CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212273Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 212273

Review #1

Drug Name/Dosage Form	VX-445/tezacaftor/ivacaftor and ivacaftor (co-packaged)/tablets
Strength	100 mg VX-445/50 mg tezacaftor/75 mg ivacaftor per tablet & 150 mg ivacaftor per tablet
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Vertex Pharmaceuticals, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*19-JUL-2019*	*All*
Amendment	*19-AUG-2019*	*Drug substance, process, biopharmaceutics*
Amendment	*03-SEP-2019*	*Drug substance, drug product, biopharmaceutics, process*
Amendment	*11-SEP-2019*	*Biopharmaceutics, process*
Amendment	*16-SEP-2019*	*Drug substance*
Amendment	*20-SEP-2019*	*Drug product, biopharmaceutics*
Amendment	*26-SEP-2019*	*Drug product, biopharmaceutics*
Amendment	*27-SEP-2019*	*Process*
Amendment	*03-OCT-2019*	*Biopharmaceutics*
Amendment	*09-OCT-2019*	*Drug Product (labeling)*
Amendment	*15-OCT-2019*	*Biopharmaceutics*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Paresma Patel	Donna Christner
Drug Product	Venkat Pavuluri	Julia Pinto
Process	Pratibha Bhat	Yong Hu
Microbiology	N/A	
Facility	Pratibha Bhat	Yong Hu
Process Analytical Technology	Hong Yang	Yong Hu

Biopharmaceutics	Kalpana Paudel	Haritha Mandula
Regulatory Business Process Manager	Florence Aisida	
Application Technical Leads	Craig M. Bertha/Sharmista Chatterjee	
Laboratory (OTR)		
Emerging Technologies Team Lead	Sharmista Chatterjee	
ORA Lead	Zhihao Peter Qui	
Environmental	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate		Sufficient information in application – same CCS component approved for Vertex NDA 206038
	Type III			Adequate		Sufficient information in application – same CCS component approved for Vertex NDA 206038

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	203188	Kalydeco® (ivacaftor) tablets
NDA	210491	Symdeko® (tezacaftor/ivacaftor; ivacaftor) tablets
IND	74633	Ivacaftor tablets
IND	132547	Tezacaftor/ivacaftor tablets

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/ Toxicology	Final	Adequate regarding potential mutagenic impurities	12-AUG-2019	Dong Zhao/Andrew Goodwin
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

N/A – The application is recommended for **approval**

II. Summary of Quality Assessments

A. Product Overview

The drug product of this NDA is a triple fixed-dose combination (FDC) immediate release (IR) tablet containing three drugs (VX-445 or elexacaftor, tezacaftor or TEZ, and ivacaftor or IVA) that are targeted to enhancing cell chloride transport that is impacted by the genetic mutations affecting the cystic fibrosis transmembrance conductance regulator (CFTR) protein. The daily dosing regimen is two triple FDC tablets in the morning and one ivacaftor tablet (approved NDA 203188) in the evening. The cystic fibrosis therapy proposed under this NDA is designed to be a treatment for patients with at least one *F508del* allele mutation, which encompasses approximately 86% of CF patients. There are currently no available disease modifying therapies for the subset of CF patients heterozygous for the *F508del* mutation and a "minimal function" CFTR mutation on the other allele. As such, this drug has been granted both Break-Through Therapy designation and Fast Track designation. The Office of Process and Facilities has performed a pre-approval inspection of (b) (4), a manufacturer of a starting material/intermediate of (b) (4), as this site had not been inspected by the Agency previously. A post-approval inspection of the Vertex, Boston drug product manufacturing site is planned.

VX-445 is a new molecular entity in the triple FDC IR tablet drug product, which is formulated with the previously approved tezacaftor/ivacaftor APIs that were in the double FDC Symdeko® Tablet drug product of NDA 210491. Tezacaftor is class II and ivacaftor is class II or IV as per the Biopharmaceutics Classification System (BCS), so they are both poorly soluble molecules. VX-445 is also poorly soluble and is class II or IV as per the BCS. As such the physicochemical properties of the drugs/formulation components are important to control, as they may impact the bioavailability of each API.

The drug product is manufactured using a continuous manufacturing (CM) process. During manufacturing, the applicant uses process analytical technology (PAT) for in-process control. Specifically, PAT data are from (b) (4) The drug product is released based on more typical end-product testing for all pertinent parameters, as opposed to real-time-release testing (RTRT), which Vertex has used for some previous applications that utilized CM.

Prior to submission of the NDA, the Agency and Vertex had a pre-NDA meeting, but no CMC topics were discussed. At a Type B CMC-only of 03-JUN-2019, the Agency recommended Vertex (b) (4) to demonstrate process robustness, and Vertex agreed. At a Type B CMC-only meeting of 19-SEP-2018, the Agency indicated that Vertex's in-process control (b) (4) is reasonable for (b) (4) but did not agree with their proposed (b) (4) At a Type C CMC-only meeting of 30-JAN-2018, the Agency agreed with Vertex's approach to (b) (4) the VX-445, and agreed to allow Vertex to submit a second drug substance manufacturing site at the time of NDA filing, but cautioned that final acceptance will depend on comparability of drug substance from the two sites. However, no second site has been proposed in the application, but there are three sites that prepare one (b) (4) intermediate.

Proposed Indication(s) including Intended Patient Population	TRIKAFTA is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the *CFTR* gene. If the patient's genotype is unknown, confirm the presence of at least one *F508del* mutation (b) (4)
Duration of Treatment	Chronic
Maximum Daily Dose	200 mg VX-445, 100 mg tezacaftor, and 300 mg ivacaftor
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

The immediate release triple FDC IR tablet contains one new molecular entity, elexacaftor (or VX-445) and two previously approved chemical entities, ivacaftor and tezacaftor. The drug substance CMC information for ivacaftor and tezacaftor are fully cross referenced to the approved NDAs for Kalydeco (NDA 203188) and Symdeko (NDA 210491), respectively, so no evaluation of those active pharmaceutical ingredients (APIs) was necessary**.** The drug substance elexacaftor (VX-445) is recommended for approval from the perspective of the drug substance reviewer in the Office of New Drug Products, Office of Pharmaceutical Quality**.**

Elexacaftor is manufactured through (b) (4) synthesis from the following starting materials: (b) (4) Sufficient detail was provided outlining the control of input materials, reaction times, process parameters and in-process controls. (b) (4)

(b) (4). The absolute configuration of the elexacaftor was confirmed by single crystal X-ray analysis. (b) (4) impurities brought into the synthesis have a higher potential to contaminate the final API. There are three sites that manufacture one of the (b) (4) intermediates of the synthesis ((b) (4)) and one site that synthesizes elexacaftor. Starting material specifications include sufficient impurity controls that are adequately justified (b) (4) to minimize any impact on the purity of the final drug substance. The proposed regulatory starting materials are considered adequate and Vertex has generally followed the recommendations of ICH Q11 for the development and manufacture of elexacaftor. The applicant provides adequate characterization data for the drug substance and specified impurities and sufficient data to demonstrate adequate control of potentially mutagenic impurities through the manufacturing process, as per ICH M7. The overall control strategy is based on the manufacturer's process understanding gained during development, and includes specifications for starting materials, reagents, solvents, catalysts and the specification for the drug substance itself. Together, these provide sufficient controls for identity, purity, strength, and quality of elexacaftor API. Clinical and registration drug substance batch data were provided and all of these were within specification acceptance criteria. Note that as per a request from the biopharmaceutics team, the applicant has tightened the acceptance criteria for control of the particle size distribution (PSD) of elexacaftor, but also has agreed to revisit these post-approval as they gain more commercial manufacturing experience. The long term and accelerated stability data provided, albeit limited, show little or no changes to the quality attributes of elexacaftor, thus the proposed retest period of (b) (4) months (with storage at (b) (4)) is supported, as per ICH Q1E.

The current triple FDC tablet dosage form of VX-445/tezacaftor/ivacaftor is similar to the previously approved double FDC tablet dosage form containing tezacaftor/ivacaftor (comparable formulation with analogous continuous manufacturing process). Thus, Vertex is building on their knowledge of the double FDC tablet by the addition of the VX-445 NME that is added as (b) (4) crystalline API. For the triple FDC, the stability studies revealed that degradation products formed were below the reporting threshold up to 6 months at accelerated (40°C/75% RH) conditions and 12 months at long-term storage (25°C/60% RH) conditions, in blister packs proposed for commercialization, with no changes reported in physical form or chiral purity of the drugs. In addition, the application included the standard three-part post-approval stability commitment. The applicant originally proposed (b) (4) But because of the limited batch data available at this time, the team did not agree with this proposal and the drug product specification has been revised accordingly. Upon our request, the applicant provided data supporting their control strategy for elemental impurities in the drug product, following ICH Q3D. As VX-445 is a NME, we requested our laboratory to verify the analytical methods for assay and quantification of degradants in the drug product, and these methods were determined to be suitable for regulatory purposes.

Other quality control methods for testing the drug product at release and after stability storage were found to be adequate based on an evaluation of the method validation reports provided in the application. The stability data provided in the application support the proposed **24 month expiry** for the FDC tablets when packaged in foil-foil blisters and stored at controlled room temperature and there were no noteworthy trending stability parameters. The applicant was granted a categorical exclusion from an Environmental assessment in accord with 21 CFR 25.31(b). In conclusion, the quality information provided in the NDA 212273 is adequate from a drug product perspective to recommend approval of the Elexacaftor (VX-445), Tezacaftor and Ivacaftor tablets (100 mg, 50 mg and 75 mg). Note that the labeling comments for the package insert listed in *Chapter IV: Labeling* below, have been adequately addressed by the applicant in the 09-OCT-2019, amendment. Other container/closure system label-related comments will be addressed in coordination with DMEPA/DPARP during negotiations with Vertex (see the Unireview filed in DARRTS).

The biopharmaceutics team recommends approval for the application. The review concluded that the three dissolution methods and associated acceptance criteria were acceptable considering that the applicant has tightened the (b) (4) in-process acceptance criterion and has provided two post-marketing commitments (PMCs) regarding improvements to the control of both VX-445 and (b) (4) PSDs. The biopharmaceutics team (with input from the biostatistics team) did not agree with the applicant's (b) (4) They also concluded that the process controls currently proposed along with those to be implemented based on PMCs for VX-445 and (b) (4) PSDs would be adequate in reducing manufacturing variation that could lead to variable drug dissolution. The ONDP Division Director has considered these opposing positions regarding (b) (4) and has concluded that the applicant's mitigation strategies for addressing factors potentially impacting drug dissolution and their understanding of and experience with approved continuous manufacturing processes and their controls, was acceptable as proposed by the applicant. Furthermore, it was concluded that the clinical need and substantial benefit that this drug product will provide for CF patients, outweighs the risks of accepting the applicant's (b) (4) proposal.

