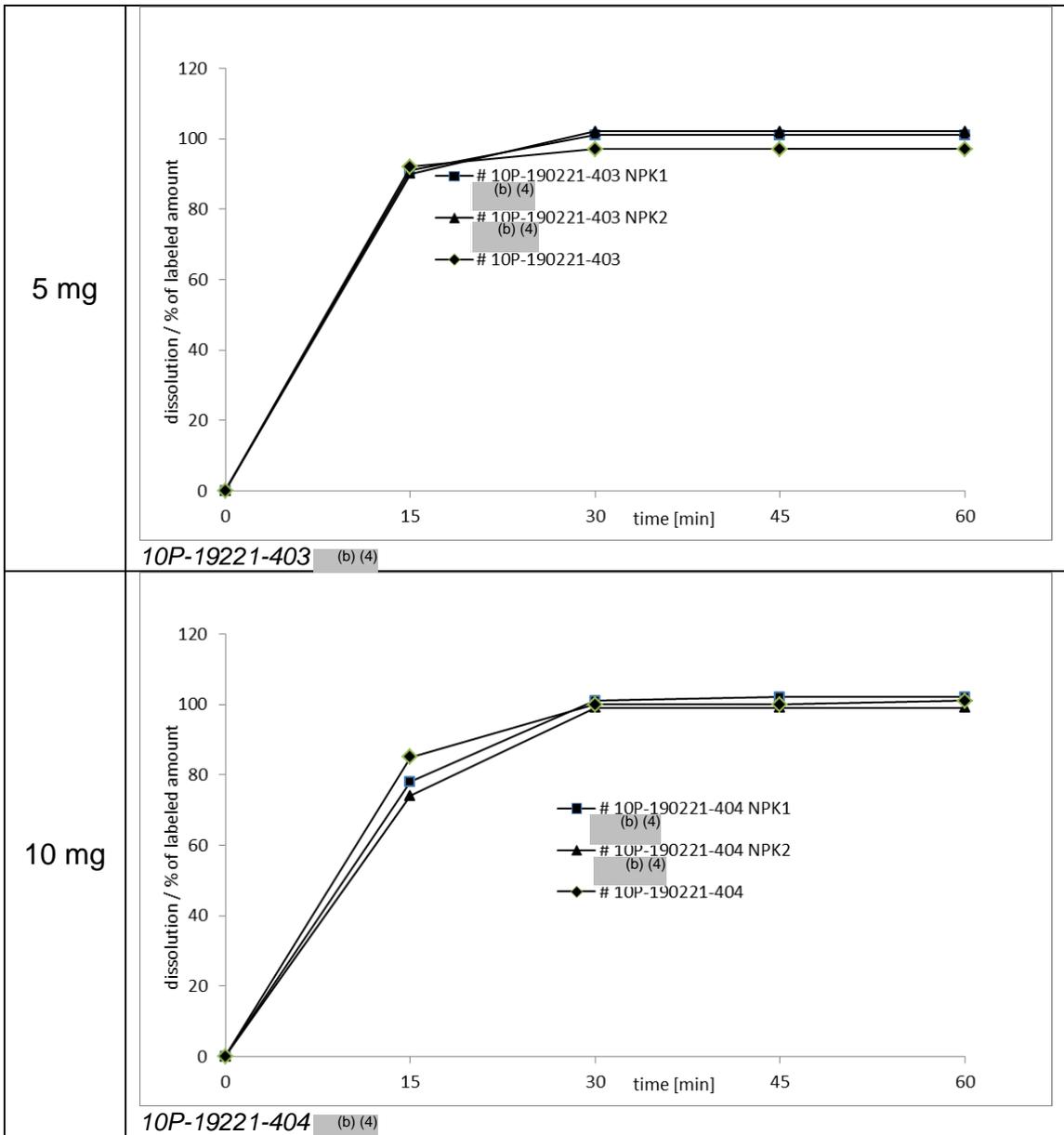
Strength	2.5 mg	5 mg	10 mg
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Hardness	(b) (4) N	(b) (4) N	(b) (4) N
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The dissolution of the batches for all strengths were nearly independent of the different (b) (4) shown in Figure 5.

