

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206038Orig1s000**

**CHEMISTRY REVIEW(S)**



Priority and Breakthrough Review

Recommendation: ~~Approval of NDA from a product quality perspective~~

NDA 206038
Review #1
Review Date: April 7, 2015

Table with 2 columns: Field Name and Value. Fields include Drug Name/Dosage Form, Strength, Route of Administration, Rx/OTC Dispensed, Applicant, and US agent, if applicable.

Quality Review Team

Table with 3 columns: Quality Review Section, Primary Reviewer, and Secondary Reviewer. Lists various review sections like Drug Substance, Drug Product, and other roles with their respective reviewers.

**Administrative**

**A. Signature Block**

Primary Reviewer Name	Electronic Signature
Edwin Jao, PhD	Edwin Jao -A <small>Digitally signed by Edwin Jao -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Edwin Jao -A, 0.9.2342.19200300.100.1.1=1300212075 Date: 2015.04.02 11:06:10 -04'00'</small>
Arthur Shaw, PhD	Arthur B. Shaw -S <small>Digitally signed by Arthur B Shaw -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA ou=People, cn=Arthur B Shaw -S 0.9.2342.19200300.100.1.1=1300057581 Date: 2015.04.02 13:12:24 -04'00'</small>
Celia Cruz, PhD	Celia Cruz -S <small>Digitally signed by Celia Cruz -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Celia Cruz -S, 0.9.2342.19200300.100.1.1=2000473041 Date: 2015.04.02 10:54:18 -04'00'</small>
Bogdan Kurtyka, PhD	Bogdan Kurtyka -S <small>Digitally signed by Bogdan Kurtyka -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bogdan Kurtyka -S, 0.9.2342.19200300.100.1.1=1300405755 Date: 2015.04.02 09:21:30 -04'00'</small>
Alex Viehmann, PhD	Alex Viehmann -S <small>Digitally signed by Alex Viehmann -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Alex Viehmann -S, 0.9.2342.19200300.100.1.1=2000287441 Date: 2015.04.02 18:25:31 -04'00'</small>
Vibhakar Shah, PhD	Vibhakar J. Shah -S <small>Digitally signed by Vibhakar J. Shah -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Vibhakar J. Shah -S, 0.9.2342.19200300.100.1.1=1300104989, cn=Vibhakar J. Shah -S Date: 2015.04.03 17:10:54 -04'00'</small>
John Duan, PhD	John Z. Duan -S <small>Digitally signed by John Z. Duan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=John Z. Duan -S, 0.9.2342.19200300.100.1.1=1300118208 Date: 2015.04.02 12:08:25 -04'00'</small>
Jessica Cole, PhD	Jessica Cole -S <small>Digitally signed by Jessica Cole -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jessica Cole -S, 0.9.2342.19200300.100.1.1=2000397920 Date: 2015.04.02 10:15:13 -04'00'</small>

Secondary Reviewer Name	Electronic Signature
Eric Duffy, PhD	Eric P. Duffy -S <small>Digitally signed by Eric P. Duffy -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA ou=People, cn=Eric P. Duffy -S 0.9.2342.19200300.100.1.1=1300062144 Date: 2015.04.06 14:35:48 -04'00'</small>
Rapti Madurawe, PhD	Rapti D. Madurawe -A <small>Digitally signed by Rapti D. Madurawe -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA ou=People, cn=Rapti D. Madurawe -A, 0.9.2342.19200300.100.1.1=1300220251 Date: 2015.04.06 14:46:16 -04'00'</small>
Sharmista Chatterjee, PhD	Sharmista Chatterjee -S <small>Digitally signed by Sharmista Chatterjee -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA ou=People, cn=Sharmista Chatterjee -S, 0.9.2342.19200300.100.1.1=1300392042 Date: 2015.04.06 12:50:56 -04'00'</small>
Mahesh Ramanadham, MS	Mahesh R. Ramanadham -S <small>Digitally signed by Mahesh R. Ramanadham -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mahesh R. Ramanadham -S, 0.9.2342.19200300.100.1.1=2000618629, Date: 2015.04.06 10:04:11 -04'00'</small>
Tapash Ghosh, PhD	Paul R. Seo -S <small>Digitally signed by Paul R. Seo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA ou=People, cn=Paul R. Seo -S, 0.9.2342.19200300.100.1.1=1300225071 Date: 2015.04.06 13:04:08 -04'00'</small>
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**B. ATL and RBPM**

**ATL:** Rapti Madurawe, PhD

**RBPM:** Youbang Liu, PhD



**Priority and Breakthrough Review**

**Recommendation: Approval of NDA from a product quality perspective**

**NDA 206038  
Review #1  
Review Date: April 7, 2015**

<b>Drug Name/Dosage Form</b>	Orkambi (lumacaftor/ivacaftor) Tablets
<b>Strength</b>	200mg/125mg (b) (4) (lumacaftor/ivacaftor)
<b>Route of Administration</b>	Oral
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Vertex Pharmaceuticals, Inc.
<b>US agent, if applicable</b>	N/A

**Quality Review Team**

<b>QUALITY REVIEW SECTION</b>	<b>PRIMARY REVIEWER</b>	<b>SECONDARY REVIEWER</b>
Drug Substance	Edwin Jao, PhD	Eric Duffy, PhD
Drug Product	Arthur Shaw, PhD	Rapti Madurawe, PhD
Drug Product Process	Celia Cruz, PhD	Rapti Madurawe, PhD
(b) (4)	Bogdan Kurtyka, PhD	Sharmista Chatterjee, PhD
Statistics	Alex Viehmann, PhD	Rapti Madurawe, PhD
Facility	Vibhakar Shah, PhD	Mahesh Ramanadham, MS
Biopharmaceutics	John Duan, PhD	Tapash Ghosh, PhD; Paul Seo, PhD
Microbiology	Jessica Cole, PhD	Bryan Riley, PhD
<b>OTHER ROLES</b>	<b>NAME</b>	
Project/Business Process Manager	Youbang Liu, PhD	N/A
Filing Review and CMC Lead	Craig Bertha, PhD	N/A
Application Technical Lead	Rapti Madurawe, PhD	N/A
Methods Validation	OTR Lab, St. Louis	N/A
OTR Liaison	Huiquan Wu, PhD	N/A

## Administrative

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### B. ATL and RBPM

ATL: Rapti Madurawe, PhD

RBPM: Youbang Liu, PhD

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# Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION:** 505b(1)

2. **RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:** All are N/A because there is sufficient information in the application.