The FDC drug product is manufactured using continuous manufacturing process on the Vertex (b) (4) There is no difference in the manufacturing process used for the later clinical batches and the intended commercial product. (b) (4)

(b) (4) The manufacturing process is similar to the approved process for NDA 210491.

The Elexacaftor drug substance is crystalline and exists as (b) (4) which is the (b) (4) form. The tezacaftor and ivacaftor drug substances are provided as (b) (4) The line rate for continuous manufacturing is (b) (4). The clinical batch sizes were between (b) (4) kg to (b) (4) kg, and the proposed batch size for commercial batch is (b) (4) kg. In response to an information request comment, Vertex confirmed that (b) (4) Although initial clinical supplies, including the initial Phase 3 clinical supplies, were manufactured at Vertex using a discontinuous (batch) process, the continuous manufacturing process utilizes the same process steps as the discontinuous process.

Using the principles of Quality by Design, multivariate design of experiments (DoEs) were used to define normal operating ranges and design space limits for critical process parameters. (b) (4)

The IPC strategy consists of: (b) (4)

(b) (4)

(b) (4) To increase the robustness of (b) (4) the firm proposed (b) (4) different from the (b) (4) submitted in previously approved applications, e.g, NDA 210491 for Tezacaftor/ivacaftor FDC tablets. (b) (4)

Overall, from a process perspective, the information in the amended application provides sufficient description of the manufacturing process and associated control strategy to provide assurance of the quality of the FDC drug product.

All the facilities listed in the application are acceptable. The site (b) (4) (FEI# (b) (4)) that is responsible for manufacturing Elexacaftor drug substance starting material as well as a critical intermediate had not been inspected previously. An expedited pre-approval inspection was requested from ORA. This site was inspected between (b) (4) and initial pre-approval inspection outcome of this site is NAI (no action indicated). Due to abbreviated review timeline and considering the firm's continuous manufacturing experience to date with previously approved products, a pre-approval inspection of Vertex's continuous drug product manufacturing site at Boston (FEI 1000513211) is not recommended. However, because of the complexity associated with the manufacturing of a three drug FDC using continuous manufacturing and the use of (b) (4) as an IPC, a post-approval inspection is warranted.

A comparability protocol was included in the submission for (b) (4) However, the Comparability Protocol was not assessed at this time due to pending concerns from the Biopharmaceutics team that are communicated as PMCs as well as the expedited review timelines. The protocol has been withdrawn from the application by the applicant.

In conclusion, the OPQ review team recommends that the application be **approved.**

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

93 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

BIOPHARMACEUTICS

Product Background:

NDA: NDA-212273-ORIG-1

Drug Product Name / Strength: Trikafta (elexacaftor/tezacaftor/ivacaftor Tablet/100mg, 50mg, 75mg)

Route of Administration: Oral

Applicant Name: Vertex Pharmaceuticals Incorporated

Submission:
Vertex Pharmaceuticals Incorporated has submitted NDA 212273 for Trikafta™ tablets triple combination (TC) therapy for the treatment of cystic fibrosis (CF). The tablet (immediate release, IR) is a fixed dose combination (FDC) of the active ingredients VX-445 (elexacaftor, ELX), tezacaftor (TEZ), and ivacaftor (IVA). 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. ELX/TEZ/IVA was granted Fast Track designation on 02/08/2017, Breakthrough Therapy Designation on 05/15/2018 and Orphan Drug Designation (ODD 18-6476) on 08/29/2018. Elexacaftor is a new molecular entity that has been developed in combination with the already approved TEZ/IVA combination regimen (Symdeko). This application includes a cross reference to the previously submitted and approved clinical, nonclinical and CMC information for both the TEZ/IVA (Symdeko) NDA 210491 and IVA (Kalydeco) NDA 203188 as applicable. The triple combination is composed of 3 CFTR modulators: 2 CFTR correctors (VX-445 and TEZ) and a CFTR potentiator (IVA).

The proposed commercial regimen is a total daily dose of ELX 200 mg, TEZ 100 mg and IVA 300 mg. It is dosed orally as follows:

- Morning dose: 2 fixed-dose combination (FDC) tablets containing VX-445 100 mg/tezacaftor 50 mg/ivacaftor 75 mg, supplied as orange, capsule shaped tablets.
- Evening dose: 1 tablet containing 150 mg IVA, supplied as a light blue, film coated, capsule shaped tablet.

The manufacture of the FDC tablets uses a continuous manufacturing process, starting with the introduction of formulation components and ending with film coated tablets. The fixed dose combination product is developed using (b) (4) (b) (4) Dissolution was found to be one of the critical quality attributes (CQAs) of the proposed drug product along with other variables such as degradation products, uniformity of dosage units, and physical form etc. The continuous process has been used for development and Phase 3 clinical resupply batches, formal stability batches, QbD DOE experiments and is the commercial manufacturing process. Based on the QbD DOE experiments, the following critical parameters were explored for possible interaction: VX445 Dv50 Particle size, ivacaftor (b) (4), texacaftor (b) (4), (b) (4) (the details of these experiments are discussed below).

Review Recommendation: **Adequate**

Review Summary:
The Biopharmaceutics review is focused on the evaluation of the dissolution method and acceptance criteria for VX-445, tezacaftor and ivacaftor in the FDC tablets, supporting drug substance (e.g. particle size distribution, PSD)/ drug product specifications (e.g. hardness, (b) (4) PSD), dissolution sampling strategy for continuous manufacturing process, and bridging between the to-be-marketed and pivotal clinical trial formulations.

Dissolution Method and Acceptance Criteria
The following dissolution methods and acceptance criteria for the release of VX-445, tezacaftor and, ivacaftor from the FDC tablet are deemed acceptable (refer to submission dated 09/11/2019):

Component	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
VX-445	II (Paddle)	75	1.8% (v/v) Tween 20 in 50 mM sodium phosphate, pH 6.8/37°C ± 0.5°C	900ml	Q = (b) (4)% in 20 minutes
Tezacaftor	II (Paddle)	75	0.2% (w/v) SLS solution in 0.1N HCl	900ml	Q = (b) (4)% in 15 minutes
Ivacaftor	II (Paddle)	65	0.4% (w/v) SLS in 50 mM sodium phosphate, pH 6.8	900ml	Q = (b) (4)% in 20 minutes

It should be noted, however, that the dissolution methods' discriminatory ability to critical attributes/process parameters is demonstrated only at earlier time points (e.g. 15 min). The proposed dissolution acceptance criterion *Q*= (b) (4)*% in 20 minutes* for VX-445 and Ivacaftor was deemed acceptable provided additional mitigation strategies are implemented for critical attributes/parameters which include the implementation of adequate controls for VX-445 particle size (D10, D50 and D90), (b) (4) particle size (D10, D50, D90) and tablet hardness based on manufacturing experience and clinical relevance.

Drug Product Specifications for Critical Quality Attributes
After several communications with the Applicant and internal discussions with the OPQ review team, the following agreement was reached related to drug product specifications for critical attributes (refer to submission dated 09/20/2019):

- (b) (4)
-
-

Dissolution Sampling Strategy for Continuous Manufacturing

(b) (4)

Post Marketing Commitment

The Applicant is requested to collect additional data as Post-Marketing Commitment (PMC) to further revise/justify the following specifications:

1. Implementation of three tier particle size specification (D10, D50, and D90) for VX-445 particle size distribution. Submission of the D10, D50 and D90 particle size distribution for at least five commercial batches along with complete dissolution profiles. These data along with similarity testing should be used to verify the design space for D50, revise D90 ranges and implement the ranges for D10.
2. Implementation of three tier particle size specification (i.e., D10, D50, and D90) for (b) (4) size. Submission of the D10, D50 and D90 size distribution for at least five commercial batches along with complete dissolution profiles. These data along with similarity testing should be used to verify the design space and set the appropriate ranges for D10, D50 and D90.

Under the PMC # 3718 the Applicant agreed to the above recommendations and will submit the newly generated data by June 2020.

Bridging of Clinical Formulations: Phase 2 (mono components) and Phase 3 (TC/FDC) formulations were bridged with a bioavailability (BA) study (study 005). Following the FDC tablet, VX-445 AUC was 15% lower and IVA AUC was 12% higher, while TEZ exposure met bioequivalence criteria. Per the Applicant, the small differences in VX-445 and IVA exposures were not considered clinically relevant. The qualification of this study is under the purview of the OCP review team (please refer to clinical pharmacology review for additional details). Phase 3 formulation and commercial formulations are the same.

List of Submissions reviewed: Dissolution data and acceptance criteria

Application 212273 - Sequence 0001 - 0001 (1) 07/19/2019 ORIG-1 /Multiple Categories/Subcategories
Application 212273 - Sequence 0006 - 0006 (6) 08/19/2019 ORIG-1 /Quality/Response To Information Request
Application 212273 - Sequence 0014 - 0014 (14) 09/11/2019 ORIG-1 /Quality/Response To Information Request
Application 212273 - Sequence 0017 - 0017 (17) 09/20/2019 ORIG-1 /Quality/Response To Information Request
Application 212273 - Sequence 0021 - 0021 (21) 10/03/2019 ORIG-1 /Quality/Response To Information Request
Application 212273 - Sequence 0023 - 0023 (23) 10/15/2019 TRIAGE-1 /Electronic Submission/Gateway

Highlight Key Outstanding Issues from Last Cycle: The Applicant is requested to implement VX-445 particle size range (D10, D50 and D90), and (b) (4) particle size distribution range (D10, D50 and D90) as PMC.

Concise Description of Outstanding Issues Remaining: None.
However, the Applicant is requested to collect additional data as PMC to further revise/justify the following specifications:1. Implementation of three tier particle size specification (D10, D50, and D90) for VX-445 particle size distribution. Submission of the D10, D50 and D90 particle size distribution for at least five commercial batches along with complete dissolution profiles. These data along with similarity testing should be used to verify the design space for D50, revise D90 ranges and implement the ranges for D10.
2. Implementation of three tier particle size specification (i.e., D10, D50, and D90) for (b) (4) size. Submission of the D10, D50 and D90 size distribution for at least five commercial batches along with complete dissolution profiles. These data along with similarity testing should be used to verify the design space and set the appropriate ranges for D10, D50 and D90.

From Biopharmaceutics perspective, NDA 212273 for Trikafta™ (VX-445/Tezacaftor/Ivacaftor/100 mg/50 mg/75 mg tablets) 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).

