

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210491Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210491
Review #1

Drug Name/Dosage Form	tezacaftor/ivacaftor tablet
Strength	100 mg tezacaftor/150 mg ivacaftor/tablet
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Vertex Pharmaceuticals, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>Original</i>	<i>28-JUN-2017</i>	<i>all</i>
<i>Amendment</i>	<i>07-JUL-2017</i>	<i>all</i>
<i>Amendment</i>	<i>10-JUL-2017</i>	<i>process/facilities</i>
<i>Amendment</i>	<i>26-JUL-2017</i>	<i>process/facilities</i>
<i>Amendment</i>	<i>31-JUL-2017</i>	<i>process/facilities</i>
<i>Amendment</i>	<i>05-SEP-2017</i>	<i>biopharmaceutics</i>
<i>Amendment</i>	<i>01-NOV-2017</i>	<i>drug substance</i>
<i>Amendment</i>	<i>03-NOV-2017</i>	<i>biopharmaceutics/process/facilities</i>
<i>Amendment</i>	<i>07-NOV-2017</i>	<i>process/facilities</i>
<i>Amendment</i>	<i>01-DEC-2017</i>	<i>biopharmaceutics/process</i>
<i>Amendment</i>	<i>02-JAN-2018</i>	<i>drug product</i>
<i>Amendment</i>	<i>04-JAN-2018</i>	<i>drug product</i>
<i>Amendment</i>	<i>05-JAN-2018</i>	<i>drug product</i>
<i>Amendment</i>	<i>09-JAN-2018</i>	<i>process/facilities</i>
<i>Amendment</i>	<i>11-JAN-2018</i>	<i>drug product</i>

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/BRANCH
Drug Substance	Sukhamaya Bain	ONDP/DNDAPI/NDBII
Drug Product	Xiaobin Shen	ONDP/ DNDPII/NDPBIV
Process	Yong Hu Hong Yang	OPF/DPAII/PABIV

Microbiology	N/A	OPF/DMA/MABII
Facility	Christina Capacci-Daniel	OPF/DIA/IABII
Biopharmaceutics	Min Li	ONDP/DB/BBIII
Regulatory Business Process Manager	Florence Aisida	OPRO/DRBPMI/RBPMBI
Application Technical Leads	Sharmista Chatterjee Craig M. Bertha	OPF/DPAII ONDP/DNDPII/NDPBIV
Laboratory (OTR)	N/A	
ORA Lead	Margaret Sands Maya Davis Sean Marcsisin	OMPT/OPQO/DPQOIV/PQIB
Environmental Analysis (EA)	N/A, but EIC estimation needed	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	III		(b) (4)	Not reviewed		Sufficient information in NDA
	III			Not reviewed		Sufficient information in NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	108105	tezacaftor (VX-661) for CF
IND	74633	ivacaftor (VTX-770) for CF
NDA	203188	ivacaftor tablets for CF

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other – process modeling/simulation	Final			Thomas O'Connor

Executive Summary

I. Recommendations and Conclusion on Approvability

N/A – OPQ recommends approval

II. Summary of Quality Assessments

A. Product Overview

The fixed dose combination drug product of tezacaftor/ivacaftor is an immediate release tablet (Symdeko™) that is indicated for the treatment of patients 12 years and older with cystic fibrosis (CF). The tezacaftor is a new molecular entity (NME with BCS class II) and the ivacaftor (BCS class II or IV) has already been approved for treatment of CF as a single ingredient (NDAs 203188, 207925) and in combination with lumacaftor (N206038). All of these drugs are targeted to enhancing cell chloride transport that is impacted by the genetic mutations affecting the cystic fibrosis transmembrane conductance regulator (CFTR) protein.

The two active substances, tezacaftor and ivacaftor, are incorporated into the fixed-dose combination tablet (b) (4)

. The tablet is manufactured by a continuous manufacturing process, involving (b) (4)

. The applicant uses similar Chemistry, Manufacturing, and Controls (CMC) for production of the drug product at their Boston, MA site as for their approved NDA 206038; fully continuous drug product manufacturing, process analytical technology, and real-time-release-testing (RTRT) as an alternative to regulatory end-product testing. One main difference here is the (b) (4)

. The applicant is proposing design spaces for both the drug product manufacture and the tezacaftor synthesis. The control strategy for Tezacaftor/ivacaftor consists of 4 levels of automated control, from the lowest level to highest level including unit operation control to set point, process design space monitoring, in-process controls (IPC) and release testing. Spectroscopic and non-spectroscopic PAT measurements are implemented for IPC and real time release testing (RTRT) for the following attributes: (b) (4)

. Two important points to note are that the primary stability data for the drug product supporting the application were from batches that were *not* prepared by the proposed continuous process for commercial production, but by a developmental

discontinuous process that used stand-alone equipment for unit operations and different (b) (4). Though the initial Phase III clinical supplies were manufactured using the discontinuous process, the resupplies for the pivotal clinical studies were manufactured using the continuous process with same equipment, similar line rates, and with the same sampling locations as will be used for commercial manufacture. Clinical batches were (b) (4) kg to (b) (4) kg, and the planned batch size for the initial commercial batch is (b) (4) kg. An expiry of 30 months is proposed and is granted, which is based on 18 months of real-time long-term stability data for three discontinuous batches 2015014, 2015015, and 2015016 and 12 months for three continuous manufactured batches, 2015044, 2016002, and 2016006. Following a review of the inspectional documents associated with all the facilities included in this application along with results from pre-approval inspection it was concluded that there are no significant, outstanding manufacturing or facility risks that prevent approval of this application.

Proposed Indication(s) including Intended Patient Population	“SYMDEKO is a combination of tezacaftor and ivacaftor, indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the <i>F508del</i> mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (<i>CFTR</i>) gene that is responsive to tezacaftor/ivacaftor based on <i>in vitro</i> data and/or clinical evidence. If the patient’s genotype is unknown, (b) (4) ”
Duration of Treatment	chronic
Maximum Daily Dose	100 mg tezacaftor; 300 mg ivacaftor (using single entity drug product previously approved)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

The fixed dose combination drug product of tezacaftor 100 mg/ivacaftor 150 mg is an immediate release tablet (Symdeko™) that is indicated for the treatment of patients 12 years and older with cystic fibrosis (CF). For the immediate release (IR) film coated tablet drug product, which is used in combination with the already approved ivacaftor IR tablets, the excipients are controlled per the compendial quality standards. The immediate container closure system is commonly used blister packaging for tablets. All batch analysis results met the proposed and acceptably justified specifications. The proposed dissolution methods for Tezacaftor and Ivacaftor are acceptable based on the

justification for the selected dissolution conditions provided in the method development. Up to 18 months of real-time stability data are provided for 3 registration batches and 3 supportive batches. All results remained relatively unchanged and indicate good product stability. Based on ICH Q1E, up to 12 months of shelf life can be extended. Thus the provided information supports the approval of the applicant requested product expiry of 30 months.

The applicant states that tezacaftor belongs to biopharmaceutics classification system (BCS) class II and ivacaftor belongs to BCS class II or IV. (b) (4)

(b) (4) formulation of the drug product. The crystalline forms of the drug substances are practically insoluble in aqueous media. Dissolution for both components is critical quality attributes (CQAs) of the proposed drug product. The biopharmaceutics assessment focused on the evaluation of: 1) the dissolution method and acceptance criterion for tezacaftor and ivacaftor FDC tablets; 2) the bridging between the tezacaftor and ivacaftor FDC to-be-marked formulation and pivotal clinical formulation; 3) the alternative dissolution testing: real time release testing (RTRT); and 4) the role of dissolution on the establishment of the manufacturing design space for tezacaftor and ivacaftor film coated tablets.

To prepare the (b) (4)

by a continuous manufacturing process,

The tablet is manufactured (b) (4)

Multivariate designs of experiments (DoEs) were performed on the integrated continuous manufacturing line to define the critical process parameters/material attributes and the design space. (b) (4)

(b) (4) The initial Phase III clinical supplies were manufactured using the discontinuous process. The resupplies for the pivotal clinical studies were manufactured using the continuous process with same equipment, similar line rates, and with the same sampling locations as will be used for commercial manufacture. Clinical batches were (b) (4) kg to (b) (4) kg, and the planned batch size for the initial commercial batch is (b) (4) kg. Process performance qualification has been carried out at the (b) (4) kg scale. The proposed maximum commercial batch size is (b) (4) kg. While clinical and commercial batch sizes vary, the continuous process is essentially scale-independent since batch size is not related to equipment scale. In addition, adequate process analytical technology (PAT) is in place to aid in process control. Though the (b) (4), there are some potential risks to (b) (4) what is currently demonstrated. Vertex has

agreed to the agency's recommendation that the approach used for increasing batch size would include a qualification protocol with an appropriate risk assessment managed by their internal Pharmaceutical Quality System. As part of the continuous process verification approach, Vertex proposes to [REDACTED] (b) (4)

The manufacturing process control strategy for Tezacaftor/ivacaftor consists of 4 levels of automated control, from the lowest level to highest level including unit operation control to set point, process design space monitoring, in-process controls (IPC) and release testing. Spectroscopic and non-spectroscopic PAT measurements are implemented for IPC and real-time-release testing (RTRT). The following PAT analytical procedures used for testing Tezacaftor/ivacaftor tablets 100/150 mg and their method validations were evaluated: [REDACTED] (b) (4)

[REDACTED] The actually sampling size is less than the target sampling size defined by the target sampling rate. RTRT approaches for identification, assay, and content uniformity were evaluated including proposed minimum sample size and method verification. Pre-approval inspection took place from 8/28/2017-9/1/2017, and 9/6/2017-9/7/2017. The requested documents related to PAT and RTRT were reviewed and were found to be adequate.

Following a review of the application, inspectional documents, and pre-approval results, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 210491 are found to be acceptable.

Overall, the Office of Pharmaceutical Quality recommends that this application be approved, from the quality perspective.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)



CHAPTER I: Drug Substance

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BIOPHARMACEUTICS

NDA: 210491

Submission Type: 505(b)1

Drug Product Name/Strength: Symdeko™ (tezacaftor/ivacaftor 100 mg/150 mg tablets and ivacaftor 150 mg tablets)

Route of Administration: Oral

Applicant Name: Vertex Pharmaceuticals Inc.

Submission:

Vertex Pharmaceuticals Incorporated is submitting a NDA for Symdeko™ (TEZ/IVA) combination therapy for the treatment of cystic fibrosis (CF). 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. TEZ/IVA was granted Breakthrough Therapy Designation by the FDA on 28 January 2014 and Orphan Drug Designation (Designation No. 17-5775) on 15 June 2017.

TEZ/IVA is a new CFTR modulator therapy containing a combination of TEZ and IVA, which act by complementary mechanisms to enhance chloride transport. It is dosed orally as follows:

- Morning dose: 1 fixed-dose combination (FDC) tablet containing 100 mg TEZ and 150 mg IVA, supplied as a yellow, film-coated tablet
- Evening dose: 1 tablet containing 150 mg IVA, supplied as a blue, film-coated tablet

Review Summary: ADEQUATE

Tezacaftor/Ivacaftor drug product is an immediate-release film coated tablet used in combination with ivacaftor immediate release tablet for the treatment of cystic fibrosis. The IR film coated tablet is a fixed dose combination (FDC) of the active pharmaceutical ingredients (APIs) tezacaftor and ivacaftor. The tezacaftor/ivacaftor FDC tablet contains 100 mg of tezacaftor and 150 mg of ivacaftor. Per the Applicant, tezacaftor belongs to BCS class II and ivacaftor belongs to BCS class II or IV. (b) (4) both tezacaftor and ivacaftor drug substances are

(b) (4) for drug product formulation. Dissolution for both components are critical quality attributes (CQAs) of the proposed drug product.

The biopharmaceutics assessment focuses on the evaluation of: 1) the dissolution method and acceptance criterion for tezacaftor and ivacaftor FDC tablets; 2) the bridging between the tezacaftor and ivacaftor FDC to-be-marked formulation and pivotal clinical formulation; 3) the

alternative dissolution testing: real time release testing (RTRT); and 4) the role of dissolution on the establishment of the manufacturing design space for tezacaftor and ivacaftor film coated tablets.

Please refer to NDA 203188 for the biopharmaceutics assessment of Ivacaftor Tablets, 150 mg¹.

1) Dissolution Method and Acceptance Criteria

The proposed dissolution methods for tezacaftor and ivacaftor are acceptable for quality control based on adequate justification for the selected dissolution conditions provided in the method development report. The agreed upon dissolution acceptance criteria for tezacaftor and ivacaftor were based on: (1) dissolution data from individual product keys (PK) of three pivotal clinical batches; (2) stability data for both APIs in tezacaftor and ivacaftor tablets; (3) tablet-to-tablet variability from individual PKs of clinical batches; and (4) risk-based assessment on dissolution performance related to (b) (4) content and (b) (4) particle size. The approved dissolution methods and acceptance criteria shown in **Table 1** below.

Table 1. Dissolution Method and Acceptance Criteria for (tezacaftor 100 mg/ivacaftor 150 mg) FDC tablet

API	USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
Tezacaftor	USP II (Paddle)	75 rpm	900 mL	37°C	0.2% SLS (w/v) in 0.1 N hydrochloric acid	NLT (b) (4)% (Q) of the label claim of Tezacaftor is dissolved in 20 minutes
Ivacaftor	USP II (Paddle)	65 rpm	900 mL	37°C	0.4% SLS (w/v) in 50 mM sodium phosphate buffer (pH 6.8)	NLT (b) (4)% (Q) of the label claim of Ivacaftor is dissolved in 30 minutes

2) Alternative dissolution testing: Real Time Release Testing (RTRT)

The RTRT dissolution method is based on a partial least square (PLS) model developed with measured in-process material attributes assessed by process analytical technology (PAT) implemented in the continuous manufacturing (CM), for the calculation of the dissolution rate (z) to predict a dissolution profile using a modified Noyes-Whitney equation. The Tezacaftor/Ivacaftor PLS dissolution rate model uses (b) (4)

(b) (4)

¹ <http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af8025f5d2>

measured in-process material attributes were selected as model inputs based on knowledge of the process and factors influencing dissolution performance. The PLS models are calibrated using the reference dissolution methods (b) (4) spanning the process design space and desired manufacturing range with various drug substance, (b) (4) and excipient lots. Based on the verification results obtained during clinical testing on the (b) (4) across the desired manufacturing range for 19 integrated continuous QbD runs and 3 QbD confirmation runs, the RTRT dissolution results are consistent with those obtained from the regulatory dissolution methods with no more than 5% of absolute difference, indicating prediction accuracy of the RTRT method to characterize the dissolution performance.

