CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218730Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) 218730
Integrated Quality Assessment

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 218730
Assessment #1

Drug Product Name	Vanzacaftor/tezacaftor/deutivacaftor tablets
Dosage Form	tablets
Strength	4/20/50 mg and 10/50/125 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Vertex Pharmaceuticals Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (SD-1)	05/02/2024	All
Amendment (SD-11)	07/08/2024	Manufacturing
Amendment (SD-14)	07/30/2024	Manufacturing
Amendment (SD-15)	08/02/2024	Drug Product
Amendment (SD-17)	08/22/2024	Manufacturing, Biopharmaceutics
Amendment (SD-20)	08/26/2024	Biopharmaceutics
Amendment (SD-23)	09/09/2024	Biopharmaceutics
Amendment (SD-25)	09/12/2024	Manufacturing
Amendment (SD-26)	09/13/2024	Drug Product
Amendment (SD-27)	09/20/2024	Drug Substance

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Sam Bain	Lawrence Perez (Donna Christner)
Drug Product	Ghaled Hamad	Craig M. Bertha
Manufacturing	Vickey He	Shu-Wei Yang
Microbiology	Vickey He	Shu-Wei Yang

Biopharmaceutics	Kalpana Paudel	Tapash Ghosh
Regulatory Business Process Manager	Emma Gimose	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
Environmental	Ghaled Hamad	Craig M. Bertha

Table of Content Links

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate		Sufficient information in application – same CCS component approved for Vertex NDA 212273
	Type III			Adequate		Sufficient information in application – same CCS component approved for Vertex NDA 21273

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	142001	VNZ/TEX/D-IVA tablets
IND	74633	Ivacaftor (IVA) tablets
IND	128544	D-IVA tablets
IND	108105	IVA/TEZ tablets
NDA	210491	IVA/TEZ tablets
NDA	203188	IVA tablets
NDA	212273	Elexacaftor/TEZ/IVA tablets

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

Office of Pharmaceutical Quality

New Drug Application (NDA) 218730
Integrated Quality Assessment (IQA)

NDA Executive Summary

1. Application/Product Information

NDA Number	218730
Applicant Name	Vertex Pharmaceuticals Inc.
Drug Product Name	Vanzacaftor (VNZ)/tezacaftor (TEZ)/deutivacaftor (D-IVA) tablets
Dosage Form	Tablet
Proposed Strength(s)	4/20/50 mg and 10/50/125 mg
NDA Classification	Type 1, 4 – NME and New Combination
Route of Administration	Oral
Maximum Daily Dose	20/100/250 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator
Drug Product Description	Cystic fibrosis is a life-shortening disease affecting more than 92K people worldwide. The proposed triple fixed-dose combination of VNZ/TEZ/D-IVA is said to cover 91% of the people with CF that have at least one *F508del* mutation in their transmembrane conductance regulator (CFTR) protein. The drug product is a triple fixed-dose combination of VNZ/TEZ/D-IVA formulated in two strengths as tablets for oral administration.
Co-packaged product information	N/A
Device information	N/A
Storage Temperature/ Conditions	Store at 20ºC - 25ºC (68ºF - 77ºF); excursions permitted to 15ºC - 30ºC (59ºF - 86ºF) [see USP Controlled Room Temperature]

	Discipline	Primary	Secondary
Review Team	*Drug Substance*	Sam Bain	Lawrence Perez (Donna Christner)
	Drug Product/ Labeling	Ghaled Hamad	Craig M. Bertha
	Manufacturing	Vickey He	Shu-Wei Yang
	Biopharmaceutics	Kalpana Paudel	Tapash Ghosh
	Microbiology	Vickey He	Shu-Wei Yang
	Other (specify)	N/A	
	RBPM	Emma Gimose	
	ATL	Craig M. Bertha	
Consults	N/A		

2. Final Overall Recommendation - *Recommend Approval*

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:
Based on the evaluation of the drug substance, drug product, manufacturing, and biopharmaceutics information, as amended, the application is recommended for approval. See footnote 1 below regarding labeling.

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

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Pending[1]
Manufacturing - Adequate
Biopharmaceutics - Adequate
Microbiology - N/A

[1] The labeling review decision is pending for this IQA due to ongoing negotiations with the applicant. There are only minor labeling deficiencies from the CMC perspective and we expect the applicant will accept our recommendations. Refer to the CMC sections of the final approved labeling.

Environmental Assessment: **Categorical Exclusion - Adequate**
QPA for EA(s): Choose Yes or No.

5. Life-Cycle Considerations
Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: N/A

Application Technical Lead Name and Date:

Craig M. Bertha, 03-OCT-2024

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BIOPHARMACEUTICS

Product Background:

NDA: NDA-218730-ORIG-1

Drug Product Name / Strength: Vanzacaftor (VNZ)/ tezacaftor (TEZ)/ deutivacaftor (D-IVA) tablet/ 10mg / 50mg / 125mg and 4mg / 20mg / 50mg

Route of Administration: Oral

Applicant Name: Vertex Pharmaceuticals Incorporated

Submission:
Vertex Pharmaceuticals Incorporated has submitted NDA 218730, Vanzacaftor (VNZ)/ tezacaftor (TEZ)/ deutivacaftor (D-IVA) tablet (immediate release, IR) for triple combination (TC) therapy for the treatment of cystic fibrosis (CF). VNZ/TEZ/D-IVA tablet is a fixed dose combination (FDC) for oral administration comprised of: vanzacaftor a new molecular entity which acts as a CFTR modulator (CFTRm), tezacaftor a previous approved CFTRm (symdeko® and trikafta®), and deutivacaftor a deuterated isotopolgue of the previously approved CFTRm ivacaftor (kalydeco®, orkambi ®, symdeko® and trikafta®). CF is a progressive, systemic, life-shortening, genetic disease that is caused by reduced quantity and/or function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein due to mutations in the *CFTR* gene. VNZ/TEZ/D-IVA was granted Fast Track designation on 30 May 2019, Rare Pediatric Disease Designation on 01 October 2020 (#RPD-2020-485) and Orphan Drug Designation (#DRU-2020-772) on 26 October 2020.

This application includes a cross reference to the previously submitted and approved clinical, nonclinical and chemistry and manufacturing controls (CMC) information for ELX/TEZ/IVA (trikafta®) NDA 212273, TEZ/IVA (symdeko®) NDA 210491 and IVA (kalydeco®) NDA 203188 as applicable. Comprehensive quality information for VNZ and D-IVA drug substances, D-IVA (b) (4) intermediate drug product, and two FDC drug products are provided in this application.

Two different strength FDC tablets have been developed: VNZ 10mg / TEZ 50mg / D-IVA 125mg and VNZ 4mg / TEZ 20mg / D-IVA 50mg. The proposed commercial dosing regimens for VNZ/TEZ/D-IVA are as follows:

Age	Weight	Dose
(b) (4)		

Both FDC tablets are made from (b) (4)

Review Recommendation: **Adequate**

Review Summary:
The Biopharmaceutics review is focused on the evaluation of dissolution method and acceptance criteria for vanzacaftor, tezacaftor, and deutivacaftor in the FDC tablets and bridging between the pivotal clinical trial and to-be-marketed formulation.

Dissolution Method and Acceptance Criteria: Adequate
The following dissolution methods and acceptance criteria for the release of vanzacaftor, tezacaftor, and deutivacaftor from the FDC tablet are deemed acceptable:

Component	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
Vanzacaftor	II (Paddle)	75	0.5% (w/v) SLS in 50 mM sodium phosphate, pH 6.8/37°C ± 0.5°C	900	NLT (b)(4)% (Q) of the label claim is d solved in 30 min
Tezacaftor	II (Paddle)	75	0.2% (w/v) SLS solution in 0.1N HCl/37°C ± 0.5°C	900	NLT (b)(4)% (Q) of the label claim is d solved in 30 min
Deutivacaftor	II (Paddle)	75	0.5% (w/v) SLS in 50 mM sodium phosphate, pH 6.8/37°C ± 0.5°C	90	NLT (b)(4)% (Q) of the label claim is dissolved in 20 min

Bridging of Clinical Formulations: Adequate
The to-be-marketed and pivotal clinical Phase 3 formulations are same. Hence, no bridging is needed.

Biowaiver Request: Not applicable
The Applicant has not requested any biowaiver. There are two strengths of the FDC. Both strengths were included in the Phase 3 clinical study (Study 105).

List of Submissions reviewed:

Application 218730 - Sequence 0001 - 05/02/2024 ORIG-1 /Multiple Categories/Subcategories
Application 218730 - Sequence 0020 - 08/26/2024 ORIG-1 /Multiple Categories/Subcategories /Quality/Response To Information Request
Application 218730 - Sequence 0023 - 09/09/2024 ORIG-1 /Multiple Categories/Subcategories /Quality/Response To Information Request

Highlight Key Outstanding Issues from Last Cycle: None. This is the first review cycle.

Concise Description of Outstanding Issues Remaining: None.

Conclusion: From Biopharmaceutics perspective, NDA 218730 for vanzacaftor, tezacaftor and deutivacaftor (D-IVA) tablets (10mg / 50mg / 125mg and 4mg / 20mg / 50mg) is recommended for APPROVAL.

BCS Designation

Reviewer's Assessment: Adequate

The Applicant has not claimed or requested any BCS classification for their drug product. However, following information has been provided in M.2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods).

VNZ
VNZ is considered to be BCS Class 2 (low solubility/high permeability) compound.

TEZ
- TEZ is classified as a BCS Class 2 compound (low solubility/high permeability). Classification of TEZ according to the BCS is summarized in the TEZ/IVA Marketing Application Module 2.7.1/Section 3.6 (Symdeko, Symkevi)
- A 100-mg dose requires 25 L of water to completely dissolve; therefore, TEZ is classified as low solubility according to BCS criteria.
- TEZ exhibited high permeability in a study conducted using the Caco-2 cell system, which is a widely accepted in vitro model to predict intestinal drug permeation in humans.

D-IVA
- IVA could not be definitively classified by the BCS (Kalydeco Marketing Authorization/ Module 2.7.1/Section 1.5).
- It has low solubility, suggesting that it is either BCS Class 2 (low solubility/high permeability) or Class 4 (low solubility/low permeability).
- Its low solubility and nonspecific binding to culture materials precluded an acceptable determination of its permeability using the Caco-2 cell system.
- Due to the structural similarities between D-IVA and IVA, D-IVA is also expected to be either BCS Class 2 or Class 4.

Solubility
The solubility of all three components in different media is provided below.

Vanzacaftor

Table 1: Solubility, Solution pH, and Physical Form of Vanzacaftor Drug Substance in Aqueous Solutions and Organic Solvents at 24 hours

Solvent	Solubility (mg/mL)	pH	USP Definition [a]	Physical Form
pH 1.0 Buffer [b]	ND	1.1	practically insoluble	Form D
pH 3.0 Buffer [c]	ND	3.0	practically insoluble	Form D
pH 5.0 Buffer [d]	ND	5.1	practically insoluble	Form D
pH 7.0 Buffer [e]	ND	7.0	practically insoluble	Form D
pH 8.0 Buffer [f]	ND	8.1	practically insoluble	Form D
pH 9.0 Buffer [g]	ND	9.0	practically insoluble	Form D
Water at RT	0.001	8.3	practically insoluble	Form D
Water at 37 °C	0.003	7.0	practically insoluble	Form D
FaSSIF at 37 °C	0.008	6.8	practically insoluble	Mixture of Form D (b) (4)
FeSSIF at 37 °C	0.013	5.7	practically insoluble	(b) (4)
Acetonitrile (MeCN)	3.2	--	slightly soluble	Form D
MeCN/Water (60/40 v/v)	4.5	--	slightly soluble	Form D

Abbreviations: FaSSIF: Fasted state simulated intestinal fluid; FeSSIF: Fed state simulated intestinal fluid, RT – Room Temperature, ND – Not Detected < 0.0003 mg/mL
[a] USP definitions: < 0.1 mg/mL: practically insoluble, 1-10 mg/mL: slightly soluble
[b] Potassium chloride and hydrochloric acid
[c] Potassium hydrogen phthalate and hydrochloric acid
[d] Potassium hydrogen phthalate and sodium hydroxide
[e] Potassium phosphate monobasic and sodium hydroxide
[f] Potassium phosphate monobasic and sodium hydroxide
[g] Boric acid, potassium chloride, and sodium hydroxide

Table 2: Solubility, Solution pH, and Physical Form of Deutivacaftor in Aqueous Solutions and Organic Solvents at 24 hours