VX-445

- VX-445 could not be classified definitively by the BCS, may be considered Class 2 or 4 per BCS criteria.
- VX-445 drug substance is practically insoluble (<0.1 mg/mL) in pH buffer solutions of pH 1.0 to pH 8.0. A 100-mg strength tablet requires >1000 mL of aqueous media to dissolve; therefore VX-445 is classified as low solubility according to BCS criteria.
- VX-445 showed high permeability (apparent permeability coefficient [Papp] >2.0) in the Caco-2 cell system. At 5 µM, the average Papp of VX-445 was high (3.08 × 10-6 cm/s) in the apical-to-basolateral direction (Module 4.2.2.2/Report M388). In addition, absolute BA of VX-445 was determined in humans and is approximately 80%, suggesting that permeability is not absorption-limiting.

TEZ

- TEZ is classified as a BCS Class 2 compound (low solubility/high permeability) (Symdeko, Symkevi Marketing Authorization/Module 2.7.1/Section 3.6).
- 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.

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.

Solubility

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

VX-445

Table 1: Solubility of VX-445 at 24 hours, 37°C[a]

Buffer/pH	VX-445 Solubility at 24 Hours (mg/mL)
0.1N HCl pH 1.0	None Detected
50 mM Sodium Acetate pH 4.5	None Detected
50 mM Sodium Phosphate pH 6.8	None Detected

[a] Solubility was measured in the presence of ivacaftor and tezacaftor (b) (4) in a ratio of 1:1:1, with a target concentration of 5 mg/mL.

Table 2: Summary of VX-445 Solubility in the Presence of Ivacaftor (b) (4) and Tezacaftor (b) (4) in Various Surfactant / Buffer Combinations at 37°C

Surfactant	Surfactant Level (% w/v)	Buffer	Solubility (mg/mL)*
(b) (4)			

Tezacaftor

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

Buffer/pH	Tezacaftor Solubility at 24 Hours (mg/mL)
0.1N HCl pH 1.0	0.004
50 mM Sodium Acetate pH 4.5	0.003
50 mM Sodium Phosphate pH 6.8	0.005

* Solubility was measured in the presence of VX-445 drug substance and ivacaftor (b) (4) in the ratio of 1:1:1, with a target concentration of 5 mg/mL.

Table 4: Summary of Tezacaftor (b) (4) Solubility in the Presence of VX-445 and Ivacaftor (b) (4) in Various Surfactant / Buffer Combinations, 37°C

Surfactant	Surfactant Level (% w/v)	Buffer	Solubility (mg/mL)[a]
			(b) (4)

Ivacaftor

Table 5: Solubility of Ivacaftor (b) (4) at 24 hours, 37°C[a]

Buffer/pH	Ivacaftor Solubility at 24 Hours (mg/mL)
0.1N HCl pH 1.0	None Detected
50mM Sodium Acetate pH 4.5	None Detected
50mM Sodium Phosphate pH 6.8	None Detected

[a] Solubility was measured in the presence of VX-445 drug substance and tezacaftor (b) (4) in the ratio of 1.0:0.5:0.75, with a target concentration of 5 mg/mL.

Table 6: Summary of Ivacaftor (b) (4) Solubility in the Presence of VX-445 DS and Tezacaftor (b) (4) in Various Surfactant / Buffer Combinations at 37°C

Surfactant	Surfactant Level (% w/v)	Buffer	Solubility (mg/mL)[a]
			(b) (4)

Dissolution: Please see below.

Drug Product

Trikafta drug product (VX-445 (elexacaftor), tezacaftor, and ivacaftor) is an immediate-release film coated tablet for oral administration in the treatment of CF. Per the Applicant, tezacaftor belongs to BCS class 2 and ivacaftor belongs to BCS class 2 or 4. (b) (4)

(b) (4)

(b) (4) VX-445 is provided as a crystalline solid. Per the Applicant, VX-445 may be considered as a class 2 or 4.

The product and process development of FDC was conducted under a Quality by Design (QbD) paradigm to ensure desired product performance in terms of quality, safety, and efficacy. Dissolution was identified as one of the CQAs for the drug product.

The composition of FDC drug product is provided below.

Table 7: Composition of VX-445/Tezacaftor/Ivacaftor Fixed Dose Combination Tablet

Component	Quality Standard	Component Function	Amount per Tablet (mg)	Content (% w/w)
Core Tablet				
				(b) (4)
Core Tablet Total				(b) (4)
Film Coat				
				(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 VX-445, tezacaftor and ivacaftor in the FDC tablets. Dissolution method and acceptance criterion for 150 mg ivacaftor tablet (for Evening dose) has been approved previously (please refer to review by Dr. Sandra Suarez dated 01/18/2012 for NDA 203188). The dissolution medium for 150 mg

ivacaftor tablet contains higher level of SLS (0.7%) compared to the medium for the release of ivacaftor from FDC tablets (0.4%).

Proposed dissolution method and acceptance criteria

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 8: Dissolution Methods for VX-445, Tezacaftor, and Ivacaftor from VX-445/Tezacaftor/Ivacaftor FDC Tablet

Component	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
VX-445	II (Paddle)	75	1.8% (v/v) Tween 20 in 50 mM sodium phosphate, pH 6.8/37°C ± 0.5°C		Q =(b) (4)% in 20 minutes
Tezacaftor	II (Paddle)	75	0.2% (w/v) SLS solution in 0.1N HCl		Q =(b) (4)% in (b) (4) minutes
Ivacaftor	II (Paddle)	65	0.4% (w/v) SLS in 50 mM sodium phosphate, pH 6.8		Q =(b) (4)% in 20 minutes

The dissolution method for tezacaftor and ivacaftor is the same as approved for previous combination product Symdeko™ (tezacaftor 100 mg /ivacaftor 150 mg tablets). Please refer to Biopharmaceutics review by Dr. Fang Wu dated 01/17/2018 for NDA 210491 (Symdeko). However, it is to be noted that since this is a new drug product containing an additional drug substance with very low solubility, the dissolution methods' adequacy is part of the focus of this review. Dissolution specifications (method and acceptance criteria) are product specific and though the method was previously approved for two of the actives (tezacaftor and ivacaftor), the adequacy of the method is reevaluated based on the interaction of all the three actives with the critical parameters affecting the dissolution of the drug product.

Dissolution data for the three pivotal clinical batches (n=6) of the FDC at release are summarized below. Pivotal clinical batches are also the registration batches.

VX-445 Dissolution Mean Results (n=6)

Timepoints (Minutes)	5	10	15	20	30	45	60	75
2018019 (% LC)	46	69	81	88	95	99	101	101
2018026 (%LC)	47	71	82	89	95	99	100	100
2018027 (%LC)	48	72	83	89	96	99	100	101

Tezacaftor Dissolution Mean Results (n=6)

Timepoints (Minutes)	5	10	15	20	30	45	60	75
2018019 (% LC)	14	65	90	97	101	102	103	103
2018026 (%LC)	20	75	93	99	102	102	102	103
2018027 (%LC)	17	68	90	97	100	101	101	101

Ivacaftor Dissolution Mean Results (n=6)

Timepoints (Minutes)	5	10	15	20	30	45	60	75
2018019 (% LC)	27	65	82	91	98	100	101	101
2018026 (%LC)	31	66	82	91	98	99	100	100
2018027 (%LC)	26	63	81	90	98	101	101	101

Dissolution method development

(b) (4)

[redacted]

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(b) (4)

Discriminating ability of the dissolution method

The Applicant has provided data for the discriminating ability of the dissolution method for all three components of the FDC tablet and the details are provided in \\cdsesub1\evsprod\nda212273\0001\m3\32-body-data\32p-drug-prod\vx-445-tez-iva-tablet-all\32p2-pharm-dev\p22-drug-produc-formulation-dev.pdf. The discriminatory power of the dissolution method was evaluated for potentially critical process parameters and material and tablet properties, namely:

VX-445
- Tablet hardness
- Ivacaftor (b) (4)
- (b) (4)
- (b) (4) particle size
- VX-445 drug substance particle size
- (b) (4)

Tezacaftor
- Tablet hardness
- Tezacaftor (b) (4)
- Tezacaftor (b) (4)
- Ivacaftor (b) (4)

- (b) (4)
- (b) (4) particle size
- (b) (4)

Ivacaftor

- Tablet hardness
- Ivacaftor (b) (4)
- Ivacaftor (b) (4)
- (b) (4)
- (b) (4) particle size
- (b) (4)

Though all attributes listed above are considered critical, no discriminating ability was demonstrated to these critical material attributes/process parameters within the ranges tested except for hardness for all the three components. The discriminating ability of the dissolution method for tablet hardness is shown in Figures 5-7 below.

Dissolution of each component from the FDC tablets prepared with a range of tablet hardness ((b) (4) kP) was evaluated using the proposed methods. As seen in these figures, there is a dissolution slowdown trend with increasing tablet hardness. At 20-minute (b) (4) TEZ and IVA will reject batches with a hardness value of (b) (4) whereas at 15-minute (b) (4) all the three methods will reject batches with a hardness value of (b) (4) kP. Note that the hardness for pivotal clinical batches ranged from (b) (4) kP.

Figure 5: USP 2 Dissolution of VX-445 from 100 mg VX-445 / 50 mg Tezacaftor / 75 mg Ivacaftor FDC Tablets Prepared with Different Tablet Hardness in 1.8% (v/v) Tween 20 in 50 mM Sodium Phosphate, pH 6.8, 75 rpm

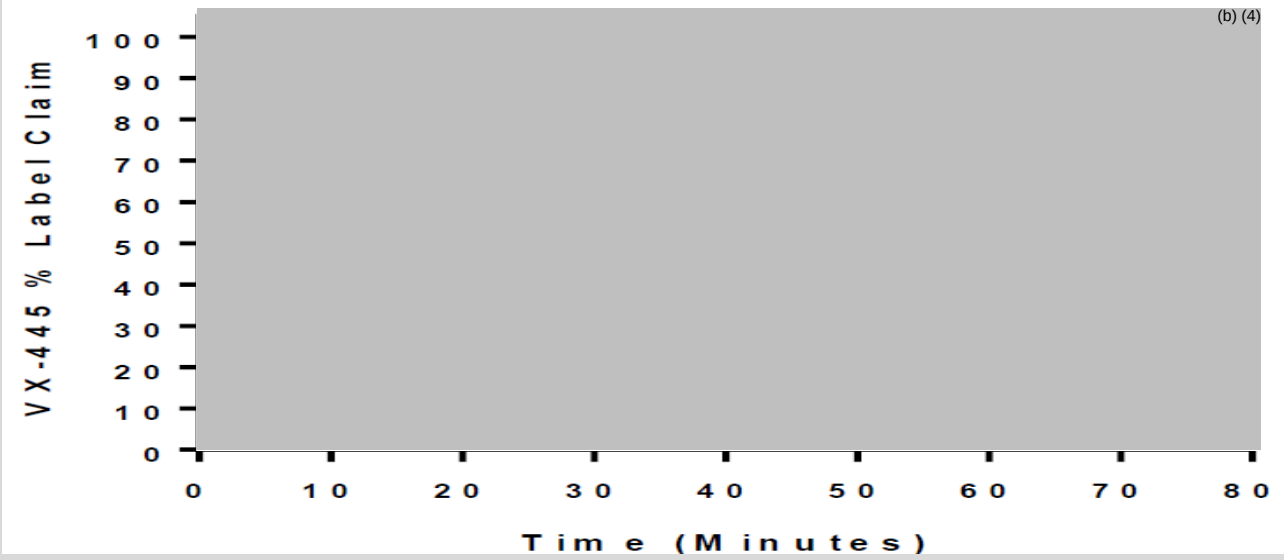


Figure 6: UPS 2 Dissolution of Tezacaftor from 100 mg VX-445 / 50 mg Tezacaftor / 75 mg Ivacaftor FDC Tablets Prepared with Different Tablet Hardness in 0.2% (w/v) SLS in 0.1N HCl, 75 rpm