DMF #	TYPE	HOLDER	ITEM REFERENCED
(b) (4)	III		(b) (4)
	III		
	IV		

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

Document	APPLICATION NUMBER	DESCRIPTION
IND	79521	Clinical Development of lumacaftor/ivacaftor
NDA	203188	Kalydeco (ivacaftor) Tablets

3. **CONSULTS:** None requested except for Methods Validation. Methods were found acceptable for control and regulatory purposes by the FDA Laboratory at St. Louis, MO.

# Executive Summary

## I. Recommendations

NDA 206-038 has provided sufficient CMC information to assure the identity, strength quality and purity of the drug product. However, this NDA is not recommended for approval at this time due to pending facility inspections. A recommendation for approval from a quality perspective can be made once an overall acceptable recommendation is issued for the facilities.

### A. Recommendation and Conclusion on Approvability

The shelf life granted is 24 months when stored at 20-25°C (room temperature).

There are no product quality deficiencies to communicate in the action letter.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

## II. Summary of Quality Assessments

### A: General

NDA 206038 provides for Orkambi, a fixed dose combination (FDC), immediate-release tablet for oral use containing 200 mg lumacaftor and 125 mg ivacaftor. Orkambi is indicated for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The two drug substances in Orkambi, lumacaftor and ivacaftor, are claimed to act respectively as a CFTR <sup>(b) (4)</sup> and a potentiator. Lumacaftor is a new molecular entity (NME) while Ivacaftor was approved for the CF arising from a number of different mutations under the Kalydeco tablet NDA 203188. NDA 206038 and its corresponding IND 79521 are designated "Breakthrough." NDA 206038 was granted a Priority review.

NDA 206038 also contains CMC information for an <sup>(b) (4)</sup>

<sup>(b) (4)</sup>

<sup>(b) (4)</sup> NDA action most likely will be for the 200/125 mg

FDC tablet.

<sup>(b) (4)</sup>

<sup>(b) (4)</sup>

NDA 206038, if approved, would represent the first fully continuous drug product manufacturing process to be approved in the US and to our knowledge, world-wide. Hence, the applicant gave authorization to include this NDA in the European Medicines Agency (EMA)-FDA Quality by Design pilot for consultative advice. All Quality information and decisions were shared with EMA during the review cycle.

The Quality review was conducted by a large team of FDA reviewers as listed in the cover page. As the integrated review template was not available at the time of NDA receipt, each primary review segment is based on the eCTD format; the Executive Summary is based on the new OPQ integrated review template.

421 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

## Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

### I. Review Cover Sheet

- 1. OMPQ Reviewer: Vibhakar Shah, Ph.D.
  
- 2. NDA/BLA Number: 206038  
 Submission Date: 11/05/2014  
 21<sup>st</sup> C. Review Goal Date: 05/05/2015  
 PDUFA Goal Date: 07/05/2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	ORKAMBIT™ (lumacaftor/ivacaftor) Tablets (Proposed)
Established or Non-Proprietary Name (USAN) and strength:	Lumacaftor/Ivacaftor Tablet
Dosage Form:	Tablet

4. SUBMISSION PROPERTIES:

Review Priority :	Original Priority
Applicant Name:	Vertex Pharmaceuticals Inc.
Responsible Organization (OND Division):	Division of Pulmonary, Allergy and Rheumatology Products

## II. Application Detail

1. INDICATION: Treatment of cystic fibrosis
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: Lumacaftor/Ivacaftor (200/125 mg, (b) (4))
4. Rx/OTC DISPENSED:  Rx  OTC
5. ELECTRONIC SUBMISSION (yes/no)?  Yes  No
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	X			One of the two drug substances, Lumacaftor, is a NME.
2.	Breakthrough Therapy Designation	X			
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		Not applicable/relevant at this stage.
7.	Rolling Submission	X			
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing	X			<p>The application proposes three distinct drug product manufacturing sites with :</p> <p>(b) (4)</p> <ul style="list-style-type: none"> <li>• Vertex, which has a fully continuous process, (b) (4)</li> </ul> <p>of the drug product.</p>
10.	Other (e.g., expedited for an unlisted reason)		X		

(b) (4)

### III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is a single comprehensive list of all involved facilities available in one location in the application?		X	Manufacturing facility Information for <i>ivacaftor</i> <sup>(b) (4)</sup> was not provided in the NDA but was cross-referenced to an approved NDA. The applicant was reminded to provide this information in an IR letter and include it on the 356h form. Applicant submitted this information in an amendment post NDA submission (11/05/2014)
12.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
13.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
14.	Do all sites indicate they are ready to be inspected (on 356h)?		X	Except for the Vertex Facility in Boston all facilities are ready for inspection. Vertex facility in Boston will be ready by Jan 07, 2015. Agency had agreed to grant this delayed timeline for the readiness of the facility for a PAI.
15.	Additional notes (non-filing issue)	X		
	1. Are all sites registered or have FEI #?	X		
	2. Do comments in PANORAMA indicate a request to participate on inspection(s)?	X		Participation on the PAIs of <sup>(b) (4)</sup> facilities has been requested.
	3. Is this first application by the applicant?		X	

\*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQ. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?	X		<p>Vertex is proposin [REDACTED] (b) (4)</p> <p>Vertex is proposing [REDACTED] (b) (4)</p> <p>Vertex has described the conditions/criteria to determine submission category [REDACTED] (b) (4)</p> <p>Reference: eCTD Sec.3.2.R.</p>

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?			<ul style="list-style-type: none"> <li>- NME</li> <li>- New complex Mfg. elements (QbD [REDACTED] (b) (4))</li> <li>- Newly constructed Mfg. area</li> </ul>
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion?	X		
	Have all EERs been updated with final PAI recommendation?		X	
19.	<p><b>From a CGMP/facilities perspective, is the application fileable?</b></p> <p>If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.</p>	X		

## IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
PET	Design Space	Continuous Mfg	Naturally derived API
<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Other (explain):			

### Manufacturing Highlights:

1. **Drug Substances:** *Lumacaftor* and *Ivacaftor* are used in the manufacture of the drug product.