For batch release, RTRT measurement of 12 segments stratified for each batch to assure that the results comply with USP <711> stage 2 criteria. The Applicant also commits to initiate a root cause investigation in the event of: (1) a dissolution prediction failing PLS model's diagnostic criteria and (2) RTRT model predicted dissolution results that do not conform to the specification.

Overall, the proposed RTRT method is acceptable as an alternative dissolution testing for batch release during continuous manufacturing for the TEZ/IVA FDC tablet.

3) The role of dissolution on the establishment of the design space for tezacaftor and ivacaftor film coated tablets (QbD)

Within the design space of critical material parameters, e.g., (b) (4), and critical process parameters, e.g. (b) (4), the dissolution process model predicted that tezacaftor and ivacaftor dissolution fall within an acceptable range and meet the set dissolution criteria.

4) Bridging between the TEZ/IVA FDC to-be-marked formulation and clinical formulation

Based on dissolution profile comparison, the to-be-marketed (TBM) formulation (produced by continuous process) and the pivotal phase III clinical formulation (produced by both discontinuous and continuous processes) showed similarity. The TBM product with deboss and the pivotal clinical batches without deboss also showed dissolution profile similarity. Therefore, the TBM formulation and clinical formulations are adequately bridged.

Concise Description Outstanding Issues Remaining: None

NDA210491 Symdeko™ (Tezacaftor/Ivacaftor Tablets (tezacaftor/ivacaftor 100 mg/150 mg tablets and ivacaftor 150 mg tablets) is recommended for APPROVAL from a biopharmaceutics perspective.

List Submissions being reviewed (table):

Submitted data	Description	Submission Date
Module 3.2.P.2 Pharmaceutical Developments	Dissolution method development part	06/28/2017
Module 3.2.P.5 Control of Drug Product	Specification Batch Analysis	06/28/2017
Module 1.11 Information Amendment: Information Not Covered Under Modules 2 to 5	Response to Request for CMC Information Received 21 August 2017	09/05/2017
	Response to Information Request dated 18 October 2017	11/03/2017
	Response to Request for CMC Information Request 3 Dated 21 November 2017	12/01/2017

1. BCS Designation

As reported by the applicant, tezacaftor, drug substance, belongs to BCS class II and ivacaftor, drug substance, belongs to BCS class II or IV. This submission does not contain a request for biowaiver based on BCS classification.

Solubility

Tezacaftor

The kinetic solubility of (b) (4) tezacaftor (b) (4) at 24 hours in water at various pH levels is shown in **Table 2**:

Table 2. Solubility of (b) (4) tezacaftor (b) (4) at 24 hours in water at various pH levels ^a

Buffer/pH	Tezacaftor (b) (4) Solubility at 24 hours (mg/mL)
0.1N HCl (~ pH 1.5)	0.077
pH 4.5 (sodium acetate buffer)	0.079
pH 6.8 (sodium phosphate buffer)	0.090
FaSSGF	0.093
FeSSGF	0.38
FaSSIF	0.10
FeSSIF	3.4

^a Solubility of tezacaftor (b) (4) was measured with the presence of ivacaftor (b) (4) in the ratio of 2:3, with a starting concentration of 5 mg/mL tezacaftor (b) (4) and 7.5 mg/mL ivacaftor (b) (4)

Ivacaftor

Reference is made to NDA 203188 Section 3.2.P.2.3 for key physicochemical characteristics of ivacaftor. Ivacaftor belongs to BCS class II or IV. However, its low solubility and non-specific binding to culture materials precluded an acceptable determination of its permeability using the Caco-2 cell system. Therefore, it could not be classified definitively (refer to Dr. John Duan’s biopharmaceutics review for NDA 206038, Orkambi™ (lumacaftor/ivacaftor) Tablets in OPQ-Final Review-1 entered into Panorama by Dr. Youbang Liu on 04/06/2015²).

Permeability

Experimental permeability data were not provided in the submission.

Reviewer’s Assessment:

The solubility for both APIs is low. Thus, dissolution may play an important role (e.g., rate-limiting factor for absorption) in their in vivo performance. Due to the demonstrated low solubility, the use of surfactants in the dissolution media are reasonable.

2. Drug Product Composition Information

Tezacaftor/ivacaftor drug product is an immediate-release film coated tablet for oral administration. The tablet is a fixed dose combination (FDC) of the active ingredients tezacaftor and ivacaftor. Both tezacaftor and ivacaftor drug substances are (b) (4)

The tezacaftor/ivacaftor FDC tablet contains 100 mg of tezacaftor and 150 mg of ivacaftor. It is a yellow film-coated tablet, debossed with “V100” on one face.

The composition of the tezacaftor/ivacaftor FDC tablet, which consists of the core tablet and film coat, is provided in **Table 3**.

Table 3. Composition of Tezacaftor/Ivacaftor Fixed Dose Combination Tablet

Component	Quality Standard	Component Function	Amount per tablet	Content (% w/w)
Core Tablet				
(b) (4)				
Ivacaftor (b) (4) ^a				
Ivacaftor drug substance	Internal standard	Active ingredient	150.00	24.61
(b) (4)				

² <http://panorama.fda.gov/project/view?ID=545b073c0005bb6abedbaa8db8152c3d>

(b) (4)

Tezacaftor ^b (b) (4)

Tezacaftor drug substance	Internal standard	Active ingredient	100.00	16.40

(b) (4)

Core Tablet Total

(b) (4)

Film Coat ^c

(b) (4)

Total Tablet Weight

609.59 100

a

b

c

d

(b) (4) contains: HPMC/Hypromellose 2910 (USP/NF/Ph.Eur.), Hydroxypropyl cellulose (USP/NF/Ph.Eur.), Titanium Dioxide (USP/NF/Ph.Eur.), Talc (USP/NF/Ph.Eur.), and Iron oxide yellow (USP/NF)

(b) (4)

Reviewer’s Assessment:

The tezacaftor/ivacaftor FDC tablet contains 100 mg of tezacaftor and 150 mg of ivacaftor. The to-be-marked formulation is a yellow film-coated tablet, debossed with “V100” on one face. The formulation used for clinical batches (e.g. batch 2016051) is without deboss. Therefore, the Applicant was asked to provide dissolution profile comparison data between the debossed product (if available) and the clinical batches without deboss (details refer to Section 7, Bridging of Formulations).

3. Dissolution Method and Acceptance Criteria

The proposed dissolution specification proposed for Tezacaftor/Ivacaftor FDC Tablet is shown in **Table 4** (refer to Table 8 and Table 11 in Module 3.2.P.2 Pharmaceutical Development)

Table 4. Proposed In Vitro Dissolution Testing Method

API	USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Proposed Acceptance Criterion
Tezacaftor	II(Paddle)	75 rpm	900 mL	37°C	0.2% SLS (w/v) in 0.1 N hydrochloric acid	NLT ^(b) ₍₄₎ % (Q) of the label claim of Tezacaftor is dissolved in 20 minutes
Ivacaftor	II(Paddle)	65 rpm	900 mL	37°C	0.4% SLS (w/v) in 50 mM sodium phosphate buffer (pH 6.8)	NLT ^(b) ₍₄₎ % (Q) of the label claim of Ivacaftor is dissolved in 30 minutes

3.1 Dissolution method

3.1.1 Tezacaftor:

3.1.1.1 What data are provided to support the adequacy of the proposed dissolution method (e.g., medium, apparatus selection, etc.)?

During the dissolution method development process for Tezacaftor, multiple parameters were selected. These parameters included a solubility enhancer (i.e., surfactant), buffer type and paddle speed, which were used in combination to develop the dissolution method. The selection of the dissolution apparatus II (paddle) is standard for the tablet solid oral dosage form.

(1) Selection of Dissolution Medium and Surfactant

(b) (4)

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(b) (4)

3.1.1.2 What data are available to support the discriminating power of the dissolution method for Tezacaftor?

According to the Applicant, the proposed dissolution method for Tezacaftor has discriminating ability for (b) (4) particle size, tablet hardness, and tablet (b) (4) as shown in **Figure 5** to **Figure 7**. The discriminatory capability of the method was not evident for Tezacaftor (b) (4) (b) (4), Tezacaftor (b) (4) and particle size, Ivacaftor (b) (4) and particle size, (b) (4) (b) (4) (Data not shown, refer to Figure 7, 8, 9 and Figure 10 in Module 3.2.P.2 Pharmaceutical Development).

(b) (4) Particle Size

Figure 5. Dissolution of Tezacaftor from 100 mg Tezacaftor/ 150 mg Ivacaftor FDC Tablets Made with Different (b) (4) Particle Sizes from (b) (4), Using Proposed Dissolution Method for Tezacaftor (n=6)

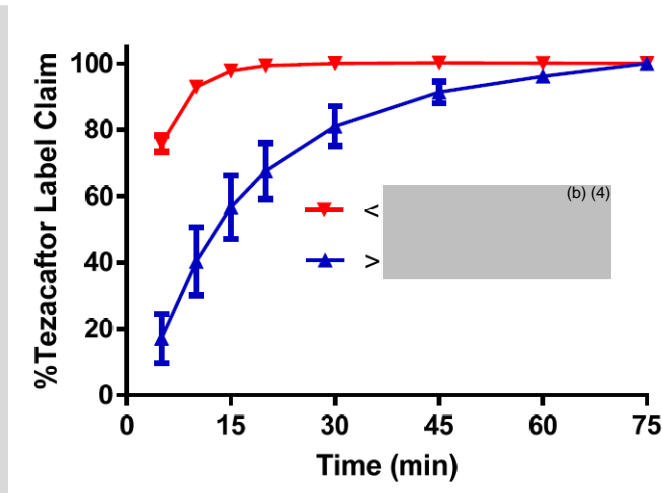


Figure 6. Dissolution of Tezacaftor from 100 mg Tezacaftor/ 150 mg Ivacaftor FDC Tablets Made with Different Tablet Hardness Using Proposed Dissolution Method for Tezacaftor (n=6)

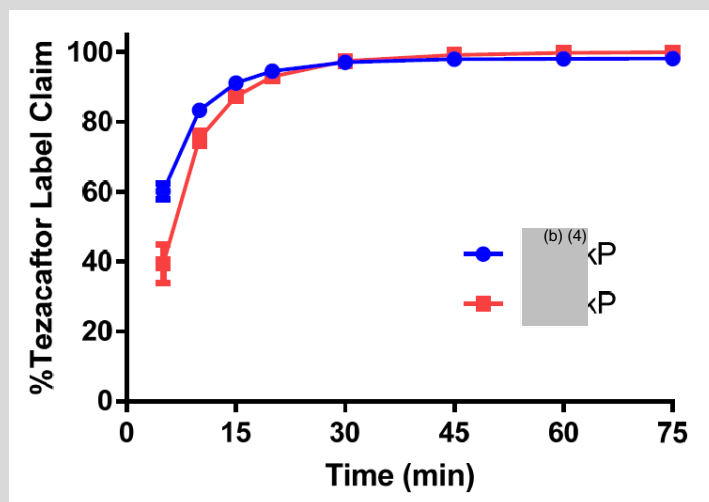
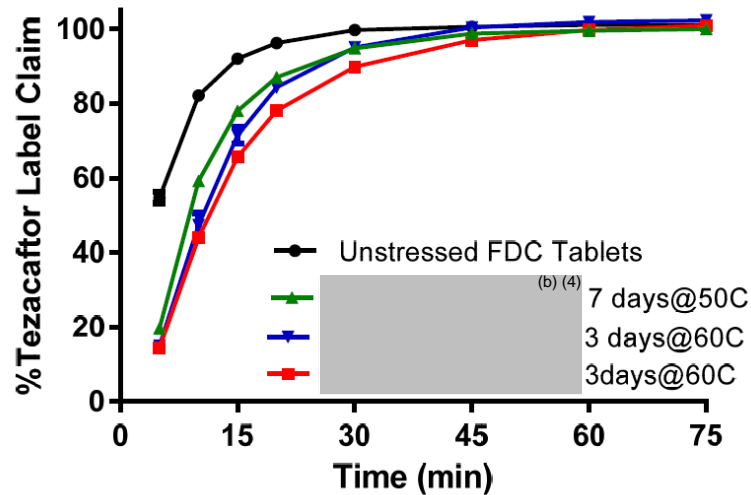


Figure 7. Effect of (b) (4) on Tezacaftor Dissolution from 100 mg Tezacaftor /150 mg Ivacaftor FDC Tablets Stressed Under Extreme Conditions Using Proposed Dissolution Method for Tezacaftor (n=3)



Reviewer’s Assessment:

The proposed dissolution method for Tezacaftor has discriminating ability for (b) (4) particle size and tablet (b) (4).

- Figure 5 showed that the dissolution method is discriminating to changes in the particle size of the (b) (4) for the tested range (<(b) (4) μm and >(b) (4) μNm; particle size range determined based on (b) (4)). With the increase of (b) (4) particle size, the dissolution rate is slowing down.
- Figure 6 showed that there is a trend of dissolution slowing down with increased tablet hardness. However, the dissolution profiles are overlaying each other indicating that the dissolution method is not discriminating to changes of tablet hardness from (b) (4) kP to (b) (4) kP.
- Figure 7 showed that tablets containing (b) (4) and stressed under high temperatures (≥ 50°C) show dissolution slow-down over time. However, as indicated by the Applicant, the (b) (4) and temperatures studied in this experiment represent extreme conditions to challenge the method, at intended storage conditions even at equilibrium (b) (4) no significant change to dissolution is expected on stability.
- Lack of discriminating ability for Tezacaftor (b) (4) content (e.g.(b) (4)%) in the formulation was observed for this method (e.g., the tablets with (b) (4) had a slightly slower release profile than the (b) (4) tablets, while the f2 calculation shows both profiles are similar (f2 = 62, refer to Module 3.2.P.2.2 Drug Product-formulation development). However, (b) (4) was implemented for both Tezacaftor (b) (4) and final FDC product specification using (b) (4) method to detect (b) (4) The specification regarding (b) (4) would mitigate the risk of undesired dissolution due to the presence of (b) (4) in the final product.

3.1.1.3 Is the proposed dissolution/release method clinically relevant? What data including but not limited to IVIVC are available to support this claim?

There is no data submitted in this NDA for assessing the clinical relevance of the proposed dissolution/release method.

3.1.1.4 Overall assessment on dissolution method: ADEQUATE

The selection of the dissolution testing condition for Tezacaftor is adequately justified based on method development information. The proposed dissolution method for Tezacaftor provides limited discriminating ability towards (b) (4) particle size and (b) (4). Overall, the selected dissolution method for Tezacaftor is acceptable for quality control purpose of the proposed drug product.