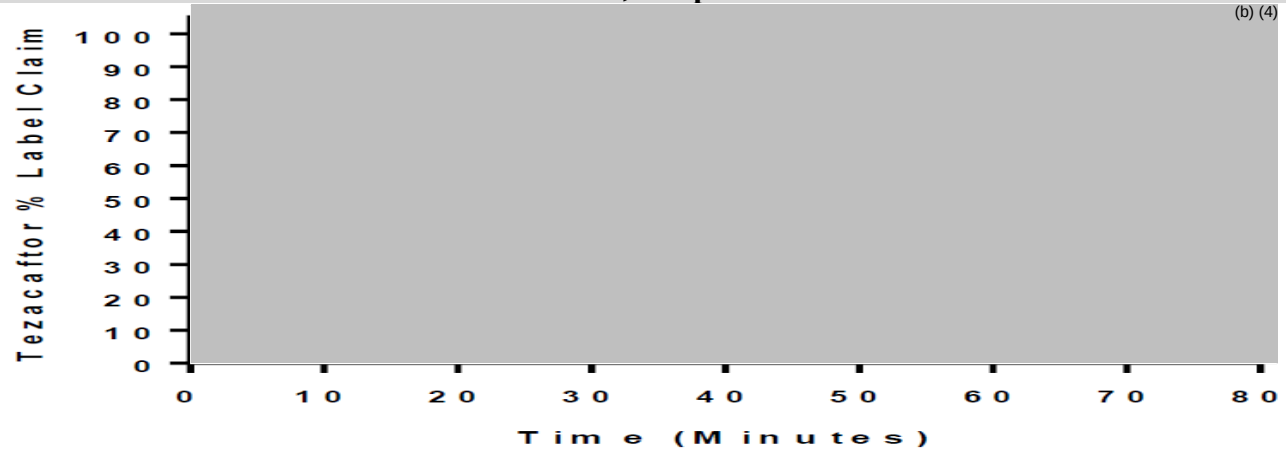
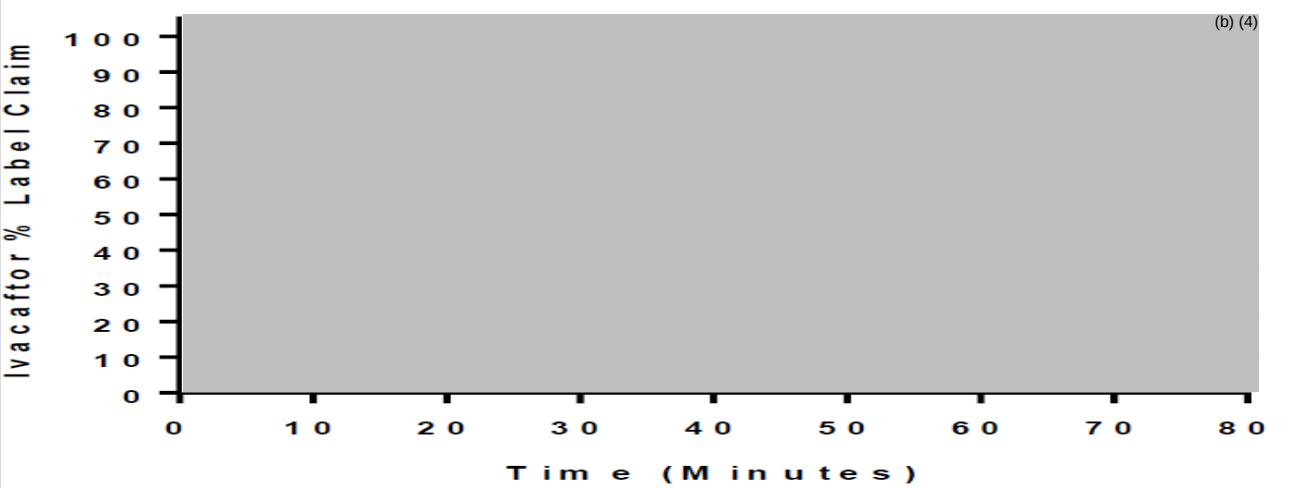


Figure 7: USP 2 Dissolution of Ivacaftor from 100 mg VX-445 / 50 mg Tezacaftor / 75 mg Ivacaftor FDC Tablets Prepared with Different Tablet Hardness in 0.4% (w/v) SLS in 50 mM Sodium Phosphate, pH 6.8, 65 rpm



Reviewer's assessment:
Based on the discriminating ability data, initial Biopharmaceutics recommendation (Refer to IR2.2) to the Applicant was to revise the ranges for the following parameters:

Parameters	Ranges observed in batches tested in Pivotal Phase 3 Trials			Proposed Acceptance criteria (AC)	Recommended Acceptance Criteria
	VX-445	Tezacaftor (b) (4)	Ivacaftor		
Particle size, µm, D50	(b) (4)	Not reported	Not reported	**Vx-455:** (b) (4) **Tezacaftor and Ivacaftor:** NA	**Vx-455:** (b) (4) **D90:** Vertex to propose a range based on observed values for batches tested in pivotal Phase 3 trials **Tezacaftor and Ivacaftor** (b) (4) Reported as per previous accepted ranges for D50 and D90.

(b) (4) **particle size, D50 µm**	(b) (4)	NA	**D50:** (b) (4) **D90:** Vertex to propose a range based on observed values for batches tested in pivotal Phase 3 trials
Core tablet hardness, kp	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	NMT (b) (4)	(b) (4)
Core tablet thickness, mm	(b) (4)	NMT (b) (4)	(b) (4)

It should be noted that the original recommendation also included revision of the (b) (4) ranges; however, the OPQ review team highly recommended against it.

In response to the IR (refer to submission dated 9/11/2019), the Applicant provided justification to maintain their proposed VX-445 particle size (D50) range based on DOE studies and a clinical study 001 and not to implement D90 range based on the D50 and D90 correlation. In addition, the Applicant was reluctant to implement/change specifications for Tezacaftor and Ivacaftor (b) (4) (b) (4) particle size, (b) (4) particle size, tablet (b) (4), tablet hardness, and tablet thickness. The specifications for tablet (b) (4) and tablet thickness were accepted as initially proposed by the Applicant based on CMC team's recommendation. Inclusion of Tezacaftor and Ivacaftor (b) (4) particle sizes were also not pursued further. A summary of the discussion for the Tezacaftor and Ivacaftor (b) (4) particle sizes, tablet (b) (4), and tablet thickness are provided below. Implementation of VX-445 PSD, (b) (4) PSD and the hardness of the tablet were pursued further, and the details are provided in Page 22.

Tezacaftor (b) (4) and Ivacaftor (b) (4) particle size

The Applicant provided cross reference to previously approved NDAs for Tezacaftor (b) (4) and Ivacaftor (b) (4) particle size. The Applicant was requested to provide particle size distribution (D50 and D90) of tezacaftor and ivacaftor (b) (4) used for preparation of each pivotal Phase 3 clinical batches and to include the specifications for the tezacaftor and ivacaftor (b) (4) directly in this application, for ease of future reviews.

In response, the Applicant noted that based on knowledge gained through multiple programs, the effect of (b) (4) (b) (4). Therefore, (b) (4) is controlled for ivacaftor (b) (4) and tezacaftor (b) (4), and (b) (4) is included in the specification for both ivacaftor (b) (4) and tezacaftor (b) (4)

Coated tablet (b) (4)

From the Biopharmaceutics perspective, (b) (4) of the drug product is considered critical for dissolution. However, the proposed specification is wide. Per the CMC reviewers, (b) (4) is also critical for (b) (4) (b) (4) The Applicant was, thus, recommended to tighten the specification for (b) (4) from NMT (b) (4) based on the pivotal clinical batches since there are no dissolution data supporting the range proposed by the Applicant.

In response, the Applicant proposed to keep the same specification since (b) (4) is not a critical quality attribute of the drug product. However, the tablet (b) (4) is controlled at release as part of the (b) (4). The

proposed (b) (4) range (NMT (b) (4)) was accepted based on CMC review team's assessment that the manufacturing process is (b) (4), and that there are no data to show that (b) (4) impacts dissolution or a change of (b) (4) the components.

Core tablet thickness

From the Biopharmaceutics perspective, core tablet thickness is considered critical as it has potential to impact dissolution. The Applicant's core tablet thickness was considered wide compared to the thickness of the pivotal clinical batches and hence, was requested to tighten it. In response, the Applicant noted that (b) (4) monitored and controlled as IPCs, though these attributes are inter-related and do not vary independently. However, the (b) (4) (b) (4) IPC has been set to ensure that tablets meet appropriate dimensions for blister packaging. The Applicant's proposed tablet thickness range was accepted. Based on CMC review team's assessment that tablet weight and hardness are tightly controlled during manufacture, which naturally constrains tablet thickness, controls on thickness was therefore considered not necessary.

On further assessment of the data provided by the Applicant, the following issues were observed with the discriminating ability of the dissolution method as stated below. The data submitted in support of the discriminating ability was not sufficient, i.e., it was generated based on dissolution profiles from 1-3 tablets. Based on current practice, data for at least 6 units should be used in support of discriminating ability of the dissolution method. In addition, no discriminating ability was demonstrated to critical material attributes and process parameters except for hardness. Moreover, there are no data supporting the clinical relevance of the proposed drug product specifications. Therefore, the Applicant was recommended (Please see IR 2 in Appendix 1) to change the dissolution acceptance criterion for all the three components to *Q (b) (4) % in 15 minutes* where discriminatory ability of the methods was demonstrated and to tighten or implement some material and process parameter specifications.