Solvent	Solubility (mg/mL)	pH	USP Definition [a]	Physical Form
pH 1.0 Buffer [b]	ND	1.2	practically insoluble	(b) (4)
pH 3.0 Buffer [c]	< 0.001	3.0	practically insoluble	
pH 5.0 Buffer [d]	< 0.001	5.0	practically insoluble	
pH 7.0 Buffer [e]	ND	7.1	practically insoluble	
Water at RT	< 0.001	8.0	practically insoluble	
Water at 37 °C	< 0.001	8.9	practically insoluble	
FaSSIF at 37 °C	0.009	6.5	practically insoluble	
FeSSIF at 37 °C	0.10	5.8	very slightly soluble	
Acetonitrile/Water (90/10)	4.8	--	slightly soluble	
Methyl ethyl ketone/Water (90/10)	110.6	--	freely soluble	
Acetonitrile	0.77	--	very slightly soluble	
Methanol	2.1	--	slightly soluble	Solvate
2-Methyltetrahydrofuran	45.4	--	soluble	N/A [f]
Acidified 2-methyltetrahydrofuran [g]	134.2	--	freely soluble	N/A [f]

Abbreviations: FaSSIF: Fasted state simulated intestinal fluid; FeSSIF: Fed state simulated intestinal fluid, RT – Room Temperature, ND – Not Detected < 0.0001 mg/mL
[a] USP definitions: < 0.1 mg/mL: practically insoluble, 0.1-1 mg/mL: very slightly soluble, 1-10 mg/mL: slightly soluble, 10-30 mg/mL: sparingly soluble, 30-100 mg/mL: soluble, 100-1000 mg/mL: freely soluble.
[b] Potassium chloride and hydrochloric acid
[c] Potassium biphthalate hydrochloric acid
[d] Potassium biphthalate sodium hydroxide
[e] Dihydrogen potassium phosphate – sodium phosphate dibasic
[f] Not enough solids were available for XRPD analysis
[g] Solution prepared by mixing 0.1N hydrochloric acid and 2-methyltetrahydrofuran and extracting the organic layer

Table 3: Tezacaftor (b) (4) Solubility at 24 hours, 37°C[a]

Buffer/pH	Tezacaftor Solubility (mg/mL)
0.1 N HCl pH 1.0	0.04
50 mM Sodium Phosphate pH 6.8	0.05

[a] Solubility was measured in the presence of vanzacaftor drug substance and deutivacaftor (b) (4) Solubility was determined at 24 hours.

Dissolution: Please see below.

Drug Product

Per the Applicant, tezacaftor belongs to BCS class 2 and deutivacaftor belongs to BCS class 2 or 4. As the solubility for both APIs are low, both tezacaftor and deutivacaftor drug substances are provided as (b) (4) intermediates for drug product formulation. Vanzacaftor is provided as a calcium salt; reference to vanzacaftor drug substance denotes the use of calcium salt Form D of the active pharmaceutical ingredient. Per the Applicant, vanzacaftor may be considered as a class 2. VNZ/TEZ/D-IVA 10/50/125 mg and 4/20/50 mg tablet strengths are weight multiples prepared (b) (4)

The composition of FDC drug product is provided below.

Table 4: Composition of VNZ/TEZ/D-IVA 10/50/125 mg Tablet

Component	Quality Standard	Component Function	Amount per Tablet (mg)	Content (% w/w)
(b) (4)				

Component	Quality Standard	Component Function	Amount per Tablet (mg)	Content (% w/w)
(b) (4)				

Table 5: Composition of VNZ/TEZ/D-IVA 4/20/50 mg Tablet

Component	Quality Standard	Component Function	Amount per Tablet (mg)	Content (% w/w)
(b) (4)				

Component	Quality Standard	Component Function	Amount per Tablet (mg)	Content (% w/w)
(b) (4)				

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: Adequate

The Biopharmaceutics review is focused on the evaluation of dissolution method and acceptance criterion for venzacaftor, tezacaftor and deutivacaftor in the FDC tablets.

Proposed dissolution method and acceptance criterion

In-vitro dissolution methods for each active were independently developed for testing FDC tablets. The following dissolution methods and acceptance criteria were initially proposed:

Table 6: Dissolution Methods for Vanzacaftor, Tezacaftor, and Deutivacaftor from Vanzacaftor/Tezacaftor/Deutivacaftor FDC Tablet

Component	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion

Vanzacaftor	II (Paddle)	75	0.5% (w/v) SLS in 50 mM sodium phosphate, pH 6.8/37°C ± 0.5°C	900	NLT (b) (4)% (Q) of the label claim is dissolved in (b) (4)min
Tezacaftor	II (Paddle)	75	.2% (w/v) LS solution in 0.1N HCl/37°C ± 0.5°C	900	NLT (b) (4)% (Q) of the label claim is dissolved in (b) (4)min
Deutivacaftor	II (Paddle)	75	0.5% (w/v) SLS in 50 mM sodium phosphate, pH 6.8/37°C ± 0.5°C	900	NLT (b) (4)% (Q) of the label claim is dissolved in 20 min

For Tezacaftor, the dissolution testing will be carried out separately per the described dissolution procedure as Tezacaftor has different medium than the other two components.

Dissolution method development

The Applicant submitted details of the dissolution method development for each component in the FDC tablet. A summary of the dissolution method development for the three components is provided below.

Vanzacaftor

(b) (4)

(b) (4)

[redacted]

Discriminating ability of the vanzacaftor dissolution method

A risk assessment was performed to identify VNZ/TEZ/D-IVA 4/20/50 mg and 10/50/125 mg tablet variants for the discriminating ability assessment of the vanzacaftor dissolution method. This

assessment involved reviewing material attributes, minor changes in tablet composition and variations in process parameter ranges that could potentially influence the release of vanzacaftor from the tablet (Table 7). Based on this assessment, tablet variants were manufactured in small scale batches to evaluate the discriminating ability of the vanzacaftor dissolution method for VNZ/TEZ/D-IVA 4/20/50 mg and 10/50/125 mg tablets. Dissolution plots are shown below for tablet variants where discriminating ability of the method is demonstrated.

Table 7: Vanzacaftor Risk Assessment Summary of Tablet Variants Identified for Dissolution Method Discriminating Ability Evaluation

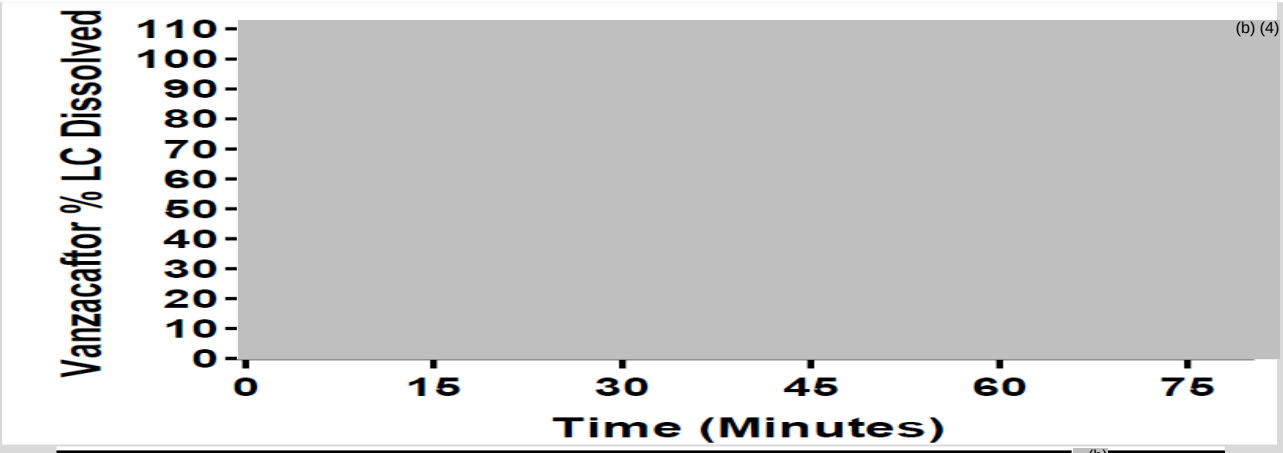
Potential to Impact Dissolution	Identified Attributes & Process Parameters	Tablet Variants for Method Discriminatory Power Evaluation
Material Attributes	• Vanzacaftor DS particle size • Deutivacaftor (b) (4) • Tezacaftor (b) (4)	• Tablets with varying vanzacaftor DS particle size • Tablets with varying deutivacaftor (b) (4) • Tablets with varying tezacaftor (b) (4)
Tablet Composition	• (b) (4) level (b) (4) • (b) (4) level (b) (4)	• Tablets with varying (b) (4) levels • Tablets with varying (b) (4) levels
Process Parameter	• Tablet (b) (4) • (b) (4)	• Tablets varying in hardness • Tablets made from (b) (4) varying (b) (4)

a Method discriminatory power to (b) (4) can be evaluated either through (b) (4) variations or by varying the tablet (b) (4) level. For vanzacaftor dissolution method discriminatory power evaluation, tablets made with varying (b) (4) levels were assessed.

Vanzacaftor DS particle size

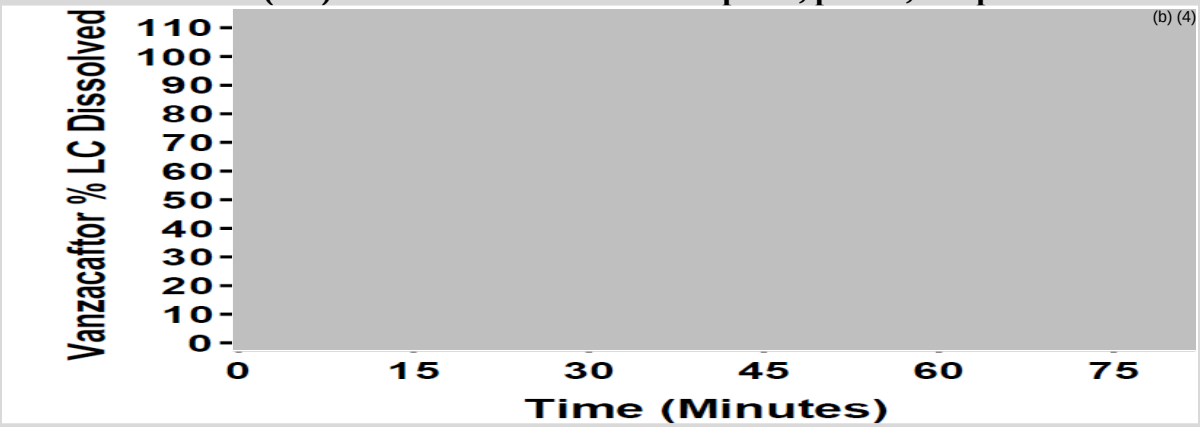
Tablets were prepared at (b) (4) (4/20/50 mg tablet: (b) (4) kp; 10/50/125 mg tablet: (b) (4) kp) with vanzacaftor drug substance of varying particle sizes (b) (4) µm) and tested. The vanzacaftor dissolution rate decreases with increasing vanzacaftor particle size for both tablet strengths as seen in the below figures.

Figure 3: Dissolution of Vanzacaftor from VNZ/TEZ/D-IVA 4/20/50 mg Tablets Prepared with Varying Vanzacaftor Drug Substance Particle Size in 0.5% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm



Vanzacaftor Particle Size (Dv50)	Vanzacaftor % LC Dissolved in (b) (4) Minutes
(b) (4) µm	89
µm	64

Figure 4: Dissolution of Vanzacaftor from VNZ/TEZ/D-IVA 10/50/125 mg Tablets Prepared with Low and High Vanzacaftor Drug Substance Particle Size in 0.5% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm



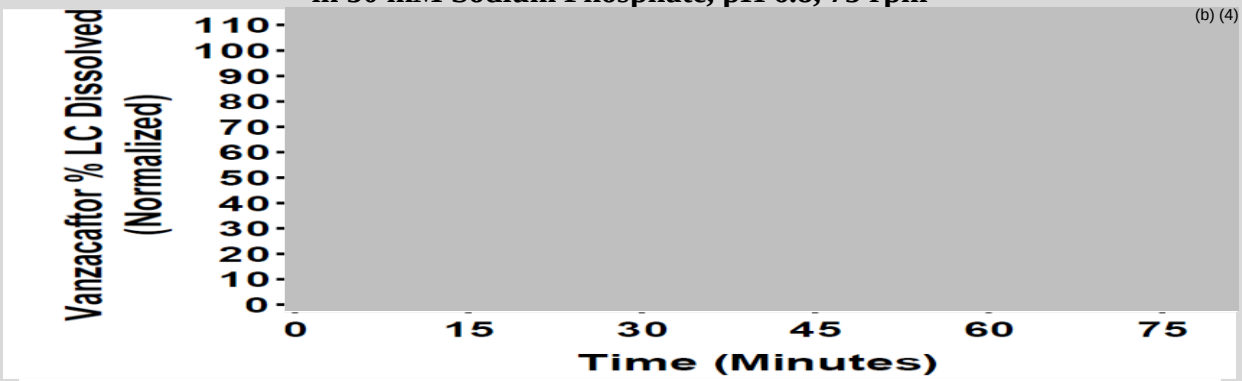
Vanzacaftor Particle Size (Dv50)	Vanzacaftor % LC Dissolved in (b) (4) Minutes
(b) (4) µm	89
µm	73

Deutivacaftor (b) (4)

Tablets were prepared at (b) (4) (4/20/50 mg tablet: (b) (4) kp; 10/50/125 mg tablet: (b) (4) kp) with deutivacaftor (b) (4) of varying (b) (4) ((b) (4) and (b) (4)) and tested. The vanzacaftor dissolution rate decreases with decreasing deutivacaftor (b) (4) for both tablet strengths as seen in the below figures.

