CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211358Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 211358
Review #1

Drug Name/Dosage Form	Orkambi (lumacaftor/ivacartor oral granules)[1]
Strengths	100/125 and 150/188 mg (lumacaftor/ivacaftor)
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Vertex Pharmaceuticals Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*07-FEB-2018*	*All*
Amendment	*20-APR-2018*	*drug substance, biopharmaceutics*
Amendment	*15-MAY-2018*	*process, drug product, biopharmaceutics*
Amendment	*11-JUN-2018*	*biopharmaceutics*
Amendment	*29-JUN-2018*	*biopharmaceutics*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Friedrich Burnett	Donna Christner
Drug Product	Venkat Pavuluri	Craig M. Bertha
Process	Hong Yang	Yong Hu
Microbiology	Hong Yang	Yong Hu
Facility	Hong Yang	Yong Hu
Biopharmaceutics	Hansong Chen	Haritha Mandula
Regulatory Business Process Manager	Florence Aisida	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	N/A	

(b) (4)

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III	(b) (4)	(b) (4)	N/A	N/A	Adequate information provided in NDA; DMF not reviewed

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	79521	lumacaftor tablets for cystic fibrosis (CF)
IND	74633	ivacaftor tablets for CF
NDA	203188	ivacaftor tablets for CF
NDA	206038	ivacaftor/lumacaftor tablets for CF

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

N/A

II. Summary of Quality Assessments

A. Product Overview

The drug product is lumacaftor/ivacaftor oral granules (proposed proprietary name: Orkambi®) and the two strength fixed dose combinations share the same formulation, with each providing either 100/125 or 150/188 mg of lumacaftor/ivacaftor, respectively. Individual doses of the drug product are packaged in foil laminate (b) (4)

The drug substances are already approved for treatment of cystic fibrosis (CF) in Orkambi® Tablets of N206038. Information supporting the lumacaftor drug substance is supplied by reference to the applicant's approved N206038 and information supporting (b) (4) of ivacaftor is provided by (b) (4) reference to the applicant's approved N203188.

The recommended daily dose for CF patients 2-5 years of age and less than 14 kg is one packet of granules of 100/125 mg lumacaftor/ivacaftor; for patients 2-5 years of age over 14 kg, the recommended daily dose is one packet of granules of 150/188 mg lumacaftor/ivacaftor. Based on the stability data for the registration stability batches, a 24 month expiration dating period is supported.

Proposed Indication(s) including Intended Patient Population	For treatment of cystic fibrosis in patients 2 years and older
Duration of Treatment	chronic
Maximum Daily Dose	300/376 mg lumacaftor/ivacaftor as granules (higher daily doses of 800/500 mg for adults are provided with tablet formulation)
Alternative Methods of Administration	tablets and granules (both oral)

B. Quality Assessment Overview

This NDA involves two drug substances, Lumacaftor (LUM) and Ivacaftor (IVA). The

applicant has provided no detailed information on either Lumacaftor or Ivacaftor in this NDA, but has cross-referenced their NDAs 206038 and 203188, which use these same drug substances for other solid oral dosage forms for CF. Therefore, no detailed review was necessary in support of this application, as we can rely on the established and approved CMC information supporting the earlier applications utilizing these drug substances.

The drug product is a fixed dose combination Orkambi® (lumacaftor/ivacaftor) oral granules dosage form with two strengths (100mg/125mg and 150mg/188mg, respectively) and is intended for weight based dosing to pediatric patients by oral administration with small volumes (~5 mL) of soft food or liquid. The FDC granules use the (b) (4) that is identical to those of the 100 mg lumacaftor/125 mg lower strength ivacaftor tablet formulation approved by the Agency under NDA 206038. The specifications proposed for the two dosage strengths are identical and adequate for their intended purposes from a quality perspective. All analytical test methods used for testing of finished drug product and corresponding method validation information were included in the submission. Based on the assessment provided in the submission, in response to the requests for information, there is a low risk for the introduction of Class 1, Class 2A, or any other elemental impurities in to the drug product.

The proposed shelf-life of **24 months** is supported by stability data up to 12 months at long term (25°C/60 % RH) and 6 months at accelerated (40°C /75 % RH) conditions. Short term in-use stability/compatibility studies demonstrated acceptable chemical stability up to 1 hour after mixing the FDC granules with water, (b) (4) juice, (b) (4), (b) (4) puree, (b) (4) yogurt, (b) (4) and (b) (4) pudding; supporting their use as media for drug administration.

The current lumacaftor/ivacaftor drug product consists of granules in a (b) (4) for oral administration. The same fixed-ratio granule formulation is used for both granule strengths of 100 mg lumacaftor/125 mg ivacaftor and 150 mg lumacaftor /188 mg ivacaftor. (b) (4)

In terms of facilities, there are seven that are utilized for the production of the drug product. Based on file review, all seven facilities are acceptable to support the approval of the application.

The Biopharmaceutics review focused on the dissolution method development, dissolution data, dissolution specification, and *in vitro* soft-food interaction study. The Applicant has adopted the dissolution methods developed for Orkambi, 200 mg/125 mg tablets for the proposed products, which is acceptable. The dissolution methods demonstrate discriminatory power (b) (4) for both lumacaftor and ivacaftor, and (b) (4) (b) (4) The Agency agrees with the following dissolution acceptance criteria: 1) Lumacaftor: NLT (b) (4) % (Q) in 20 minutes; 2) Ivacaftor NLT (b) (4) % (Q) in 15 minutes. From a biopharmaceutics perspective, the drug products were found to be compatible with those soft-foods studied, assuming the oral granules are intended to be mixed with food and administered within a short time-frame, as indicated in the patient instructions.

Some minor modifications to the labels and labeling are warranted and will be addressed during labeling negotiations and in conjunction with DMEPA recommendations.