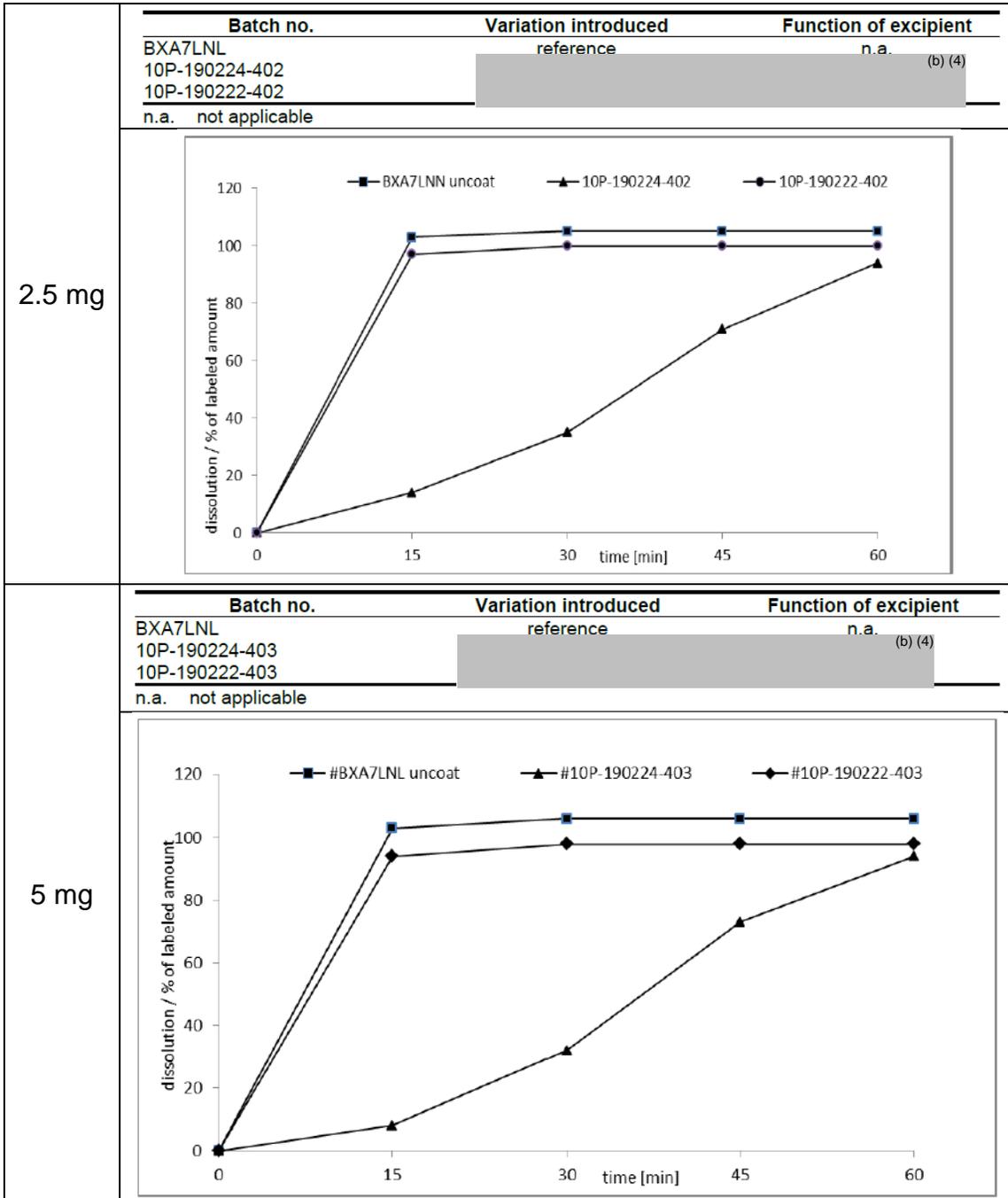
**Figure 5. Dissolution profiles of Vericiguat tablets, comparison of different (b) (4) using the same tablet blend, 0.01 M HCl pH 2, 75 rpm, mean of n=12, 37 °C**