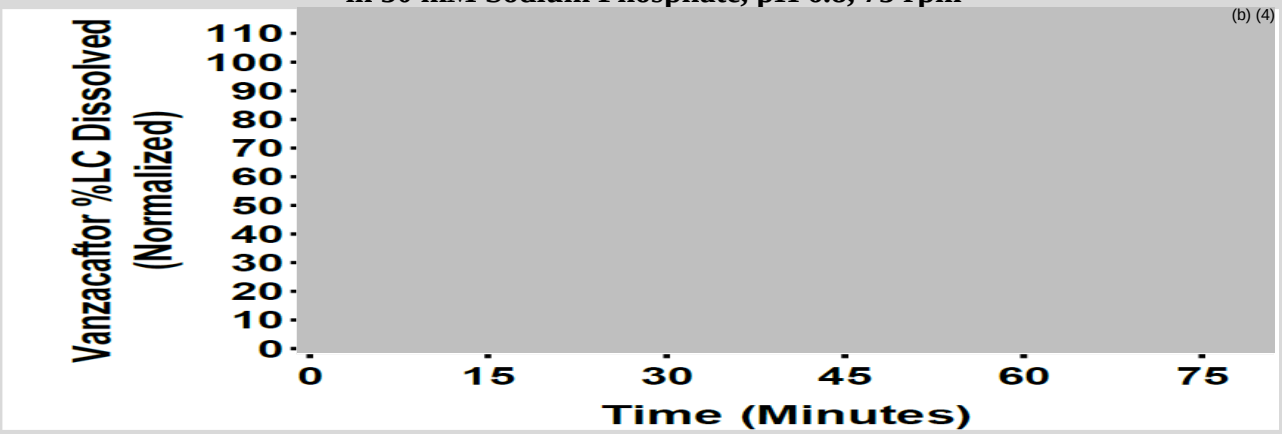
Figure 5: Dissolution of Vanzacaftor from VNZ/TEZ/D-IVA 4/20/50 mg Tablets Prepared with Varying Deutivacaftor (b) (4) in 0.5% (w/v) SLS

in 50 mM Sodium Phosphate, pH 6.8, 75 rpm



Deutivacaftor (b) (4)	Vanzacaftor % LC Dissolved in (b) (4) Minutes
(b) (4)	70
	85

Figure 6: Dissolution of Vanzacaftor from VNZ/TEZ/D-IVA 10/50/125 mg Tablets Prepared with Varying Deutivacaftor (b) (4) in 0.5% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm



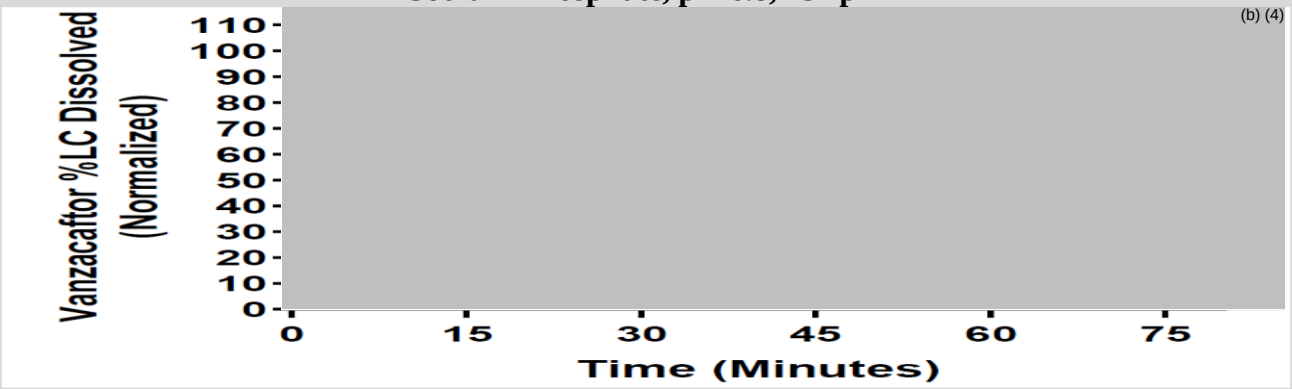
Deutivacaftor (b) (4)	Vanzacaftor % LC Dissolved in (b) (4) Minutes
(b) (4)	73
	85

(b) (4) level

Tablets were prepared at (b) (4) (4/20/50 mg tablet: (b) (4); 10/50/125 mg tablet: (b) (4) kp) with (b) (4) levels spanning (b) (4)% target composition and tested. The vanzacaftor dissolution rate decreases with decreasing (b) (4) for both tablet strengths as seen in the below figures.

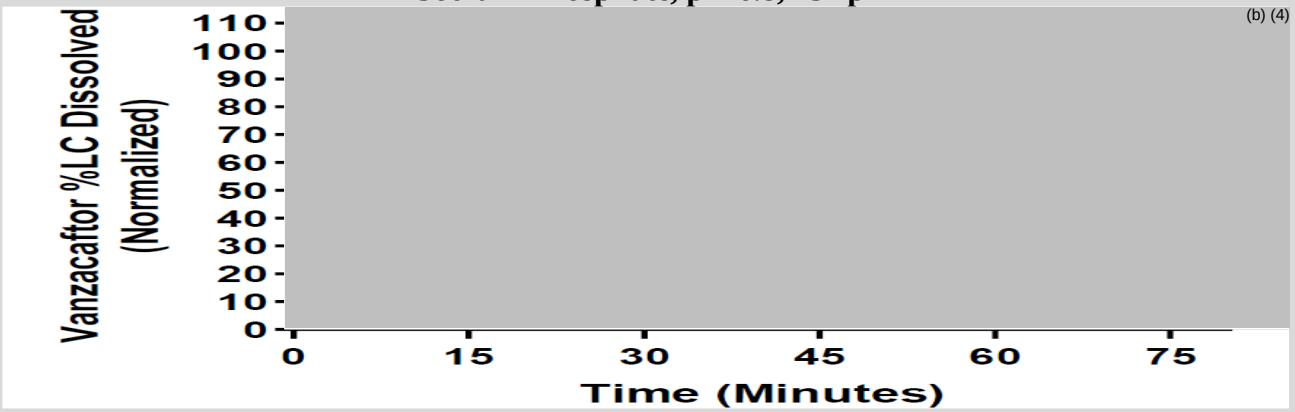
Figure 7: Dissolution of Vanzacaftor from VNZ/TEZ/D-IVA 4/20/50 mg Tablets Prepared with Varying (b) (4) Levels in 0.5% (w/v) SLS in 50 mM

Sodium Phosphate, pH 6.8, 75 rpm



(b) (4) Levels	Vanzacaftor % LC Dissolved in (b) (4) Minutes
(b) (4) % Target	87
(b) (4) % Target	55

Figure 8: Dissolution of Vanzacaftor from VNZ/TEZ/D-IVA 10/50/125 mg Tablets Prepared with Varying (b) (4) Levels in 0.5% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm

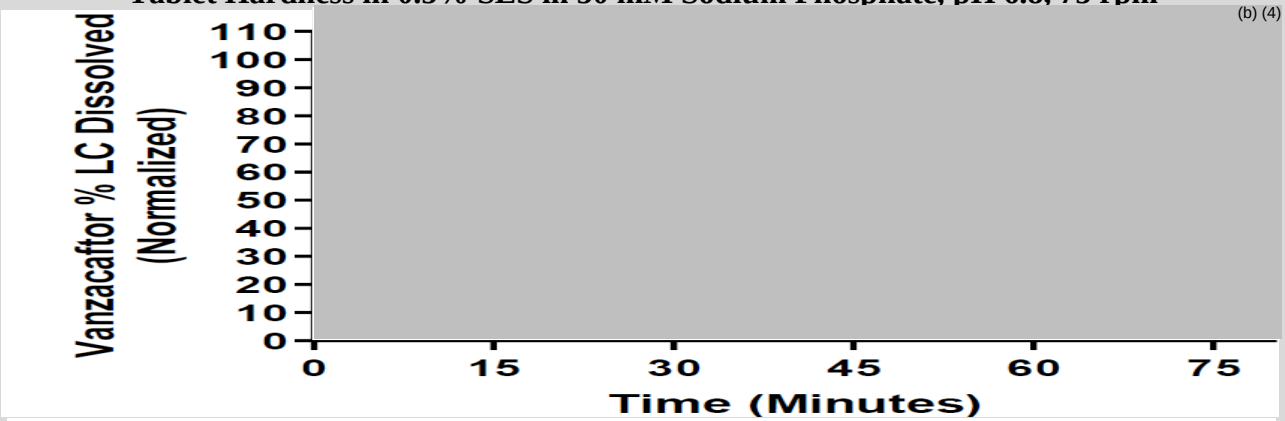


(b) (4) Levels	Vanzacaftor % LC Dissolved in (b) (4) Minutes
(b) (4) % Target	88
(b) (4) % Target	70

Tablet hardness

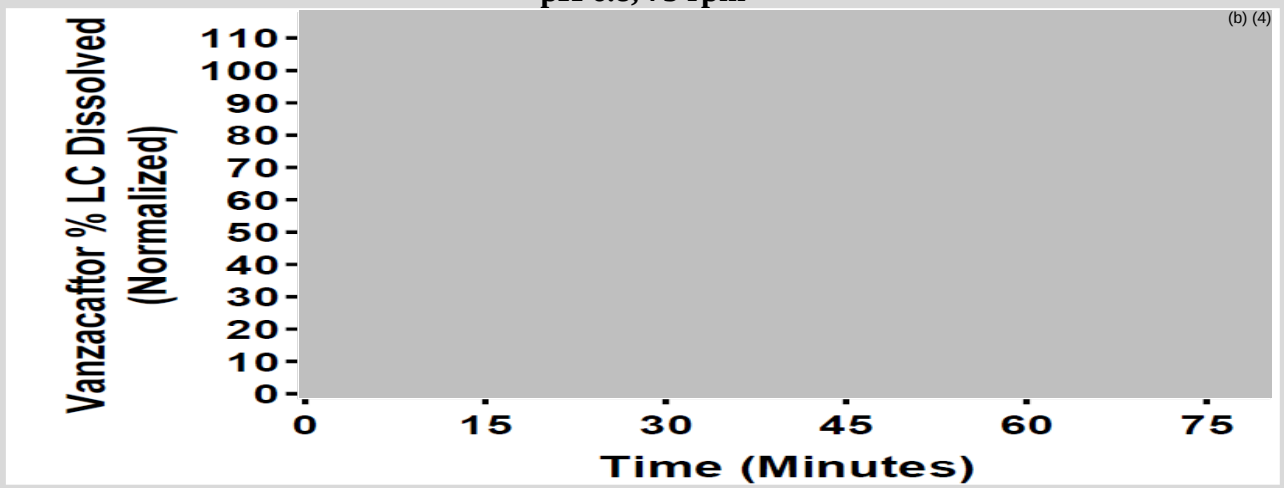
Tablets of varying hardnesses (4/20/50 mg tablet: ~ (b) (4) kp; 10/50/125 mg tablet: ~ (b) (4) kp) were prepared and tested. The vanzacaftor dissolution rate decreases with increasing tablet hardness for both tablet strengths as seen in the below figures.

Figure 9: Dissolution of Vanzacaftor from VNZ/TEZ/D-IVA 4/20/50 mg Tablets of Varying Tablet Hardness in 0.5% SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm



Tablet Hardness (kp)	Vanzacaftor % LC Dissolved in (b) (4) Minutes
(b) (4)	94
	92
	91
	89
	80

Figure 10: Dissolution of Vanzacaftor from VNZ/TEZ/D-IVA 10/50/125 mg Tablets of Varying Tablet Hardness in 0.5% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm



Tablet Hardness (kp)	Vanzacaftor % LC Dissolved in (b) (4) Minutes
(b) (4)	93
	93
	90
	88
	81

Tezacaftor (b) (4)

The method showed little discrimination for tablets prepared with tezacaftor (b) (4) ranging in (b) (4) from (b) (4) for both tablet strengths.

(b) (4) **level**

The vanzacaftor dissolution method shows little discrimination to (b) (4) level. Tablets were prepared at (b) (4) (4/20/50 mg tablet: (b) (4) kp; 10/50/125 mg tablet: (b) (4) kp) with (b) (4) level spanning (b) (4) % target composition. A small but measurable change in vanzacaftor dissolution was observed for both tablet strengths.