The application is recommended for **approval** from the CMC/quality perspective.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

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BIOPHARMACEUTICS

Product Background:

Vertex developed Orkambi (lumacaftor/ivacaftor), 200 mg /125 mg tablets, which were approved by FDA under NDA 206038 on 7/2/2015. Orkambi (lumacaftor/ivacaftor) tablets are indicated for the treatment of CF patients aged 12 years and older and homozygous for the F508del-CFTR mutation in the CFTR gene. Later, the Applicant submitted NDA 206038 S005 to propose a new strength, 100 mg /125 mg tablets for an indication extension to include patients aged 6 through 11 years, which was approved by FDA on 8/31/2016.

In this NDA, Vertex proposed a new dosage form of granules in 2 strengths (100 mg /125 mg and 150 mg/188 mg lumacaftor/ivacaftor per packet), and seek approval under NDA 211358 through 505 (b) (1) pathway. These two new strengths are indicated for the treatment of cystic fibrosis (CF) in patients 2 years and older who are homozygous for the F508del-CFTR mutation in the CFTR gene.

The proposed product is an age-appropriate formulation for administration orally from the sachets and mixed with a small amount of soft food or liquid.

NDA/ANDA: NDA 211358

Drug Product Name / Strength: Lumacaftor/Ivacaftor FDC Granules 100 mg /125 mg and 150 mg/188 mg

Route of Administration: Oral

Applicant Name: Vertex Pharmaceuticals Incorporated (Vertex)

Review Summary:

The Biopharmaceutics review focuses on the dissolution method development, dissolution data, dissolution specification, and In-Vitro Soft-food Interaction Study.

The Applicant adopted the dissolution methods developed for Orkambi, 200 mg /125 mg tablets for the proposed products, which is acceptable. The dissolution methods demonstrate discriminatory power towards the changes in Granule Particle Size, (b) (4) for both lumacaftor and ivacaftor, and (b) (4). The following dissolution acceptance criteria have been set agreed upon with the Applicant:

Lumacaftor	Ivacaftor
NLT (b) (4)% (Q) in 20 minutes	NLT (b) (4)% (Q) in 15 minutes

The Applicant conducted In-Vitro Soft-food Interaction Study and concluded that the proposed products are compatible with soft food.

From the Biopharmaceutics perspective, this Reviewer concludes that NDA 211358 for Lumacaftor/Ivacaftor FDC Granules 100 mg /125 mg and 150 mg/188 mg is ADEQUATE for approval.

List Submissions being reviewed (table):

2/7/2018	NDA 211358 /Original submission
4/20/2018	eCTD-0002/Response to Biopharmaceutics Information Requests
5/15/2018	eCTD-0006/Response to Biopharmaceutics Information Requests
6/11/2018	eCTD-0007/Response to Biopharmaceutics Information Requests

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining:

None.

BCS Designation

Reviewer's Assessment:

The Applicant reported lumacaftor (LUM) is a BCS Class II drug, which has low solubility and high permeability. The Applicant also reported that ivacaftor (IVA) has low solubility; however, they could not classify IVA as BCS II or BCS IV drug (b) (4)

Solubility:

The lumacaftor drug substance is practically insoluble in water and buffer solutions of pH 1.0 to pH 8.0 (range: <0.05 µg/mL to 0.099 mg/mL.

FeSSI
FeSSI

The solubility of ivacaftor (IVA) could not be located in the submission.

Permeability:

(b) (4)

Dissolution: See the Biopharm review below.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

I. Components and composition of Lumacaftor/Ivacaftor FDC Granules Formulations used in Phase 3 Clinical and Primary Stability Studies

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Total

(b) (4)

(b) (4)

(b) (4)

(b) (4)

II. Dissolution method

The Applicant stated that they employed the dissolution methods developed for Orkambi, 200 mg /125 mg tablets to conduct dissolution tests.

Table 1. The proposed dissolution methods for Lumacaftor/Ivacaftor FDC Granules 100 mg /125 mg and 150 mg/188 mg

	Lumacaftor	Ivacaftor
Apparatus	USP apparatus –II (paddle)	USP apparatus –II (paddle)
Speed	65 rpm	65 rpm
Dissolution media	900 mL of 0.5% (w/v) CTAB in 50 mM sodium acetate buffered solution, pH 4.5	900 mL of 50 mM sodium phosphate buffered 0.4% (w/v) SLS solution, pH 6.8
Volume	900 mL	900 mL
Sampling times	20 minutes	(b) (4) minutes
Temperature	(b) (4)	
Filtration		(b) (4)
Analysis		
Proposed specification	NLT (b) (4)% (Q) in 20 minutes	NLT (b) (4)% (Q) in (b) (4) minutes

III. The discriminatory power of the proposed dissolution methods

The Applicant used two independent in-vitro dissolution methods for lumacaftor and ivacaftor, respectively.

The Applicant stated that the dissolution profiles of 100 mg lumacaftor / 125 mg ivacaftor and 150 mg lumacaftor / 188 mg ivacaftor are not dose dependent. The Applicant compared the mean dissolution profiles of two strengths for both lumacaftor and ivacaftor and found that they are the same (Figures 1 and 2). Therefore, the conclusions obtained from experiments performed on one dose strength apply to both dose strengths.

The dissolution profile of the 75 mg / 125 mg FDC granules formulation was not collected because this formulation was only used for a sensory study (013).

Reviewer's assessment

The response is adequate.

IR 1 Item 2

Submit comparative multipoint dissolution profiles on 75 mg /125 mg FDC granule formulation and the commercial formulation 100 mg/ 125 mg FDC granules and 150 mg /188 mg FDC granules by using the proposed dissolution method. The dissolution profiles of the 75 mg/ 125 mg FDC granule should be similar to those of the commercial formulations (e.g. by the calculation of f2 if appropriate).

The Applicant's response to IR 1 Item 2

The complete dissolution data for in-use stability studies is provided in Section 1.11.1 Response to Request for Information 28 March 2018 – In-use Stability Studies in Food.

Reviewer's assessment

The response is adequate. The provided data was thoroughly reviewed under section: In-Vitro Soft-food Interaction Study.

Biopharmaceutics Information Request 2

The second Biopharmaceutics IR was sent to the Applicant on 5/1/2018. On 5/15/2018, the Applicant responded to the IR. The following are the Biopharmaceutics IR, the Applicant's response, and this Reviewer's assessment of the Applicant's response.