3.1.2 Ivacaftor:

3.1.2.1 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

As the FDC tablets contains the same (b) (4) ivacaftor (b) (4) as Kalydeco® (ivacaftor) oral granules, the selection of surfactant, buffer type, pH and paddle speed is based on the Kalydeco® (ivacaftor) granules dissolution method as described in NDA 207925 Submission. Also, refer to biopharmaceutics review for NDA207925 by Dr. Karen Riviere³.

3.1.2.2 What data are available to support the discriminating power of the dissolution method for Ivacaftor?

According to the Applicant, the proposed dissolution method for Ivacaftor has discriminating ability for ivacaftor (b) (4) (b) (4) particle size, tablet hardness, tablet (b) (4) as shown in **Figure 8** to **Figure 11**, but not for Ivacaftor (b) (4) and Particle Size, Tezacaftor (b) (4) and Particle Size, (b) (4) (Data not shown, refer to Figure 16, Figure 17, and Figure 18 in Module 3.2.P.2 Pharmaceutical Development).

Ivacaftor (b) (4)

Figure 8. Dissolution of Ivacaftor from 100 mg Tezacaftor/ 150 mg Ivacaftor FDC Tablets (b) (4), in pH 6.8 Sodium Phosphate Buffer, 0.4% (w/v) SLS using USP Apparatus 2 (n=12)

³ file:///C:/Users/WUF/Downloads/NDA%20207925%20Biopharmaceutics%20Review.pdf

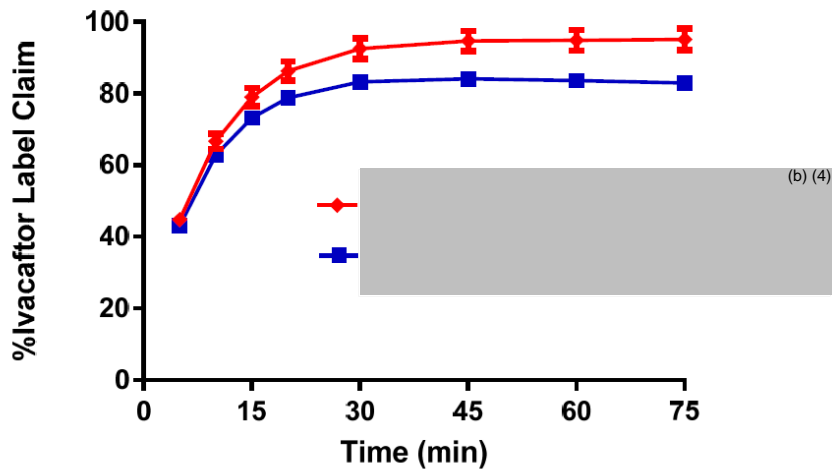


Figure 9. Dissolution of Ivacaftor from 100 mg Tezacaftor/ 150 mg Ivacaftor FDC Tablets Made with Different (b) (4) Particle Sizes from (b) (4), in pH 6.8 Sodium Phosphate Buffer, 0.4% (w/v) SLS using USP Apparatus 2 (n=6)

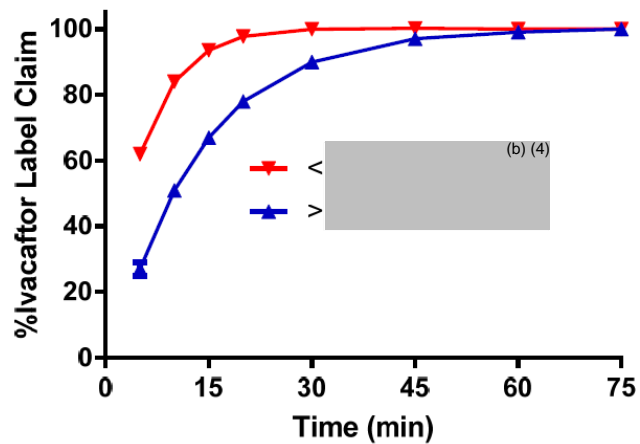


Figure 10. Dissolution of Ivacaftor from 100 mg Tezacaftor/ 150 mg Ivacaftor FDC Tablets Made with Different Tablet Hardness, in pH 6.8 Sodium Phosphate Buffer, 0.4% (w/v) SLS using USP Apparatus 2 (n=6)

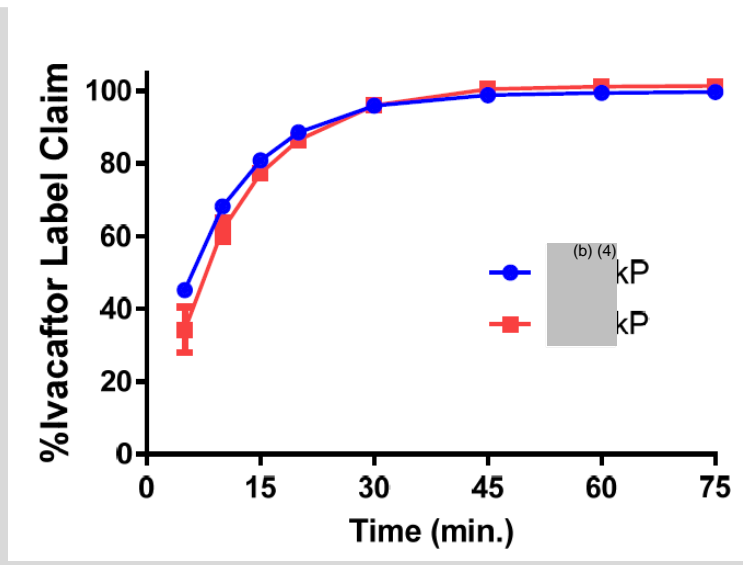
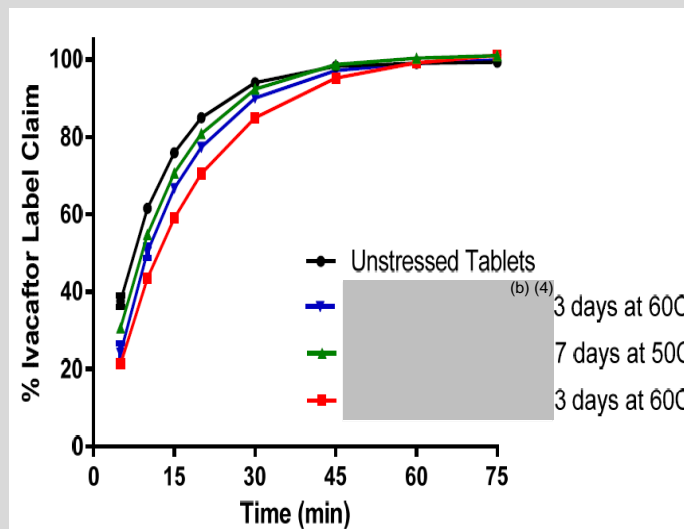


Figure 11. Dissolution of Ivacaftor from 100 mg Tezacaftor/ 150 mg Ivacaftor FDC Tablets Stressed Under Extreme Conditions, in pH 6.8 Sodium Phosphate Buffer, 0.4% (w/v) SLS using USP Apparatus 2 (n=3)



Reviewer’s Assessment:

The proposed dissolution method for Ivacaftor has limited discriminating ability for Ivacaftor (b) (4), (b) (4) Particle Size, Tablet (b) (4).

- Figure 8 showed that ivacaftor dissolution method is discriminative to (b) (4) in ivacaftor (b) (4). With (b) (4) (b) (4), the dissolution rate slowed down. While with the proposed dissolution acceptance criterion “Q (b) (4) % in 30 min” for Ivacaftor, the batch with (b) (4) (b) (4) most likely cannot be rejected. However, it is noted that the content of (b) (4) in (b) (4) in

the Ivacaftor (b) (4) and final FDC product was controlled with a specification (b) (4) detected by performing (b) (4), which mitigates the risk of undesirable dissolution due to the presence of (b) (4).

- Figure 9 showed that the dissolution method is discriminating to changes in the particle size of the (b) (4) for the tested range (<(b) (4) μm and >(b) (4) μm; particle size range determined based on (b) (4)). With the increase of (b) (4) particle size, the dissolution rate is slowing down.
- Figure 10 showed that there is a trend of dissolution slowing down with increased tablet hardness, however, the dissolution profiles are overlaying each other indicating that the dissolution method is not discriminating to changes of tablet hardness from (b) (4) kP to (b) (4) kP.
- Figure 11 showed that tablets containing (b) (4) and stressed under high temperatures (≥ 50°C) show dissolution slow-down over time. However, as indicated by the Applicant, the (b) (4) temperatures studied in this experiment represent extreme conditions to challenge the method. At intended storage conditions even at equilibrium (b) (4) no significant change to dissolution is expected on stability when packaged in proposed configurations.

3.1.2.3 Is the proposed dissolution/release method clinically relevant? What data including but not limited to IVIVC are available to support this claim?

There is no data submitted in this NDA for assessing the clinical relevance of the proposed dissolution/release method.

3.1.2.4 Overall assessment on dissolution method for Ivacaftor: ADEQUATE

Reviewer’s Assessment:

The selection of the dissolution testing condition for Ivacaftor is adequately justified based on method development information provided in NDA 207925⁴. This method also provides limited discriminating ability towards (b) (4) content, (b) (4) particle size and (b) (4). Overall, the selected dissolution method for Ivacaftor is acceptable for quality control purpose of the proposed drug product.

3.2. Dissolution Acceptance Criterion

The proposed dissolution acceptance criteria for Tezacaftor and Ivacaftor are shown in **Table 6**.

Table 6. The proposed dissolution acceptance criteria for 100 mg Tezacaftor/ 150 mg Ivacaftor FDC Tablets

Amount of Tezacaftor Dissolved	Amount of Ivacaftor Dissolved
NLT (b) (4)% (Q) at 20 minutes	NLT (b) (4)% (Q) at 30 minutes

⁴ file:///C:/Users/WUF/Downloads/NDA%20207925%20Biopharmaceutics%20Review.pdf

3.2.1 What are the dissolution data of the biobatches used in the pivotal clinical trial?

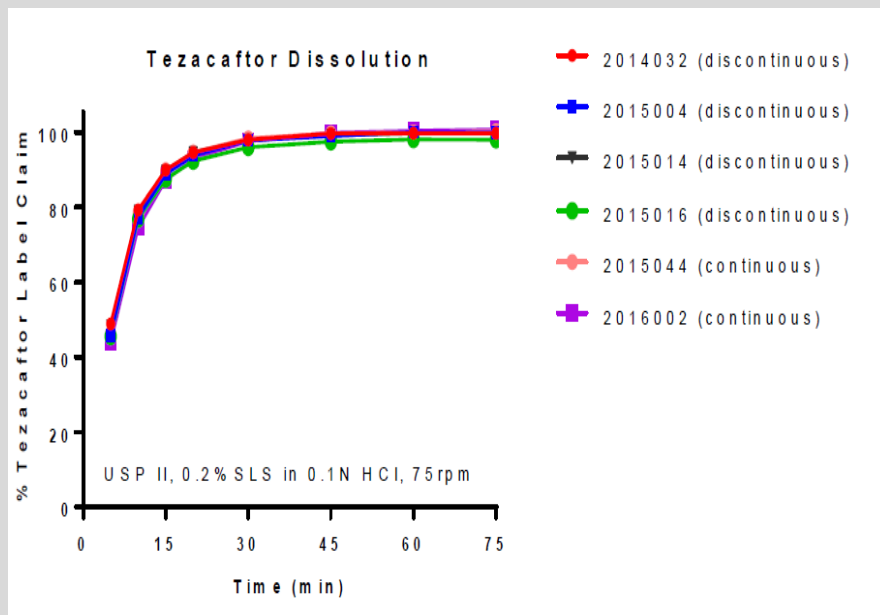
To obtain the dissolution data for biobatches used in the pivotal clinical trials, the following IR was communicated to the Applicant on 08/21/2017.

“Provide complete dissolution profile data (individual, mean, range, relative standard deviation or CV% of the data and graphical profiles) for all the bio-batches used in the pivotal phase 3 clinical trials.”

Applicant’s responses dated 09/05/2017

Dissolution profile data for the tezacaftor/ivacaftor FDC tablets batches used in pivotal phase 3 clinical trials VX14-661-106 and VX14-661-108 (Lots 2014032, 2015004, 2015014, 2015016, 2015044, and 2016002) are provided in **Figure 12** for Tezacaftor and **Figure 13** for Ivacaftor.

Figure 12. Tezacaftor dissolution profile data for the tezacaftor/ivacaftor FDC tablets batches used in pivotal phase 3 clinical trials VX14-661-106 and VX14-661-108



The individual dissolution data of batches 2105044 and 2016002 are shown in **Table 7** and **Table 8**.

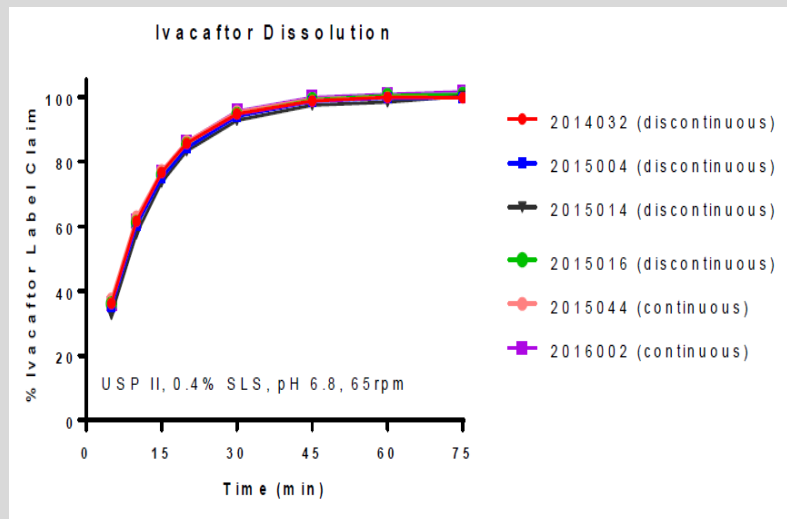
Table 7. Tezacaftor % label claim dissolved, Batch 2015044 (by continuous manufacturing)

Time (min.)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Vessel 7	Vessel 8	Vessel 9	Vessel 10	Vessel 11	Vessel 12	Mean	Range	%RSD
5	(b) (4)												46	(b) (4)	12.2
10	(b) (4)												79	(b) (4)	1.6
15	(b) (4)												90	(b) (4)	1.2
20	(b) (4)												95	(b) (4)	1.6
30	(b) (4)												98	(b) (4)	2.0
45	(b) (4)												100	(b) (4)	2.1
60	(b) (4)												100	(b) (4)	2.2
75	(b) (4)												100	(b) (4)	2.2

Table 8. Tezacaftor % label claim dissolved, Batch 2016002 (by continuous manufacturing)

Time (min.)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Vessel 7	Vessel 8	Vessel 9	Vessel 10	Vessel 11	Vessel 12	Mean	Min.	%RSD
5	(b) (4)												39	(b) (4)	26.3
10	(b) (4)												75	(b) (4)	4.6
15	(b) (4)												87	(b) (4)	1.6
20	(b) (4)												93	(b) (4)	1.3
30	(b) (4)												98	(b) (4)	1.8
45	(b) (4)												100	(b) (4)	2.2
60	(b) (4)												100	(b) (4)	2.3
75	(b) (4)												101	(b) (4)	2.5

Figure 13. Ivacaftor dissolution profile data for the tezacaftor/ivacaftor FDC tablets batches used in pivotal phase 3 clinical trials VX14-661-106 and VX14-661- 108



The individual dissolution data of batches 2105044 and 2016002 are shown in **Table 9** and **Table 10**.