In response, the Applicant provided additional data (DOE run data for 3 units) in support of discriminating ability of the dissolution methods (refer to submission dated 9/11/2019), the summary of which is provided below.

Additional Method Discrimination Assessment Using QbD Process Development Results

The ranges for critical parameters used in DOE experiments are shown below. The actual Vx-445 D50 range used was (b) (4) µm.

Table 9: Material Attribute and Process Parameter Ranges Studied in QbD DOE

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APPENDIX A

Clinical Study 001

The Applicant submitted population PK report from clinical study 001 (cohort D evaluated PK and efficacy). This PK study evaluated two strengths 50 mg and 100 mg of VX-455 tablet formulations with different PSD. VX-445 drug substance with a D50 of (b) (4) µm and (b) (4) µm were dosed (Table 9). Based on OCP team's assessment which was communicated in a review team meeting, Appendix g, changes in VX-445 particle size distribution (in the range of (b) (4) microns) does not affect the systemic exposure of the drug and thus its efficacy (see table and figure below). Hence, the Applicant was requested to implement VX-445 particle size range (D50) from (b) (4) µm in support of this study. In response, the Applicant counter-proposed a D50 ranging from (b) (4) µm considering that VX-445 drug substance with D50 ranging from (b) (4) µm was evaluated during drug product process development, and resulting tablets met the acceptance criteria for all drug product CQAs. Although the Applicant's rationale for justifying wider PSD ranges that those tested in the PK study is not relevant in support of establishing clinically relevant specifications, due to lack of additional PK data, the proposal was found acceptable from Biopharmaceutics perspective, since according to the clinical review team, there is no safety signal based on the data submitted to evaluate whether higher Cmax values (eg. due to potential faster release from smaller particles) would be of safety concern.

Table 10: Details on PK study 001

Tablet Lot	Tablet Description	VX-445 Dv50 (µm)	Study	Dose
2016063	100 mg VX-445	(b) (4)	Study 001, Cohort D1	100 mg VX-445
2017037	50 mg VX-445		Study 001, Cohort D2	100 mg VX-445
			Study 005	200 mg VX-445 (administered with 100 mg TEZ and 150 mg IVA)
2018019	100/50/75 mg VX-445/TEZ/IVA FDC	(b) (4)	Study 005 Study 102 Study 103 Study 105	200 mg VX-445, 100 mg TEZ, 150 mg IVA

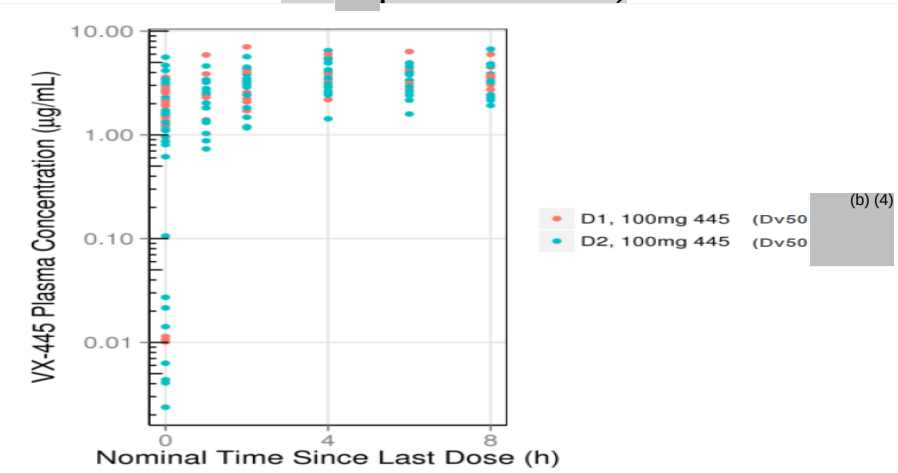
Table 11: Population PK Analysis Results-Study 001

Group	VX-445 Dose	Genotype	N	$AUC_{0\text{-}24h}$ (h*mcg/mL)	C_{avg} (mcg/mL)	C_{max} (mcg/mL)	T_{max} (h)	C_{min} (mcg/mL)	$t_{1/2}$ (h)
CC3A	100	HV	6	92.2 (13.2) [73.3,108]	3.84 (0.552) [3.05,4.51]	4.78 (0.624) [3.77,5.49]	5.1 (2.42) [2.5,9.9]	2.9 (0.493) [2.32,3.51]	48.4 (6) [41.1,57.5]
CC1A	200	HV	5	200 (58) [124,282]	8.32 (2.42) [5.16,11.7]	10.2 (2.83) [6.63,14.4]	7.7 (1.35) [5.4,8.6]	6.5 (2.08) [3.71,9.21]	53.5 (12.2) [41.2,66.9]
CC2A	280	HV	6	263 (56.8) [179,315]	11 (2.37) [7.46,13.1]	13.6 (2.69) [9.46,16]	4.9 (1.58) [4.1,8.5]	8.31 (2.14) [5.37,10.2]	49.9 (12.8) [38.2,73.2]
TC-low-D2	50	F/MF	10	39.2 (16.5) [8.89,60.6]	1.63 (0.688) [0.371,2.52]	2.23 (0.788) [0.967,3.41]	3.65 (2.66) [2.1,9.9]	1.14 (0.571) [0.0588,1.98]	24.6 (7.94) [7.91,36.2]
TC-mid-D1	100	F/MF	8	103 (66.9) [51.1,246]	4.3 (2.79) [2.13,10.2]	5.25 (2.86) [2.89,11.4]	3.55 (1.67) [2.2,7.6]	3.46 (2.7) [1.45,9.08]	40.4 (23.2) [20.2,82.1]
TC-mid-D2	100	F/MF	14	68.3 (25.8) [37,125]	2.85 (1.07) [1.54,5.2]	3.89 (1.18) [2.54,6.32]	3.45 (0.861) [2,5.4]	1.96 (0.973) [0.637,4.13]	25.3 (8.32) [12.2,43]
TC-high-D2	200	F/MF	21	173 (71.9) [65.3,387]	7.23 (3) [2.72,16.1]	9.83 (3.62) [4.03,20.2]	3.3 (0.611) [1.9,4]	5 (2.47) [1.62,12.3]	25.1 (6.95) [15.1,44.7]
TC2-high	200	F/MF	21	178 (114) [98.5,651]	7.4 (4.76) [4.11,27.1]	9.56 (4.72) [6.14,28.8]	3.5 (0.49) [1.9,3.9]	5.54 (4.78) [2.32,25.5]	32.1 (23.8) [15.9,131]
TC-high-E	200	F/F	21	175 (68) [23,340]	7.31 (2.83) [0.957,14.2]	9.55 (2.92) [3.57,17.4]	3.6 (1.87) [2.3,10.8]	5.42 (2.65) [0.00367,11.4]	30.6 (15.5) [6.32,87.2]

Results are presented in the following format: mean (standard deviation) [minimum, maximum] except for T_{max} which is reported as median (standard deviation) [minimum, maximum]

•TC-low-D2 (50 mg strength with (b) (4) microns)
•D1 received 100 mg strength with (b) (4) microns

Figure 15: VX-445 Plasma Concentration from Study 001 Cohorts D1 ((b) (4) µm VX-445 Dv50) and D2 (b) (4) µm VX-445 Dv50)



Bridging of Formulations

Reviewer's Assessment: Adequate

Bridging of formulations used in clinical studies

Table 11 lists the formulations of VX-445, TEZ, and IVA that were used in each clinical study in the VX-445/TEZ/IVA TC development program. Early Phase 1 and 2 studies used individual VX-445 tablets and either individual TEZ and IVA tablets or TEZ/IVA FDC tablets. An FDC tablet that contained all components of the TC (VX-445, TEZ, and IVA) was then developed for use in Phase 3 (Studies 102, 103, and 105) and commercialization.

Table 12: Formulations of VX-445, TEZ, IVA, and D-IVA Used in Clinical Studies in the TC Development Program

Clinical Study Number (Cohort)			Abbreviated Formulation Description	Formulation Description
Phase 1	Phase 2	Phase 3		
VX-445				
001 (A7)	--	--	IV solution	1 mg/mL solution in 25 mM phosphate buffer (diluted to 0.1 mg/mL with isotonic saline)
001 (A, B, C), 006	--	--	Tablet (20 mg)	20-mg tablet
002, 005 (A1, A3), 009	001 (D, E, F)	--	Tablet (50 mg)	50-mg tablet
001 (A, B, C)	001 (D)	--	Tablet (100 mg)	100-mg tablet
003	--	--	Solution in capsule	25-mg capsule using solution of [^{14}C]-VX-445 in Phosal53 MCT
TEZ				
005 (A1), 006	001 (F)	--	Tablet (50 mg)	50-mg tablet using (b) (4) mg/g TEZ (b) (4)
IVA				
001 (C), 002	001 (D, E)	102, 103, 105 (evening dose)	Tablet (150 mg)[a]	150-mg tablet using (b) (4) mg/g IVA (b) (4)
D-IVA[b]				
005 (A1), 006	001 (F)	--	Tablet (50 mg)	50-mg tablet using (b) (4) mg/g D-IVA (b) (4)
TEZ/IVA FDC				
001 (C), 002, 005 (A3)	001 (D, E)	103	FDC tablet (100 mg/ 150 mg)[c]	100-mg TEZ/150-mg IVA FDC tablet using (b) (4) mg/g TEZ and IVA (b) (4)
VX-445/TEZ/IVA FDC				
005 (A3)	--	102, 103, 105 (morning dose)	FDC tablet (100 mg/ 50 mg/75 mg)	100-mg VX-445/50-mg TEZ/75-mg IVA FDC tablet using (b) (4) mg/g TEZ and IVA (b) (4)
VX-445/TEZ/D-IVA FDC[b]				
005 (A1, B)	--	--	FDC tablet (100 mg/ 50 mg/75 mg)	100-mg VX-445/50-mg TEZ/75-mg D-IVA FDC tablet using (b) (4) mg/g TEZ and D-IVA (b) (4)

Source: Module 3/Section 3.2.P.2.2 – VX-445/TEZ/IVA Tablet for composition of formulations
D-IVA: deuterated IVA (VX-561); FDC: fixed-dose combination; IV: intravenous; IVA: ivacaftor; MCT: medium-chain triglyceride; (b) (4) TC: triple combination; TEZ: tezacaftor
Note: See Section 2.2 and the clinical study reports for study details.
[a] Same composition as commercial IVA tablet (Kalydeco).
[b] D-IVA, a deuterated version of IVA that is not part of the intended commercial formulation, was evaluated in a subset of studies within the VX-445 TC development program.
[c] Same composition as commercial TEZ/IVA tablet (Symdeko/Symkevi).