IR 2 Item 1

In Module 3.2. P.2.2. Drug Product Formulation Development, you reported that the proposed dissolution method has discriminatory power towards the changes in Granule Particle Size, (b) (4) and stability; however, you did not provide detailed data to support your conclusion. Specifically, submit the complete dissolution data (individual, mean, SD, %RSD, and profiles) for Figures 2-6 and Figure 8-12 to the Agency for review.

The Applicant's response to IR 2 Item 1

The complete dissolution data for Figures 2-6 and 8-12 in Section 3.2.P.2.2 Formulation Development are included in the appendix of this IR response.

The complete dissolution data of the QbD batches included in Section 3.2.P.2.2 Formulation Development are normalized to the (b) (4) dissolution values. The complete dissolution data of all other batches in Section 3.2.P.2.2 were not normalized. Therefore, Figures 4, 9, and 10 in Section 3.2.P.2.2 have been normalized and the updated section is re-submitted with this response.

Reviewer's assessment

The response is adequate. Part of the dissolution data are listed in Appendix I for details. All data are thoroughly reviewed under sub-sections: the discriminatory power of the proposed dissolution methods and Dissolution data and specification.

IR 2 Item 2

Submit the complete dissolution data (individual, mean, SD, %RSD, and profiles) of the batches used in Study VX15-809-014 to the Agency for review.

The Applicant's response to IR 2 Item 2

The complete dissolution data for the batches used in Study VX15-809-014 are included in the appendix of this IR response.

Reviewer's assessment

The response is adequate.

IR 2 Item 3

You just provided the (b) (4) time point (i.e. (b) (4) minutes) dissolution data for the batches listed in Table 2 of Module 3.2.P.5.4 Batch Analyses. Submit the complete dissolution data (individual, mean, SD, %RSD, and profiles) of these batches to the Agency for review

The Applicant's response to IR 2 Item 3

The complete dissolution data for the batches listed in Table 2 of Section 3.2.P.5.4 Batch Analyses are included in the appendix of this IR response.

Reviewer's assessment

The response is adequate. The requested dissolution data are listed in Appendix I for details. All data are thoroughly reviewed under sub-sections: Dissolution data and specification.

IR 2 Item 4

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(b) (4)

Biopharmaceutics Information Request 3

The third Biopharmaceutics IR was sent to the Applicant on 6/6/2018. On 6/8/2018, the Applicant responded to the IR. The following are the Biopharmaceutics IR, the Applicant's response, and this Reviewer's assessment of the Applicant's response.

IR 3 Item 1

In the response dated May 15, 2018 to CMC Information Request Question 10 dated May 1, 2018, you made the following statement:

"The bioperformance of the large FDC granules (d50: (b) (4)) and the Phase 3 Granules (d50: ~ (b) (4) were not directly compared. However, based on a phase 1 BA study (VX15-809-014), bioavailability of the FDC tablets and the large FDC granules are comparable based on the drug exposure (AUC). When comparing the exposure data across the phase 3 studies of granules (study VX15-809-115) and FDC tablets (study VX15-809-109), the range of LUM and IVA exposures were similar. Therefore, in-vivo exposures (AUC) are expected to be similar between the large FDC granules (d50: (b) (4) and the phase 3 granules (d50: (b) (4) ." Provide detailed comparative data to support this statement.

The Applicant's response to IR 3 Item 1

The AUC data from the Phase 1 BA study (VX15-809-014) comparing the FDC tablets and the large FDC granules in healthy adult subjects are were included in Tables 2 and 3 in Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods.

The AUC data from the two phase 3 studies of FDC granules (VX15-809-115) and FDC tablets (VX15-809-109) in pediatric CF patients are shown in the table below. The AUC data by age group were also submitted through responses to Information Request dated 23Oct2017 for PPSR.

N: number of subjects

Reviewer's assessment

The response is adequate. The information was reviewed under subsection: Dissolution data and specification.

IR 3 Item 2

Lot B16029 and Lot 6064308 were used in Part A and Part B of Study VX15-809-115, respectively. These two lots were manufactured in different sites. The granule particle size of Lot 6064308 was reported to be around (b) (4) However, the granule particle size of Lot B16029 could not be located in the submission. Submit the detailed information (including components and composition, and granule particle size) of Lot B16029 to the Agency for review.

The Applicant's response to IR 3 Item 2

The components and composition of FDC granules in lots B16029 and 6064308 are the same, please refer to Section 3.2.P.1 Description and Composition, Table 1 for the information. The d50 granule particle size of lot B16029 is (b) (4)

Reviewer's assessment

The response is adequate.

IR 3 Item 3

In the submission, you stated that the proposed dissolution specifications (i.e. NLT (b) (4) in (b) (4) minutes) for both lumacaftor and ivacaftor are clinically relevant. However, this statement is not supported by sufficient data because you did not conduct a clinical study to compare whether the FDC granules with d50= (b) (4) are bioequivalent to the FDC granules with d50= (b) (4)

Your proposed dissolution specification for lumacaftor (NLT (b) (4) in 20 minutes) is acceptable because it can ensure only the granules with smaller particle size (b) (4) can meet this proposed specification. But the proposed dissolution for ivacaftor is not acceptable because it is not sufficient to reject the granules with larger granule particle size (b) (4) We recommend the following specification for ivacaftor:

NLT (b) (4) (Q) in 15 minutes

Acknowledge your acceptance of the above dissolution acceptance criterion for ivacaftor and update the drug product specification tables in Module 3.2. P.5.1. Specifications and other relevant parts of your NDA submission accordingly.

The Applicant's response to IR 3 Item 3

The Vertex agrees with the Agency's recommended ivacaftor dissolution specification of NLT (b)(4)% (Q) in 15 minutes. Vertex commits to update the drug product specification table in Section 3.2.P.5.1 and other relevant parts of the NDA accordingly and will submit these changes as a separate amendment.