Table 9. Ivacaftor % label claim dissolved, Batch 2015044 (by continuous manufacturing)

Time (min.)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Vessel 7	Vessel 8	Vessel 9	Vessel 10	Vessel 11	Vessel 12	Mean	Range	%RSD
5	(b) (4)												37	(b) (4)	3.7
10	(b) (4)												63	(b) (4)	1.8
15	(b) (4)												77	(b) (4)	1.8
20	(b) (4)												86	(b) (4)	2.0
30	(b) (4)												95	(b) (4)	2.4
45	(b) (4)												99	(b) (4)	2.7
60	(b) (4)												100	(b) (4)	2.6
75	(b) (4)												101	(b) (4)	2.6

Table 10. Ivacaftor % label claim dissolved, Batch 2016002 (by continuous manufacturing)

Time (min.)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Vessel 7	Vessel 8	Vessel 9	Vessel 10	Vessel 11	Vessel 12	Mean	Range	%RSD
5	(b) (4)												36	(b) (4)	6.3
10	(b) (4)												62	(b) (4)	2.4
15	(b) (4)												77	(b) (4)	1.6
20	(b) (4)												86	(b) (4)	1.7
30	(b) (4)												96	(b) (4)	2.0
45	(b) (4)												100	(b) (4)	2.4
60	(b) (4)												101	(b) (4)	2.4
75	(b) (4)												101	(b) (4)	2.2

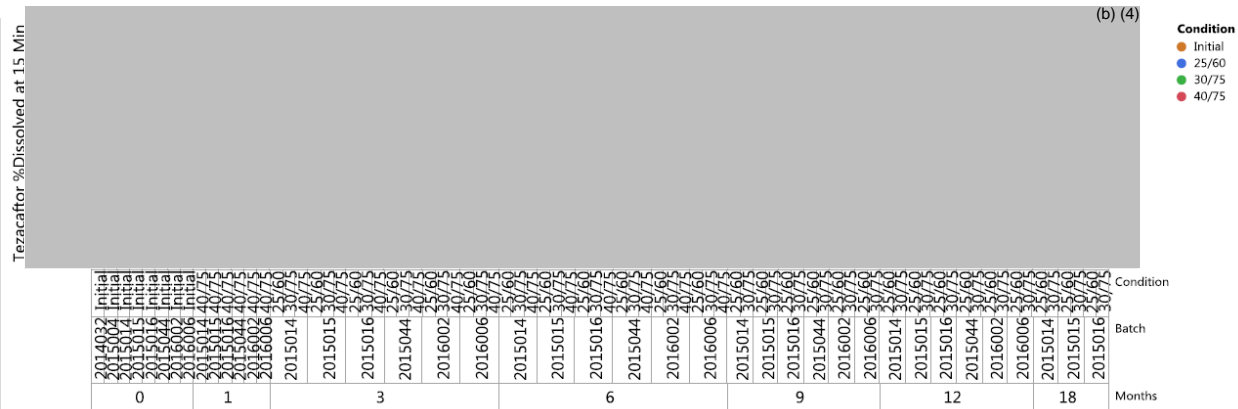
Reviewer’s Assessment: Based on the dissolution data shown in **Table 7** to **Table 10** for biobatches (batch #2015044 and #2016002), the proposed dissolution acceptance criteria of “NLT (b) (4) % (Q) of the labeled amount of tezacaftor dissolved in 20 minutes and NLT (b) (4) % (Q) of the labeled amount of ivacaftor dissolved in 30 minutes” is permissive for the proposed drug product. Therefore, the following data-driven dissolution acceptance criterion is recommended: “NLT (b) (4) % (Q) of the labeled amount of tezacaftor dissolved in 15 minutes and NLT (b) (4) % (Q) of the labeled amount of Ivacaftor dissolved in 20 minutes”. The IR comment⁵ was communicated to the Applicant in the Information Request IR#2 dated 10/17/2017.

Summary of the Applicant’s responses dated 11/3/2017:

- The tezacaftor release and stability dissolution results at 15 minutes are shown in **Figure 14**.

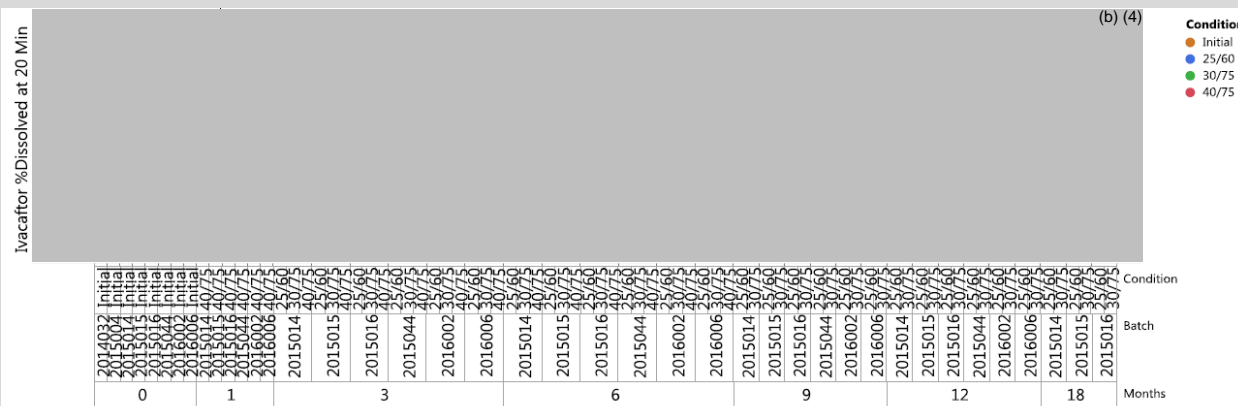
Figure 14. 100 mg Tezacaftor / 150 mg Ivacaftor FDC Tablets, Tezacaftor 15 minutes Dissolution Release and Stability Results

⁵ A complete list of Information Requests (IRs) is provided in the Appendix of this review.



- The ivacaftor release and stability dissolution results at 20 minutes are shown in **Figure 15**.

Figure 15. 100 mg Tezacaftor / 150 mg Ivacaftor FDC Tablets, Ivacaftor 20 minutes Dissolution Release and Stability Results



- Monte Carlo evaluation of the probability of failing the Stage 1 (S1) acceptance criteria, as defined in USP <711>, was performed by the Applicant using the dissolution results at release for all pivotal clinical batches and the dissolution results on stability for all storage conditions for primary and supportive stability lots. The Monte Carlo analysis results are summarized in **Table 11** for both ivacaftor and tezacaftor. The Applicant used all available stability data for the Monte Carlo evaluations to ensure a more accurate assessment of the variability.

Table 11. Monte Carlo Evaluation of Probability of Failing USP <711> Stage 1 for Pivotal Clinical and Stability Batches^a

API	Q ^{(b) (4)} Acceptance Criteria (minutes)	Mean %LC Dissolved	Probability (%) of Failing USP <711> S ₁
Tezacaftor	15	88	28
	20	94	0
Ivacaftor	20	85	94
	30	95	4

^a Based on 100,000 repetitions

According to the Applicant, the Monte Carlo analysis indicates that tightening the dissolution acceptance criterion to NLT ^{(b) (4)}% (Q) of the label claim dissolved in 15 minutes for tezacaftor and NLT ^{(b) (4)}% (Q) of the label claim dissolved in 20 minutes for ivacaftor is not appropriate as the acceptance limit of Tezacaftor would require Stage 2 (S2) testing for 28% of release or stability samples and the acceptance limit Ivacaftor would require Stage 2 (S2) testing for 94% of the release or stability samples. Therefore, the proposed dissolution specification of NLT ^{(b) (4)}% (Q) of the labeled claim of tezacaftor dissolved in 20 minutes and ivacaftor dissolved in 30 minutes is appropriate.

- Further evaluation of the clinical batches manufactured by CM process was performed by Monte Carlo simulation to assess the probability of failing the USP <711> acceptance criteria. For this analysis Vertex tested one tablet per active run for each PK (about ^{(b) (4)}) throughout the batch. The tezacaftor per PK dissolution results at 15 minutes and 20 minutes are shown in **Figure 16**. The ivacaftor per PK dissolution results at 20 minutes and 30 minutes are shown in **Figure 17**. The results of the Monte Carlo evaluation are summarized in **Table 12** and **Table 13** for tezacaftor and ivacaftor, respectively.

Figure 16. 100 mg Tezacaftor / 150 mg Ivacaftor FDC Tablets, Tezacaftor (VX-661) 15 minutes and 20 minutes Per PK Dissolution Results

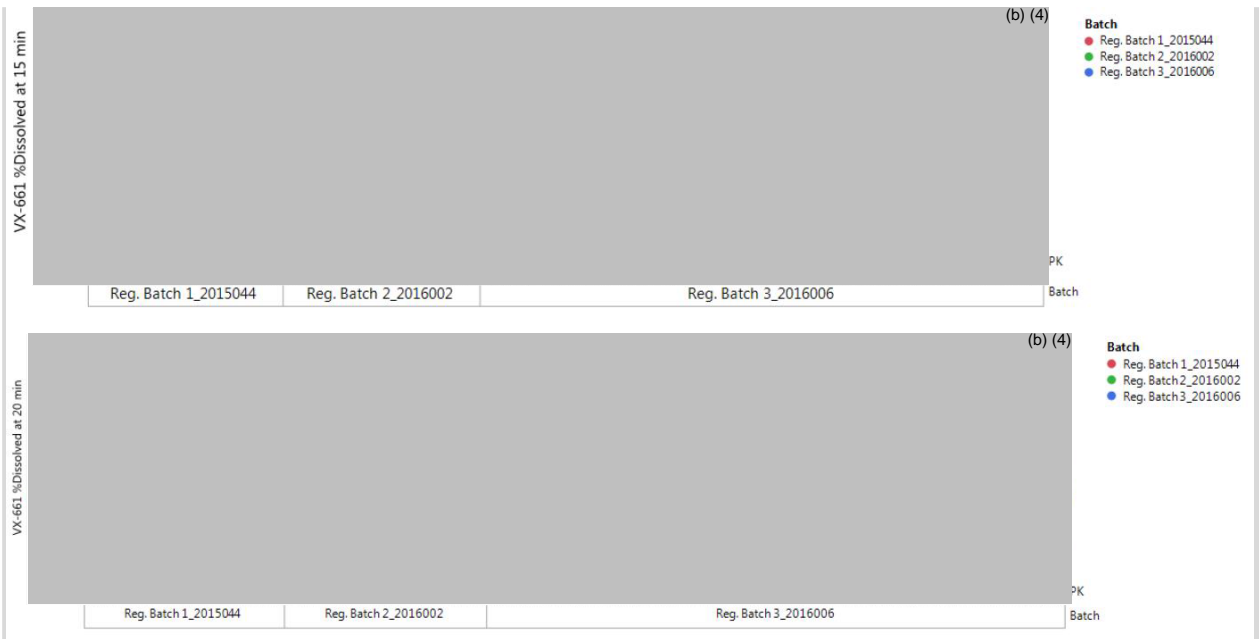


Figure 17. 100 mg Tezacaftor / 150 mg Ivacaftor FDC Tablets, Ivacaftor (VX-770) 20 minutes and 30 minutes Per PK Dissolution Results



Table 12. Monte Carlo Evaluation of Probability of Failing USP <711> Criteria for Tezacaftor for Continuously Manufactured Clinical Batches^a

Batch	Q ^{(b) (4)} Acceptance Criteria (minutes)	Probability (%) of Failing USP <711> S ₁	Probability (%) of Failing USP <711> S ₂	Probability (%) of Failing USP <711> S ₃
2015044	15	97	0	0
	20	0	0	0
2016002	15	100	51	52
	20	61	0	0
2016006	15	100	0	0
	20	18	0	0

^a Using per PK dissolution results at time of manufacture based on 10,000 repetitions

Table 13. Monte Carlo Evaluation of Probability of Failing USP <711> Criteria for Ivacaftor for Continuously Manufactured Clinical Batches^a

Batch	Q ^{(b) (4)} Acceptance Criteria (minutes)	Probability (%) of Failing USP <711> S ₁	Probability (%) of Failing USP <711> S ₂	Probability (%) of Failing USP <711> S ₃
2015044	20	44	0	0
	30	0	0	0
2016002	20	82	0	0
	30	0	0	0
2016006	20	72	0	0
	30	0	0	0

^a Using per PK dissolution results at time of manufacture based on 10,000 repetitions

According to the Applicant, tightening the acceptance criteria to 15 minutes for tezacaftor and 20 minutes for ivacaftor would reduce the effectiveness of trending S₂ occurrence due to the high probability for S₂ testing as summarized above. Therefore, the dissolution acceptance criteria of NLT ^{(b) (4)}% (Q) of the label claim dissolved in 20 minutes for tezacaftor and NLT ^{(b) (4)}% (Q) of the label claim dissolved in 30 minutes for ivacaftor are more appropriate for continual improvement and life cycle management.