Parameter	Yes	No	Comment
Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	<i>Lumacaftor</i> is an NME. <i>Ivacaftor</i> is the known drug substance of Vertex's approved NDA 203188, Kalydeco® tablet (approved 31-JAN-2012), indicated for the treatment of cystic fibrosis in patients 6 yrs. and older.

### Drug Substance Manufacturing Process flow chart/diagram (see eCTD Section 3.2.S.2.2)

The flow diagram for the synthesis of the drug substance, *lumacaftor* at (b) (4) is reproduced below in **Figure -1a** from the NDA. For *ivacaftor* synthesis and manufacturing process, Vertex has cross referenced their approved NDA 203188. The flow diagram for the synthesis of *ivacaftor* is reproduced in **Figure 1b** below from the NDA 203188.

### Drug Intermediate:

The drug intermediate, (b) (4)

(b) (4)

### 2. Drug Product:

Parameter	Yes	No	Comment
Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?	X		See below for more information.

### Drug Product Manufacturing Process flow chart/diagram (see eCTD Section 3.2.P.3.3)

The *ivacaftor* tablet is manufactured by (b) (4) and its flow chart is reproduced in **Figure -2** from the NDA. *Lumacaftor/ivacaftor* FDC tablets are manufactured at three facilities (b) (4) and Vertex) with (b) (4)

The flow charts, associated process parameters, and in-process controls for the manufacturing processes at these three facilities are reproduced below in **Figures 3-6** from the NDA.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

### Drug substance and Drug Product Manufacturing Facilities Inspection Status Chart

Facility	FEI	District Short	Country Code	Responsibility	Profile	Inspection History	FACTS ID	Inspection Dates	Most Recent Milestone	Most Recent Compliance Status	Comment
			(b) (4)	DS: Lumacaftor Manufacture, Packaging, labeling and Release testing DS: Ivacaftor Manufacture, Packaging, and Release testing	CSN	(b) (4)	-	-	OC Recommendation	AC	NME Based on Inspection Review , and DO Recommendation
				DS: Lumacaftor Release and Stability testing	CTL		-	-	Submitted to DO	PN	
				DS: Ivacaftor Manufacturer, Release and, Stability Testing	CSN		-	-	To be submitted to OC	PN	N203188/S-011,AP Need to be entered in PANORAMA
				DPI: Ivacaftor (b) (4) Manufacture and release testing	NEC CSN		-	(b) (4)	Inspection completed	PN	
				Ivacaftor Tablet: Manufacture, Release and Stability testing	TCM		-	-	Submitted to DO	PN	
				Ivacaftor/Lumacaftor Tablet: Manufacture, Release and Stability testing	TCM		-	(b) (4)	Inspection Assigned	PN	
				Ivacaftor/Lumacaftor Tablet: Manufacture, Release and Stability testing Ivacaftor Tablet: Stability testing	TCM		-	(b) (4)	Inspection assigned	PN	

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

Facility	FEI	District Short	Country Code	Responsibility	Profile	Inspection History	FACTS ID	Inspection Dates	Most Recent Milestone	Most Recent Compliance Status	Comment
Vertex Pharmaceuticals, Inc., Boston, MA	1000513211	NEW	US	Lumacaftor: Release and Stability testing Ivacaftor Tablet: Release and Stability testing Ivacaftor/Lumacaftor Tablet: Manufacture, Release and Stability testing	TCM	TCM [AC, (b) (4)]  CSN, CTX [AC, (b) (4)]	-	Dates to be confirmed	Inspection assigned*	PN	*Inspection dates are being finalized by the NEW-DO
(b) (4)	(b) (4)	(b) (4)	(b) (4)	Ivacaftor/Lumacaftor Tablet: Release and stability testing Ivacaftor Tablet: Stability testing	CTL	(b) (4)	-		Submitted to DO	PN	
				Ivacaftor/Lumacaftor Tablet: Packaging, and labeling Ivacaftor Tablet: Packaging, and labeling	TCM		-	-	OC Recommendation	AC	Based on Profile
				Ivacaftor Tablet: Packaging, labeling Ivacaftor/Lumacaftor Tablet: Packaging, labeling	TCM		-	-	OC Recommendation	AC	Based on Inspection Review , and DO Recommendation
				Ivacaftor/Lumacaftor Tablet: Stability testing (microbiology testing only)	CTL		-	-	OC Recommendation	AC	Based on Inspection Review , and DO Recommendation

AC: Acceptable; NA: Not Applicable; TBD: To be determined; PN: Pending; AP: Approved; DS: Drug substance; DP: Drug product; DPI: drug Product Intermediate

## V. Overall Conclusions and Recommendations

<b>Is the application fileable? (yes/no)</b>	<b>YES</b>
<p><b>At this time, is a KTB/KTM warranted for any PAI? (yes – site / no):</b></p> <p>To facilitate pre-approval Inspections of three different facilities, manufacturing the drug product, the following information should be considered:</p> <ul style="list-style-type: none"> <li>– Recommend transmitting a KTB to the lead investigator for the mfg. process at (b) (4)</li> <li>– Recommend transmitting KTMs or other appropriate documents to the lead investigators for the mfg. processes at (b) (4) and Vertex, Boston.</li> </ul>	<b>YES</b>
<b>Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no):</b>	<b>NO</b>
<b>Comments for 74 Day Letter</b>	<b>None</b>
1.	
2.	
3.	