Reviewer's assessment

The response is adequate.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment:

See subsection: Dissolution data and specification for details.

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: N/A

In-Vitro Soft-food Interaction Study

Reviewer's Assessment:

The lumacaftor/ivacaftor FDC granules are dosed orally to young pediatric patients by mixing the formulation with a small volume of soft foods or liquids. The Applicant conducted additional dissolution tests to evaluate the compatibility of the granules mixed with small volumes (5 mL) of selected liquids and soft foods (i.e. apple juice, carrot puree, and yogurt).

I. Dissolution method for in vitro food compatibility

The Applicant used the same dissolution method to conduct in vitro food compatibility studies. However, the Applicant modified the sample preparation and introduction of the sample into the dissolution vessels as follows:

"Add 5 mL of food matrix to the granules from a (b)(4) and stir until all the granules are dispersed in the food matrix. Hold the mixture for 1 hour at ambient conditions. Quantitatively transfer the mixture to the dissolution vessel (n=6) with ~30 mL of dissolution medium from each vessel and start dissolution testing".

II. Soft food and liquid compatibility

In vitro soft food stability dissolution was conducted on both 150 mg Lumacaftor / 188 mg Ivacaftor FDC Granules and 100 mg Lumacaftor / 125 mg Ivacaftor FDC Granules with apple juice, carrot puree, and yogurt. The initial dissolution and 12 months' stability data are summarized in the following tables:

Table 11. Mean lumacaftor dissolution data of 100 mg Lumacaftor / 125 mg Ivacaftor FDC Granules for in use stability, initial and 12 months

Lot number /Time Point (min)	5	10	15	20	30	45	60	75
100/125 mg Lot W033179 with apple juice, T0	92	99	101	102	103	104	105	106
100/125 mg Lot W033179 with apple juice, 12 months	91	97	99	101	102	103	104	104
100/125 mg Lot W033179 with Carrot Puree, T0	100	103	104	105	105	105	106	106
100/125 mg Lot W033179 with Carrot Puree, 12 months	98	101	101	102	102	103	103	103
100/125 mg Lot W033179 with Yogurt, T0	96	103	103	104	104	100	105	105
100/125 mg Lot W033179 with Yogurt, 12 months	86	90	93	94	96	97	98	102

Table 12. Mean ivacaftor dissolution data of 100 mg Lumacaftor / 125 mg Ivacaftor FDC Granules for in use stability, initial and 12 months

Lot number /Time Point (min)	5	10	15	20	30	45	60	75
100/125 mg Lot W033179 with apple juice, T0	68	89	95	98	101	102	103	103
100/125 mg Lot W033179 with apple juice, 12 months	75	89	93	95	97	99	99	100
100/125 mg Lot W033179 with Carrot Puree, T0	75	92	97	99	100	100	100	101
100/125 mg Lot W033179 with Carrot Puree, 12 months	79	90	94	95	96	97	97	98
100/125 mg Lot W033179 with Yogurt, T0	67	89	96	98	101	101	102	101
100/125 mg Lot W033179 with Yogurt, 12 months	66	82	89	92	95	96	97	98

Table 13. Mean lumacaftor dissolution data of 150 mg Lumacaftor / 188 mg Ivacaftor FDC Granules for in use stability, initial and 12 months

Lot number /Time Point (min)	5	10	15	20	30	45	60	75
150/188 mg Lot W033182 with apple juice, T0	91	97	99	100	101	102	103	104
150/188 mg Lot W033182 with apple juice, 12 months	92	97	100	101	102	103	103	104
150/188 mg Lot W033182 with Carrot Puree, T0	98	101	102	103	103	103	103	103
150/188 mg Lot W033182 with Carrot Puree, 12 months	98	101	102	102	103	103	103	103
150/188 mg Lot W033182 with Yogurt, T0	86	96	97	100	100	104	104	106

150/188 mg Lot W033182 with Yogurt, 12 months	78	84	87	89	91	93	95	100

Table 14. Mean ivacaftor dissolution data of 150 mg Lumacaftor / 188 mg Ivacaftor FDC Granules for in use stability, initial and 12 months

Lot number /Time Point (min)	5	10	15	20	30	45	60	75
150/188 mg Lot W033182 with apple juice, T0	73	87	92	95	97	99	100	100
150/188 mg Lot W033182 with apple juice, 12 months	75	87	92	94	96	97	98	99
150/188 mg Lot W033182 with Carrot Puree, T0	76	89	94	96	98	98	99	100
150/188 mg Lot W033182 with Carrot Puree, 12 months	76	87	91	92	94	95	95	96
150/188 mg Lot W033182 with Yogurt, T0	59	80	88	93	96	98	98	98
150/188 mg Lot W033182 with Yogurt, 12 months	65	81	88	91	93	94	94	95

Figure 16. Mean lumacaftor dissolution profiles of 100 mg Lumacaftor / 125 mg Ivacaftor FDC Granules for in use stability, initial and 12 months