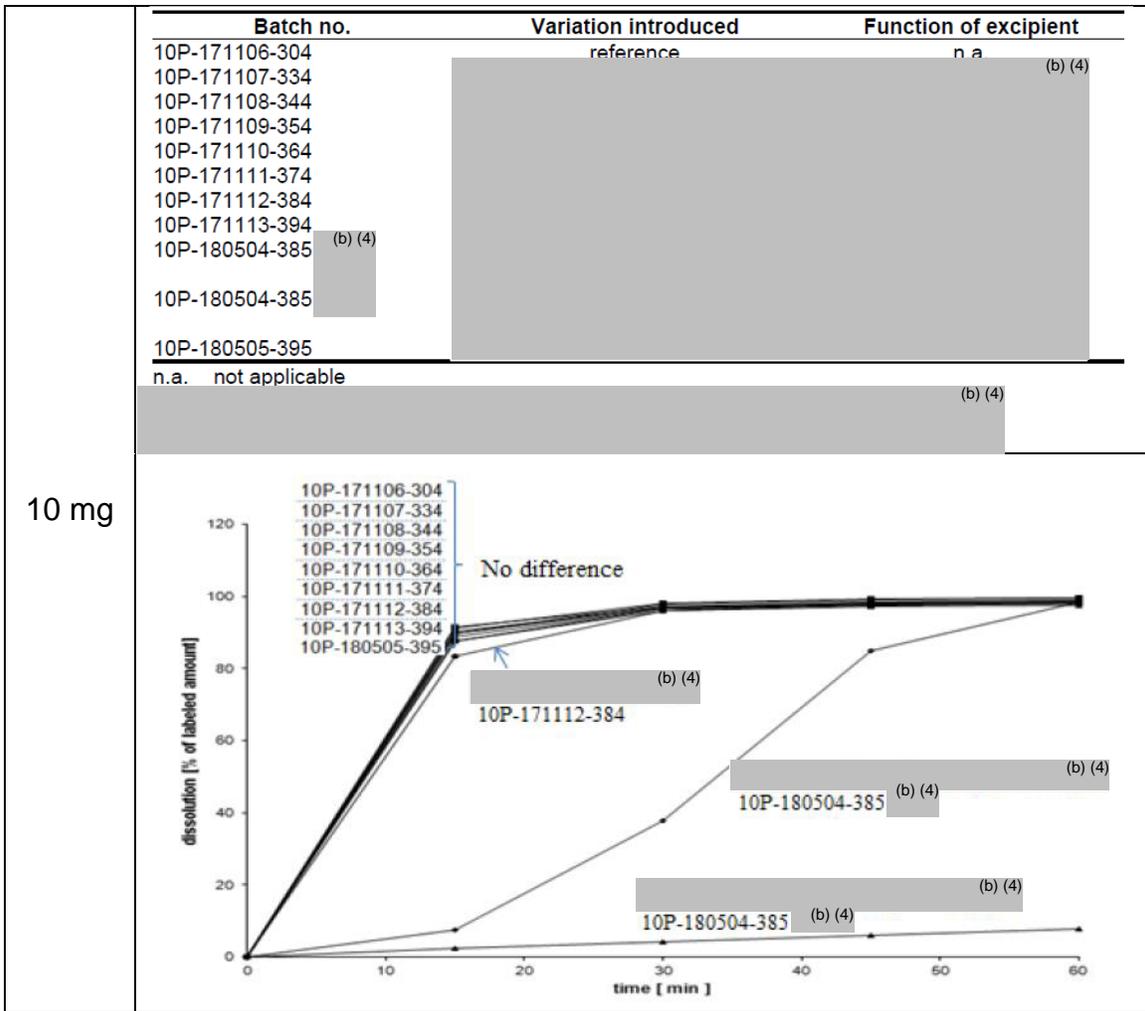




**Excipient variables:** Data obtained for 10 mg strength revealed that variations in formulation, such as (b) (4) led to a significant impaired dissolution, whereas variations, such as type of (b) (4) type of (b) (4) (b) (4) from different supplier, or reduction of the amount of (b) (4) in the formulation did not lead to a relevant impact on dissolution. The results revealed that the formulation without (b) (4) as a major variation showed significant slower dissolution as shown in Figure 6.