Multivariate assessment of the method's discriminating ability

Tablets prepared as part of a multivariate QbD study evaluating the impact to dissolution with respect to vanzacaftor drug substance particle size, tezacaftor (b) (4), deutivacaftor (b) (4), (b) (4) were tested. A range of the dissolution responses (4/20/50 mg tablet: 82 to 99% LC; 10/50/125 mg tablets: 83 to 99 % LC) were obtained for the tablet variants tested providing further evidence of the method's discriminating ability (Figures below).

Figure 11: Dissolution of Vanzacaftor from VNZ/TEZ/D-IVA 4/20/50 mg Tablets Prepared as Part of a Multivariate QbD Study in 0.5% SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm

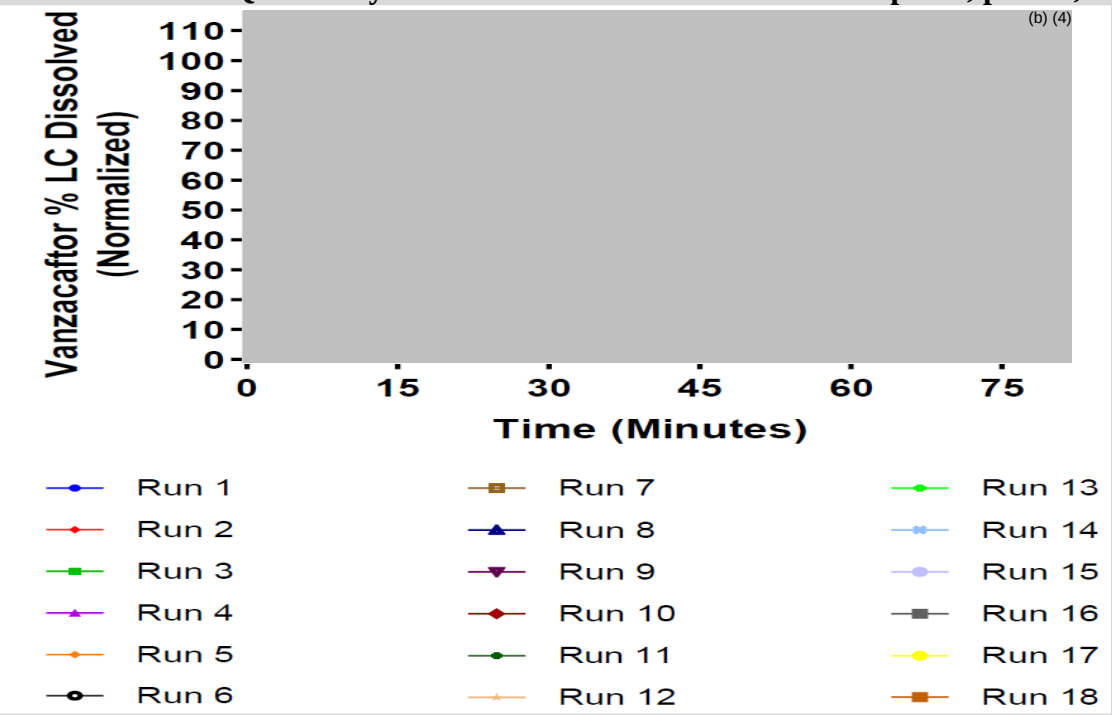
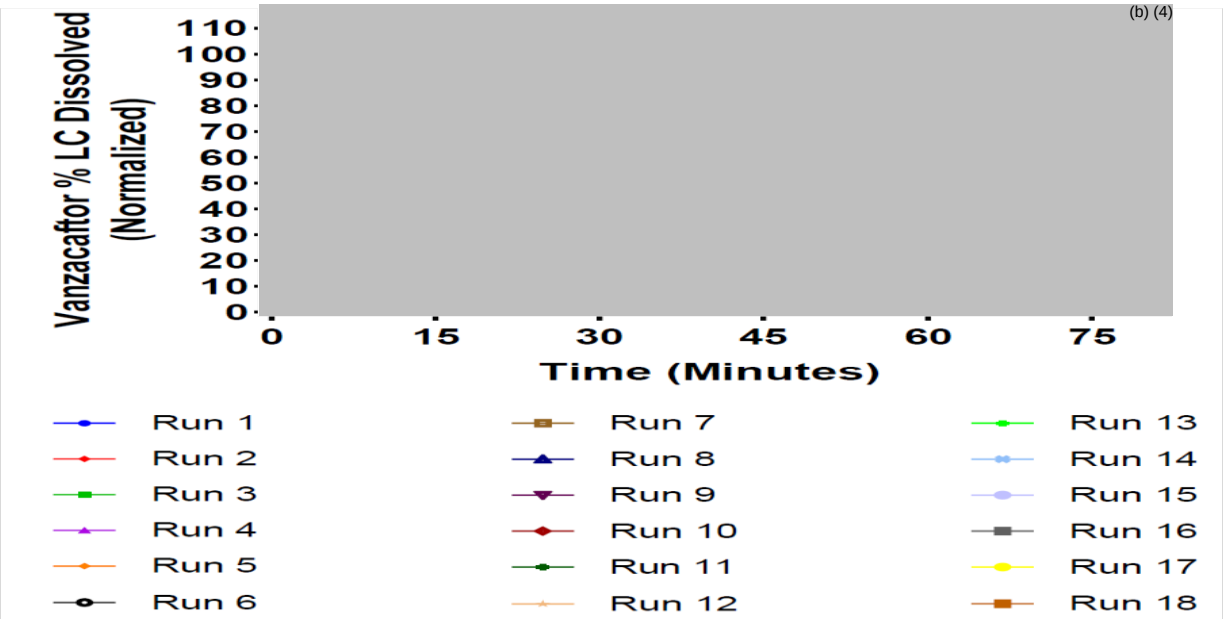


Figure 12: Dissolution of Vanzacaftor from VNZ/TEZ/D-IVA 10/50/125 mg Tablets Prepared as Part of a Multivariate QbD Study in 0.5% SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm

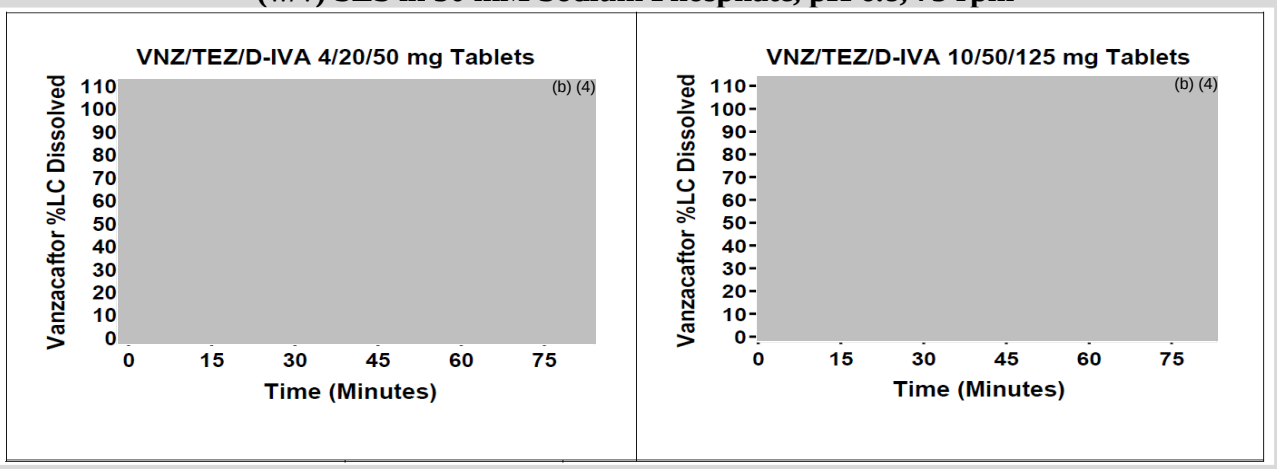


In conclusion, the Applicant has developed a dissolution method for determining the release of vanzacaftor from VNZ/TEZ/D-IVA 4/20/50 mg and 10/50/125 mg tablets. The method is sensitive with respect to material attributes, minor changes in tablet composition and variations in process parameter ranges that could potentially influence the release of vanzacaftor from the tablet. The proposed method is suitable for QC purposes for release and stability testing.

Dissolution acceptance criterion

The proposed vanzacaftor dissolution acceptance criterion is not less than (b) (4)% (Q) of the label claim is dissolved in (b) (4) minutes. The dissolution profiles of vanzacaftor for pivotal clinical batches are shown below.

Figure 13: Dissolution of Vanzacaftor for Pivotal VNZ/TEZ/D-IVA Tablet Lots in 0.5% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm



Tablet Strength	Lot	Vanzacaftor %LC Dissolved at (b) (4) minutes
4/20/50 mg	3209516R	87
	3213216R	85
	3213814R	79
10/50/125 mg	3199049R	88
	3202291R	89
	3206839R	90
	3210851R	90
	3216645R	88

Based on the submitted in vitro dissolution profile data, the proposed dissolution acceptance criterion for vanzacaftor is (b) (4) and not acceptable. An IR (see in Appendix) was sent to implement the acceptance criterion of *Q=* (b) (4) *in* (b) (4) *minutes* based primarily on the provided dissolution profile data of pivotal batch/registration batches. In the response, the Applicant accepted Agency recommendation for the higher strength but proposed to retain the same for the lower strength. It is unusual that the lower strength (4/20/50) demonstrates slower dissolution rate compared to the higher strength (10/50/125) at the beginning. However, in order to maintain a uniform dissolution method and acceptance criterion, the Agency recommended *NLT* (b) (4) *% (Q) at 30 minutes* for both strengths, which the Applicant accepted.

Tezacaftor

(b) (4)

(b) (4)

Discriminating Ability of the Tezacaftor Dissolution Method

The discriminating ability of the dissolution method was evaluated for potentially critical process parameters and material and tablet properties as listed in the below table:

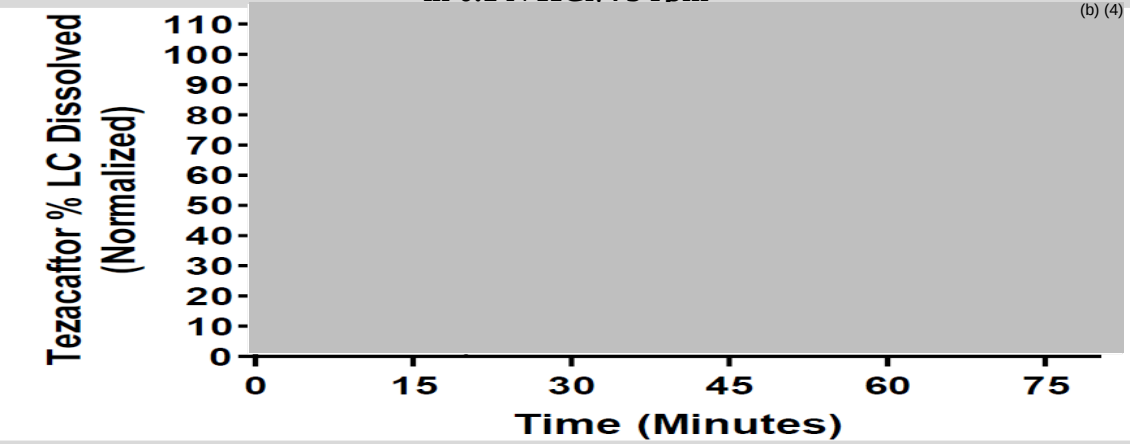
Table 8: Tezacaftor Risk Assessment Summary of Tablet Variants Identified for Method Discriminating Ability Evaluation

Potential to Impact Dissolution	Identified Attributes & Process Parameters	Tablet Variants for Method Discriminatory Power Evaluation
Material Attributes	• Deutivacaftor (b) (4) (b) (4) • Tezacaftor (b) (4) (b) (4)	• Tablets with varying deutivacaftor (b) (4) (b) (4) • Tablets with varying tezacaftor (b) (4) (b) (4)
Tablet Composition	• (b) (4) level (b) (4) • (b) (4) level (b) (4)	• Tablets with varying (b) (4) levels • Tablets with varying (b) (4) levels
Process Parameter	• Tablet (b) (4) • (b) (4)	• Tablets varying in hardness • Tablets made from (b) (4) varying in (b) (4) (b) (4)

1. Method discriminatory power to lubrication can be evaluated either through (b) (4) variations or by varying the tablet (b) (4) level. For tezacaftor dissolution method discriminatory power evaluation, tablets made with varying (b) (4) levels were assessed.

Dissolution plots are shown below for tablet variants where the dissolution method is found to be sensitive.