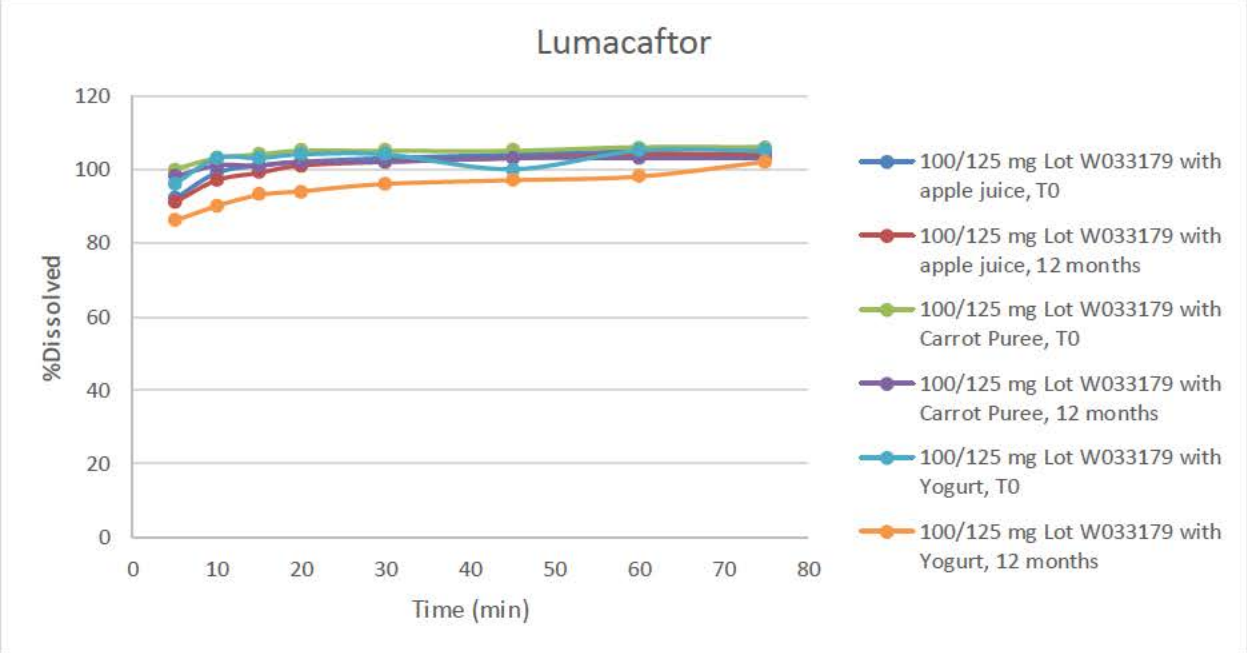


Figure 17. Mean ivacaftor dissolution profiles of 100 mg Lumacaftor / 125 mg Ivacaftor FDC Granules for in use stability, initial and 12 months

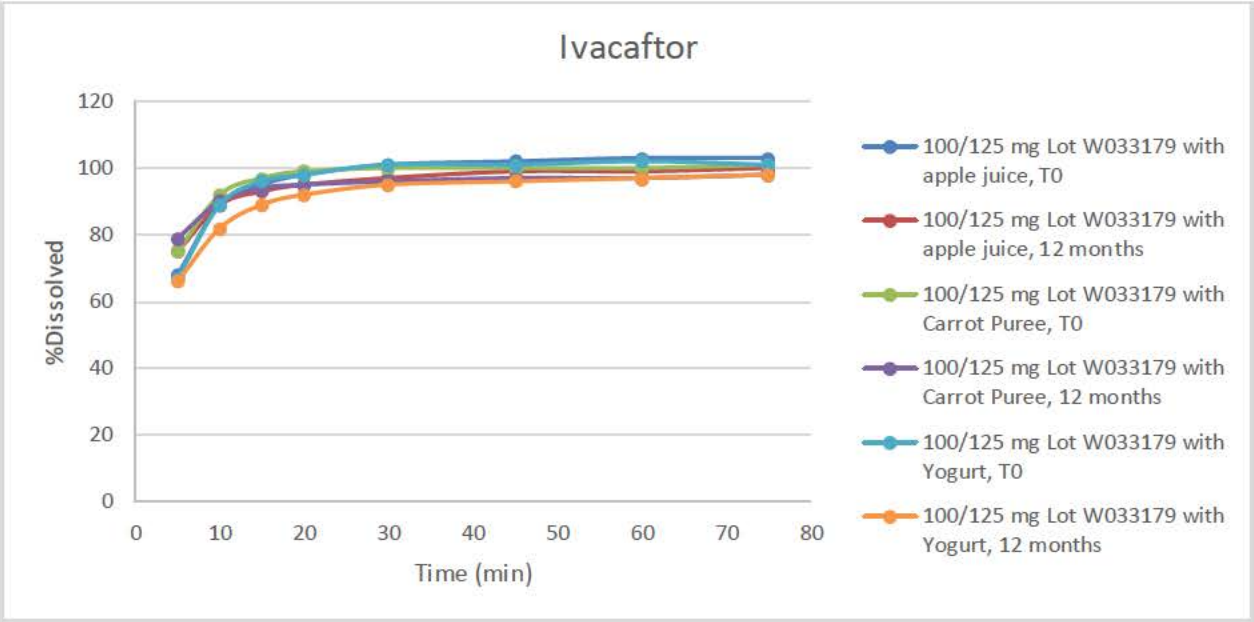


Figure 18. Mean lumacaftor dissolution profiles of 150 mg Lumacaftor / 188 mg Ivacaftor FDC Granules for in use stability, initial and 12 months