Reviewer's Assessment:

- To support the proposed acceptance criterion, the Applicant provided dissolution data from all pivotal clinical batches and exhibit batches at release and stability testing as well as individual PKs for three exhibit/clinical batches (batch # 2015044, 2016002 and 2016006). The data showed that mean dissolution ^{(b) (4)}% at 15 minutes for Tezacaftor and mean dissolution ^{(b) (4)}% at 20 minutes for Ivacaftor for all the studied release and stability batches up to 18-month long term stability (**Figure 14** and **Figure 15**).
- It is noted that the dissolution data of Tezacaftor from individual PK (**Figure 16**) of the three exhibit batches shows variations at 15 mins that might lead to a high rate of Stage 2 testing

with the recommended dissolution acceptance criterion “Q = (b) (4) % in 15 min” for Tezacaftor. Based on the discriminating ability of the dissolution method of Tezacaftor, tightening dissolution acceptance criterion to “Q = (b) (4) % in 15 min” might not provide additional discriminating power than that proposed “Q = (b) (4) % in 20 min” towards critical material attributes (e.g., (b) (4) content, (b) (4) particle size) or process parameters (e.g., hardness) while the risk of Tezacaftor dissolution has been mitigated by controlling (b) (4) content to be absent in the final product and manufacturing design space. Overall, the proposed dissolution acceptance criterion of “Q = (b) (4) % in 20 min” for Tezacaftor is considered acceptable

- We still have concerns regarding the Applicant’s proposed dissolution acceptance criterion of “Q = (b) (4) % in 30 min” for Ivacaftor because this specification for Ivacaftor would not be able to discriminate the batches with (b) (4) particle size < (b) (4) μm and > (b) (4) μm from (b) (4).

Therefore, the comments were further conveyed to the Applicant dated 11/21/2017 to investigate the dissolution behavior of ivacaftor when (b) (4) particle size are within the design space (details refer to list of deficiencies at the end of the review):

“Provide D10, D50 and D90 of (b) (4) particle size that were observed for each of the pivotal clinical batches; and Provide the D10, D50, D90 of (b) (4) particle size range produced within the process design space and provide ivacaftor dissolution profile data (e.g. at 5, 10, 15, 20, 30, 45, 60 and 75 minutes) within the above (b) (4) particle size range”.

Summary of the Applicant’s responses dated 12/1/2017:

(b) (4) particle size (D10, D50, D90) for the pivotal clinical batches is provided in **Table 14**. Differences between the results of the (b) (4) methods are expected due to the differences in the (b) (4) techniques of the two methods. In addition, batches 2015044 and 2016002 were manufactured using (b) (4), resulting in a (b) (4) particle size range than that achieved when manufacturing within the final commercial design space (utilizing (b) (4))

Table 14. (b) (4) Particle Size (Laser Diffraction) for Batches used in Pivotal Clinical Studies

Batch	(b) (4)
2014032 ^a	
2015004 ^a	
2015014 ^a	
2015016 ^a	
2015044	
2016002	

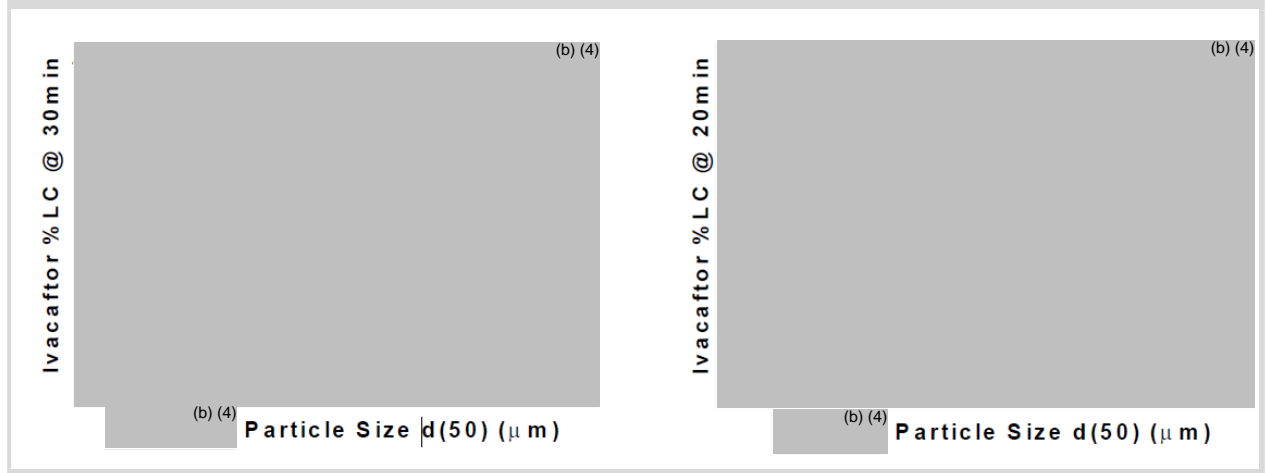
^aManufactured using discontinuous process

NA = not available

The experiments described in 3.2.P.2.2 Drug Product Formulation Development tezacaftor/Ivacaftor Tablet were performed to evaluate the discriminatory power of the dissolution methods with respect to (b) (4) particle size using two segregated groups of extreme particle size populations that are not representative of actual particle size distributions achieved during manufacture operating within the design space. These tablets were generated for the sole purpose of evaluating method discrimination by (b) (4) above (b) (4) μm and less than (b) (4) μm .

In addition, (b) (4) particle size is constrained by process parameter controls and the range of D50 values observed across the continuous manufacturing QbD experimental space is small ($\sim$ (b) (4) μm to $\sim$ (b) (4) μm , measured using the (b) (4) particle size method). QbD experiments have shown that dissolution performance is driven by 1) (b) (4) and 2) (b) (4), with no observed impact of (b) (4) particle size on ivacaftor dissolution performance when manufacturing within the design space as can be seen in **Figure 18**.

Figure 18. Ivacaftor Dissolution at 30 Minutes and 20 Minutes as a Function of (b) (4) Particle Size



RTRT dissolution profiles and USP II dissolution profiles (data for commercial batches are not available) are provided in **Table 15** and **Table 16**, respectively for each of the QbD batches used to define (integrated continuous QbD runs 1 - 20) and confirm (QbD confirmation runs 1 – 3, run at different conditions) the design space, and for 5 continuously manufactured clinical batches and 5 commercial batches.

Table 15. RTRT Dissolution Profiles of Ivacaftor for the Integrated Continuous QbD Runs, QbD Confirmation Runs, Continuously Manufactured Clinical Batches, and Commercial Batches

Batch	RTRT Dissolution Profile (ivacaftor %LC)							
	5 min	10 min	15 min	20 min	30 min	45 min	60 min	75 min
QbD, Run 1	42	65	78	87	96	101	102	102
QbD, Run 2 ^a	39	61	74	83	93	99	100	100
QbD, Run 3	46	69	81	89	97	100	100	100
QbD, Run 4 ^a	41	63	77	85	95	100	101	101
QbD, Run 5	45	68	81	89	97	101	101	101
QbD, Run 6	46	69	82	90	98	102	102	102
QbD, Run 7 ^a	39	61	74	83	93	98	99	99
QbD, Run 8	46	69	82	89	97	100	100	100
QbD, Run 9 ^a	40	62	76	85	95	101	103	103
QbD, Run 10 ^a	44	66	79	87	95	99	99	99
QbD, Run 11	51	75	87	94	100	101	101	101
QbD, Run 12 ^a	43	66	79	87	96	100	101	101
QbD, Run 13	50	72	84	91	97	98	98	98
QbD, Run 14 ^a	45	68	81	89	98	101	101	101
QbD, Run 15	51	74	85	92	97	98	98	98
QbD, Run 16	53	76	88	94	100	101	101	101
QbD, Run 17 ^a	45	67	80	88	96	99	99	99
QbD, Run 19	41	63	77	85	94	100	100	100
QbD, Run 20	47	70	82	90	97	99	99	99
Confirmation Run 1	41	64	77	86	95	100	101	101
Confirmation Run 2	41	63	76	84	94	99	100	100
Confirmation Run 3	38	60	73	82	92	99	100	100
GMP Lot 2015044 ^b	43	65	79	87	96	101	101	101
GMP Lot 2016002 ^b	42	64	78	86	96	101	102	102
GMP Lot 2016006 ^b	41	63	77	86	96	101	103	103
GMP Lot 2016051 ^b	47	70	83	90	97	100	100	100
GMP Lot 2017016 ^b	47	69	82	89	96	99	99	99
GMP Lot 237.10035.01 ^c	46	68	81	88	96	98	98	98
GMP Lot 237.10035.02 ^c	46	68	81	88	95	98	98	98
GMP Lot 237.10035.03 ^c	45	68	80	88	96	99	99	99
GMP Lot 237.10043.01 ^c	46	68	81	89	96	99	100	100
GMP Lot 237.10043.02 ^c	47	69	82	89	97	99	99	99

(b) (4)

^a Clinical batch
^c Commercial batch

Table 16. Average USP II Dissolution Profiles for the Integrated Continuous QbD Runs, QbD Confirmation Runs, and Continuously Manufactured Clinical Batches

Batch	Average Ivacaftor % Label Claim Dissolved ^a							
	5 min	10 min	15 min	20 min	30 min	45 min	60 min	75 min
QbD, Run 1	41	66	80	88	95	99	99	99
QbD, Run 2 ^b	30	58	74	84	95	100	101	101
QbD, Run 3	49	74	86	93	98	99	99	99
QbD, Run 4 ^b	22	55	73	84	94	99	100	100
QbD, Run 5	50	72	84	91	97	100	101	101
QbD, Run 6	52	75	86	92	98	100	100	99
QbD, Run 7 ^b	32	60	75	84	95	99	101	101
QbD, Run 8	51	72	84	91	97	100	101	100
QbD, Run 9 ^b	22	55	73	84	93	97	98	98
QbD, Run 10 ^b	35	66	81	90	98	100	101	101
QbD, Run 11	52	73	85	91	98	100	101	101
QbD, Run 12 ^b	36	67	82	90	97	99	99	99
QbD, Run 13	40	66	79	88	95	98	99	99
QbD, Run 14 ^b	39	66	79	87	95	98	99	99
QbD, Run 15	57	77	88	92	97	98	98	98
QbD, Run 16	57	78	89	94	99	100	100	100
QbD, Run 17 ^b	51	73	84	91	96	98	98	98
QbD, Run 19	35	60	74	84	92	97	98	98
QbD, Run 20	51	72	83	90	94	96	97	98
Confirmation Run 1	45	68	81	89	96	99	99	100
Confirmation Run 2	34	62	77	86	96	100	101	101
Confirmation Run 3	27	52	68	78	91	99	101	102
GMP Lot 2015044	37	63	77	86	95	99	100	101
GMP Lot 2016002	36	62	77	86	96	100	101	101
GMP Lot 2016006	36	61	75	84	94	98	99	100
GMP Lot 2016051	42	67	81	90	98	102	102	101
GMP Lot 2017016	39	64	79	87	96	100	101	101

^a n = 3 for integrated continuous QbD runs 1-14 and 16-17; n = 2 for integrated continuous QbD run 15; n=1 for integrated QbD runs 19-20; n = 5 for Confirmation Runs 1 and 2; n = 6 for Confirmation Run 3; n = 12 for GMP lots 2015044, 2016002, and 2016006; n = 6 for GMP lots 2016051 and 2017016.

(b) (4)

Reviewer’s Assessment:

- The dissolution data provided in the responses can meet the Agency’s recommended limit of “NLT ^{(b) (4)} (Q) of the labelled amount of Ivacaftor dissolved in 20 minutes” at stage 2. However, the Applicant proposed dissolution acceptance criterion of “NLT ^{(b) (4)} % (Q) of the labelled amount of Ivacaftor dissolved in 30 minutes” is considered acceptable based on the totality of the data for the following reasons: 1) within the ^{(b) (4)} particle size range seen across manufacturing design space, the risk of not meeting the % ^{(b) (4)} at 20 minutes is low; 2)

the risk of undesired ivacaftor dissolution is further mitigated by controlling ivacaftor (b) (4) content to be absent in the final product.

- Per internal OPQ team discussion, the discrepancy between (b) (4) measurements of (b) (4) particle size shown in **Table 14** may be due to the different approach of measurement, which is commonly seen. Therefore, no further IR was sent regarding this issue.

In the teleconference with the Applicant dated 11/30/2017, we communicated with the Applicant that the preliminary evaluation of their responses to IR dated 11/21/2017 are acceptable.

4. Alternative Dissolution Method using RTRT Dissolution Model

The RTRT dissolution model for the prediction of batch dissolution for tezacaftor and ivacaftor is based on measured in-process material attributes assessed at (b) (4)

The measured in-process material attributes were selected as model inputs based on knowledge of the process and factors influencing dissolution performance at the time of batch release. Details refer to Module 3.2.P.2.3 Manufacturing Process Development-Introduction to Process Controls and RTRT.

The Ishikawa diagram describing the relationship between measured in-process materials attributes, process parameters, raw material attributes, and dissolution performance are shown in **Figure 19**.

Figure 19. Dissolution model Ishikawa Diagram

RTRT Dissolution Model Ishikawa Diagram

(b) (4)

4.1 Tezacaftor Model Development, Calibration and Verification

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Overall, the RTRT model method can serve as a basic alternative dissolution method during the continuous manufacturing based on the following reasons:

- 1) The Applicant provided satisfactory justification for the selection of input parameters for the RTRT model, which is based on the significance of the impact of input parameters on drug release.
- 2) The Applicant performed the calibration and verification of the RTRT model by showing the similar prediction outcomes with those obtained from the regulatory dissolution methods (the absolute differences for Tezacaftor% LC dissolved at 20 minutes and for Ivacaftor% LC dissolved at 30 minutes between two methods are <5%).
- 3) Examples have been shown to demonstrate that the RTRT model can detect non-conforming batches and an out of specification investigation will be initiated once RTRT dissolution result does not conform to the specification.
- 4) For batch release using the RTRT method, the measurement of 12 segments stratified for each batch to assure that the results comply with USP <711> stage 2 criteria.

5. Dissolution Process Model for Supporting Manufacturing Process Design Space in QbD

5.1 Integrated (b) (4) QbD Experimental Design

Integrated continuous QbD experiments were conducted on the continuous manufacturing (CM) (b) (4) investigating both material properties and process. (b) (4)

(b) (4) integrated continuous QbD experiments were conducted on the continuous manufacturing (CM) (b) (4) for assessing CMAs and CPPs that impact dissolution (refer to Module 3.2.P.2.3 Manufacturing Process Development-tezacaftor/ivacaftor Tablet⁷). The evaluated parameters included both material properties such as (b) (4) and process parameters such as (b) (4) within certain range. Once the design spaces of these parameters are finalized, dissolution models which describe them, or which are used as part of the control strategy, are finalized.