## REVIEW AND APPROVAL

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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VIBHAKAR J SHAH  
12/23/2014

VIPULCHANDRA N DHOLAKIA  
12/23/2014

## APPLICATION INFORMATION

<b>NDA Number</b>	206038
<b>Submission Date</b>	7/30/2014 (rolling submission)
<b>Complete Application Submission Date</b>	Expected early November 2014
<b>Product name, generic name of the active</b>	Lumacaftor/Ivacaftor tablets
<b>Dosage form and strength</b>	Tablets (200/125 mg, (b) (4))
<b>Applicant</b>	Vertex Pharmaceuticals
<b>Clinical Division</b>	DPARP
<b>Type of Submission</b>	Original NDA
<b>Biopharmaceutics Primary Reviewer</b>	John Duan, PhD
<b>Biopharmaceutics Team Leader</b>	Tapash Ghosh, PhD
<b>Acting CMC Lead</b>	Craig M. Bertha, PhD

Lumacaftor/ivacaftor tablets are a fixed dose combination (FDC) drug product for the treatment of cystic fibrosis. (b) (4)

(b) (4)  
1) two (b) (4)  
*200mg lumacaftor/125 mg ivacaftor FDC drug tablets twice a day;*

Only the lumacaftor active is a new molecular entity (NME) and it is considered to be Biopharmaceutics Classification System (BCS) Class II (low solubility – high permeability). Currently, there is insufficient information regarding the permeability of ivacaftor, but considering that it is practically insoluble or insoluble in water, it would be either a BCS Class II (low solubility - high permeability) or Class IV (low solubility - low permeability) drug. The FDC immediate release tablets (b) (4) (b) (4) contain common compendial grade excipients, but also

(b) (4)

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use [redacted] (b) (4)

**Start of Applicant Material**

Component	Quality Standard	Component Function	200 mg/125 mg	
			Amount per tablet (mg)	Content (% w/w)
[redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4)
Lumacaftor drug substance	In house standard	Active Ingredient Drug product	200.00	[redacted] (b) (4)
Ivacaftor	NDA 203188			
Microcrystalline cellulose	USP/NF			
Croscarmellose sodium	USP/NF			
Sodium lauryl sulfate	USP/NF			
Povidone	USP/NF			
[redacted] (b) (4)	USP			
[redacted] (b) (4)	USP/NF			
[redacted] (b) (4)	USP/NF			
Magnesium stearate	USP/NF			
<b>Film Coat</b>	[redacted] (b) (4)			
[redacted] (b) (4)	DMF No. [redacted] (b) (4) USP			
<b>Print Ink</b>	[redacted] (b) (4)			
[redacted] (b) (4) Black	DMF No. [redacted] (b) (4)			
<b>Total Tablet Weight</b>			<b>582.5</b>	<b>100.0</b>

**End of Applicant Material**

[redacted] (b) (4)  
the application also reflects Vertex's ambitious development approach to this drug product. The application proposes three distinct drug product manufacturing sites: [redacted] (b) (4)  
[redacted] (b) (4)  
3) Vertex, which [redacted] (b) (4)  
has a fully continuous process, [redacted] (b) (4)  
[redacted] (b) (4) of the drug product. This last proposed site, in particular, introduces new regulatory considerations, which have been discussed with the applicant during multiple CMC meetings under I79521.

1. Drug Name: Lumacaftor/ivacaftor tablets (no proprietary name or Trademark is proposed at this time)

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Although there is no formal policy, the chemistry classification codes for the drug product (see draft of MaPP 7500.3) would appear to be types 1 and 4 (**New Molecular Entity and New Combination**). The ivacaftor active is already approved for treatment of cystic fibrosis as an immediate release oral tablet under N203188.

The Quality Target Product Profile (QTPP) for the drug product is that it is:

- safe and efficacious
- bioavailable
- for oral administration
- immediate release fixed-dose combination tablet
- 24 months expiry at room temperature packaged in blisters

2. RECEIVED DATE: 31-JUL-2014 (CMC section only: pre-submission; PDUFA “clock” does not start)

3. RELATED REVIEW DOCUMENTS:

**a. Drug Master Files listed on 356h form or in DMF (b) (4):**

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	3	(b) (4)	(b) (4)	06-JAN-2014	This file has not been reviewed for this particular item, but it is used for packaging of at least two approved oral drug products
	3			28-JAN-2014	Section 154 was found to be adequate for an oral drug product (reviewed); Section 155 has no apparent reviews
	4			24-JUN-2014	(b) (4) has been reviewed and found adequate for an oral drug product; There are no apparent reviews of (b) (4)
				20_NOV-2013	(b) (4) has been reviewed and found adequate for an oral drug product

**b. Recommended Consults**

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	<input type="checkbox"/>	X	Applicant claims to have followed ICH Q1E for stability data evaluation
Clin Pharm	<input type="checkbox"/>	X	

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EES	X	<input type="checkbox"/>	ONDQA PM informed of CMC pre-submission on 01-AUG-2014. EER pending submission as PDUFA "clock" does not start until complete application is submitted.
Pharm/Tox	X	<input type="checkbox"/>	<p>There are 24 potential drug related impurities (see S.3.2) related to the NME lumacaftor, and some of these include (b) (4)</p> <p>[REDACTED]</p> <p>For those impurities listed above that are allowed by the acceptance criteria to exceed the qualification thresholds of ICH Q3A and Q3B, and for those with structural alerts that exceed the qualification thresholds for genotoxic and carcinogenic impurities, a consult should be forwarded to the pharmacologist for assessment of the associated toxicological data submitted.</p> <p>Depending on the ingredients in the (b) (4) coatings that have not been reviewed in DMF (U) (4), a consult to the pharmacologist may be needed if the components are non-compendial and not listed in the inactive ingredient guide for use with other oral dosage forms.</p>
Methods Validation	X	<input type="checkbox"/>	Lumacaftor is an NME, thus, the drug substance and drug product impurities methods will be sent to the Agency laboratory for assessment.
EA	<input type="checkbox"/>	<input type="checkbox"/>	It is expected that the applicant will submit the environmental analysis section in November 2014, i.e., it is not included in the July 2014 pre-submission.
New Drug Micro	<input type="checkbox"/>	X	Jessica Cole, PhD has been assigned as the microbiologist reviewer for this application.
CDRH	<input type="checkbox"/>	X	N/A
Other	<input type="checkbox"/>	X	N/A