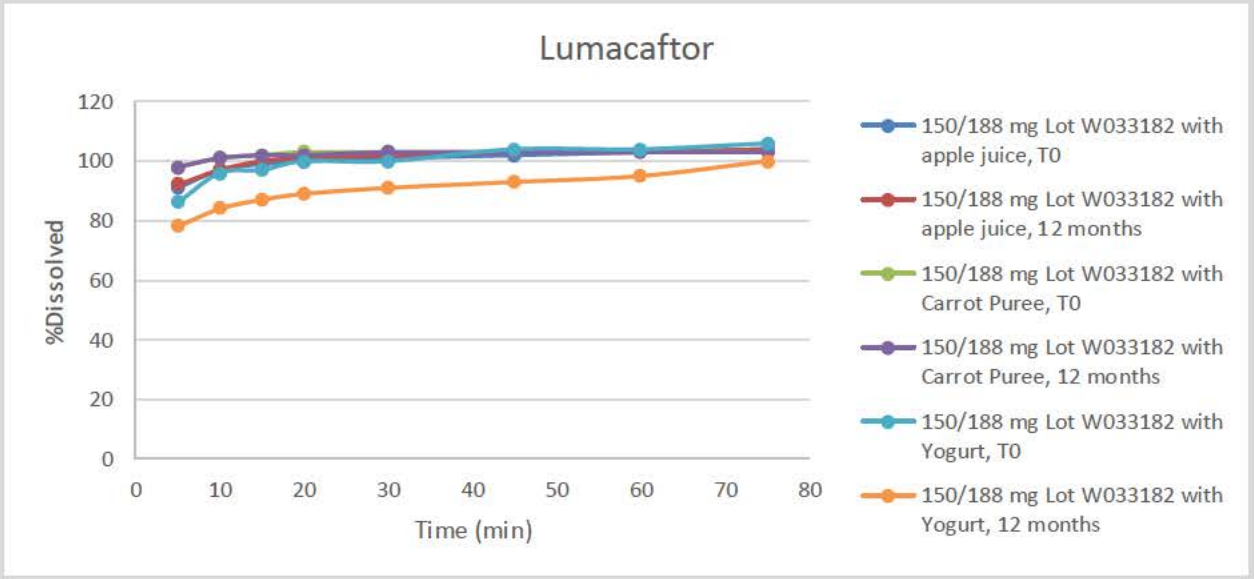
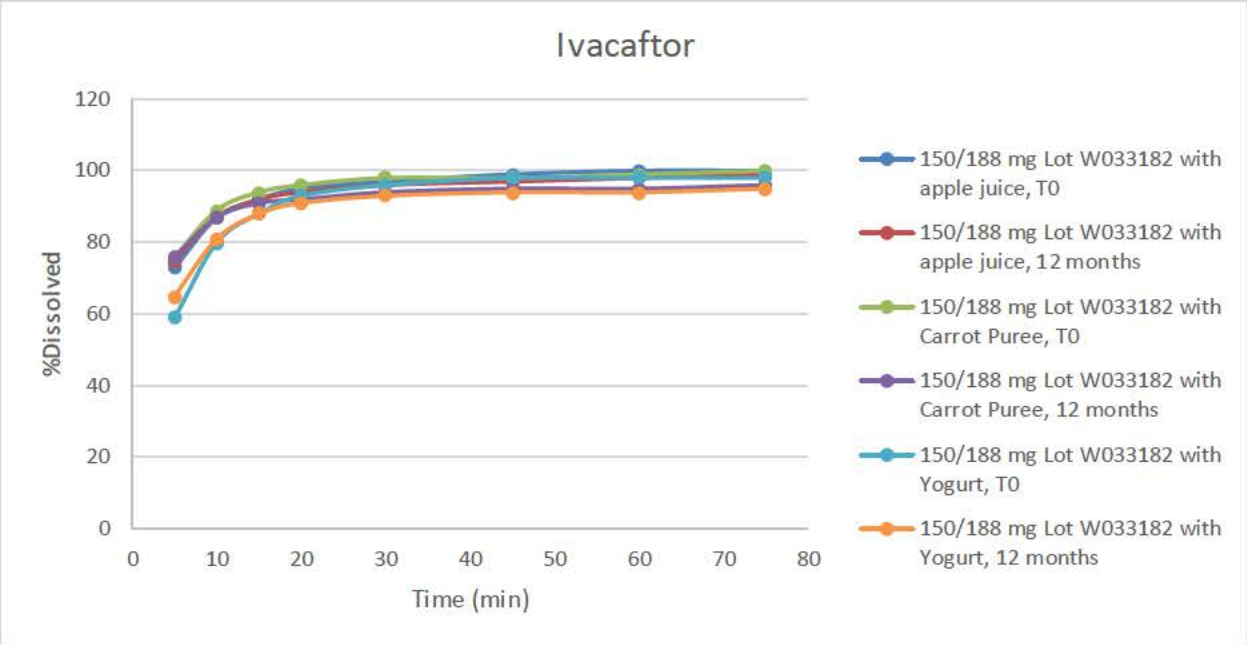


Figure 19. Mean ivacaftor dissolution profiles of 150 mg Lumacaftor / 188 mg Ivacaftor FDC Granules for in use stability, initial and 12 months



The data show that lumacaftor and ivacaftor dissolution for release and stability tests is not affected after the FDC granules were mixed with apple sauce and carrot puree. However, lumacaftor release in the FDC Granules significantly decreases after the mixture of the FDC granules and whole milk yogurt was stored at 30°C /75% RH for 12 months, although ivacaftor dissolution remains unchanged.

(b) (4)

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Bridging of Formulations

Reviewer's Assessment:

Lot B16029 and Lot 6064308 were used in Part A and Part B of Study VX15-809-115, respectively. These two lots were manufactured in different sites. The dissolution data show that Lot B16029 and Lot 6064308 have similar dissolution profiles based on the calculated f2s (Lumacaftor: f2=59.51; Ivacaftor: no f2 is calculated for both lots dissolve (b) (4) % in (b) (4) minutes). In addition, these two lots have similar AUCs based on the population PK model per Clinical Pharmacology review.

Biowaiver Request

Reviewer's Assessment: N/A

R Regional Information

Comparability Protocols

Reviewer's Assessment:

Post-Approval Commitments

Reviewer's Assessment:

Lifecycle Management Considerations

List of Deficiencies: None

Primary Biopharmaceutics Reviewer Name and Date:

Hansong Chen, Pharm.D., Ph.D., 6/11/2018

Biopharmaceutics reviewer

OPQ/ONDP/DB

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Haritha Mandula, Ph.D. 6/14/2018

Hansong Chen

Digitally signed by Hansong Chen
Date: 6/18/2018 11:20:42AM
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Haritha Mandula

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Date: 6/18/2018 01:27:55PM
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LABELING

IQA Review Guide Reference

{For NDA 211358}

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	ORKAMBI® (lumacaftor/ivacaftor)
Dosage form, route of administration	Granules, Oral
Controlled drug substance symbol (if applicable)	Not applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Oral granules: Unit-dose packets of lumacaftor 100 mg and ivacaftor 125 mg; lumacaftor 150 mg and ivacaftor 188 mg.

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	The entire content of each packet of oral granules should be mixed with one teaspoon, 5 mL, of age appropriate soft food or liquid and the mixture completely consumed. Some examples of soft foods include puréed fruits, flavored yogurt or pudding, and milk or juice. Food should be at room temperature or below. Each packet is for single use only. Once mixed, the product has been shown to be stable for one hour, and therefore should be ingested during this period.