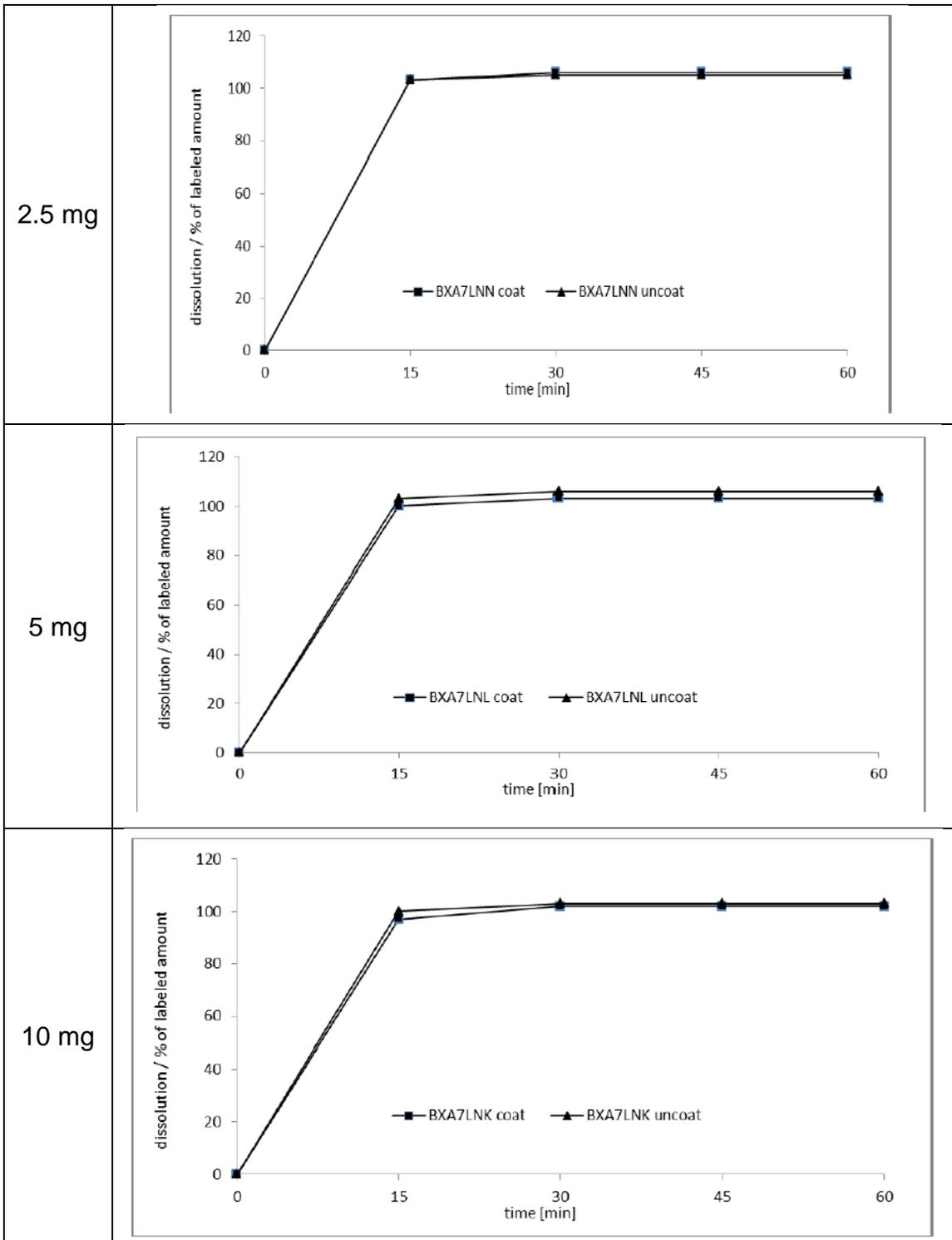
**Figure 6. Dissolution profiles of Vericiguat tablet batches (all uncoated), influence of variations in formulation composition on dissolution, 0.01 M HCl pH 2, 75 rpm, 37 °C, mean of n=12, except for batch BXA7LNN (mean of n=6)**





**Coating:** The effect of coating on the dissolution was investigated using coated and uncoated tablets, and the results showed that no difference between dissolution profiles of them was observed shown in Figure below.

**Figure. Dissolution profiles of Vericiguat tablet batches, influence of coating on dissolution, coated and uncoated batches, 0.01 M HCl pH 2, 75 rpm, 37 °C, mean of n=6 (uncoated) and n=12 (coated)**



**Assessment: {Adequate}**

It is noted that the proposed dissolution method was used during batch release testing of clinical phase II and III and stability studies.

The Applicant demonstrated that the study results revealed the discriminatory power and robustness of the proposed method using batches with variations, such as CMAs and CPPs.

The changes in PSD of the API and excipient ( (b) (4) ) significantly affected dissolution profiles whereas other factors, such as temperature, speed, and hardness had no impact on dissolution of the proposed products across all strengths. The clinical batches prepared under the proposed API specification ( $X_{90} \leq (b) (4) \mu\text{m}$ ) showed that the dissolution profiles were comparable, but the dissolution profiles of the development batch prepared with uncontrolled PSD (b) (4) failed the recommended acceptance criterion of  $\text{NLT}_{(b) (4)} \% (Q)$  in 15 min (see acceptance criterion section below).

In general, a lower agitation speed is preferred for IR dissolution method, however, the proposed speed (75 rpm) was found acceptable since the method with 75 rpm is able to discriminate batches with meaningful variation in critical material attribute, API particle size.

The proposed dissolution method is found acceptable for the quality control of the proposed drug product (all strengths).