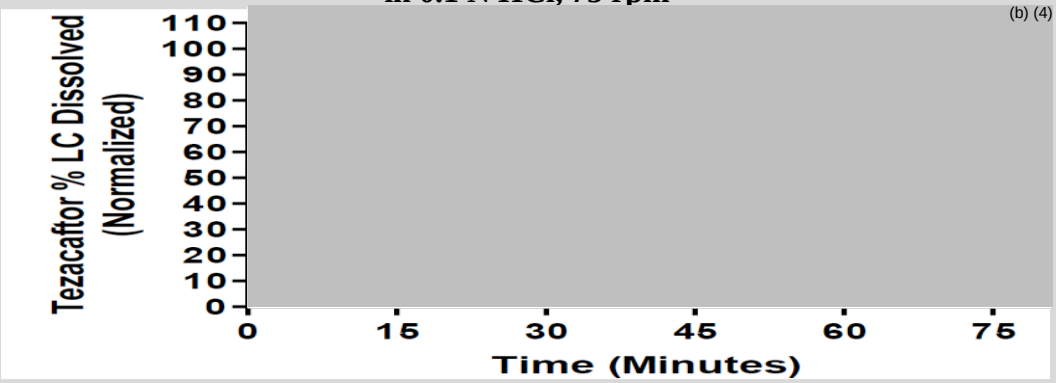
Figure 14: Dissolution of Tezacaftor from VNZ/TEZ/D-IVA 4/20/50 mg Tablets Prepared with Varying Deutivacaftor (b) (4) in 0.2% (w/v) SLS in 0.1 N HCl, 75 rpm



Deutivacaftor (b) (4)	Tezacaftor % LC Dissolved in (b) (4) Minutes
(b) (4)	55
	79

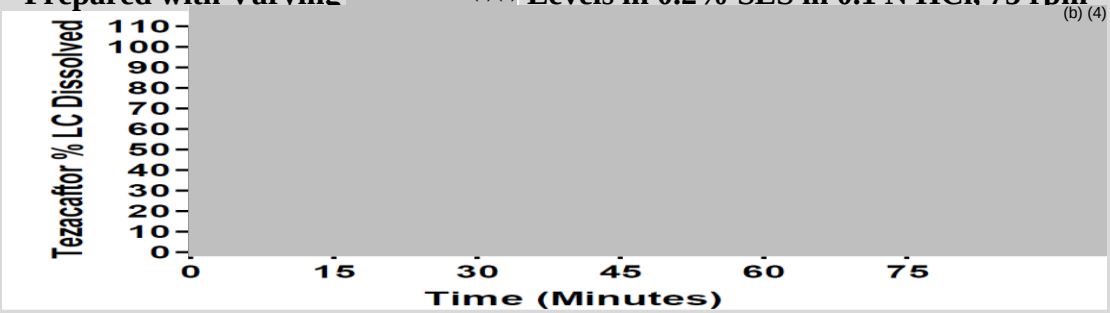
Figure 15: Dissolution of Tezacaftor from VNZ/TEZ/D-IVA 10/50/125 mg Tablets Prepared with Varying Deutivacaftor (b) (4) in 0.2% (w/v) SLS

in 0.1 N HCl, 75 rpm



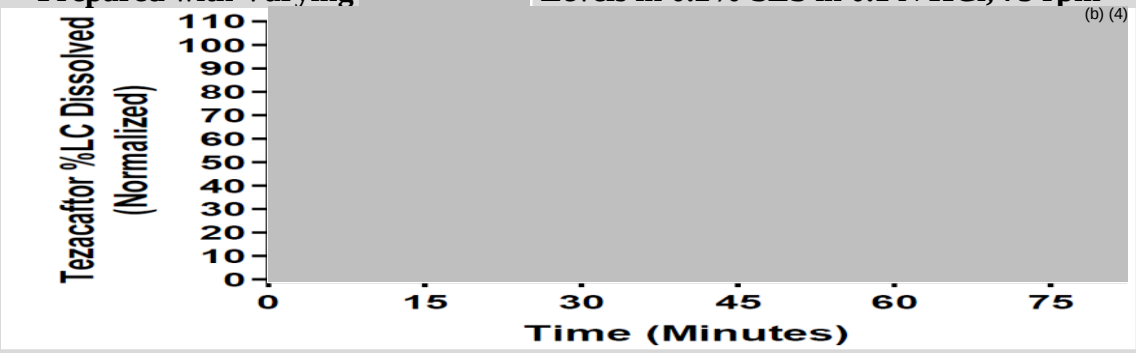
Deutivacaftor (b) (4)	Tezacaftor % LC Dissolved in (b) (4) Minutes
(b) (4)	61
	85

Figure 16: Dissolution of Tezacaftor from VNZ/TEZ/D-IVA 4/20/50 mg Tablets Prepared with Varying (b) (4) Levels in 0.2% SLS in 0.1 N HCl, 75 rpm



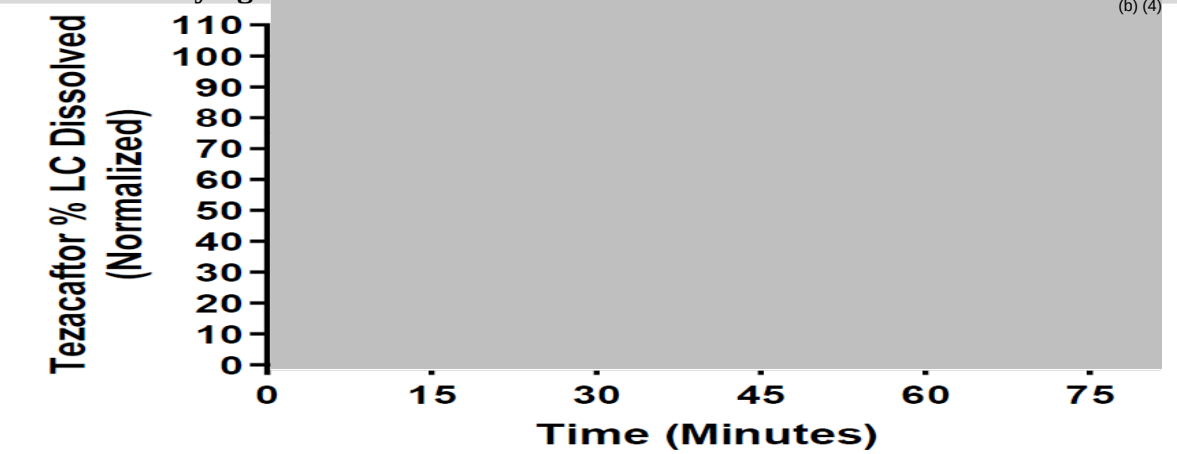
(b) (4) Levels	Tezacaftor % LC Dissolved in (b) (4) Minutes
(b) (4) Target	93
Target	23

Figure 17: Dissolution of Tezacaftor from VNZ/TEZ/D-IVA 10/50/125 mg Tablets Prepared with Varying (b) (4) Levels in 0.2% SLS in 0.1 N HCl, 75 rpm



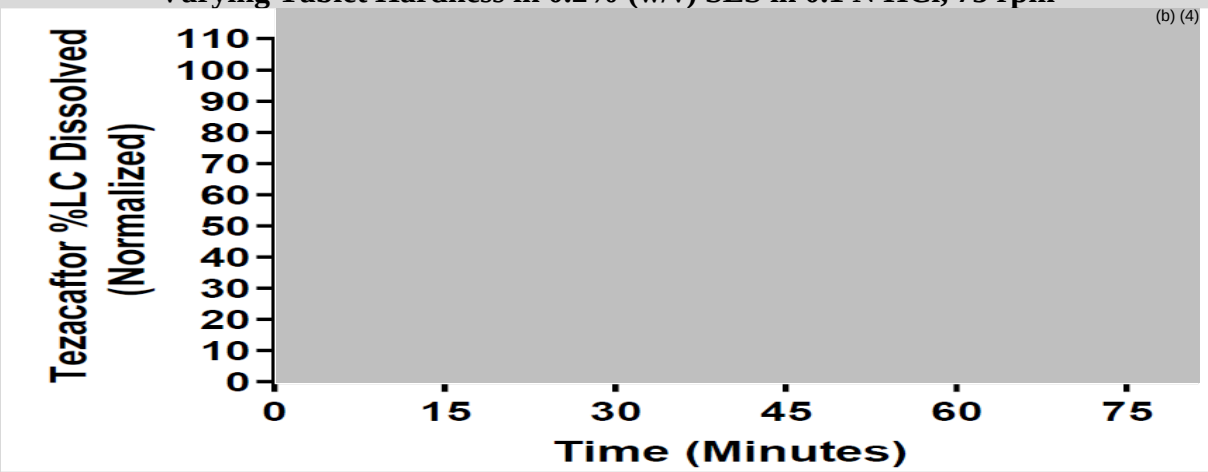
(b) (4) Levels	Tezacaftor % LC Dissolved in (b) (4) Minutes
(b) (4) Target	94
Target	69

Figure 18: Dissolution of Tezacaftor from VNZ/TEZ/D-IVA 4/20/50 mg Tablets of Varying Tablet Hardness in 0.2% (w/v) SLS in 0.1 N HCl, 75 rpm



Tablet Hardness (kp)	Tezacaftor % LC Dissolved in (b) (4) Minutes
(b) (4)	99
	98
	97
	92
	76

Figure 19: Dissolution of Tezacaftor from VNZ/TEZ/D-IVA 10/50/125 mg Tablets of Varying Tablet Hardness in 0.2% (w/v) SLS in 0.1 N HCl, 75 rpm



Tablet Hardness (kp)	Tezacaftor % LC Dissolved in (b) (4) Minutes
(b) (4)	99
	98
	95
	92
	78

Tezacaftor (b) (4)

The tezacaftor dissolution method showed little discrimination for tablets prepared with tezacaftor (b) (4) ranging in (b) (4) from (b) (4) for both tablet strengths.

(b) (4) **Level**

The method shows little discrimination to (b) (4) level. Tablets were prepared at (b) (4) (4/20/50 mg tablet: (b) (4) kp; 10/50/125 mg tablet: (b) (4) kp) with (b) (4) level spanning (b) (4) target composition. A small but measurable change in tezacaftor dissolution was observed for both tablet strengths.

Multivariate Assessment of the Method's Discriminating Ability

Tablets prepared as part of a multivariate QbD study evaluating the impact to dissolution with respect to vanzacaftor drug substance particle size, tezacaftor (b) (4), deutivacaftor (b) (4) were tested. A range of the dissolution responses (4/20/50 mg tablet: 82 to 99% LC; 10/50/125 mg tablets: 83 to 99 % LC) were obtained for the tablet variants tested providing further evidence of the method's discriminating ability (Figures below).

Figure 20: Dissolution of Tezacaftor from VNZ/TEZ/D-IVA 4/20/50 mg Tablets Prepared as Part of a Multivariate QbD Study in 0.2% (w/v) SLS in 0.1 N HCl, 75 rpm