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Oral granules: Unit-dose packets
Strengths: in metric system	lumacaftor 100 mg/ivacaftor 125 mg or lumacaftor 150 mg/ivacaftor 188 mg per packet
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	white to off- white granules

4. ***Section 11 Description***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	ORKAMBI®
Dosage form and route of administration	granules for oral administration
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Not applicable, oral drug product
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Lumacaftor is cystic fibrosis transmembrane conductance regulator (CFTR) and Ivacaftor is a CFTR potentiator.
Chemical name, structural formula, molecular weight	Lumacaftor : chemical name: 3-[6-({[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropyl]carbonyl}amino)-3-methylpyridin-2-yl]benzoic acid; Ivacaftor chemical name: N (2,4-di-tert-butyl 5 hydroxyphenyl)-1,4-dihydro 4 oxoquinoline 3 carboxamide; Mol. wt. for lumacaftor and ivacaftor are 452.41 and 392.49, respectively; Mol. formula for lumacaftor is C24H18F2N2O5 and for ivacaftor is C24H28N2O3.
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Both drugs are practically insoluble.

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	lumacaftor 100 mg/ivacaftor 125 mg per packet
Available units (e.g., bottles of 100 tablets)	56-count carton (contains 56 unit-dose packets) same applicable for both strengths.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Supplied as small white to off-white granules and enclosed in unit dose packets. **NDC** 51167-900-01 **NDC** 51167-500-02
Special handling (e.g., protect from light)	None
Storage conditions	Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for Vertex Pharmaceuticals Incorporated 50 Northern Avenue Boston, MA 02210

Reviewer's Assessment of Package Insert: Adequate.

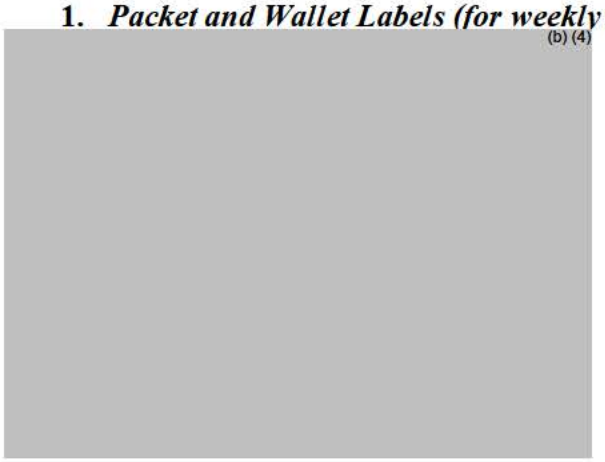
Information provided in the PI complies with relevant regulatory requirements from CMC perspective.

II. Labels:

Note: Only one each of the carton, wallet and sachet representative samples was reproduced below. Except for the color schemes and dosage statement both strengths use the same packaging configurations for primary package (b) (4) and secondary carton.

1. ***Packet and Wallet Labels (for weekly dosing)***

(b) (4)



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

Item	Information provided in the container label ((b) (4) and wallet carton)	Information provided in the Outer carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Acceptable Font sizes for Proprietary and established names of drugs	Acceptable Font sizes for Proprietary and established names of drugs
Dosage strength	Lumacaftor/Ivacaftor 100 mg / 125 mg; or 150 mg/ 188 mg per packet	Lumacaftor/Ivacaftor 100 mg / 125 mg; or 150 mg/ 188 mg per packet
Net contents	Net content in mg or g was no included on the packet (primary container). 14 packets per wallet pack	56 packets per carton, with 4 individual wallets with 14packets per wallet
"Rx only" displayed prominently on the main panel	Present on both	Present
NDC number (21 CFR 207.35(b)(3)(i))	Present on both	Present
Lot number and expiration date (21 CFR 201.17)	Space available, but didn't indicate where batch number and Expiry date will be included on either the packet (b) (4) or wallet.	Space available, but didn't indicate where batch number and Expiry date will be included.
Storage conditions	Not included on either the packet (b) (4) or the Wallet pack for weekly dosing.	Store at USP controlled room temperature [20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F)].
Bar code (21CFR 201.25)	Present on packet (b) (4)	
Name of manufacturer/distributor	Present on both Vertex Pharmaceuticals Incorporated	Vertex Pharmaceuticals Incorporated
And others, if space is available	Individual AM /PM dosing makers provided for all day of the week on Wallet pack. Instructions for preparing the dose included.	None

Reviewer's Assessment of Labels: Inadequate

- Storage conditions statement should be included on the wallet label, at the minimum, if there is not adequate space on the primary package (b) (4).
- Net contents of the package should be expressed in metric units, i.e. g or mg, on the primary pack (b) (4) independent of the dosage strength.

- Space where Batch # and Expiry date are printed on the packet (b) (4), wallet or outer carton was not marked.

List of Deficiencies:

Provide revised text for (b) (4) (packet), Wallet and outer cartons with the following information included

1. Storage condition should be included on the wallet label, at the minimum, in case there is not adequate space on the primary package (b) (4).
2. Net contents of the package should be expressed in metric units, i.e. g or mg, independent of the dosage strength on the primary pack (b) (4).
3. Indicate (mark) space where Batch number and Expiry date are printed on primary packet (b) (4) wallet and outer carton.

Overall Assessment and Recommendation: Approvable, only up on revising the text with changes proposed as above.

Primary Labeling Reviewer Name and Date:

Venkateswara R. Pavuluri, Ph. D., R. Ph.; 03-JUL-2108

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Craig M. Bertha, Ph. D.