QbD design of Experiment (refer to page 31 in Module 3.2.P.2.3 Manufacturing Process Development-tezacaftor/ivacaftor Tablet)

(b) (4) design of experiments (DoE) (**Figure 28**) was performed to evaluate the impact of material attributes and process parameters on drug product CQA (**Table 33**)

⁷ <\\cdsesub1\evsprod\nda210491\0015\m3\32-body-data\32p-drug-prod\tezacaftor-ivacaftor-tablet-all\32p2-pharm-dev\manf-proc-dev-commercial-tezacaftor-ivacaftor-fdc-tablet.pdf>

Reviewer's Assessment:

- As shown in **Figure 32**, Ivacaftor [REDACTED] (b) (4) are the critical material and process parameters for Ivacaftor dissolution, respectively.
- The dissolution profiles data of batches manufactured with [REDACTED] (b) (4) and Ivacaftor [REDACTED] (b) (4) were not provided. The comparisons of the above profiles using f2 test were not provided either. However, as shown in **Figure 32**, within the design space of [REDACTED] (b) (4), the Ivacaftor dissolution at 30 minutes are all over 90%, supporting the established design space.
- For the assessment on the impact of process parameters on CQAs other than dissolution, refer to the Drug Process Chapter of the OPQ IQA entered into Panorama by Dr. Yong Hu⁸.

⁸ <http://panorama.fda.gov/task/view?ID=5980e4590066f3428ae81a5585edeffe>

6. Bridging of Formulations

Formulations of Tezacaftor/Ivacaftor Used in Clinical Studies are shown in the following Table:

Table 39. Formulations/ of Tezacaftor/Ivacaftor Used in Clinical Studies

Formulation Description (Abbreviated)	Formulation Description	Tezacaftor/Ivacaftor Clinical Study Number (abbreviated)		
		Phase 1	Phase 2	Phase 3
Tezacaftor/ivacaftor FDC (50 mg/150 mg)	50 mg tezacaftor/150 mg ivacaftor fixed dose combination tablet using (b) (4) tezacaftor and ivacaftor	004	--	--
Tezacaftor/ivacaftor FDC (100 mg/150 mg)	100 mg tezacaftor/150 mg ivacaftor fixed dose combination tablet using (b) (4) tezacaftor and ivacaftor	006, 008		106, 107, 108, 110

a (b) (4)

b

Phase 3 pivotal studies included a 100 mg tezacaftor/150 mg ivacaftor FDC tablet that utilized (b) (4) tezacaftor and ivacaftor (b) (4) Ivacaftor (b) (4) is an existing commercial drug product intermediate. The (b) (4) was used for late stage clinical trials and commercialization.

100-mg TEZ/150-mg IVA, film-coated fixed-dose combination (FDC) tablet (batch numbers 2014032, 2015004, 2015014, 2015016, 2015044, and 2016002) was used in Phase 3 Study 106; TEZ 100-mg/IVA 150-mg, film-coated fixed-dose combination (FDC) tablets (batch numbers 2015004, 2015016, 2016006) was used in Phase 3 Study 107; TEZ 100 mg/IVA 150 mg fixed-dose combination (FDC) tablet (batch number 2015016, 2015044, 2014032) was used in Phase 3 Study 108.

The batch size for batch 2014032 and batch 2015004 is (b) (4) tablets (equivalent to about (b) (4) kg as each tablet weight is 0.609g, calculated by this reviewer); batch size for batch 2015014 is (b) (4) tablets (equivalent to about (b) (4) kg as each tablet weight is 0.609g, calculated by this reviewer). batch size for batch 2015006 is (b) (4) tablets (equivalent to about (b) (4) kg as each tablet weight is 0.609g, calculated by this reviewer) (Refer to Table 1 in Module 3.2.P.2.3 Manufacturing Process Development-Tablet). Initial commercial batch size target will be (b) (4) kg (refer to Module 3.2.P.3.2 Batch Formula). Proposed maximum commercial batch size is (b) (4) kg.

Reviewer's Assessment:

Bridging between batch size of the commercial batches and bio-batches used in the pivotal clinical trials

- Initial commercial batch size target will be (b) (4) kg (refer to Module 3.2.P.3.2 Batch Formula) and the later proposed maximum commercial batch size is (b) (4) kg, which is within 10-fold differences of clinical batch size (up to (b) (4) kg). Therefore, no further bridging data is necessary regarding the batch size.

Bridging between to-be-marked formulation and bio-batch used in the pivotal clinical trials

- The to-be-marketed product has the same formulation with the product used in the pivotal clinical studies. The initial phase III clinical batches and primary stability batches were manufactured by discontinuous process.
- Although in Phase 3 clinical studies (pivotal), batches manufactured by CM with same formulation as the to-be-market product also were used to evaluate the efficacy and safety of the proposed product, dissolution profile comparisons (multimedia as well as QC medium) between the batches manufactured by CM and the Phase 3 clinical formulations produced by discontinuous process) were requested to confirm no impact of dissolution due to the process transfer.
- In addition, dissolution profile comparison is needed for supporting the bridging between the debossed to-be-marketed product and the clinical batches without deboss.

IR#1: The following IR was communicated to the Applicant dated 08/21/2017.

- *“For bridging purpose, provide dissolution profile comparison data between the exhibit batches (to-be-marketed formulation manufactured by continuous manufacturing) and the clinical batches used in Phase III trials manufactured by discontinuous process (e.g., Batch 2014032, 2015004 and 2015014).*
- *Provide dissolution profile comparison data between the debossed product (if available) and the clinical batches without deboss.”*

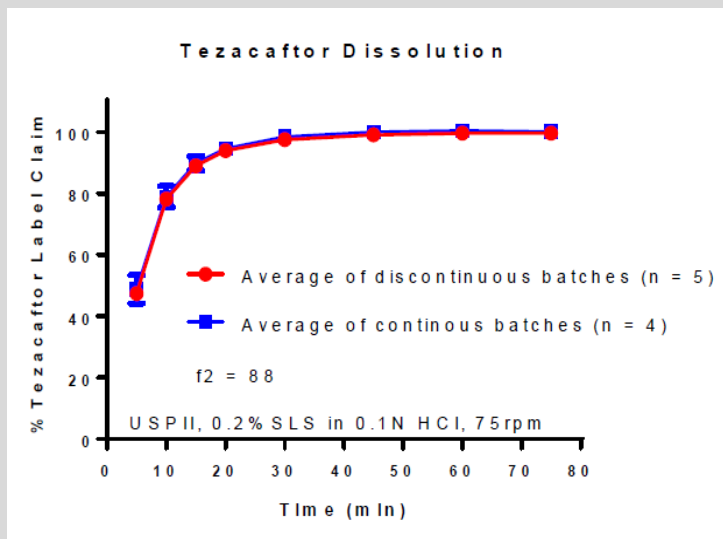
Responses were received dated 09/05/2017

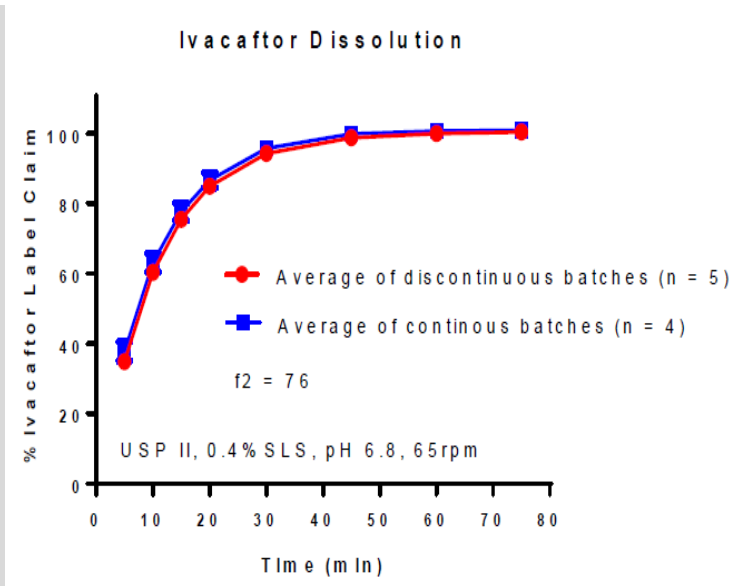
Table 40 provides an overview of the tablet lots manufactured by the discontinuous process used in pivotal phase 3 studies and all the to-be-marked formulation lots manufactured by the continuous process. A graphical comparison and dissolution data from the average dissolution profiles from the tezacaftor/ivacaftor FDC tablets manufactured using the discontinuous and continuous processes are provided in **Figure 33**.

Table 40. Manufacturing Process of 100 mg Tezacaftor/ 150 mg Ivacaftor Tablets for Dissolution Comparison

Lot Number	Manufacturing Process
2014032	Discontinuous
2015004	Discontinuous
2015014	Discontinuous
2015015	Discontinuous
2015016	Discontinuous
2015044	Continuous
2016002	Continuous
2016006	Continuous
2016051	Continuous

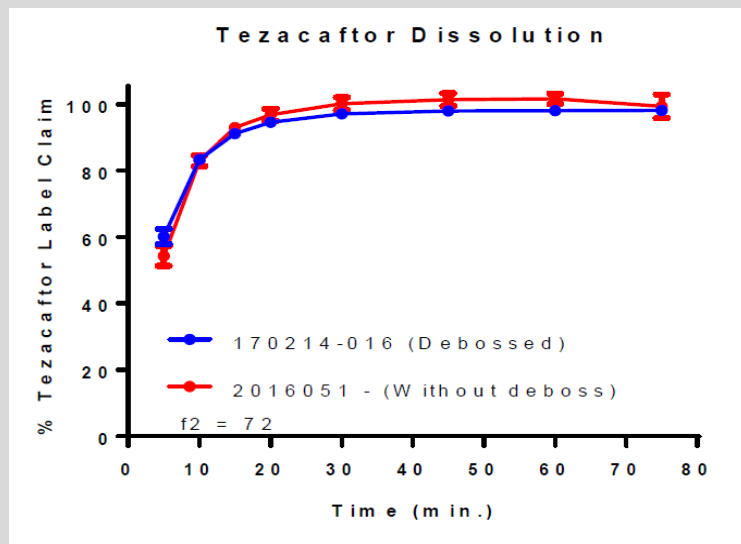
Figure 33. Dissolution Comparison (average) of 100 mg Tezacaftor/ 150 mg Ivacaftor FDC Tablets Manufactured Continuously and Discontinuously

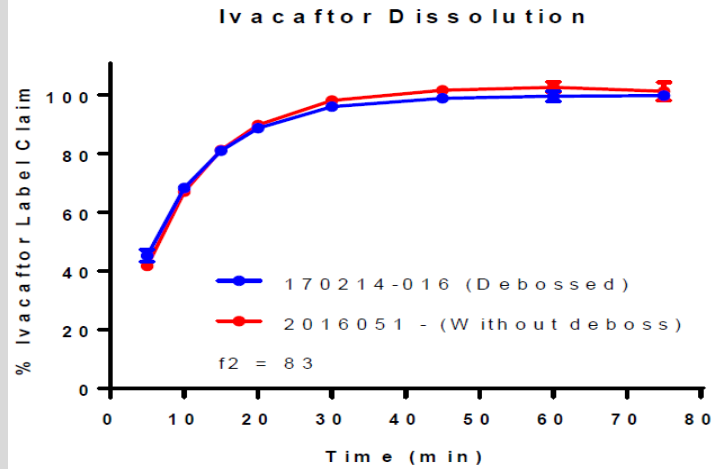




A graphical dissolution profile comparison, including f_2 values, of the tezacaftor/ivacaftor FDC tablet clinical batch 2016051 and debossed development tablet batch 170214-016, both manufactured using the continuous process is shown in **Figure 34**.

Figure 34. Comparison of 100 mg Tezacaftor/ 150 mg Ivacaftor FDC Tablets with and Without Debossing ($f_2=72$ for Tezacaftor and $f_2=83$ for Ivacaftor)





Reviewer's Assessment:

- Per this request, the dissolution profile comparisons were provided which showed similarity between clinical formulation (produced by discontinuous process and continuous process) and to-be-marked formulations (produced by continuous process) which confirmed to have no impact in dissolution by changing discontinuous process to CM. The dissolution profile comparisons were also provided which showed similarity between debossed to-be-marketed product and the clinical batches without deboss.
- The Applicant's response is acceptable.

Primary Biopharmaceutics Reviewer Name and Date:

Fang Wu, Ph. D.

Biopharmaceutics Reviewer
 Division of Biopharmaceutics
 Office of New Drugs Products

Date: 12/11/2017, updated on 12/27/2017, 01/11/2018

Secondary Reviewer Name and Date:

Min Li, Ph. D.

Secondary Biopharmaceutics Reviewer
 & Biopharmaceutics Lead (acting)
 Division of Biopharmaceutics
 Office of New Drugs Products
 Date: 1/16/2018

Tertiary Reviewer Name and Date:

Kimberly Raines, Ph. D.

I concur with the primary reviewer assessment.

Tertiary Biopharmaceutics Reviewer
& Branch Chief (acting)
Division of Biopharmaceutics
Office of New Drugs Products
Date: 01/12/2018

APPENDIX

Information Requests communicated to the Applicant throughout the Review Cycle

Biopharmaceutics Comments for 1st IR dated 08/21/2017:

- *Provide complete dissolution profile data (individual, mean, range, relative standard deviation or CV% of the data and graphical profiles) for all the bio-batches used in the pivotal phase 3 clinical trials.*
- *For bridging purpose, provide dissolution profile comparison data between the exhibit batches (to-be-marketed formulation manufactured by continuous manufacturing) and the clinical batches used in Phase III trials manufactured by discontinuous process (e.g., Batch 2014032, 2015004 and 2015014).*
- *Provide dissolution profile comparison data between the debossed product (if available) and the clinical batches without deboss.*
- *In regards to RTRT dissolution model included in Module 3.2.P.2.3 Manufacturing Process Development-5.2.3 Dissolution, we are unable to locate raw modeling data for model development and calibration. Direct us to the location of the submission or provide complete modeling data including but not limited to program files, input and output data for model development and calibration/validation. Provide the details (in tables) of the formulation and process parameter information of individual batches or segments selected for model development and calibration/validation or direct us to the location of such data.*

Biopharmaceutics Comments for #2 IR dated 10/18/2017:

- *Provide justification on the selection of 0.2% SLS in 0.1N HCl rather than (b) (4) (b) (4) as dissolution medium for Tezacaftor.*
- *Note that your proposed dissolution acceptance criteria of “NLT (b) (4)% (Q) of the labeled amount of tezacaftor dissolved in 20 minutes and NLT (b) (4)% (Q) of the labeled amount of Ivacaftor dissolved in 30 minutes” is permissive and not supported by the dissolution data from the pivotal clinical batches. The mean dissolution profile data from pivotal clinical batches support the following acceptance criterion, “NLT (b) (4)% (Q) of the labeled amount of tezacaftor dissolved in 15 minutes and NLT (b) (4)% (Q) of the labeled amount of Ivacaftor dissolved in 20 minutes”. The above acceptance criterion is recommended for batch release and stability testing of your proposed drug product. Justify your proposed acceptance criteria for both APIs, e.g. in terms of the clinical relevance of your proposed specification. Alternatively, update the dissolution specification with the Agency’s recommended acceptance criteria accordingly.*
- *Justify the selection of the input variables included in the tezacaftor and ivacaftor PLS model, e.g., provide the rationale for including variables such as (b) (4)*

(b) (4)
in the dissolution model.