**c. Other Applications or Submissions to note (if any):**

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND	Submitted 19-OCT-2007, currently active	79521	Initial IND submission was for lumacaftor; Combination with ivacaftor was added in amendment dated 23-OCT-2012

(b) (4)

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NDA	Approved 31-JAN-2012	203188	Application for Kalydeco® (ivacaftor) Tablets (150 mg) for treatment of patients 6 yrs. and older for cystic fibrosis
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**d. Previous Communications with the Applicant to note (see module 1.6.3 for complete detail):**

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IR letter	10-JAN-2008	IND 79521	CMC related comments re: structural alerts, testing for (b) (4) drug substance stability, drug product data, and specifications as per ICH Q6A
Meeting Minutes	25-FEB-2013	IND 79521	EOP2 CMC meeting re: drug substance starting materials, control strategy; product bridging with dissolution data, stability plan and expiry, dissolution method
Meeting Minutes	19-JUL-2013	IND 79521	CMC Guidance (type B) re: drug product traceability, definition of batch, Bill of Materials and (b) (4) validation strategy (b) (4)
Pre-Operational Visit Memo	24-OCT-2013	IND 79521, (b) (4)	(b) (4)
Meeting Minutes	30-OCT-2013	IND 79521	CMC Guidance (type B) re: dissolution method, (b) (4) and detection, QbD approach, rolling submission
Meeting Minutes	14-FEB-2014	IND 79521	CMC Guidance (type B) re: control strategies, design space for manufacturing, dissolution methodology
Meeting Minutes	16-MAY-2014	IND 79521	CMC Guidance (type B) re:

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			submission plan, stability & expiry, dissolution specification, (b) (4) control strategy, (b) (4)
Pre-Operational Visit Memo	(pending)	IND 79521, Vertex (b) (4) site 7/15/2014 to 7/16/2014	FDA Pre-Operational Visit Vertex –Annex, One Harbor Drive, Boston, MA

## OVERALL PRODUCT QUALITY CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
<input type="checkbox"/>	<input type="checkbox"/>	N/A – this is a pre-submission of most, but not all of the CMC section

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	N/A – this is a pre-submission; reviewers may send coordinated information requests as needed

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
X	<input type="checkbox"/>	

Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
X	<input type="checkbox"/>	Please convey the comments listed on pages 18 of this filing review to the Applicant.

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**Does the submission contain any of the following elements?**

	Yes	No	Comments
Botanical Products	<input type="checkbox"/>	X	
Combination Products	<input type="checkbox"/>	X	
Nanotechnology	<input type="checkbox"/>	X	
PET	<input type="checkbox"/>	X	
QbD Elements	X	<input type="checkbox"/>	(b) (4) proposed for the Vertex site with the (b) (4) where material attributes are assessed with (b) (4) (identification, assay, dissolution, dosage form uniformity, physical forms of APIs); Separate control strategies proposed at all three manufacturing sites (b) (4) Vertex, (b) (4) (b) (4)
SPOTS	<input type="checkbox"/>	X	

<b>Is a team review recommended?</b>		
Yes	No	Suggested expertise for team
<input type="checkbox"/>	<input type="checkbox"/>	N/A - A team is already assigned by the Division Director: Drs. Arthur Shaw (drug product), Celia Cruz (process), John Duan (biopharmaceutics), Edwin Jao (drug substance), Vibhakar Shah (facilities)

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**Drug Product Risk Assessment**

DP attribute/ CQA (200/125 mg lumacaftor/ ivacaftor)	Factors that can impact the CQA <sup>3</sup>	O <sup>4</sup>	S <sup>4,5</sup>	D <sup>4</sup>	FMEC A RPN #	Comment & considerations
Appearance	(b)(4)	1	3	4	12	(b)(4)
Identification [lumacaftor (L)/ ivacaftor (I)]	<ul style="list-style-type: none"> <li>incorrect APIs formulated</li> </ul>	1	3	1 (IR) 2 (Raman)	3 6	<ul style="list-style-type: none"> <li>lumacaftor and ivacaftor specifications include specific ID tests (IR spectroscopy)</li> <li>cGMP requires multiple checks during formulation</li> <li>all control strategies use specific end-product testing for identification of the APIs, but Vertex can use in-line Raman (with chemometric models) in addition to standard IR spectroscopy</li> </ul>
Assay	<ul style="list-style-type: none"> <li>assay/purity of input</li> </ul>	1	3	2	6	<ul style="list-style-type: none"> <li>lumacaftor specification includes a criterion for assay</li> </ul>

<sup>3</sup> As there are three distinct manufacturing sites (b)(4), and Vertex) with some manufacturing differences, there may be some slight differences regarding the probabilities of occurrence (O) and detectability (D) between sites, thus, the values provided in the table are general estimates, e.g., assuming RTR models are valid, higher sample rates (every one or two minutes) at Vertex may lead to better detectability of CQA failures

<sup>4</sup> O = Probability of Occurrence; S = Severity of Effect; D = Detectability

<sup>5</sup> 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.