Table 13: Composition of VX-445 and VX-445/Tezacaftor/Ivacaftor FDC Tablets Used in Phase 1, 2, and 3

Component	Component Function	Tablet Content (% w/w)		
		20 mg, 50 mg, and 100 mg VX-445 Tablets	100 mg VX-445/ 50 mg Tezacaftor/ 75 mg VX-561 FDC Tablet	100 mg VX-445/ 50 mg Tezacaftor/ 75 mg Ivacaftor FDC Tablet
(b) (4) VX-445 Drug Substance	Active			(b) (4)
Tezacaftor (b) (4)	Active			
VX-561 (b) (4)	Active			
Ivacaftor (b) (4)	Active			
Microcrystalline cellulose				(b) (4)
Lactose monohydrate				
Croscarmellose sodium				
Sodium stearyl fumarate				
(b) (4				
Sodium stearyl fumarate				
Microcrystalline cellulose				
Magnesium stearate				
(b) (4)				
Film Coat				
				(b) (4)

A BA study (Study 005) was conducted to evaluate the VX-445/TEZ/IVA FDC tablet used in Phase 3 studies as compared to the tablets used in Phase 2. In this study (Cohort A3), the relative BA of the VX-445/TEZ/IVA FDC formulation (Phase 3/commercial formulation) was compared to the VX-445 tablet and TEZ/IVA FDC tablet (Phase 2 formulations) in the fed state (2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods Page 20 of 31).

Following the VX-445/TEZ/IVA FDC tablet, VX-445 AUC was 15% lower and IVA AUC was 12% higher, while TEZ exposure met bioequivalence criteria relative to exposures following the VX-445 tablet and TEZ/IVA FDC tablet (Table 13). Per the Applicant, the small differences in VX-445 and IVA exposures were not considered clinically relevant, and therefore the VX-445/TEZ/IVA FDC tablet evaluated in Study 005 was used in Phase 3. The qualification of this study is under the purview of the OCP review team.

Table 14: Relative BA of VX-445, TEZ, and IVA in the FDC Formulation (Test) Compared to VX-445 Tablet and TEZ/IVA FDC Tablet (Reference) (Study 005, Cohort A3)

N	Analyte	PK Parameter	GLSM Ratio (Test/Reference)	90% CI (Upper, Lower)
VX-445/TEZ/IVA FDC tablet (2 × 100 mg/50 mg/75 mg [Phase 3 FDC tablet]) versus VX-445 tablet (4 × 50 mg) + TEZ/IVA FDC tablet (1 × 100 mg/150 mg)[a]				
14	VX-445	C_{max}	0.725	0.637, 0.825
		$AUC_{0-\infty}$	0.850	0.759, 0.953
	TEZ	C_{max}	0.976	0.902, 1.06
		$AUC_{0-\infty}$	0.985	0.886, 1.09
	IVA	C_{max}	1.11	0.991, 1.24
		$AUC_{0-\infty}$	1.12	0.969, 1.30

Source: Study 005 CSR/Table 11-4
BA: bioavailability; FDC: fixed-dose combination; GLSM: geometric least squares mean; IVA: ivacaftor; PK: pharmacokinetics; TEZ: tezacaftor
[a] VX-445/TEZ/IVA dose: 200 mg/100 mg/150 mg.

The Applicant has noted that that in the Phase 3 studies (Studies 102 and 103), VX-445/TEZ/IVA was administered with the same FDC tablets as the commercial formulation.

In Pharmaceutical development report, the Applicant mentioned that the initial clinical supplies, including the initial Phase 3 clinical supplies were manufactured using a discontinuous process. In response to an IR, the Applicant confirmed that the Pivotal clinical batch 2018019 was manufactured using a discontinuous process, whereas batches 2018026 and 2018027 were manufactured using the continuous manufacturing process. However, it is of no concern as continuous manufacturing process utilized the same processing steps as the discontinuous process and all three batches have similar dissolution profiles for all the three components.

Biowaiver Request

Reviewer's Assessment: The Applicant has not requested any biowaiver. There is only one strength of the FDC.

Conclusions and recommendation

From Biopharmaceutics perspective, NDA 212273 for VX-445 (elexacaftor), tezacaftor, and ivacaftor Tablets (100mg, 50mg, and 75mg), is recommended for APPROVAL.

The Applicant is requested to collect additional data as PMC to further revise/justify the following specifications:

1. Implementation of three tier particle size specification (D10, D50, and D90) for VX-445 particle size distribution. Submission of the D10, D50 and D90 particle size distribution for at least five commercial batches along with complete dissolution profiles. These data along with similarity testing should be used to verify the design space for D50, revise D90 ranges and implement the ranges for D10.
2. Implementation of three tier particle size specification (i.e., D10, D50, and D90) for (b) (4) size. Submission of the D10, D50 and D90 size distribution for at least five commercial batches along with complete dissolution profiles. These data along with similarity testing should be used to verify the design space and set the appropriate ranges for D10, D50 and D90.

Appendix B

List of Deficiencies

Information Request 1 (IR 1)

We are in the process of reviewing your NDA and have identified the lack of some relevant information/data. In order to continue reviewing your submission, provide the following:

1. Complete dissolution profile data (individual, mean, %RSD, mean graphical profiles, n=12/batch) for all the pivotal Phase 3 clinical and primary stability batches. Also provide complete batch information (batch no. and batch manufacturing date, site, size, and the dates of dissolution testing) for all lots.

2. Complete dissolution data (individual, mean, %RSD, f2 calculations where appropriate) for all dissolution profiles related to the discriminating ability of VX-455 (section 2.2.4.), Tezacaftor (section 2.3.4.), and Ivacaftor (section 2.4.4.) component of the FDC tablet provided in Drug Product Formulation Development report.

3. Drug product batch numbers used for each of the Phase 3 clinical studies for the FDC tablet in a tabular format. Identify each clinical study.

4. Submit the following information (not limited to) for all the batches tested in pivotal Phase 3 clinical trials in a tabular format (an example shown below):

a. Particle and (b) (4) size distribution (e.g. D10, D50 and D90) for the three active ingredients
b. (b) (4) for all three active ingredients
c. Tablet hardness
d. (b) (4)
e. Tablet weight range
f. Core tablet thickness

Example Table

Clinical Studies and Batches of fixed dose combination used	Critical Parameters	Corresponding Value (vx-445)	Corresponding Value (Tezacaftor)	Corresponding Value (Ivacaftor)
Study 005 VX-445 100-mg/ TEZ 50-mg/ IVA 75-mg FDC tablets (Lot 2018019)	Particle size distribution			
	(b) (4) size distribution			
	(b) (4)			
	Tablet hardness			
	(b) (4)			
	Tablet weight range			
	Core tablet thickness			

5. In Pharmaceutical development report, you have mentioned that the initial clinical supplies, including the initial Phase 3 clinical supplies were manufactured using a discontinuous process. Please confirm that the Pivotal clinical batches (2018019, 2018026, and 2018027) were manufactured using continuous manufacturing process.

6. Dissolution profiles inside and outside the ranges tested in pivotal clinical trials for the following variables:

a. Drug and (b) (4) particle size distribution for all active components.
b. (b) (4) for all active components
c. Tablet weight
d. (b) (4)
e. Core tablet thickness
f. Tablet hardness

7. Information on the control strategy for (b) (4) content.

8. Detailed information on the sampling strategy for dissolution testing under continuous manufacturing process. Please provide clarification on the following:

a. Are the units randomly sampled?
b. If taken from every segment, how many per segment?

c. What is the procedure for sampling selection if segment number varies?

Information Request 2 (IR 2)

We acknowledge the data submitted on 08/20/2019 in response to the previous IR. The data submitted in support of the discriminating ability is not sufficient, i.e., it was generated based on dissolution profiles from 1-3 tablets. Based on current practice, data for at least 6 units should be used in support of discriminating ability of the dissolution method. In addition, no discriminating ability was demonstrated to critical attributes and parameters except for hardness. Moreover, there are no data supporting the clinical relevance of the proposed drug product specifications. Thus, we cannot reach a conclusion on the adequacy of the dissolution method at this time. However, recognizing the benefit that this product is expected to bring to the patient population, and to ensure consistent safety and efficacy to the batches tested in pivotal clinical trials, in the interim, we have the following recommendations as a path forward.

1. Revise the dissolution acceptance criteria for batch release and stability testing of your proposed drug product to:

Component	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Recommended Acceptance criteria
VX-445	II (Paddle)	75	1.8% (v/v) Tween 20 in 50 mM sodium phosphate, pH 6.8/37.0°C ± 0.5°C	900ml	Q (b) (4)% in 15 minutes
Tezacaftor	II (Paddle)	75	0.2% (w/v) SLS solution in 0.1N HCl / 37.0°C ± 0.5°C	900ml	Q % in 15 minutes
Ivacaftor	II (Paddle)	65	0.4% (w/v) SLS in 50 mM sodium phosphate, pH 6.8 /37.0°C ± 0.5°C	900ml	Q % in 15 minutes

In addition, revise the process parameters settings/ranges accordingly.

As an alternative, if the proposed change to the dissolution acceptance criteria would warrant major changes to the control strategy that includes current settings for process parameter ranges (e.g. change in DSL (design space limits), then we may consider revising the recommended dissolution acceptance criteria to (b) (4). Note however, that we will be amenable to this revision provided that you tighten the acceptance criteria of and include some additional in-process controls that are important to ensure the in vitro and in vivo performance of the drug product based on the characteristics of the batches tested in pivotal Phase 3 clinical trials.

2. Revise (as recommended below) and propose the acceptance criteria (AC) ranges for the critical material attributes to reflect the values for these in place when manufacturing the pivotal clinical batches:

Parameters	Ranges observed in batches tested in Pivotal Phase 3 Trials			Proposed Acceptance criteria (AC)	Recommended Acceptance Criteria
	VX-445	Tezacaftor (b) (4)	Ivacaftor		
Particle size, µm, D50	(b) (4)	Not reported	Not reported	**Vx-455:** (b) (4) **Tezacaftor and Ivacaftor:** NA	**Vx-455:** (b) (4) **D90:** Vertex to propose a range based on observed values for batches tested in pivotal Phase 3 trials **Tezacaftor and Ivacaftor** (b) (4) Reported as per previous accepted ranges for D50 and D90.
(b) (4) **particle size, D50 µm**	NA, (b) (4)			NA	**D50:** (b) (4) **D90:** Vertex to propose a range based on observed values for batches tested in pivotal Phase 3 trials
Core tablet hardness, kp	(b) (4)			(b) (4)	(b) (4)
Coated tablet (b) (4) **(b) (4) w/w**	(b) (4)			NMT (b) (4)	(b) (4)
Core tablet thickness, mm	(b) (4)			NMT	

Because of the low solubility for each drug substance, we consider PSD for VX-445 drug substance, (b) (4) ivacaftor and tezacaftor, and the drug product (b) (4) size to have a potential to impact the *in vitro* and *in vivo* performance of the drug product. Therefore, as listed on the table above, we are recommending that a specification for D50 and D90 be implemented for (b) (4) VX-455 API, TEZ/IVA (b) (4) and the drug product (b) (4) size. The proposed ranges should reflect the data from the pivotal Phase 3 batches.