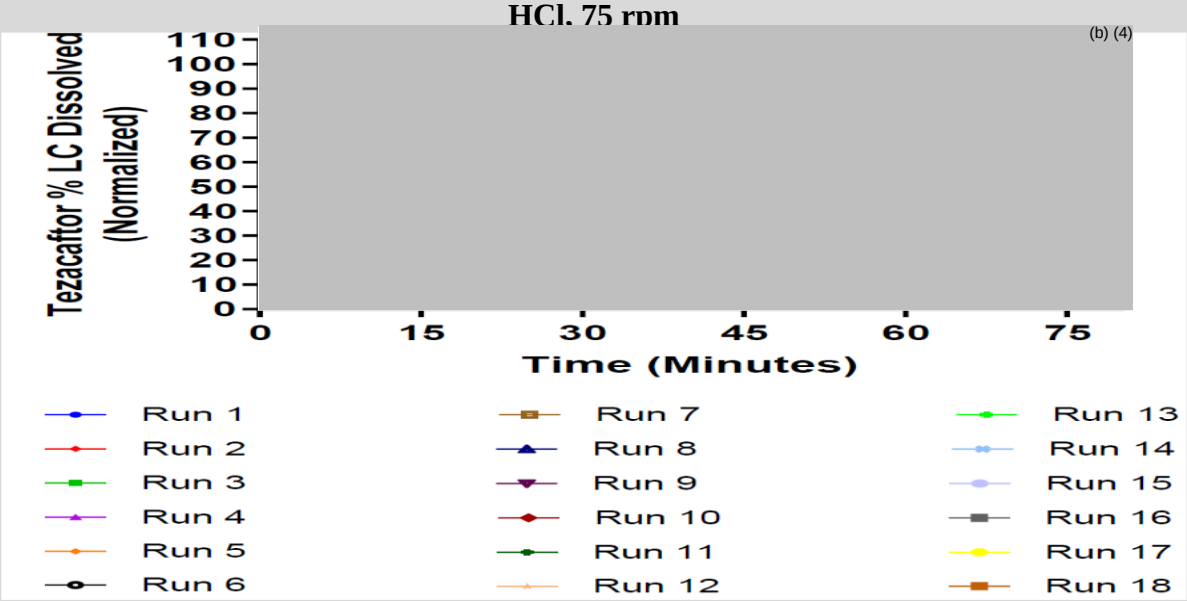
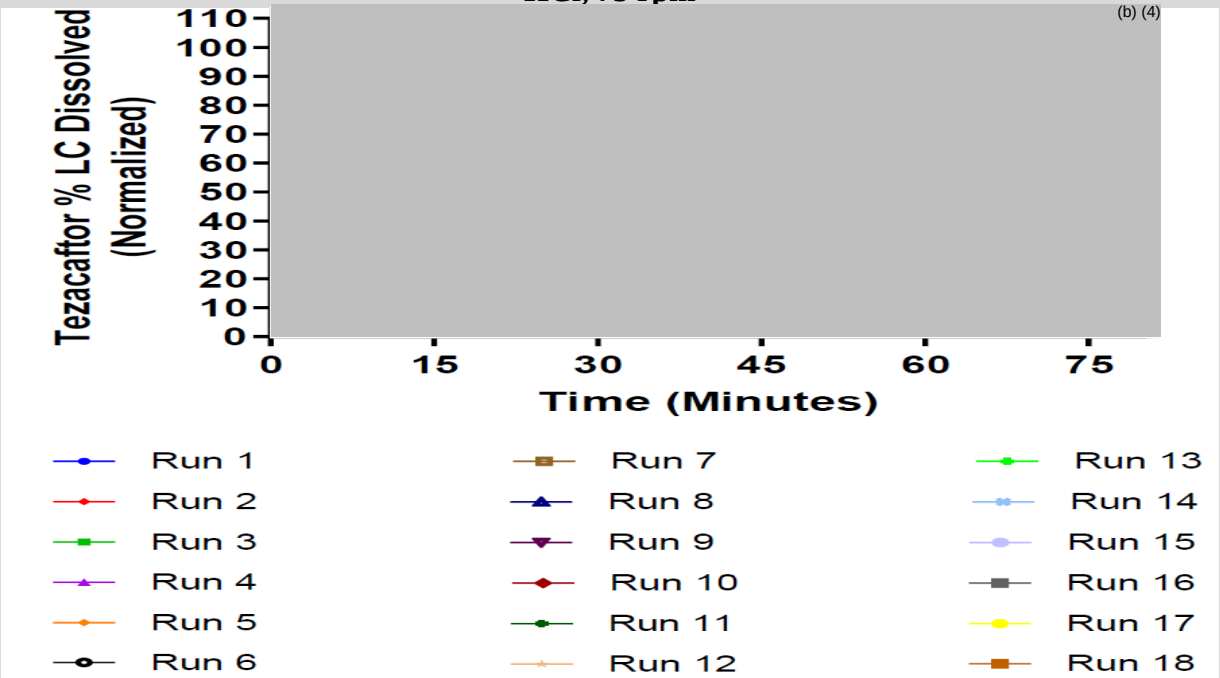


Figure 21: Dissolution of Tezacaftor from VNZ/TEZ/D-IVA 10/50/125 mg Tablets

Prepared as Part of a Multivariate QbD Study in 0.2% (w/v) SLS in 0.1 N HCl, 75 rpm

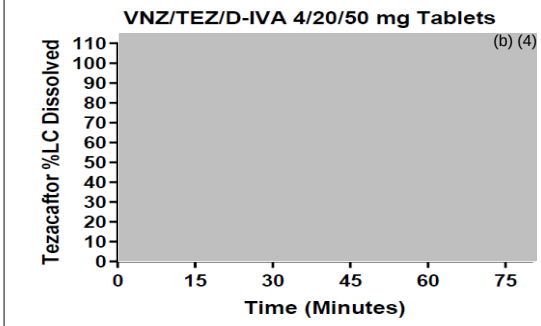


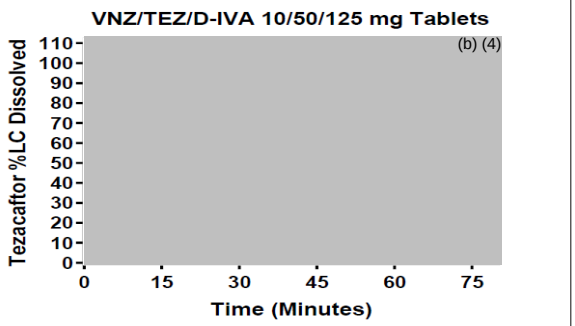
In conclusion, the Applicant has developed a dissolution method for the release of tezacaftor from VNZ/TEZ/D-IVA 4/20/50 mg and 10/50/125 mg tablets. The method is sensitive with respect to material attributes, minor changes in tablet composition and variations in process parameter ranges that could potentially influence the release of tezacaftor from the tablet. The proposed method is suitable for QC purposes.

Dissolution acceptance criterion

The proposed tezacaftor dissolution acceptance criterion is not less than (b) (4)% (Q) of the label claim is dissolved in (b) (4) minutes. Based on the submitted in vitro dissolution profile data (profiles in the figures below) for the clinical lots, the proposed dissolution acceptance criterion for tezacaftor is (b) (4) and not acceptable. An IR (see in Appendix) was sent to implement the acceptance criterion of *Q*= (b) (4)*% in* (b) (4) *minutes* based primarily on the provided dissolution profile data of pivotal batch/registration batches. In the response, the Applicant accepted Agency recommendation for the higher strength but proposed to retain the same for lower strength. In order to maintain a uniform dissolution method and acceptance criterion, *NLT* (b) (4)*% (Q) at 30 minutes* was recommended for both strengths, which the Applicant has accepted.

Figure 22: Dissolution of Tezacaftor from Pivotal VNZ/TEZ/D-IVA Tablet Lots in 0.2% (w/v) SLS in 0.1 N HCl, 75 rpm





Tablet Strength	Lot	Tezacaftor %LC Dissolved at (b) (4) minutes
4/20/50 mg	3209516R	87
	3213216R	88
	3213814R	85
10/50/125 mg	3199049R	92
	3202291R	89
	3206839R	96
	3210851R	94
	3216645R	90

Deutivacaftor

(b) (4)

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(b) (4)

Discriminating Ability of the Deutivacaftor Dissolution Method

The discriminating ability of the dissolution method was evaluated for potentially critical process parameters and material and tablet properties as listed in the below table:

Table 9: Deutivacaftor Risk Assessment Summary of Tablet Variants Identified for Method Discriminating Ability Evaluation

Potential to Impact Dissolution	Identified Attributes & Process Parameters	Tablet Variants for Method Discriminatory Power Evaluation
Material Attributes	• Deutivacaftor (b) (4) • Tezacaftor (b) (4)	• Tablets with varying deutivacaftor (b) (4) • Tablets with varying tezacaftor (b) (4)
Tablet Composition	• (b) (4) level (b) (4) • (b) (4) level (b) (4)	• Tablets with varying (b) (4) levels • Tablets with varying (b) (4) levels
Process Parameter	• Tablet (b) (4) • (b) (4)	• Tablets varying in hardness • Tablets made from (b) (4) varying in (b) (4) (b) (4)

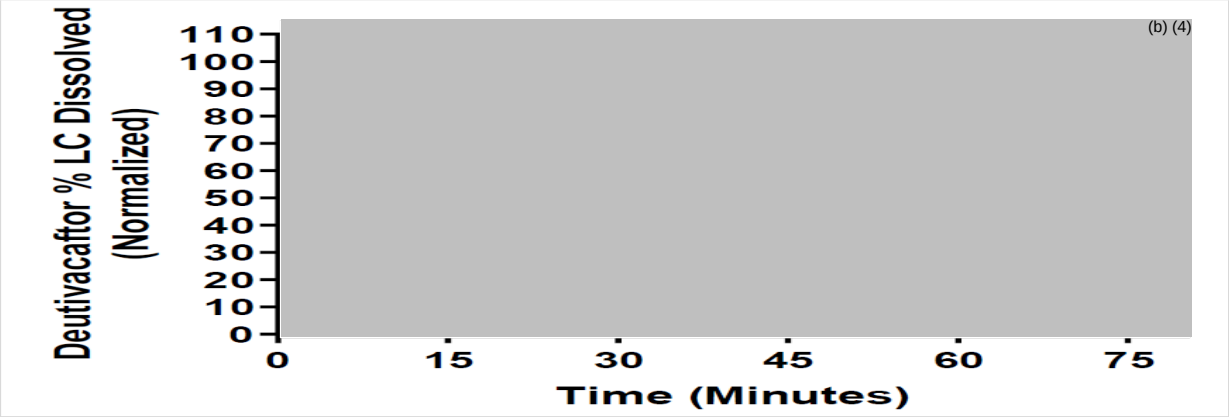
. Method discriminatory power to (b) (4) can be evaluated either through (b) (4) variations or by varying the tablet (b) (4) level. For deutivacaftor dissolution method discriminatory power evaluation, tablets made with varying (b) (4) levels were assessed.

Dissolution plots are shown below for tablet variants where the dissolution method is found to be sensitive.

Deutivacaftor (b) (4)

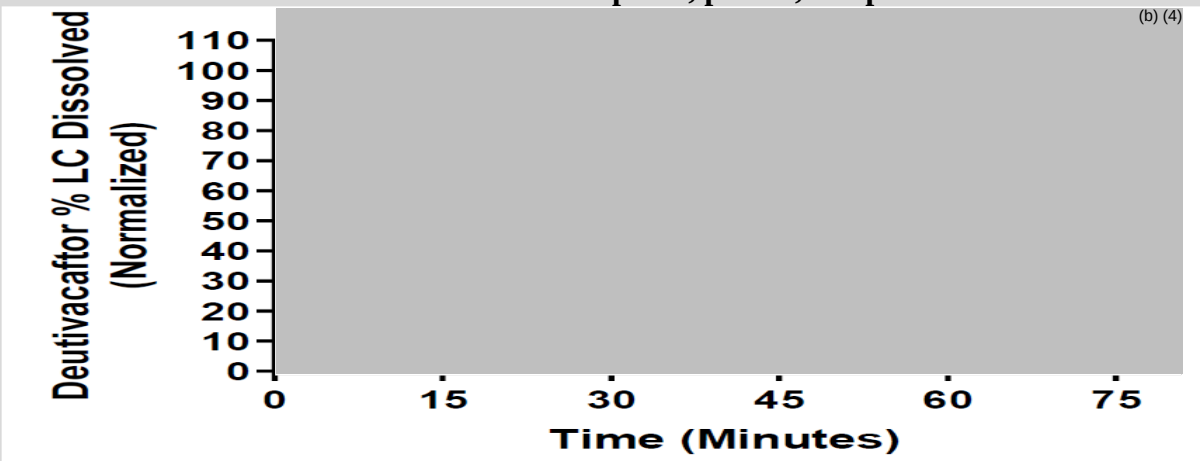
Tablets were prepared at (b) (4) (4/20/50 mg tablet: (b) (4) kp; 10/50/125 mg tablet: (b) (4) kp) with deutivacaftor (b) (4) of varying (b) (4) and tested. The deutivacaftor dissolution rate decreases with decreasing deutivacaftor (b) (4) for both tablet strengths (Figures below).

Figure 25: Dissolution of Deutivacaftor from VNZ/TEZ/D-IVA 4/20/50 mg Tablets Prepared with Varying Deutivacaftor (b) (4) in 0.5% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm



Deutivacaftor (b) (4)	Deutivacaftor % LC Dissolved in 20 Minutes
(b) (4)	74
	85

Figure 26: Dissolution of Deutivacaftor from VNZ/TEZ/D-IVA 10/50/125 mg Tablets Prepared with Varying Deutivacaftor (b) (4) in 0.5% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm



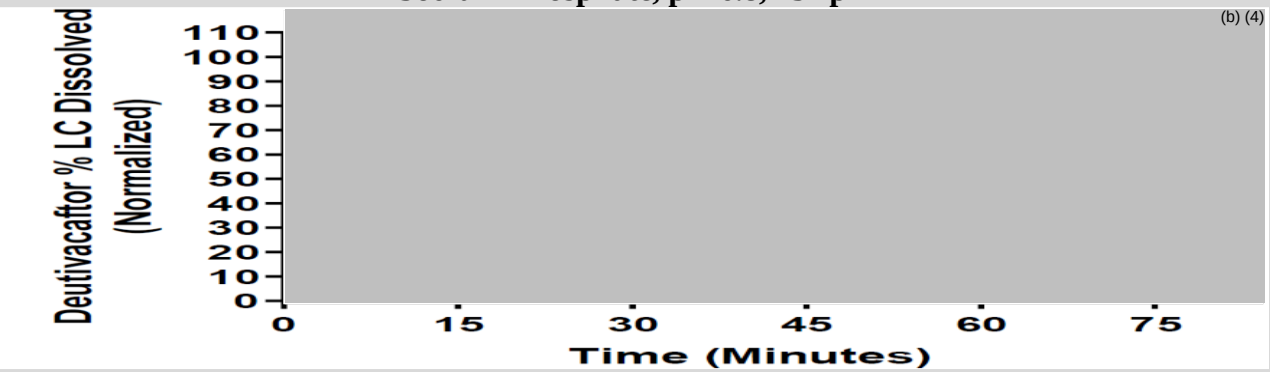
Deutivacaftor (b) (4)	Deutivacaftor % LC Dissolved in 20 Minutes
(b) (4)	78
	85

(b) (4) Level

Tablets were prepared at (b) (4) (4/20/50 mg tablet: (b) (4) kp; 10/50/125 mg tablet: (b) (4) kp) with (b) (4) levels spanning (b) (4) target composition and tested. The deutivacaftor dissolution rate decreases with decreasing (b) (4) for both tablet strengths (Figures below).