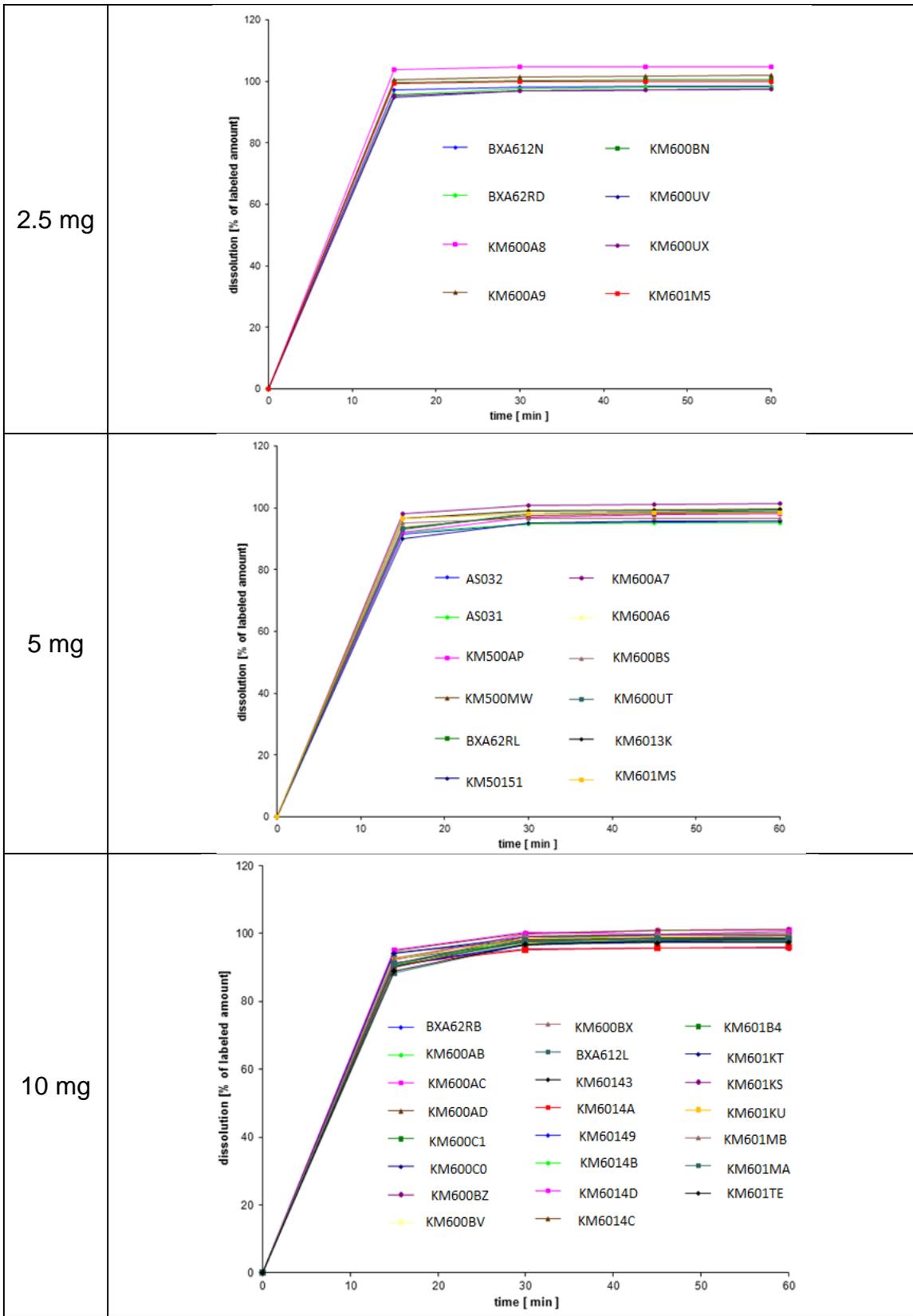
#### **B.4 DISSOLUTION ACCEPTANCE CRITERION**

The proposed dissolution acceptance criterion for quality control of Vericiguat tablets is  $\text{NLT}_{(b) (4)} \% (Q)$  after (b) (4) minutes.