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**Drug Product Risk Assessment**

	<p>lumacaftor</p> <ul style="list-style-type: none"> <li>assay/purity of input ivacaftor (b) (4)</li> <li>(b) (4) variability during (b) (4) (API assay ratio potentially affected)</li> <li>degradation of APIs during (b) (4)</li> <li>(b) (4)</li> <li>(b) (4)</li> <li>(b) (4)</li> </ul>					<p>that are said to assure this CQA is met</p> <ul style="list-style-type: none"> <li>ivacaftor (b) (4) specification includes a criterion for assay which is said to assure this CQA is met</li> <li>(b) (4) included for core tablet weight</li> <li>end product or (b) (4) testing (Vertex only) for drug product assay</li> <li>(b) (4)</li> <li>(b) (4)</li> <li>(b) (4)</li> <li>(b) (4)</li> <li>(b) (4)</li> </ul>
Degradation Products	<ul style="list-style-type: none"> <li>high degradant levels in the (b) (4) (lumacaftor) and the (b) (4) (ivacaftor)</li> <li>processing increases degradant levels (b) (4)</li> <li>(b) (4)</li> <li>degradation of APIs on stability</li> </ul>	1	3	2	6	<ul style="list-style-type: none"> <li>lumacaftor does not degrade in stability studies and the specification includes criteria to ensure conformance of the drug product to the CQA</li> <li>applicant claims (b) (4) stability studies show “no significant” degradation of ivacaftor; (b) (4) specification has tests with acceptance criteria for degradants</li> <li>applicant claims no degradants were detected in studies involving (b) (4)</li> <li>applicant claims that no degradation products were detected in (b) (4)</li> <li>applicant claims that in coating experiments, the tablet degradant CQA was not impacted</li> </ul>



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**Drug Product Risk Assessment**

						detectability over common sampling for standard dissolution testing
Uniformity of Dosage Units (lumacaftor, (b) (4))  Uniformity of Dosage Units (ivacaftor, (b) (4))	<ul style="list-style-type: none"> <li>variation of physical properties of variability of input materials (lumacaftor (b) (4) other excipients) may impact CU</li> <li>processing parameters for all stages of manufacturing to compression may impact CU</li> <li>segregation of (b) (4)</li> </ul>	3 (I) 2 (L)	3	4	36 (I) 24 (L)	<ul style="list-style-type: none"> <li></li> <li></li> <li></li> <li></li> <li></li> </ul>
Microbial limits <sup>6</sup>	<ul style="list-style-type: none"> <li>(b) (4)</li> <li></li> <li>quality of input materials</li> </ul>	1	3	5	15	<ul style="list-style-type: none"> <li>applicant proposes testing on stability only</li> <li></li> <li></li> <li></li> </ul>
Physical form (lumacaftor)  Physical form (ivacaftor)	<ul style="list-style-type: none"> <li>physical forms of drug substances could be altered during manufacturing (b) (4)</li> </ul>	4 (I) 3 (L)	3	4	48 (I) 36 (L)	<ul style="list-style-type: none"> <li></li> <li></li> <li></li> <li></li> </ul>

<sup>6</sup> Evaluation to be done by the microbiology team (as per microbiology pilot). Note that tablets are tested for microbial parameters on stability only.

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**Drug Product Risk Assessment**

	<ul style="list-style-type: none"><li>physical forms of drug substances are potentially altered with time</li></ul>					<p>no impact on either drug substance physical form for the studied ranges</p> <ul style="list-style-type: none"><li></li><li></li><li></li><li></li></ul>

## CMC Summary: Critical Issues and Complexities

*(This section is formatted to expand as far as needed by author.)*

The drug product of NDA 206038 from Vertex is proposed for the treatment of cystic fibrosis. It is a combination drug product that contains an already approved compound (ivacaftor from NDA 203188) and a NME (lumacaftor). Information about the synthesis and controls for the ivacaftor can be examined by cross-reference to NDA 203188. The current NDA does include information and data supporting the CMC for the lumacaftor drug substance. (b) (4)

(b) (4), some of which have been addressed and discussed at the multiple pre-application meetings held under IND 79521 and during pre-operational site visits. The following is a summary of the main issues that underlie and relate to the development of the drug product that may need to be considered by the reviewing team during the evaluation of the application.

- (b) (4) the chemist reviewing this portion of the application may need to consult with the pharmacologist depending on the levels of associated impurities in the lumacaftor drug substance.
- The Agency agreed with the applicant's proposed starting materials (b) (4) for the synthesis of the NME lumacaftor, but there were stipulations involving (b) (4)
- The applicant proposes (b) (4) The applicant also presents some information associated to (b) (4)
- The applicant has a control strategy that is said to assure the correct physical forms of both drug substances (b) (4)

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- The clinical team has indicated that it is likely that the dosage form that they will be considering for approval is the 200/125 mg (lumacaftor/ivacaftor) combination (b) (4)  
[Redacted]
- For the (b) (4) combination drug products, the applicant proposes *three different manufacturing sites* (b) (4) and Vertex), (b) (4)  
[Redacted] The applicant is expected to provide data that demonstrate that no matter at which site (and associated control strategy) the drug product is produced, it will have comparable quality, and that this quality is reflective of that for the drug product used in the pivotal clinical studies. (b) (4)  
[Redacted]
- Because continuous drug product manufacturing processes are used at (b) (4) and Vertex, this has brought about new regulatory issues that have been discussed and considered and for which precedents may be set with action on this NDA:
  - The applicant uses (b) (4),” to refer to the material corresponding to (b) (4) in the continuous manufacturing process; (b) (4)  
[Redacted]
  - (b) (4)
  - Definition of a drug product batch
  - (b) (4)
  - (b) (4)
  - Defining a Bill of Materials for a “batch” of drug product
- The specification for the drug product includes alternate testing for the Vertex site, as part of a (b) (4) control strategy, which will have many associated issues that are unique, from a historical regulatory perspective:
  - Models are proposed for release of drug product for assay, dissolution, and content uniformity

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- Models require maintenance as data are updated
- As part of the control strategy for the continuous manufacturing at the Vertex site, the applicant will need to outline testing scenarios when there are problems with the alternate methodology associated with

(b) (4)

**Description of Facility Related Risks or Complexities (i.e. foreign sites, large number of sites involved, etc.)**

(b) (4)

There is added complexity in that both the (b) (4) and (b) (4). This may lead to atypical GMP considerations with respect to sampling, testing, documentation, etc., at these sites. Also, the latter of these two sites with continuous manufacturing also plans to use (b) (4)

## **Biopharmaceutics Filing Review: Summary, Critical Issues and Complexities**

### **BIOPHARMACEUTICS INITIAL ASSESSMENT**

#### **Biopharmaceutics Summary**

There are four major review issues from the biopharmaceutics perspective.