- Provide justification on the limit set for (b) (4) of Tezacaftor and Ivacaftor PLS model. Provide plots of the (b) (4) (b) (4) statistics for detecting samples that are unusual due to “extreme” values in the input data (e.g., hardness, (b) (4) particle size).
- In your response dated 09/05/2017, your verification of the RTRT dissolution models was based on the dissolution results at 20 minutes for Tezacaftor and at 30 minutes for Ivacaftor. Provide additional verification data at other time points (e.g., $Q = \frac{(b)(4)}{(4)}\%$ at 15 minutes for Tezacaftor and $Q = \frac{(b)(4)}{(4)}\%$ at 20 minutes for Ivacaftor) for the design space confirmation runs on the (b) (4) the development batches, the independent test set and/or other relevant batches.
- Provide additional verification data to demonstrate the capability of the model to detect nonconforming batches (e.g., batches with slower dissolution) and what the feedback steps are.

Biopharmaceutics Comments for #3 IR which was conveyed to the Applicant dated 11/21/2017:

We have reviewed your response dated 11/03/2017 and have the following comments with respect to the dissolution specification.

1. The Agency’s previous recommendation for dissolution acceptance criterion of “NLT $\frac{(b)(4)}{(4)}\%$ (Q) of the labeled amount of Ivacaftor dissolved in 20 minutes” is supported by clinical, stability, and individual PK data. Your proposed dissolution acceptance criterion of “ $Q = \frac{(b)(4)}{(4)}\%$ at 30 minutes” for Ivacaftor would not be able to discriminate the batches with (b) (4) particle size $< \frac{(b)(4)}{(4)} \mu\text{m}$ and $> \frac{(b)(4)}{(4)} \mu\text{m}$ from (b) (4). To support your proposed acceptance criterion of “NLT $\frac{(b)(4)}{(4)}\%$ (Q) in 30 minutes” for Ivacaftor, the following data is needed:

- Provide D10, D50 and D90 of (b) (4) particle size that were observed for each of the pivotal clinical batches.
- Provide the D10, D50, D90 of (b) (4) particle size range produced within the process design space and provide ivacaftor dissolution profile data (e.g. at 5, 10, 15, 20, 30, 45, 60 and 75 minutes) within the above (b) (4) particle size range, if available. Alternatively, provide ivacaftor dissolution profile data (e.g. for the batch at upper bound of the (b) (4) particle size in RTRT dissolution model calibration data set).

2. Additionally, confirm the individual segment dissolution data along with the mean (n=12), range and RSD predicted by the RTRT model will be reported for batch release during commercial manufacturing.



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Wu

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DP attribute/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	Lifecycle considerations
Appearance	- Film coating step considered critical to appearance CQA (parameter variation) (b) (4) - Variability of (b) (4) particles size - Coating parameter variation - Legibility of debossing	4	3	2	24	(b) (4)	Risk low	Assuming the manufacturing process remains within the established design space, appearance would be acceptable since development DOEs have demonstrated acceptable appearance within the design space.
ID ³ (tezacaftor)	- Incorrect elucidation of structure - Absolute configuration of APIs not established	4	3	3	36	(b) (4)	Risk low	- To demonstrate (b) (4) specificity for the following changes: - transfer to a new site - change in instrumentation - to demonstrate specificity of method in cases of manufacture of other products than currently manufactured on the (b) (4) this can be followed up during surveillance inspection(s) - Ensure calibration models associated with the spectroscopy method are updated and verified

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 N203188 reviews for the elucidation of ivacaftor structure and the associated control strategy to assure identity.

⁴ See: Flack, HD *On Enantiomorph-Polarity Estimation* Acta Cryst. **A39** (1983), 876-881. A Flack parameter of zero is indicative of the correct assignment and a value of one indicates an inverted structure.

						(b) (4)		as needed over the lifecycle.
Assay	(b) (4) variability of tezacaftor (b) (4) (b) (4) variability of ivacaftor (b) (4) •Variable (b) (4) (b) (4) particle size variability •Degradation of (b) (4) APIs during processing (see degradation CQA below) •Variable tablet weight •Assay/purity of input tezacaftor •Assay/purity of input ivacaftor (b) (4) (b) (4) variability	2	3	2	12		Risk low	•Evaluate adequacy of sampling frequency if there is a change in equipment type, line rates, etc. •Ensure (b) (4) model (for monitoring active content) are updated and verified as needed over the lifecycle.
Degradation Products /Purity	•High degradant levels in the tezacaftor and ivacaftor (b) (4) (b) (4) •Degradation of APIs in fixed-dose combination drug product on stability •Presence of elemental impurities •Presence of (b) (4)	2	3	5 RTRT	30		Risk low	•Both the APIs are stable, however degradants (although listed in the DP spec) are tested only on stability and not at product release •Stability and forced degradation study data showed no degradation under any condition. •Minor changes to the manufacturing process and site are unlikely to significantly impact DP stability. •When major changes to the manufacturing process and changes that impact incoming material quality are made (e.g., addition of a new API or (b) (4) site, changes to API or (b) (4) process, etc.),

						(b) (4)	need to confirm no degradation products over stability
Dissolution	(b) (4) variability of tezacaftor (b) (4) (b) (4) (b) (4) particle size variability (b) (4) in drug product •Tablet hardness •Tablet (b) (4)	3	3	3 RTRT	27		Risk low •Dissolution model maintenance and update need to be evaluated over lifecycle. •Any changes to (b) (4) properties due to change in site, or any changes to the manufacturing process, that can impact the attributes that are input to the dissolution model, could potentially impact dissolution model prediction. Additionally, Vertex's criticality assessment is based on the Desired Manufacturing Ranges (DMRs). If the DMRs change in the future, the criticality should be re-evaluated.
Uniformity of Dosage Units (content uniformity or	(b) (4) variability of tezacaftor (b) (4) (b) (4)	3	3	2	18		Risk low •Changes to following can impact CU and need to be evaluated: -Change to (b) (4) may affect many CM aspects (e.g. (b) (4))

CU)	(b) (4) particle size and (b) (4) variability (b) (4) variability Input excipient variability (b) (4)							(b) (4)
Microbial limits	(b) (4) increasing above acceptance criteria - Microbial growth during processing (film coating) - Quality of input materials - No microbial limits testing proposed for drug product release	2	3	5	30		Risk low	Full waiver of microbial limits testing over stability is supported under the current conditions. If manufacturing hold time and hold times of (b) (4) coating (b) (4) are extended, would need added justification and reevaluation of above agreement.
Physical form	- Input materials contain (b) (4) 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 (b) (4)) - Comparability protocol is included that pertains to the management of post approval changes to (b) (4)	2	3	3	18		Risk is low	In process control for detection of any form conversion

	firm proposes to use this protocol multiple times for (b) (4)								



Craig
Bertha

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Sharmista
Chatterjee

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NDA 210491 ONDP Filing Review

Application #: 210491

Submission Type: 505(b)(1)

**Established/Proper Name:
tezacaftor/ivacaftor**

**Applicant: Vertex
Pharmaceuticals Inc.**

Letter Date: 28-JUN-2017

Dosage Form: tablet

**Chemical Type: 1
(tezacaftor)**

Stamp Date: 28-JUN-2017

**Strengths: 100 mg
tezacaftor/150 mg
ivacaftor/tablet**

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?	X		1. Provide any available stability data for tezacaftor drug substance manufactured at the (b) (4) commercial site. 2. Provide the quantitative composition of the (b) (4) film coat, or provide a Letter of Authorization allowing our review of a drug master file from (b) (4) that contains this information.

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	☒	☐	Tezacaftor is an NME (ivacaftor is not)
2.	Botanical ¹	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☐	☒	
8.	Transdermal ¹	☐	☒	
9.	Pediatric form/dose ¹	☐	☒	
10.	Locally acting drug ¹	☐	☒	
11.	Lyophilized product ¹	☐	☒	
12.	First generic ¹	☐	☒	(b) (4)
13.				
14.	Oral disintegrating tablet ¹	☐	☒	

¹ Contact Office of Testing and Research for review team considerations

NDA 210491 ONDP Filing Review

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
15.	Modified release product ¹	☐	☒	
16.	Liposome product ¹	☐	☒	
17.	Biosimilar product ¹	☐	☒	
18.	Combination Product _____	☐	☒	
19.	Other: continuous manufacturing; expiry proposed; cross-reference for ivacaftor _____ (b) (4)	☒	☐	- Drug product manufacturing utilizes a continuous process starting _____ (b) (4) each drug substance; the applicant also proposes alternative test methods using _____ (b) (4) for real-time release testing (RTRT) of the drug product; note the primary stability data are being obtained on drug product <i>not</i> prepared by the planned continuous process, but by a developmental discontinuous process (uses standalone equipment for unit operations and _____ (b) (4) <i>differ</i> between the discontinuous and the proposed continuous manufacturing processes; see attachment) - Expiry of 30 months is proposed, based on 18 months of real-time long-term stability data for three discontinuous batches 2015014, 2015015, and 2015016 and 12 months for three continuous manufactured batches, 2015044, 2016002, and 2016006 - As per the 07-JUL-2017, amendment, the applicant has confirmed that cross-reference is made to their approved NDA 203188 for all information about the ivacaftor _____ (b) (4)

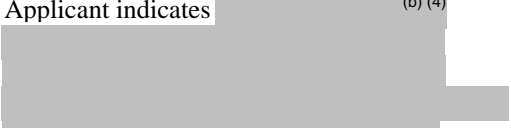
Regulatory Considerations				
20.	USAN Names Assigned	☒	☐	
21.	End of Phase II/Pre-NDA Agreements	☒	☐	EoP2 (see minutes of 30-JUL-2015, meeting for IND 108105 for more detail): 1) preliminary agreement on drug substance starting materials; 2) Vertex agreed to provide chiral purity assessment for tezacaftor for all drug substance and drug product stability batches; 3) there was general agreement with the overall control strategy proposed for the drug product, but clarification of various aspects were requested: material traceability and segregation/rejection, product key definition, sampling/measurement frequency vs. residence time, batch definition, _____ (b) (4), _____ (b) (4), control of _____ (b) (4)

NDA 210491 ONDP Filing Review

				(b) (4) in drug product, control strategy for physical form of each API in the drug product, impact of (b) (4) on CQAs (e.g., assay, dissolution), and material properties of (b) (4) 3) Vertex agreed to provide 3-6 months of stability data from 2 drug product batches prepared with the proposed continuous process, plus the 12 months of data from 3 batches prepared with the discontinuous process (see section B.19 above); 4) the plan for control of the (b) (4) in the dosage form were found to be acceptable, but there was no agreement on the appropriate threshold for reporting; 5) Vertex agreed to assess the discriminating power of the dissolution method toward (b) (4); 6) Agency agreed with Vertex approach to setting of dissolution acceptance criteria. • Type B CMC (see minutes of 14-SEP-2016, meeting for detail): this meeting involved a discussion of the process validation expectations and there was clarifying discussion, but no clear agreements evident from the minutes • Type B CMC (see minutes of 16-MAY-2017, meeting for detail): Vertex presented an overall summary of their quality-by-design (QbD) approach and FDA was in general agreement, but there was some clarifying discussion
22.	SPOTS (Special Products On-line Tracking System)	☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	☐	☐	Unknown
24.	Comparability Protocol(s) ²	☒	☐	In the R section, the applicant provides a comparability protocol (CP) for post-approval changes (b) (4) Note: CQA acceptance criteria, non-CQA specifications, incoming material attribute ranges, equipment with different operating principles are not covered by the CP
25.	Other <u>RTRT</u> and methods _____	☒	☐	The applicant proposes real-time release testing, but this is alternative, not regulatory

² Contact Post Marketing Assessment staff for review team considerations

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				testing; these RTRT methods (see table 7 P.2.3 for PAT technology for each RTRT release test parameter) will need to provide the same or increased assurance that the drug product has the required identity, strength, quality, purity, or potency as compared to the regulatory methods; note that with RTRT, there will be no testing for related substances at the time of drug product release	
Quality Considerations					
26.	Drug Substance Overage	☐	☒	However, the MBR mentions “overages” in the tablet component bill of materials, even though no mention of overage usage could be found in the P section of module 3.	
27.	Design Space	Formulation	☐	☒	
28.		Process	☒	☐	The manufacturing process parameters that make up the design space include (b) (4)  (non-critical); see P.2.3, Manufacturing Process Development
29.		Analytical Methods	☐	☒	
30.		Other	☒	☐	Multiple steps of the tezacaftor synthesis have parameters that are a part of the synthesis design space (see table 77 in S.2.6 for parameter normal operating ranges and design space limits for steps 1a, 2a, 3a, 4a, 4b, 5a, and 5b parameters (see fig. 1 in S.2.2 for synthesis scheme)
31.	Real Time Release Testing (RTRT)	☒	☐		
32.	Parametric Release in lieu of Sterility Testing	☐	☒		
33.	Alternative Microbiological Test Methods	☐	☒		
34.	Process Analytical Technology (PAT) ¹	☒	☐	See figure 5 in P.2.3 for the PAT positions for the (b) (4) 	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐	
36.		Excipients	☒	☐	(b) (4)
37.		Microbial	☐	☒	
38.	Unique analytical methodology ¹	☒	☐	Alternative methods are considered unique, but regulatory methods are not	
39.	Excipients of Human or Animal Origin	☐	☒		
40.	Novel Excipients	☐	☒		
41.	Nanomaterials ¹	☐	☒		
42.	Hold Times Exceeding 30 Days	☐	☒		
43.	Genotoxic Impurities or Structural Alerts	☒	☐	Applicant indicates (b) (4) 	

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				(b) (4) have structural alerts. However, in addition, the following potential impurities also have structural alerts (most are (b) (4) apart from those that have the same alert (b) (4))
44.	Continuous Manufacturing	☒	☐	For drug product manufacturing process
45.	Other unique manufacturing process ¹	☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	☒	☐	Yes, if alternative test methods are used for release as opposed to the regulatory methods
47.	New delivery system or dosage form ¹	☐	☒	
48.	Novel BE study designs	☐	☐	To be evaluated by the clinical pharmacology group
49.	New product design ¹	☐	☒	
50.	Other	☐	☐	

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Applicant requests a categorical exclusion as per 21 CFR 25.31(b); note that the estimation of the expected introduction concentrations (EIC) for both APIs have been given and are said to be less than 1 ppb for each.
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? ³ Is there sufficient information in the following sections to conduct a review? ☐ Drug Substance ☐ Drug Product ☐ Appendices ☐ Facilities and Equipment ☐ Adventitious Agents Safety Evaluation ☐ Novel Excipients ☐ Regional Information ☐ Executed Batch Records ☐ Method Validation Package ☐ Comparability Protocols	☒	☐	☐	• Applicant has been asked (06-JUL-2017, IR) to confirm that all information supporting the ivacaftor drug substance and (b) (4) are to be found in the approved NDA 203188 (which seems to be implied but not specifically stated in the application); see B.19 above • The application provides master batch records for manufacture of drug substance by two manufacturers (b) (4); manufacture of the tezacaftor (b) (4) and drug product manufacture at Vertex, as well as a “representative” executed batch record for drug product (lot number 2016002, used in clinical studies VX14-661-106 and -110, and for supportive stability) (technically, as

³ Not all pages of the application were checked for legibility.