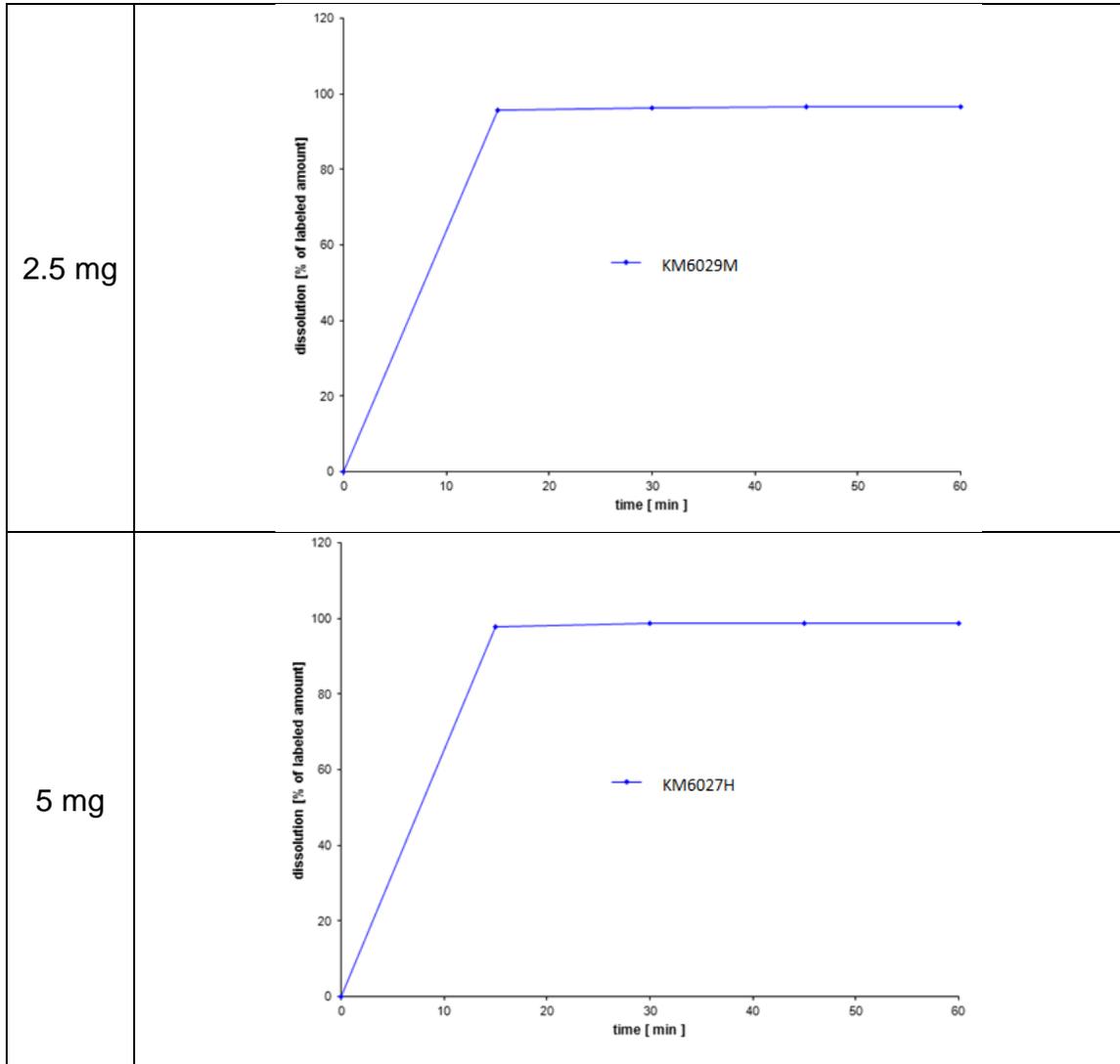
Dissolution data of batches used during clinical phase I to III as well as of the proposed commercial drug products are shown in Figure 7, 8, and 9. Further details on the dissolution data are shown in the link below<sup>1</sup>.