3. We acknowledge that PSD ranges have already been approved for the tezacaftor and ivacaftor (b) (4) and that you are providing cross reference to previously approved NDAs. However, in order to complete our evaluation, provide particle size distribution (D50 and D90) of Tezacaftor and Ivacaftor (b) (4) used for preparation of each pivotal Phase 3 clinical batches. We also recommend that you include the specifications for the tezacaftor and ivacaftor (b) (4) directly in this application, for ease of future reviews.

These ranges for critical material attributes and process parameters recommended above may be revised, upon approval (e.g., via supplement to the NDA) of the drug product as needed and supported with additional data that demonstrate not only the discriminating ability of the dissolution method, but its clinical relevance.

(b) (4)

(b) (4)

[redacted]

Information Request 3 (IR 3)

You mentioned in your presentation (during the T-con on 09/04/2019) that in Phase 1/2 studies, VX-445 drug substance with D50 of (b) (4) µm were dosed and showed similar exposure in humans. We request that you provide the data that demonstrates bioequivalence in in vivo exposure of VX-445 with these two particle sizes to support your proposed particle size specifications. If you have already provided the data, direct us to the appropriate location in the NDA submission to aid with the review of this submission. These data should include (not limited to):

1. Protocol detailing the study design on the PK study, including the number of subjects, concomitant drug administration, etc.
2. Individual and mean PK parameter values with statistical analyses including 90% CI of the geometric mean ratio of relevant PK parameters.
3. Detailed information on the batches used including batch size, batch number, components and composition of the formulation, particle size distribution (D10, D50, D90) for the VX-455 and (b) (4) hardness, (b) (4), ranges of manufacturing process parameters, etc.

We request that this information be submitted by 09/10/2019.

Information Request 4 (IR 4)

We acknowledge the additional data submitted on 09/11/2019 in response to the IR.

Based on current practice, data on at least 6 units should be used in support of discriminating ability of the dissolution method. Note that you provided DOE run data for 3 units in support of discriminating ability for your methods. However, given the low variability and the benefit that this product will bring to the

patient population, we have reached the conclusion that the data are sufficient to support the discriminatory ability of the methods.

You proposed to maintain the acceptance criterion, Q= (b) (4)% in 20 minutes, for VX-445 and Ivacaftor. However, we would like to emphasize that the discriminatory ability to critical attributes/process parameters is demonstrated not only with acceptable dissolution method but with tighter acceptance criteria. Given that your dissolution methods are acceptable based on risk assessment, your proposed dissolution acceptance criterion Q= (b) (4)% in 20 minutes for VX-445 and Ivacaftor is acceptable provided additional mitigation strategies are implemented which include the implementation of adequate controls for hardness, particle size for VX-445 and (b) (4) particle size as follows.

1. Based on clinical study 001 VX-445 particle size of (b) (4) µm demonstrated no significant change in efficacy. Implement VX-445 particle size range (D50) of (b) (4) µm. The correlation that you provided for D90 is inadequate since it encompasses range only up to (b) (4) µm while the upper end of proposed range for D50 is (b) (4) µm. Therefore, implement a range for D90 as well.
2. Implement a hardness range of (b) (4) kP as supported by pivotal clinical batches.
3. Implement (b) (4) particle size distribution (e.g., D10, D50 and D90) as supported by pivotal clinical batches.

These recommended drug product specifications may be revised, upon approval (e.g., via a Supplement to the NDA) of the drug product as needed and supported with additional data such as modeling and simulation.

Information Request 5 (IR 5)

Biostatistics/Biopharmaceutics IR

(b) (4)

(b) (4)

Submit an updated drug product specification table reflecting this recommendation.

2. Commit to providing the following as a PMC commitment*:*
1. Implement three tier particle size specification (D10, D50, and D90) for VX-445 particle size distribution. Note that your proposed D50 specification of (b) (4) µm is acceptable.
2. Provide the D10 and D90 particle size distribution for at least five commercial batches. Revise D90 based on additional data such as dissolution profiles collected for these commercial batches manufactured using particle sizes in the proposed ranges.
3. Implement (b) (4) particle size distribution (e.g., D10, D50 and D90). Provide the (b) (4) particle size distribution for at least five commercial batches.

The following information request and PMC request were drafted but not conveyed to the Applicant based on a Memo written by Dr. Wendy Wilson which overrode them (refer to review in Panorama dated 10/16/2019):

OPQ/Statistics IR

(b) (4)

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(b) (4)

Please acknowledge this proposal in writing by 10/14/2019.

Primary Biopharmaceutics Reviewer Name and Date: Kalpana Paudel, Ph.D. 10/17/19
Secondary Reviewer Name and Date: Haritha Mandula, Ph.D. 10/17/19
Tertiary Reviewer Name and Date: Sandra Suarez Sharp, Ph.D. 10/17/19

Kalpana Paudel

Digitally signed by Kalpana Paudel
Date: 10/17/2019 11:15:37AM
GUID: 562e1e15002f200f35c6ccac959cdb34

Haritha Mandula

Digitally signed by Haritha Mandula
Date: 10/17/2019 11:19:36AM
GUID: 508da6fb000282df41459408f32a1ce0

Sandra Suarez

Digitally signed by Sandra Suarez
Date: 10/17/2019 11:21:48AM
GUID: 5033874b000046a4a8b9c51d6f5bd8ba
Comments: Thanks Kalpana and Haritha for all your hard work on this. Best, SAndra

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRIKAFTA™ (elexacaftor/tezacaftor/ivacaftor) tablets; (ivacaftor) tablets,	TRIKAFTA™
Established name(s)	(elexacaftor/tezacaftor/ivacaftor) tablets; (ivacaftor) tablets,	*Change to*: (elexacaftor, tezacaftor and ivacaftor) tablets; (ivacaftor) tablets, co-packaged
Route(s) of administration	for oral use	for oral use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: □ (b) (4) co-packaged as elexacaftor 100 mg/ tezacaftor 50 mg/ivacaftor 75 mg fixed dose combination tablets and ivacaftor 150 mg tablets.	*Change to*: Tablets: fixed dose combination containing 100 mg elexacaftor, 50 mg tezacaftor and 75 mg ivacaftor. Co-packaged with: Tablets: 150 mg ivacaftor
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not applicable	Acceptable

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.	Not applicable for Oral tablets	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Not applicable for tablet for oral administration	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets (2), co-packaged	
Strength(s) in metric system	Elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg; ivacaftor150 mg	*Change to*: Elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg; ivacaftor150 mg
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not applicable	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg tablets are orange, capsule-shaped, and debossed with "T100" on one side and plain on the other. Ivacaftor 150 mg tablets are light blue, capsule-shaped, and printed with "V 150" in black ink on one side and plain on the other.	*Change to*: Elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg tablets are orange, capsule-shaped, and debossed with "T100" on one side and plain on the other. Ivacaftor 150 mg tablets are light blue, capsule-shaped, and printed with "V 150" in black ink on one side and plain on the other.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not applicable	
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.	Not applicable	

1.2.3 Section 11 (DESCRIPTION)

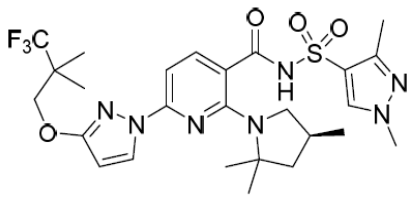
Appears this way on original

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRIKAFTA; elexacaftor/tezacaftor/ivacaftor; ivacaftor	*Change to*: TRIKAFTA; elexacaftor, tezacaftor and ivacaftor; ivacaftor
Dosage form(s) and route(s) of administration	Tablets; for oral use	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Not applicable	

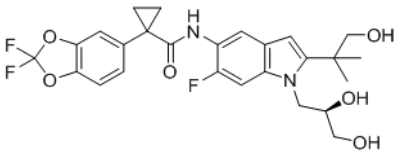
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	*elexacaftor/tezacaftor/ivacaftor tablet core contain*: hypromellose, hypromellose acetate succinate, sodium lauryl sulfate, crosscarmellose sodium, microcrystalline cellulose, and magnesium stearate. The film coat contains hypromellose, hydroxypropyl cellulose, titanium dioxide, talc, iron oxide yellow, and iron oxide red *ivacaftor tablet core contain:* colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The film coat contains carnauba wax (b) (4), FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.	Acceptable
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.	Not applicable for oral tablets	

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		
Statement of being sterile (if applicable)	Not applicable	
Pharmacological/ therapeutic class	No information on pharmacological class included	*To be included*: Elexacaftor and tezacaftor are CFTR correctors, while ivacaftor is a CFTR potentiator
Chemical name, structural formula, molecular weight	See attached information at the end of the table	
If radioactive, statement of important nuclear characteristics.	Not applicable	
Other important chemical or physical properties (such as pKa or pH)	No information provided for the three drugs	

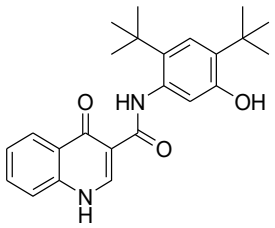
Elexacaftor: chemical name of elexacaftor is N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl] pyridine-3-carboxamide; molecular formula is C26H34N7O4SF3; molecular weight is 597.66; structural formula:



Tezacaftor: chemical name of tezacaftor 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; molecular formula is $C_{26}H_{27}N_2F_3O_6$; molecular weight is 520.50; structural formula:



Ivacaftor: chemical name is N-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide; molecular formula is $C_{24}H_{28}N_2O_3$; molecular weight is 392.49; structural formula:



Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	None	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets	
Strength(s) in metric system	Fixed dose combination tablets containing 100 mg of elexacaftor, 50 mg of tezacaftor and 75 mg of ivacaftor. Ivacaftor tablets containing 150 mg of ivacaftor.	Acceptable
Available units (e.g., bottles of 100 tablets)	84-count tablet carton (b) (4) (4 (b) (4) wallets, each (b) (4)	*Change to*: 84-count tablet carton (b) (4) (4 (b) (4) wallets, each wallet containing 14 Elexacaftor, tezacaftor and ivacaftor tablets and 7 ivacaftor tablets)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	elexacaftor/tezacaftor/ivacaftor tablets are supplied as orange, capsule shaped tablets; debossed with "T100" on one side and plain on the other. Ivacaftor tablets are supplied as light blue, film coated, capsule shaped tablets; is printed with the characters "V 150" in black ink on one side and plain on the other. NDC 51167-331-01	*Change to*: elexacaftor, tezacaftor and ivacaftor tablets are supplied as orange, capsule shaped tablets; debossed with "T100" on one side and plain on the other. Ivacaftor tablets are supplied as light blue, film coated, capsule shaped tablets; is printed with the characters "V 150" in black ink on one side and plain on the other. NDC 51167-331-01
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not scored	

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.	Not applicable	

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.)	Not applicable;	
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."	Not applicable	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20ºC 25ºC (68ºF 77ºF); excursions permitted to 15ºC 30ºC (59ºF 86ºF) [see USP Controlled Room Temperature].	Acceptable
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	Not applicable	

natural rubber latex. Avoid statements such as “latex-free.”		
Include information about child-resistant packaging	No information included	May be included as needed

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for Vertex Pharmaceuticals Incorporated 50 Northern Avenue Boston, MA 02210	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Patient Information):

Drug Product Name to be revised as **TRIKAFTA™ (elexacaftor, tezacaftor and ivacaftor) 100 mg, 50 mg and 75 mg; and (ivacaftor) 150 mg tablets** throughout the text of PI and Patient information.