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C. FILING CONSIDERATIONS					
					per regulation 21 CFR 314.50(d)(1)(i)(b), Vertex should have also supplied executed batch records for BE batches and all primary stability batches, but the Agency often agrees to just accept a representative executed batch record alone) • There is a comparability protocol proposed in R for changes to the (b) (4) (OLDP participation requested) • MV information is provided in R for tezacaftor drug substance, tezacaftor (b) (4) and the drug product (OTR participation requested)
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ☐ Name of facility, ☐ Full address of facility including street, city, state, country ☐ FEI number for facility (if previously registered with FDA) ☐ Full name and title, telephone, fax number and email for on-site contact person. ☐ Is the manufacturing responsibility and function identified for each facility, and ☐ DMF number (if applicable)	☒	☐	☐	• There are five drug substance manufacturing sites: two (b) (4) sites and one (b) (4) site for tezacaftor and ivacaftor manufacture, a (b) (4) site for ivacaftor manufacture, and a (b) (4) site for tezacaftor manufacture. Note: the (b) (4) sites are <i>not</i> listed as drug substance manufacturers in S.2.1, but are on the 356h) • There is a separate (sixth) (b) (4) site for stability testing of both APIs.
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ☐ Is a manufacturing schedule provided? ☐ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☐	☐	☒	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? ³ Is there sufficient	☒	☐	☐	• Batch analyses are provided for tezacaftor manufactured using the

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C. FILING CONSIDERATIONS					
	information in the following sections to conduct a review? ☐ general information ☐ manufacture ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only ☐ characterization of drug substance ☐ control of drug substance ○ Includes data to demonstrate comparability of drug substance to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ☐ reference standards or materials ☐ container closure system ☐ stability ○ Includes data establishing stability of the drug substance through the proposed retest period and a stability protocol describing the test methods used and time intervals for assessment			intended commercial process at the two intended commercial manufacturing sites (b) (4), however, no executed batch records have been provided, only master batch records (blank); the API team does not consider this a filing issue. • Tezacaftor drug substance stability data are only provided for (b) (4) sourced API, not (b) (4)-sourced API; the API team will request any available stability data from the (b) (4) site in the 75 day letter (see C.3 above)	
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible?³ Is there sufficient information in the following sections to conduct a review? ☐ Description and Composition of the Drug Product ☐ Pharmaceutical Development ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development ☐ Manufacture ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to	☐	☒	☐	• Note that the P section is broken down into two distinct parts, each having the CTD format: 1) tezacaftor (b) (4) drug product intermediate; 2) drug product • Tablets that have been used to support the application are <i>not</i> debossed, as will be the commercial tablets proposed for marketing (applicant claims “this does not impact safety, efficacy, or stability of the tablets”) • The application includes the qualitative composition of the (b) (4) film coating, but not the quantitative

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C. FILING CONSIDERATIONS					
	support the proposed filter? ☐ Control of Excipients ☐ Control of Drug Product - o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) - o Includes data to demonstrate process consistency (i.e. data on process validation lots) - o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) - o Analytical validation package for release test procedures, including dissolution ☐ Reference Standards or Materials ☐ Container Closure System (CCS) - o Include data outlined in container closure guidance document ☐ Stability - o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ☐ APPENDICES ☐ REGIONAL INFORMATION				information, either directly or by reference to a DMF (the applicant will be asked for this information in the 75 day letter) • No executed batch records are provided with the application for the production of the tezacaftor (b) (4) but have now been provided for one batch of the ivacaftor/tezacaftor tablet drug product (see C.2 above) • The applicant claims that the clinical batches of drug product “were manufactured using the same equipment, using similar line rates, and with the same sampling locations as will be used for commercial manufacture...therefore, process performance, IPC data, and batch-to-batch variation for the clinical batches are relevant to understanding commercial process performance.” Presumably batch-to-batch variation can be assessed by an examination of release and stability data for the clinical batches of drug product; see from Attachment below that not all clinical batches were manufactured with the continuous process. • For MV, see C.2 above. • Tezacaftor reference standard information referenced to S.5. • CCS is a (b) (4) blister and DMF reviews may be necessary for the (b) (4) backing film and the Al foil laminate lidding, depending on how much detail is or is not in the NDA
8.	Does the application contain dissolution data? • Is the dissolution test part of the DP specifications? Does the application contain the dissolution method development report including data supporting the discriminating ability?	☒			• Dissolution method development information is included in the submission. However, the adequacy of the proposed dissolution method and specification will be a review issue. Information request for additional data to support the discriminating ability of the proposed dissolution method for tezacaftor may be needed. • Dissolution modeling for RTRT is included in this submission (Refer to section 3.2.P.2.3 Introduction to Process Controls and RTRT-

C. FILING CONSIDERATIONS																												
				Tezacaftor/Ivacaftor Tablet), while no sufficient data was included in the submission for supporting the model development and validation. Information request for the dissolution model is needed. The proposed dissolution method is as follows: For Tezacaftor in 100 mg Tezacaftor/ 150 mg Ivacaftor FDC Tablets: <table border="1"> <thead> <tr> <th>Parameter</th> <th>Selection</th> </tr> </thead> <tbody> <tr> <td>Apparatus</td> <td>USP II(Paddle)</td> </tr> <tr> <td>Agitation Speed</td> <td>75 rpm</td> </tr> <tr> <td>Medium</td> <td>0.2% (w/v) SLS in 0.1N HCl</td> </tr> <tr> <td>Volume</td> <td>900mL</td> </tr> <tr> <td>Temperature</td> <td>37.0°C (b) (4)</td> </tr> </tbody> </table> (Refer to Table 8 in Module 3.2.P.2 Pharmaceutical Development) For Ivacaftor in 100 mg Tezacaftor/ 150 mg Ivacaftor FDC Tablets: <table border="1"> <thead> <tr> <th>Parameter</th> <th>Selection</th> </tr> </thead> <tbody> <tr> <td>Apparatus</td> <td>USP II(Paddle)</td> </tr> <tr> <td>Agitation Speed</td> <td>65 rpm</td> </tr> <tr> <td>Medium</td> <td>50 mM sodium phosphate buffered 0.4% (w/v) SLS, pH 6.8</td> </tr> <tr> <td>Volume</td> <td>900mL</td> </tr> <tr> <td>Temperature</td> <td>37.0°C (b) (4)</td> </tr> </tbody> </table> (Refer to Table 11 in Module 3.2.P.2 Pharmaceutical Development)	Parameter	Selection	Apparatus	USP II(Paddle)	Agitation Speed	75 rpm	Medium	0.2% (w/v) SLS in 0.1N HCl	Volume	900mL	Temperature	37.0°C (b) (4)	Parameter	Selection	Apparatus	USP II(Paddle)	Agitation Speed	65 rpm	Medium	50 mM sodium phosphate buffered 0.4% (w/v) SLS, pH 6.8	Volume	900mL	Temperature	37.0°C (b) (4)
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C. FILING CONSIDERATIONS					
9.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	PK results from the 100 mg tezacaftor/150 mg ivacaftor FDC tablet in Study 006 and the individual tezacaftor and ivacaftor tablets dosed in Studies 101 and 103 suggested that the FDC tablet provides comparable exposure and PK as the individual tablets (Module 2.7.1/Section 3.3). Office of Clinical Pharmacology will review the comparative BA studies.
10.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	☐	☒	☐	• The to-be-marketed product has the same formulation with the product used in the pivotal clinical studies. However, the initial phase III clinical batches and primary stability batches were manufactured by discontinuous process while the to-be-marketed product is manufactured by continuous process. A bridging between phase III clinical batches manufactured by discontinuous process and the to-be-marketed product made by continuous process is needed. As the CM process uses the same principle (b) (4) with similar equipment units as the discontinuous process, the change to CM may not be considered as a high risk. • Dissolution profile comparisons (multimedia as well as QC medium) between the to-be-marketed and the Phase 3 clinical formulations (produced by discontinuous process and continuous process) will be necessary for the bridging. • The dissolution profile comparison is needed for supporting the bridging between the debossed to-be-marketed product and the clinical batches without deboss.
11.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type	☐	☒	☐	No, there is only one strength for this proposed product

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C. FILING CONSIDERATIONS					
	of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.				
12.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	Not applicable because this is Immediate Release Tablet dosage form
13.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	Not applicable because this is Immediate Release Tablet dosage form
14.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☒	☐	According to the Applicant, Tezacaftor is a BCS class II and Ivacaftor is a BCS class II or IV drug.
REGIONAL INFORMATION AND APPENDICES					
15.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐	
16.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☐	☒	☐	No executed batch records for drug substance production have been provided, only a master batch record; assuming the drug substance was manufactured under GMP conditions, it would be expected that batch records would be available, however, these may need translation
17.	Is the following information available in the Appendices for Biotech Products [3.2.A]? ☐ facilities and equipment - o manufacturing flow; adjacent areas - o other products in facility - o equipment dedication, preparation, sterilization and storage - o procedures and design features to prevent contamination and cross-contamination ☐ adventitious agents safety evaluation (viral and non-viral) e.g.: - o avoidance and control procedures - o cell line qualification - o other materials of biological origin - o viral testing of unprocessed bulk - o viral clearance studies - o testing at appropriate stages of production ☐ novel excipients	☐	☐	☒	
18.	Are the following information available for Biotech Products: ☐ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: - o LAL instead of rabbit pyrogen - o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be	☐	☐	☒	

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C. FILING CONSIDERATIONS				
	marketed with summaries of test results for those samples			

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Initial Risk Assessment for Drug Product CQAs

DP attribute/ CQA (100/150 mg tezacaftor/ ivacaftor)	Factors that can impact the CQA	O ⁴	S ^{4,5}	D ⁴	FMEC A RPN #	Comment & considerations
Appearance	• film coating step considered critical to appearance CQA (parameter variation) • (b) (4) • variability of (b) (4) particles size • coating parameter variation • legibility of debossing	4	3	2	24	(b) (4)
Identification ⁶ (tezacaftor)	• incorrect elucidation of structure • absolute configuration of APIs not established	4	3	3	36	

⁴ O = Probability of Occurrence; S = Severity of Effect; D = Detectability

⁵ 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)

⁶ Refer to N203188 reviews for the elucidation of ivacaftor structure and the associated control strategy to assure identity.

⁷ See: Flack, HD *On Enantiomorph-Polarity Estimation* Acta Cryst. **A39** (1983), 876-881. A Flack parameter of zero is indicative of the correct assignment and a value of one indicates an inverted structure.

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Initial Risk Assessment for Drug Product CQAs

(b) (4)

Assay	• (b) (4) variability of tezacaftor (b) (4) • (b) (4) variability of ivacaftor (b) (4) • variable (b) (4) • (b) (4) variability • (b) (4) particle size variability • degradation of (b) (4) APIs during processing (see degradation CQA below) • variable tablet weight	2	3	2	12	

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Initial Risk Assessment for Drug Product CQAs

(b) (4)

	• assay/purity of input tezacaftor • assay/purity of input ivacaftor (b) (4) • (b) (4) variability				
Degradation Products/Purity	• high degradant levels in the tezacaftor and ivacaftor (b) (4) • (b) (4) • degradation of APIs in fixed-dose combination drug product on stability • presence of elemental impurities • presence of (b) (4)	2	3	5 (with RTR testing)	30

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Initial Risk Assessment for Drug Product CQAs

						(b) (4)
Dissolution	• (b) (4) variability of tezacaftor (b) (4) • (b) (4) variability of ivacaftor (b) (4) • (b) (4) • variability • (b) (4) particle size variability • (b) (4) in drug product • tablet hardness • tablet (b) (4) •	3	3	3(with RTR testing)	27	

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Initial Risk Assessment for Drug Product CQAs

(b) (4)

Uniformity of Dosage Units (content uniformity or CU)	• (b) (4) variability of tezacaftor (b) (4) • (b) (4) variability of ivacaftor (b) (4) • (b) (4) • variability • (b) (4) particle size and (b) (4) variability • (b) (4) variability • input excipient variability (b) (4)	3	3	2	18	
Microbial limits ⁸	• (b) (4) increasing above acceptance criteria • microbial growth during processing (film coating) • quality of input materials • no microbial limits testing proposed for drug product release	2	3	5	30	

⁸ Evaluation to be done by the microbiology team; Note that tablets are tested for microbial parameters on stability only.

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Initial Risk Assessment for Drug Product CQAs

Physical form	- input materials contain (b) (4) 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 (b) (4))	2	3	3	18



(b) (4)

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Attachment

Start of Applicant Material

Table 1 Manufacturing Summary of Tezacaftor/ Ivacaftor FDC Tablets

Bulk Tablet Lot Number	Date of Manufacture	Use	Theoretical Batch Size (Tablets)	Model Generation	Model Verification	Stability
2014032 ^a	OCT2014	Clinical	(b) (4)			
2015004 ^a	NOV2014	Clinical				
2015014 ^a	FEB2015	Clinical				X
2015015 ^a	FEB2015	Clinical				X
2015016 ^a	FEB2015	Clinical				X
2015044	NOV2015	Clinical				X
2016002	JAN2016	Clinical				X
2016006	JAN2016	Clinical				X
160420-014,1-17	APR2016	Development		X		
161121-014, 1-4	NOV2016	Development		X		
2016051	NOV2016	Clinical				
170214-016	FEB2017	Development			X	
170214-017	FEB2017	Development			X	
170214-018	FEB2017	Development			X	

^a Manufactured using discontinuous process

^b Batch sizes varied between approximately (b) (4) tablets and (b) (4) tablets

End of Applicant Material



Craig
Bertha

Digitally signed by Craig Bertha
Date: 7/25/2017 07:47:28AM
GUID: 50841a6500098a9383c817879a6a84d