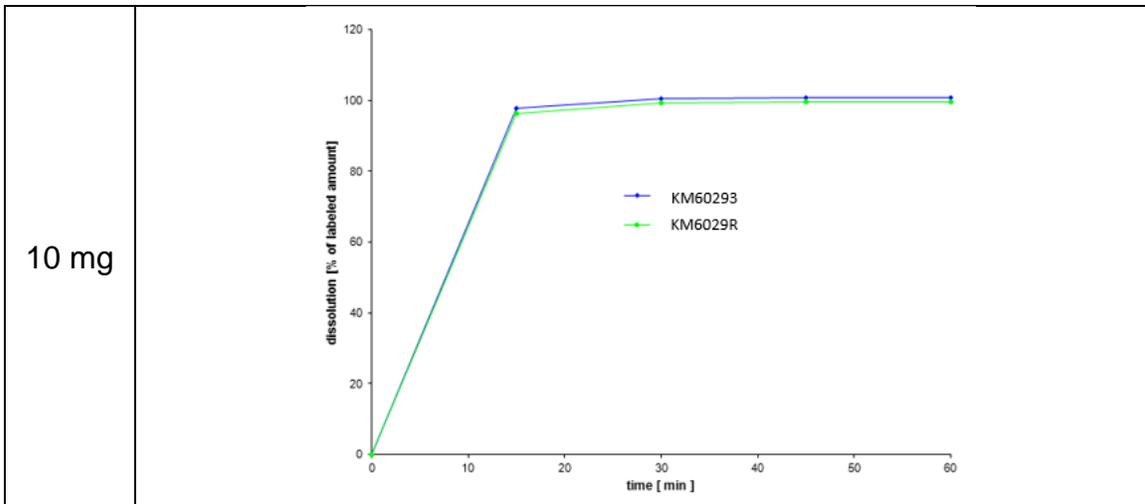
**Figure 7. Vericiguat coated tablet batches used in phase I – III clinical trials. Batches were manufactured at pilot scale. Dissolution testing was performed using USP paddle apparatus 2, 900 mL 0.01 M HCl pH 2, 75 rpm, 37 °C, (mean of n=6 or n=12)**

<sup>1</sup> \\CDSESUB1\evsprod\nda214377\0001\m3\32-body-data\32p-drug-prod\vericiguat-coated-tablet\32p2-pharm-dev\pharmaceutical-development-2-2.pdf