Venkateswara Pavuluri

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Date: 7/04/2018 04:00:28PM
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Craig Bertha

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Date: 7/05/2018 05:41:42AM
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ONDP Filing Review - NDA 211358

Attachment - Final Risk Assessment

DP attribute/ CQA	Factors that may impact the CQA	O[1]	S[4, 2]	D[4]	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Lifecycle considerations or comments
Appearance	• color of input materials • (b) (4)	3	3	2	18	• appearance must meet drug product acceptance criteria, mainly a visual examination for color (subjective) • lumacaftor, ivacaftor (b) (4), and microcrystalline cellulose (MC) (b) (4)		
Identification	• (b) (4) •	1	3	1	3	• the specification for the lumacaftor requires a specific identification by (b) (4) • the specification for the ivacaftor (b) (4) includes a specific identity test by (b) (4) • cGMP requires multiple checks during formulation of the identity of drug product components • control strategy includes testing of final drug product by (b) (4) (b) (4)		
Assay	• assay/purity of input ivacaftor (b) (4) lumacaftor, and excipients • incorrect weighing of (b) (4) • (b) (4) • variation of (b) (4) (b) (4)	3	3	2	18	• ivacaftor (b) (4) specification includes a criterion for assay and purity, e.g. degradants and residual solvents • ivacaftor (b) (4) is claimed to have "good chemical and physical stability" (refer to NDA 203188 for details) • lumacaftor specification includes a criterion for assay and purity (e.g., degradants, residual solvents, inorganic residue on ignition) • excipients meet quality standard of USP/NF, which is suitable for solid oral dosage forms • cGMP compliance should control (b) (4) • IPCs included for (b) (4) • Seal integrity must pass for packets (test details not given)		
Degradation Products	• poor packet seal integrity • high degradant levels in the ivacaftor (b) (4) and lumacaftor • compatibility of ivacaftor and lumacaftor with excipients • degradation of APIs (b) (4)	2	3	3	18	• IPC for packet seal integrity (no details provided, however) • applicant claims (b) (4) stability studies show "good chemical and physical stability"; ivacaftor (b) (4) specification has tests with acceptance criteria for degradants • lumacaftor specification includes a criterion for assay and purity (e.g., degradants, residual solvents, inorganic residue on ignition) • the formulation for the granules is the same as used for the (b) (4) tablet drug product already approved under		

[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" was used throughout)

ONDP Filing Review - NDA 211358

Attachment - Final Risk Assessment

	[redacted]					N206038 • stability studies show no degradation products above [redacted] % for 12 months at 25 C/60%RH and for 6 months at 40 C/75%RH		
Dissolution	• variability of input materials (e.g., bulk density of ivacaftor [redacted], lumacaftor [redacted]) • [redacted] • line rate • variable granule [redacted] content • [redacted] • [redacted]	2	3	3	18	• variability of particle size of lumacaftor (D50 o[redacted]) did not significantly impact dissolution • [redacted] • DoE runs resulting in granules with higher than allowable [redacted] content still met dissolution requirements • granule particle size remained in narrow range ([redacted] with chosen process parameter ranges and over this range dissolution of lumacaftor and ivacaftor met their acceptance criteria		
Uniformity of Dosage Units (ivacaftor/lumacaftor have high drug loads)	• high or low assay of ivacaftor [redacted] and lumacaftor • [redacted] • variability of input materials (e.g., bulk density of ivacaftor [redacted], lumacaftor [redacted]) • variable packet fills • line rate • [redacted]	2	3	4	24	• [redacted] of 30 and 47% for [redacted] • ivacaftor [redacted] and lumacaftor have assay acceptance criteria in their respective specifications • from the executed batch record for bulk granule lot 6064308, blend uniformity appeared to meet the requirement [redacted] • Content Uniformity results for all primary stability and clinical batches met the requirements of USP <905> • DoE studies indicated that [redacted] • [redacted] • acceptable BA (phase 1) and dissolution behavior was observed with granule sizes much larger [redacted] than those commonly produced with the proposed design space		
Microbial	• [redacted] content increasing above acceptance criteria	1	3	2	6	• [redacted] ivacaftor [redacted] said to be "hostile to microorganisms" [redacted]		

limits	• quality of input materials					• microbial limits testing of lumacaftor and ivacaftor (b) (4) show low bioburden and absence of specified organisms (testing will not be performed routinely) • granule lots meet microbial limit requirements and have water activities less than 0.60 (USP <1112> indicates water activity below this level will prevent growth of even the most prolific bacteria/yeast/mold) • microbial testing will be performed on all routine commercial stability lots of the granules with specification acceptance criteria consistent with USP <1111>		
Physical forms	• physical forms of drug substances (b) (4) • change of drug substance (b) (4)	4 (1)	3	4	48	• applicant claims that all samples of produced granules from the DoE experiments (b) (4) • applicant claims there is no change to the physical forms of the lumacaftor and ivacaftor on stability; no routine testing for physical form is planned for routine stability studies (b) (4) • food compatibility studies are poorly supported with data: o mixing granules with fat containing foods led to formation of ivacaftor (b) (4) but applicant states that these have "comparable" solubility to the original ivacaftor (b) (4) in the granules (expected to have similar BA); phase 3 studies included fat containing foods o applicant states that in-use food stability was examined for granule lots W033179 and W033182 at the 12 month time-point for 30 C/75%RH storage (to be annual thereafter), but these data were not provided in P.8.3 as expected	12	• Applicant conducted (b) (4) experiments to determine the potential for conversion of the lumacaftor to (b) (4) ivacaftor; formulation was found to be stable. • Stability studies also demonstrated that there was no propensity for these form changes to occur with routine storage. • Studies with soft food showed adequate physical stability within a one hour period, sufficient for intended usage.
Elemental impurities	• elemental impurities in input lumacaftor, ivacaftor (b) (4) excipients • elemental impurities introduced by manufacturing equipment (b) (4)	1	3	5	15	• the levels of elemental impurities in lumacaftor and ivacaftor (b) (4) and the manufactured granules were found consistently to be (b) (4) below the Q3D option 1 limits; no routine testing for elemental impurities is proposed • See related IR comments in attachment 2		
Residual solvents	• residual solvents in lumacaftor • residual solvents in ivacaftor (b) (4) • (b) (4)	1	3	5	15	• applicant refers to controls for lumacaftor residual solvents as per NDA 206038 • applicant refers to controls for ivacaftor (b) (4) residual solvents in NDA 203188 • (b) (4)		

Craig Bertha

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