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

3.0 CARTON AND CONTAINER LABELING

3.1 Wallet Inside Label

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	trikafta™ (elexacaftor/tezacaftor/ivacaftor) and (Ivacaftor) tablets	*To be changed to:* trikafta™ (elexacaftor, tezacaftor and ivacaftor) 100 mg, 50 mg and 75 mg; (ivacaftor) tablets
Dosage strength	100 mg/50 mg/75 mg and (ivacaftor) 150 mg	100 mg, 50 mg and 75 mg; 150 mg
Route of administration	No specific text to indicate the route of administration on the wallet or outer carton.	*To include*: "For Oral Use." before the text "Swallow tablets whole with fat-containing food" on wallet card and carton.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not applicable	
Net contents (e.g. tablet count)	84 tablets 4-wallets (14 elexacaftor/tezacaftor/ivacaftor and 7 ivacaftor tablets)	*Change text to*: 4-wallets (14 elexacaftor, tezacaftor and ivacaftor tablets and 7 ivacaftor tablets)
"Rx only" displayed on the principal display	Rx Only	
NDC number	NDC 51167-331-01 on both Wallet and Carton	
Lot number and expiration date	EXP MM/YYYY LOT XXXXXXX	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Not applicable	

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	Not applicable	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not applicable	
Bar code	(b) (4)  GTIN XXXXXXXXXXXXXX S/N XXXXXXXXXXX	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Vertex Pharmaceuticals Incorporated, Boston, MA 02210	
Medication Guide (if applicable)	Patient Information and Prescribing information are included in the carton	
No text on Ferrule and Cap overseal	Not applicable	
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.	Each orange tablet marked with "T100" contains: Elexacaftor 100 mg Tezacaftor 50 mg Ivacaftor 75 mg Each light blue tablet marked with "V 150" contains: Ivacaftor 150 mg	
And others, if space is available		The wallet card (inside or outside text as space allows) should contain the composition statement as on Carton Each orange tablet marked with "T100" contains: Elexacaftor 100 mg Tezacaftor 50 mg Ivacaftor 75 mg Each light blue tablet marked with "V 150" contains: Ivacaftor 150 mg

Assessment of Carton and Container Labeling: Inadequate

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

ITEMS FOR ADDITIONAL ASSESSMENT

Prescribing Information

HIGHLIGHTS

1. Revise Product Name as "TRIKAFTA™ (elexacaftor, tezacaftor and ivacaftor) tablets; (ivacaftor) tablets, co-packaged for oral use"
2. Revise DOSAGEFORMS and STRENGTHS as "Tablets: fixed dose combination containing 100 mg elexacaftor, 50 mg tezacaftor and 75 mg ivacaftor, Co-packaged with Tablets: 150 mg ivacaftor (3)"

3 DOSAGE FORMS AND STRENGTHS

1. Revise text in section 3 as
    a. "TRIKAFTA is a co-package of 150 mg strength ivacaftor tablets with fixed dose combination tablets containing elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg. The elexacaftor, tezacaftor and ivacaftor tablets are orange, capsule shaped, and debossed with "T100" on one side and plain on the other. The ivacaftor tablets are light blue, capsule shaped, and printed with "V 150" in black ink on one side and plain on the other."

11 DESCRIPTION

1. Revise the sentences in description as
    a. "TRIKAFTA is co package of elexacaftor, tezacaftor and ivacaftor fixed dose combination tablets with ivacaftor tablets. Both tablets are for oral administration."
    b. "The elexacaftor, tezacaftor and ivacaftor tablets are available as an orange, capsule shaped, film coated fixed-dose combination tablet containing 100 mg of elexacaftor, 50 mg of tezacaftor, 75 mg of ivacaftor, ….."

16 HOW SUPPLIED/STORAGE AND HANDLING

1. Revise the text in section 16 as
    a. "TRIKAFTA is supplied as a co-packaged blister pack sealed in to a printed wallet (b) (4) containing elexacaftor, tezacaftor and ivacaftor fixed

dose combination tablets and ivacaftor tablets. Four such wallets are placed in a printed outer carton. The elexacaftor, tezacaftor and ivacaftor tablets are supplied as orange, capsule shaped tablets; each containing 100 mg of elexacaftor, 50 mg of tezacaftor and 75 mg of ivacaftor."

b. "84 count tablet carton (b) (4) NDC 51167-331-01 (4 (b) (4) wallets, each wallet containing 14 Elexacaftor, tezacaftor and ivacaftor tablets and 7 ivacaftor tablets)

Wallet and Carton

1. Revise the established name of drug product as (elexacaftor, tezacaftor and ivacaftor) 100 mg, 50 mg and 75 mg; (ivacaftor) tablets.
2. Include the words "For Oral Use." before the text "Swallow tablets whole with fat-containing food" on wallet card and carton.
3. Change Net Contents to: 4-wallets (14 elexacaftor, tezacaftor and ivacaftor tablets and 7 ivacaftor tablets).

Wallet (Inner / Outer flap)

1. Include the following composition statements on the wallet card, either inside or outside as space allows. Primary container should contain the composition statement as on Carton.

   Each orange tablet marked with "T100" contains:

   Elexacaftor 100 mg
   Tezacaftor 50 mg
   Ivacaftor 75 mg

   Each light blue tablet marked with "V 150" contains:

   Ivacaftor 150 mg

Overall Assessment and Recommendation:

Acceptable, subject to making above recommended changes to the text in PI, Wallet and Carton.

Primary Labeling Assessor Name and Date: **Venkateswara R. Pavuluri, Ph. D., R. Ph.; 29-SEP-2019**

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Julia C. Pinto, Ph. D.; 30-SEP-2019

Venkateswara Pavuluri

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Julia Pinto

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NDA 212273 IQA – Final Risk Assessment

DP CQA	Factors that may impact the CQA	O[1]	S[1, 2]	D[1]	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Comments/Lifecycle considerations
Appearance	▪Film coating (b) (4) considered critical to appearance CQA; coating parameter variation (those parameters not in proposed design space) ▪Legibility of debossing ▪Friability problems with (b) (4) cores	4	3	3	36	(b) (4)	2x3x3=18	(b) (4) resulted in tablets that consistently met the appearance specification; executed batch record for registration batch 2018026, indicated that tablet hardness determined (b) (4) So long the manufacturing process remains within the established design space, appearance would be acceptable
ID[3] (VX-445)	▪Incorrect elucidation of structure ▪No tests to assure correct chirality of VX-445	4	3	3	36		2x2x3=12	Applicant provides control for chiral purity by including a specification test (b) (4) and the chiral center has low risk of epimerization

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of "3" will be used throughout)
[3] Refer to N210491 review for the elucidation of ivacaftor and tezacaftor structures and the associated control strategies to assure identities.
[4] (b) (4)

NDA 212273 IQA – Final Risk Assessment

Assay	(b) (4)	2	3	2	12	(b) (4)		The agency has proposed a PMC to implement 3 tier particle size specification for (b) (4) particle size Ensure (b) (4)) are updated and verified as needed over the lifecycle
Degradation Products /Purity	▪High degradant levels in the tezacaftor and ivacaftor (b) (4) ▪High degradant level in VX-445 (b) (4) ▪Degradation of APIs in fixed-dose combination drug product on stability ▪Presence of elemental impurities ▪Presence of (b) (4)	2	3	5	30		2x3x2=12	Applicant has agreed to test the drug product for degradants at release
Dissolution (all actives)	(b) (4) variability of tezacaftor (b) (4) (b) (4) variability of ivacaftor (b) (4)	3	3	3	27		3x3x2=18	Applicant has committed to monitoring (b) (4) particle size and proposing acceptance criteria (PMC); also

	VX-445 particle size variability ▪Variation in (b) (4) (b) (4) particle size variability ▪API (b) (4) ▪Variable tablet hardness (b) (4) ▪Tablet (b) (4) ▪Coating weight variation					(b) (4)		adequate controls are in place for (b) (4) Agency has proposed implementing a 3-tier particle size specification to control VX 445 particle size. The firm also agreed to implement (b) (4) Biopharmaceutics team has found the dissolution methods to be sufficiently discriminating to be able to detect changes in process parameters and material attributes; applicant has tightened the tablet hardness range (b) (4)
Uniformity of Dosage Units (content uniformity or CU)	(b) (4) variability of tezacaftor (b) (4) (b) (4) variability of ivacaftor (b) (4) VX-445 PSD variability (b) (4) variability	2	3	2	12			(b) (4)

						(b) (4)		(b) (4)
Microbial limits	▪Bioburden from components of formulation (b) (4) above acceptance criteria ▪Microbial growth during processing (b) (4) ▪Quality of input materials ▪No microbial limits testing proposed for drug product at release	1	3	5	15			Full waiver of micro limits testing over stability is supported under the current conditions. If manufacturing hold time and hold times of (b) (4) are extended, would need added justification and reevaluation of above agreement
Physical form	▪Input materials contain crystalline APIs ▪Physical forms of drug substances are potentially altered during manufacture ▪Physical forms of drug substances are potentially altered with time during shelf life (i.e., ivacaftor and/or tezacaftor crystallize,	3	3	3	27		2x3x3=18	Applicant has a test to assure the correct physical form of VX-445 prior to manufacturing drug product and physical form is monitored during drug substance stability studies; full evaluation of drug product stability test results and forced

	VX-445 converts to other polymorph)					(b) (4)		degradation studies for the drug product, risk of physical form conversions of VX-445, tezacaftor, and ivacaftor is now considered to be low

Craig Bertha

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/s/

CRAIG M BERTHA
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