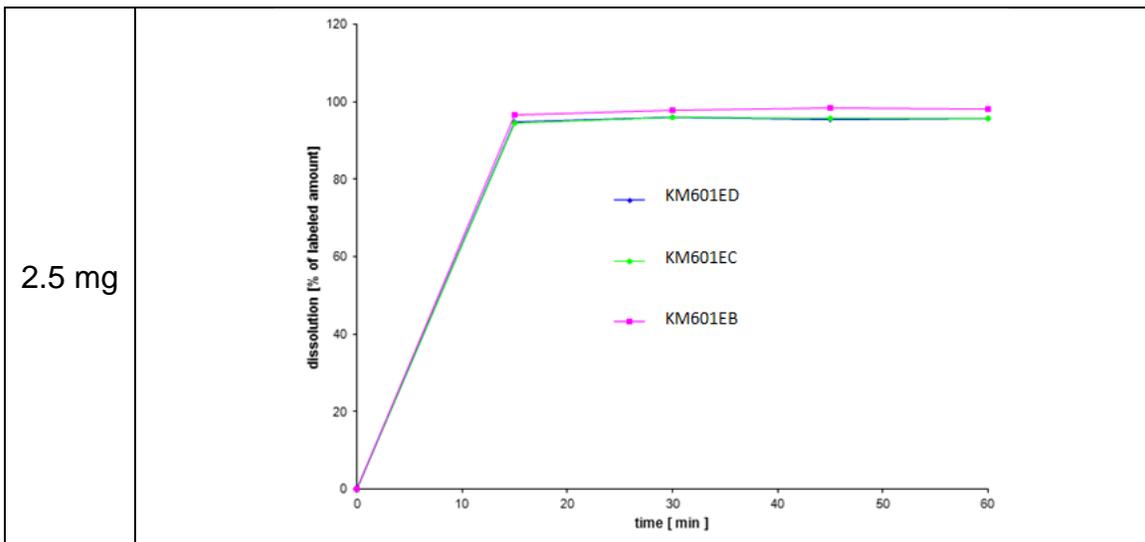


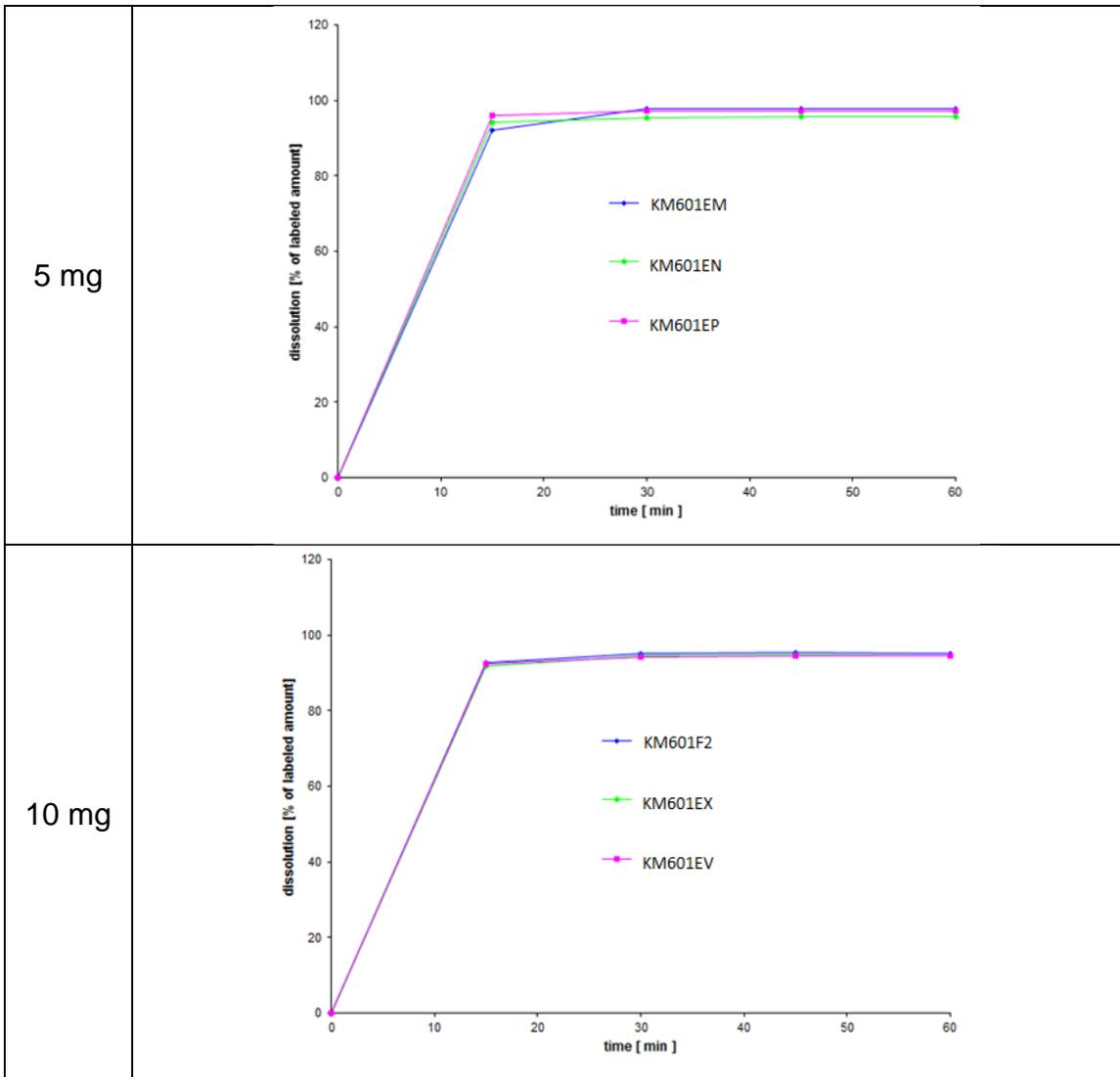
**Figure 8. Vericiguat coated tablet batches (used in phase III) manufactured at production scale. Dissolution testing was performed using USP paddle apparatus 2, 900 mL 0.01 M HCl pH 2, 75 rpm, 37 °C, (mean of n=6)**





**Figure 9. Vericiguat coated tablet proposed commercial drug product manufactured at pilot scale. Dissolution testing was performed using USP paddle apparatus 2, 900 mL 0.01 M HCl pH 2, 75 rpm, 37 °C, (mean of n=6). Data of three different batches used for primary stability testing are shown.**





The Applicant proposed that the provided dissolution profiles of clinical and commercial batches complied with the proposed acceptance criterion of NLT  $(b) (4)$  % (Q) in  $(b) (4)$  minutes.

**Assessment: {Adequate}**

The proposed dissolution acceptance criterion was  $(b) (4)$  and thus based on dissolution data of phase 3 clinical trial batches, an acceptance criterion of NLT  $(b) (4)$  % in  $(b) (4)$  minutes was recommended via the IR dated 09/01/2020. Further, Vericiguat dissolution at 15-minute time point demonstrated more discriminating ability of the proposed method towards batches with different API PSD as mentioned above. In the Applicant's response to the IR date 09/15/2020, the Applicant acknowledged and accepted the Agency's recommendation. The

dissolution specifications for the proposed drug products were updated with the recommendation.

#### **B8 BIOWAIVER REQUEST**

Biowaiver is not necessary and applicable since the proposed drug products for all strengths were tested in dose proportionality studies and phase 3 clinical trials.

#### **R. REGIONAL INFORMATION**

Comparability Protocols: N/A

Post-Approval Commitments: N/A

Lifecycle Management Considerations: N/A



Min Sung  
Suh

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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MOHAN K SAPRU  
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