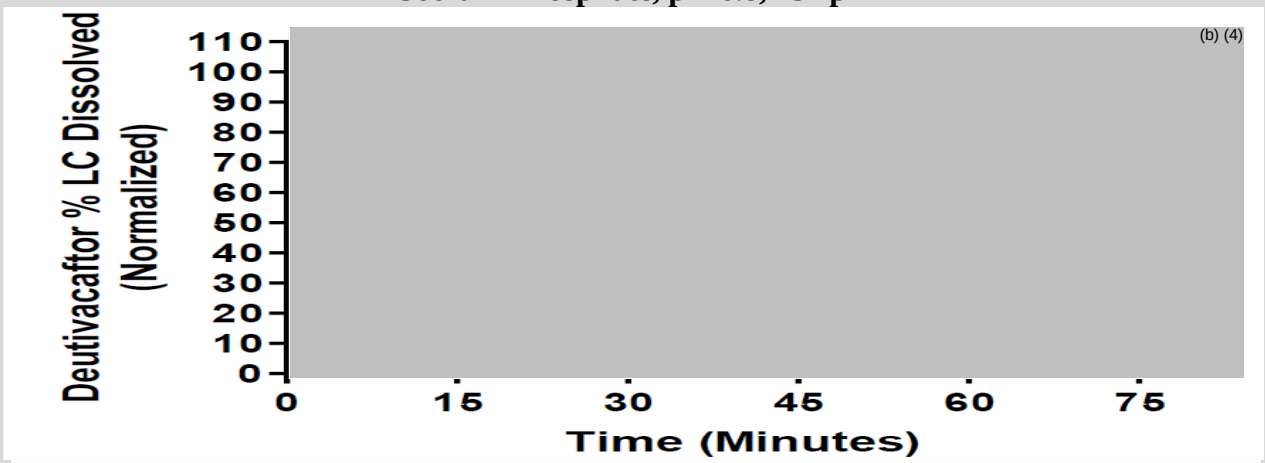
Figure 27: Dissolution of Deutivacaftor from VNZ/TEZ/D-IVA 4/20/50 mg Tablets Prepared with Varying (b) (4) Levels in 0.5% (w/v) SLS in 50 mM

Sodium Phosphate, pH 6.8, 75 rpm



(b) (4) Levels		Deutivacaftor % LC Dissolved in 20 Minute
(b) (4)	Target	91
	Target	55

Figure 28: Dissolution of Deutivacaftor from VNZ/TEZ/D-IVA 10/50/125 mg Tablets Prepared with Varying (b) (4) Levels in 0.5% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm

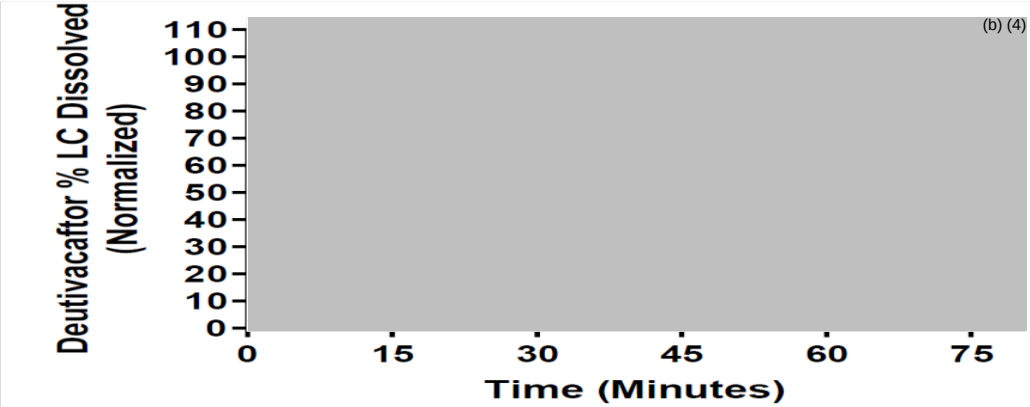


(b) (4) Levels		Deutivacaftor % LC Dissolved in 20 Minutes
(b) (4)	Target	91
	Target	72

Tablet Hardness

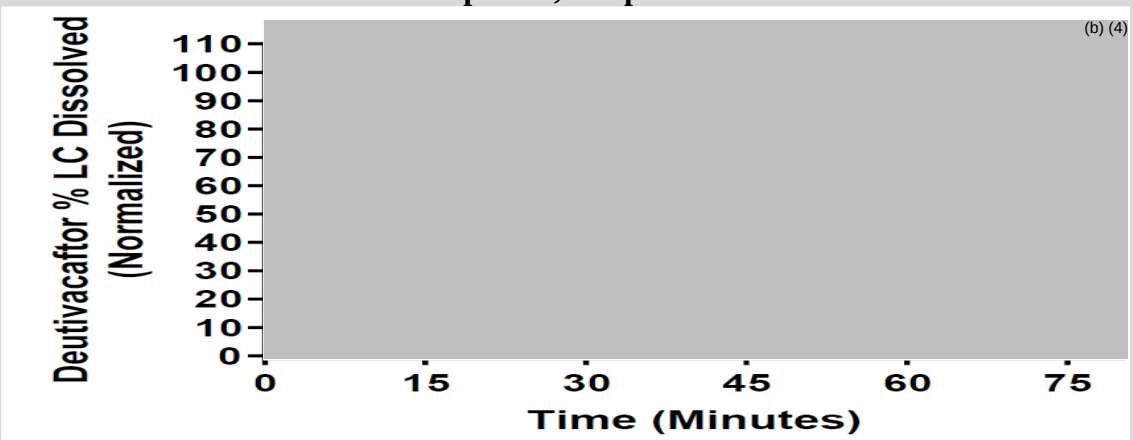
Tablets of varying hardnesses (4/20/50 mg tablet: (b) (4) kp; 10/50/125 mg tablet: (b) (4) kp) were prepared and tested. The deutivacaftor dissolution rate decreases with increasing tablet hardness for both tablet strengths (Figures below).

Figure 29: Dissolution of Deutivacaftor from VNZ/TEZ/D-IVA 4/20/50 mg Tablets of Varying Tablet Hardness in 0.5% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm



Tablet Hardness (kp)	Deutivacaftor % LC Dissolved in 20 Minutes
(b) (4)	97
	95
	93
	91
	80

Figure 30: Dissolution of Deutivacaftor from VNZ/TEZ/D-IVA 10/50/125 mg Tablets of Varying Tablet Hardness in 0.5% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm



Tablet Hardness (kp)	Deutivacaftor % LC Dissolved in 20 Minutes
(b) (4)	96
	95
	91
	88
	80

Multivariate Assessment of the Method's Discriminating Ability

Tablets prepared as part of a multivariate QbD study evaluating the impact to dissolution with respect to vanzacaftor drug substance particle size, tezacaftor (b) (4), deutivacaftor (b) (4) were tested. A range of the dissolution responses (4/20/50 mg tablet: 82 to 99% LC; 10/50/125 mg tablets: 83 to 99 % LC) were obtained for the tablet variants tested providing further evidence of the method's discriminating ability (Figures below).

Figure 31: Dissolution of Deutivacaftor from VNZ/TEZ/D-IVA 4/20/50 mg Tablets Prepared as Part of a Multivariate QbD Study in 0.5% (w/v) SLS in 50 mM sodium phosphate, pH 6.8, 75 rpm

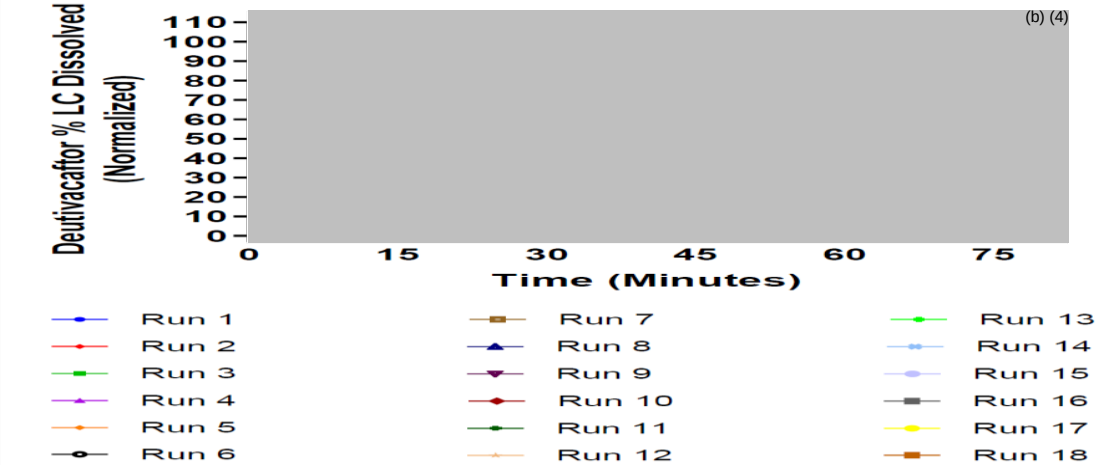
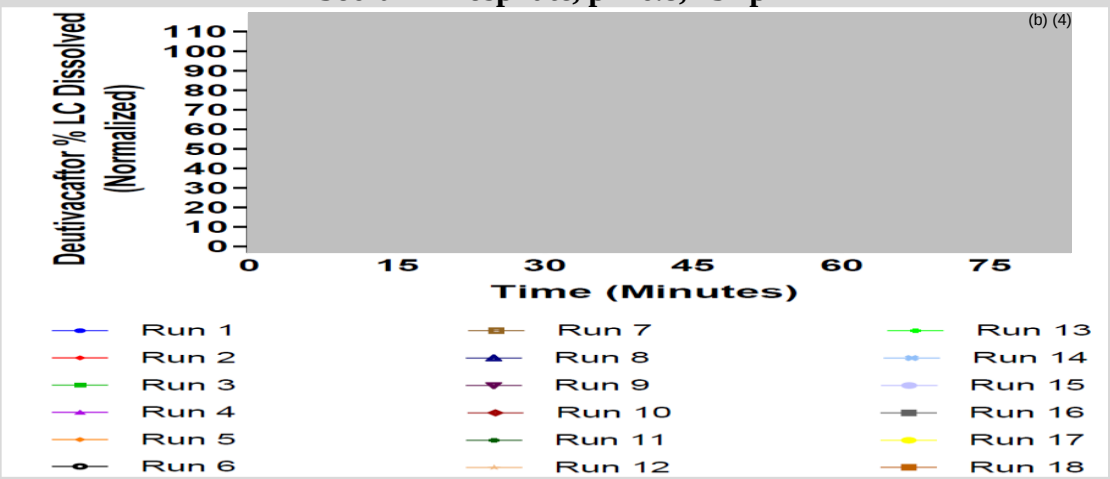


Figure 32: Dissolution of Deutivacaftor from VNZ/TEZ/D-IVA 10/50/125 mg Tablets Prepared as Part of a Multivariate QbD Study in 0.5% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm

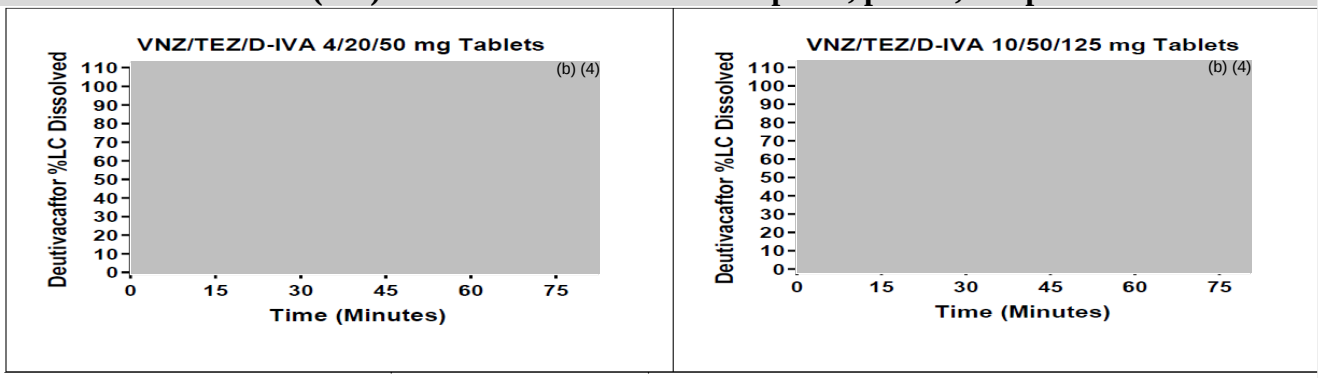


In conclusion, the Applicant has developed a dissolution method for the release of deutivacaftor from VNZ/TEZ/D-IVA 4/20/50 mg and 10/50/125 mg tablets. The method is sensitive with respect to material attributes, minor changes in tablet composition and variations in process parameter ranges that could potentially influence the release of deutivacaftor from the tablet. The proposed method is suitable as a QC method for release and stability testing.

Dissolution acceptance criterion

The deutivacaftor dissolution acceptance criterion is not less than (b) (4)% (Q) of the label claim is dissolved in 20 minutes. Based on the dissolution profile data provided for clinical batches (figures below), the proposed dissolution acceptance criterion is acceptable.

Figure 33: Dissolution of Deutivacaftor from Pivotal VNZ/TEZ/D-IVA Tablet Lots in 0.5% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 75 rpm



Bridging of Formulations

Reviewer's Assessment: Adequate
Pivotal Phase 3 formulation and commercial formulations are same.

Formulations used in clinical studies
As shown in tables below, drug product formulations used during development include an oral suspension, a solution, and various tablet dose strengths which were used in various clinical studies.

Table 10: Formulations of Vanzacaftor used in clinical studies

Formulation Description	Clinical Study Number (abbreviated)		
	Phase 1	Phase 2	Phase 3
Vanzacaftor[a] (b) (4) suspension	001	--	--
[^{14}C]Vanzacaftor[b] (b) (4) solution	004	--	--
Vanzacaftor[a] 5 mg tablet	001, 003, 005, 006, 007, 013	001 Part D, 101	--

[a] vanzacaftor calcium salt Form A
[b] [^{14}C]vanzacaftor calcium salt

Table 11: Formulations of Tezacaftor used in clinical studies

Formulation Description	Clinical Study Number (abbreviated)		
	Phase 1	Phase 2	Phase 3
Tezacaftor 50 mg tablet[a]	003, 005, 006	101	--

[a] (b) (4)

Table 12: Formulations of Deutivacaftor used in clinical studies

Formulation Description	Clinical Study Number (abbreviated)		
	Phase 1	Phase 2	Phase 3
D-IVA 25 mg tablet[a]	--	561-101	--
D-IVA 50 mg tablet[a]	003, 005, 006, 561-001	101, 561-101	--

[a] (b) (4)

Table 13: Formulations of VNZ/TEZ/D-IVA used in clinical studies

Formulation Description	Clinical Study Number (abbreviated)		
	Phase 1	Phase 2	Phase 3
VNZ[a]/TEZ[b]/D-IVA[c] 20/100/150 mg tablet	003	--	
VNZ[a]/TEZ[b]/D-IVA[c] 10/50/125 mg tablet	005, 008, 009	--	102, 103, 104, 105, 106
VNZ[a]/TEZ[b]/D-IVA[c] 4/20/50 mg tablet	009	--	105, 106

[a] Vanzacaftor drug substance
[b] (b) (4)
[c]

The Applicant noted that although VNZ calcium salt form A was used in the 5mg tablet formulation, VNZ calcium salt form D (VNZ drug substance) was identified and was developed for use in the Phase 3 studies and commercialization as it has been demonstrated to be chemically and physically stable during development and it is the most stable form at conditions relevant to the manufacturing process. The relative BA of an FDC of VNZ (Form D)/TEZ/D-IVA 20/100/150 mg was compared with separate tablets of VNZ (Form A), TEZ, and D-IVA (Study 003). Exposure from VNZ (Form D) were lower than exposures from VNZ (Form A), and the VNZ dose was adjusted to 20 mg of the active moiety of VNZ for further development.

Biowaiver Request

Reviewer's Assessment: The Applicant has not requested any biowaiver. There are two strengths of the FDC. Both strengths were used in the Phase 3 study (Study 105). Comparable exposure between the VNZ/TEZ/D-IVA 4/20/50 mg tablet and the VNZ/TEZ/DIVA 10/50/125 mg tablet was confirmed in a BA study (Study 009).

Conclusions and recommendation

From Biopharmaceutics perspective, NDA 218730 for vanzacaftor, tezacaftor and deutivacaftor (D-IVA) tablets (10mg / 50mg / 125mg and 4mg / 20mg / 50mg) is recommended for APPROVAL.

Appendix

List of Deficiencies communicated to the Applicant during current review cycle

(b) (4)

1.

1.

Primary Biopharmaceutics Reviewer: *Kalpana Paudel, Ph.D.*
Secondary Reviewer Name: *Tapash Ghosh, Ph.D.*

Kalpana Paudel

Digitally signed by Kalpana Paudel
Date: 9/13/2024 10:27:33AM
GUID: 562e1e15002f200f35c6ccac959cdb34

Tapash Ghosh

Digitally signed by Tapash Ghosh
Date: 9/13/2024 11:04:32AM
GUID: 508da7230002a2433ddcef616ca190df

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	218730
Assessment Cycle Number	1
Drug Product Name	VNZ/TEZ/D-IVA. VNZ 10mg / TEZ 50mg / D-IVA 125mg and VNZ 4mg / TEZ 20mg / D-IVA 50mg.

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	5
Patient Information	Adequate	
Instruction for Use (IFU)	Adequate	
Container Labels	Choose an item.	
Carton Labeling	Adequate	

Brief Description of Outstanding Issues:

- Pharmacological statement must be added to section 11 per the labeling review tool.
- Carton label does not contain equivalency statement for vanzacaftor "4 mg (equivalent to 4.24 mg of vanzacaftor calcium dihydrate)" or "10 mg (equivalent to 10.6 mg of vanzacaftor calcium dihydrate)".
- The applicant did not submit a container label in the NDA-218730 submission.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0026, 26	09/11/2024	Draft Labeling

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

Submitted on September 11, 2024, SDN 0026

(b) (4)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline

[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral 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.[8]	N/A	

Assessment: *Adequate*

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the	N/A	

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)
[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments
[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
patient and healthcare practitioner(s) who administer the drug		
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Adequate*

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

Tablets:

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	Adequate	
A description of the identifying characteristics of the dosage forms, including shape, color,	Adequate	

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
coating, scoring, imprinting, and color and clarity of the solution, when applicable.		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: *Adequate*

1.2.3 Section 11 (DESCRIPTION)[14]

[TRADENAME] is a fixed-dose combination tablet for oral use, (b) (4)

The [TRADENAME] tablets are available as:

(b) (4) 10 mg of vanzacaftor (equivalent to 10.6 mg vanzacaftor calcium dihydrate), 50 mg of tezacaftor, 125 mg of deutivacaftor; and (b) (4) 4 mg of vanzacaftor (equivalent to 4.24 mg vanzacaftor calcium dihydrate), 20 mg of tezacaftor, 50 mg of deutivacaftor.

Each tablet contains the following inactive ingredients: croscarmellose sodium, hypromellose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet film coating contains Brilliant Blue FCF aluminum lake/FD&C Blue #1, carmine, hydroxypropyl cellulose, hypromellose, iron oxide red, talc, and titanium dioxide.

The active ingredients of [TRADENAME] are described below.

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

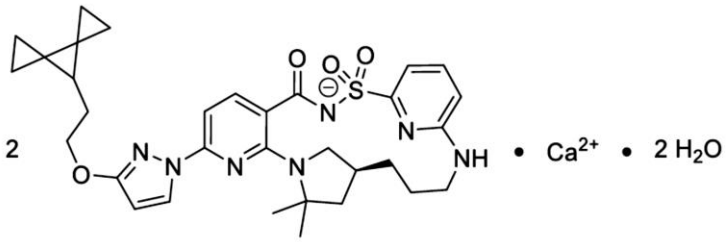
Vanzacaftor

Vanzacaftor is provided as a calcium salt. Vanzacaftor calcium dihydrate is a white solid that is practically insoluble in water (< 0.1 mg/mL).

Its chemical name is calcium bis((14S)-8-[3-(2-{dispiro[2.0.2⁴.1³]heptan-7-yl}ethoxy)pyrazol-1-yl]-12,12-dimethyl-2,2,4-trioxo-2λ⁶-thia-3,9,11,18,23-pentaazatetracyclo[17.3.1.1¹¹,¹⁴.0⁵,¹⁰]tetracosa-1(23),5,7,9,19,21-hexaen-3-ide) dihydrate.

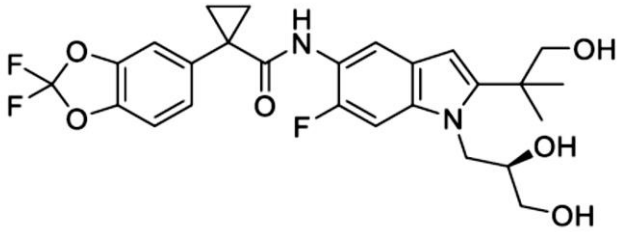
Its molecular formula is C32H38N7O4S·Ca0.5·H2O and its molecular weight is 654.82.

Vanzacaftor calcium dihydrate has the following structural formula:



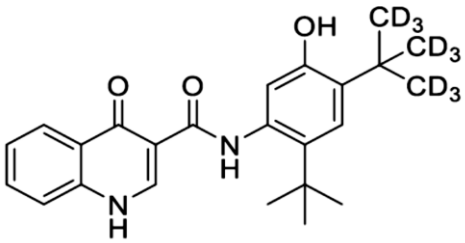
Tezacaftor

Tezacaftor is a white to off-white solid that is practically insoluble in water (< 5 microgram/mL). Its chemical name is 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl} cyclopropane-1-carboxamide. Its molecular formula is C26H27N2F3O6, and its molecular weight is 520.50. Tezacaftor has the following structural formula:



Deutivacaftor

Deutivacaftor is a white to off-white solid that is practically insoluble in water (< 0.1 mg/mL). Its chemical name is N-(2-(tert-butyl)-5-hydroxy-4-(2-(methyl-d3) propan-2-yl-1,1,1,3,3,3-d6) phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. Its molecular formula is C24H19D9N2O3, and its molecular weight is 401.55. Deutivacaftor has the following structural formula:



Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	Adequate	
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in	N/A	

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].		
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Inadequate	Pharmacological statement must be added to section 11 per the labeling review tool.
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	N/A	
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

Assessment: *Inadequate*

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

How Supplied:

(b) (4)

Store at 20ºC - 25ºC (68ºF - 77ºF); excursions permitted to 15ºC - 30ºC (59ºF - 86ºF) [see USP Controlled Room Temperature].

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the	Adequate	

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
active moiety. No equivalency statement.		
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	NDC 51167-121-01 NDC 51167-135-01
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral 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 (see USP <659>).	N/A	
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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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."*[21]	Adequate	
Include information about child-resistant packaging[22] (if chosen by manufacturer).	N/A	

Assessment: ***Adequate***

1.2.5 Other Sections of Labeling

N/A.

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

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

Assessment: *Adequate*

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

2.0 PATIENT LABELING

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	
Special preparation instructions (if applicable).	Adequate	
Storage and handling information (if applicable).	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	N/A	
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

3.2 Carton Labeling

The applicant did not submit a container label in the NDA-218730 submission.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Choose an item.	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Choose an item.	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Choose an item.	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Inadequate	Choose an item.	Carton label does not contain equivalency statement for vanzacaftor "4 mg (equivalent to 4.24 mg of vanzacaftor calcium dihydrate) or 10 mg (equivalent to 10.6 mg of vanzacaftor calcium dihydrate).
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Choose an item.	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Choose an item.	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Choose an item.	

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

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[29] § 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.

Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Choose an item.	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Choose an item.	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	Choose an item.	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	Choose an item.	
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Choose an item.	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Choose an item.	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Choose an item.	
Adequate directions for use: "Recommended Dosage: See	Adequate	Choose an item.	

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Prescribing Information" [§ 201.5 & 201.55].			
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Choose an item.	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Choose an item.	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Choose an item.	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Choose an item.	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Choose an item.	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31]	N/A	Choose an item.	
And others if space is available.	N/A	Choose an item.	

Assessment of Carton Labels and Container Labeling: *Adequate*
The container label was not included in the NDA-218527 submission by the applicant.

[31] USP General Notices 3.20 Indicating Conformance

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

- Pharmacological statement must be added to section 11 per the labeling review tool.
- Carton label does not contain equivalency statement for vanzacaftor “4 mg (equivalent to 4.24 mg of vanzacaftor calcium dihydrate) or 10 mg (equivalent to 10.6 mg of vanzacaftor calcium dihydrate).
- The applicant did not submit a container label in the NDA-218730 submission.

Primary Drug Product Assessor Name and Date:
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Drug Product Reviewer
OPQ/OPQA II/ Division VII/Unit 1

Secondary Assessor Name and Date:
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Supervisory chemist
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Ghaled Hamad

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Julia Pinto

Digitally signed by Julia Pinto
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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.

/s/

CRAIG M BERTHA
10/03/2024 08:22:33 AM