1. Formulation changes:

A summary of formulations used throughout clinical development is provided. Initial clinical studies were conducted with lumacaftor only and included a lumacaftor suspension formulation used in early Phase 1 clinical studies and a lumacaftor capsule formulation used in subsequent Phase 1 and early Phase 2 studies. Clinical development then moved to combination therapy and ivacaftor was added to the regimen. Early Phase 1/2 clinical studies used individual lumacaftor and ivacaftor tablets. A bioavailability study (Study 007) was completed that supported the use of fixed dose combination (FDC) tablets in Phase 3 clinical studies. The Phase 3 pivotal studies included 2 dosing regimens and used both the lumacaftor/ivacaftor FDC tablet, 200/125 mg and the lumacaftor/ivacaftor FDC tablet, 200/83 mg. Additionally, in the Phase 3 regimen that utilized the lumacaftor/ivacaftor FDC tablet, 200/83 mg, an individual ivacaftor, 125 mg tablet was also dosed. (b) (4)

However, lumacaftor/ivacaftor FDC tablets, 200/125 mg and lumacaftor/ivacaftor FDC tablets, 200/83 mg used in the clinical studies were coated

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with the same pink film coat and were not printed, (b) (4)

printing was added to commercial tablets. Phase 3 supplies manufactured at (b) (4)

The linkage between the to-be-marked formulation and the clinical formulation should be provided.

2. Dissolution methodologies and acceptance criteria:

The following dissolution method and acceptance criterion were proposed.

For lumacaftor:

Apparatus: USP Apparatus 2 (paddle)  
Paddle Speed: 65 RPM  
Temperature: 37.0 ± 0.5°C  
Medium: 0.5% (w/v) CTAB in 50 mM sodium acetate trihydrate buffer (pH 4.5)  
Volume: 900 mL  
Pull Times: 30 minutes  
Filter: (b) (4)  
Acceptance limit:  $Q = \frac{(b)}{(4)}\%$  of labeled claim at  $\frac{(b)}{(4)}$  minutes.

For Ivacaftor:

Apparatus: USP Apparatus 2 (paddle)  
Paddle Speed: 65 RPM  
Temperature: 37.0 ± 0.5°C  
Medium: 0.4% (w/v) SLS in 50 mM sodium phosphaste buffer (pH 6.8)  
Volume: 900 mL  
Pull Times: 20 minutes  
Filter: (b) (4)  
Acceptance limit:  $Q = \frac{(b)}{(4)}\%$  of labeled claim at 20 minutes.

The dissolution methods were discussed and agreed during IND stage. However, the acceptance criteria will be further evaluated.

3. Alternative dissolution method: (b) (4)

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(b) (4)

4. QbD and Design space:

Product and manufacturing process development was conducted under a Quality by Design (QbD) paradigm which ensures that the desired product performance in terms of quality, safety, and efficacy is achieved. The overall QbD strategy is depicted in the following figure.

(b) (4)

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(b) (4)

**Critical Review Issues**

Critical review issues identified during filing are as follows.

- The linkage between the to-be-marketed and the clinical formulations.
- The suitability of the proposed dissolution acceptance criterion.
- The dissolution model for (b) (4)
- The evaluation of the impact of dissolution in QbD and design space.

**Comments for Day 74-Letter**

The following comments should be conveyed to the Applicant:

1. Provide dissolution profile comparisons between the to-be-marketed and the clinical formulations and among the formulations manufactured by different processes.
2. Provide information for the formulations used in study 007, including the formulation number, batch number, detailed composition, and the dissolution data.
3. Provide the raw data to support the following figures and tables in Section 3.2.P.2.3: Figure 4, Table 13, Table 14, Figure 7, Figure 12, Table 24, Table 25, Figure 13, Figure 14, Table 26, Table 27, Figure 15 – 20, Table 34 – 37, Table 43, Figure 24, Figure 30 – 34, Table 57 – 66. Please note that although the figures or tables only present the dissolution data at a specific time point (b) (4) the available dissolution data at other time points (b) (4) should be provided.
4. Provide data to support the (b) (4) proposed for (b) (4)
5. Provide the results of the investigations for the (b) (4) between different manufacturing sites.

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The following parameters for the ONDQA’s Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

<b>ONDQA-BIOPHARMACEUTICS</b>				
<b><u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING</b>				
	<b>PARAMETER</b>	<b>YES</b>	<b>NO</b>	<b>COMMENT</b>
1.	Does the application contain dissolution data?	X		3.2.P.2.2, 3.2.P.5.3
2.	Is the dissolution test part of the DP specifications?	X		3.2.P.5.1
3.	Does the application contain the dissolution method development report?	X		3.2.P.2.2
4.	Is there a validation package for the analytical method and dissolution methodology?	X		3.2.P.5.3
5.	Does the application include a biowaiver request?		X	
6.	Does the application include an IVIVC model?		X	
7.	Is information such as BCS classification mentioned, and supportive data provided?		X	
8.	Is information on mixing the product with foods or liquids included?		X	
9.	Is there any <i>in vivo</i> BA or BE information in the submission?	X		Comparative pharmacokinetic studies were conducted to compare different formulations. To be submitted.
10.	Is there a modified-release claim? If yes, address the following:		X	
	a.) Is there information submitted to support the claim in accordance with 320.25(f)?		X	
	b.) Is there information on the potential for alcohol-induced dose dumping?		X	

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<b>B. FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	<b>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	X		
12.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not applicable.
13.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	X		Please convey the comments listed on pages 18 of this filing review to the Applicant.

## FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL					
	Parameter	Yes	No	N/A	Comment
14.	Is the CMC section organized adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	
15.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Are all the pages in the CMC section legible?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	All pages examined for production of this IQA were legible.
17.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X	<input type="checkbox"/>	<input type="checkbox"/>	Information related to topics discussed at meetings held under IND 79521 appear to be included, however adequacy is yet to be determined during the review

B. FACILITIES*					
	Parameter	Yes	No	N/A	Comment
18.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X	<input type="checkbox"/>	<input type="checkbox"/>	See the Form 356h
19.	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? <b>This question is not applicable for synthesized API.</b>	<input type="checkbox"/>	<input type="checkbox"/>	X	

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20.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X	<input type="checkbox"/>	<input type="checkbox"/>	
21.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X	<input type="checkbox"/>	<input type="checkbox"/>	

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22.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X	<input type="checkbox"/>	<input type="checkbox"/>	
23.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	<input type="checkbox"/>	X	<input type="checkbox"/>	Many of the sites are listed as “not ready” at this time of the pre-submission

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	Yes	No	N/A	Comment
24.	Has an environmental assessment report or categorical exclusion been provided?	<input type="checkbox"/>	X	<input type="checkbox"/>	This will be required at the time of full NDA submission

D. MASTER FILES (DMF/MAF)					
	Parameter	Yes	No	N/A	Comment
25.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X	<input type="checkbox"/>	<input type="checkbox"/>	Refer to table of DMF information above.

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STOP

<b>E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
26.	Does the section contain a description of the DS manufacturing process?	X	<input type="checkbox"/>	<input type="checkbox"/>	For the lumacaftor NME
27.	Does the section contain identification and controls of critical steps and intermediates of the DS (in process parameters)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
28.	Does the section contain information on impurities?	X	<input type="checkbox"/>	<input type="checkbox"/>	
29.	Does the section contain information regarding the characterization of the DS?	X	<input type="checkbox"/>	<input type="checkbox"/>	
30.	Does the section contain controls for the DS?	X	<input type="checkbox"/>	<input type="checkbox"/>	
31.	Has stability data and analysis been provided for the drug substance?	X	<input type="checkbox"/>	<input type="checkbox"/>	No statistical analyses have been performed for any of the parameters.
32.	Does the application contain Quality by Design (QbD) information regarding the DS?	X	<input type="checkbox"/>	<input type="checkbox"/>	
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	X	<input type="checkbox"/>	
34.	Does the section contain container and closure information?	X	<input type="checkbox"/>	<input type="checkbox"/>	

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<b>F. DRUG PRODUCT (DP)</b>					
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
35.	Does the section contain quality controls of excipients?	X	<input type="checkbox"/>	<input type="checkbox"/>	
36.	Does the section contain information on composition?	X	<input type="checkbox"/>	<input type="checkbox"/>	
37.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	<input type="checkbox"/>	X	<input type="checkbox"/>	The manufacturing description does not include any information regarding labeling or packaging, however the executed batch records for the drug product prepared at (b) (4) does describe the details of these processes.
38.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X	<input type="checkbox"/>	<input type="checkbox"/>	
39.	Is there a batch production record and a proposed master batch record?	X	<input type="checkbox"/>	<input type="checkbox"/>	The pre-submission includes executed batch records for (b) (4) the combination product from each of the three proposed manufacturing sites. These are said to be batches that are "representative" of those used in the clinical studies. No master batch records are provided for any of these three sites.
40.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X	<input type="checkbox"/>	<input type="checkbox"/>	The P.2 section does include the formulation development history, but the final to-be-marketed fixed dose combination tablets were used in phase 3, so no linkage is necessary.
41.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	<input type="checkbox"/>	<input type="checkbox"/>	(b) (4) blisters are planned as the commercial packaging for the drug product.
42.	Does the section contain controls of the final drug product?	X	<input type="checkbox"/>	<input type="checkbox"/>	(b) (4) is planned for the Vertex product site.

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43.	Has stability data and analysis been provided to support the requested expiration date?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Data are provided in the pre-submission, but no associated statistical analyses. For the 200/125 mg strength, 12 months of data are provided from (b)(4) drug product (n = 3 batches), 6-9 months for 3 batches from (b)(4), but no 3 months for drug product from Vertex. The applicant plans to update the stability data at the time of the full NDA submission. We were in general agreement with the stability plan (see minutes for 25-FEB-2013, meeting).
44.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See description of "QbD elements" above.
45.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The Vertex site will use PAT to facilitate RTR for the drug product.

**G. METHODS VALIDATION (MV)**

	Parameter	Yes	No	N/A	Comment
46.	Is there a methods validation package?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

**H. MICROBIOLOGY**

	Parameter	Yes	No	N/A	Comment
47.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	<input type="checkbox"/>	<input type="checkbox"/>		The microbiology team has been informed of the submission of this application and will make a determination of any review necessary, as per the pilot.

**I. LABELING**

	Parameter	Yes	No	N/A	Comment
48.	Has the draft package insert been provided?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Not included in the pre-submission
49.	Have the immediate container and carton labels been provided?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Not included in the pre-submission
50.	Does section contain tradename and established name?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	No trademark is proposed yet for the drug product, however, the established names of lumacaftor and ivacaftor are in the USAN dictionary.

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<b>J. FILING CONCLUSION</b>					
	Parameter	Yes	No	N/A	Comment
51.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	X	<input type="checkbox"/>	<input type="checkbox"/>	This may need to be updated once the complete application is received for review.
52.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	<input type="checkbox"/>	<input type="checkbox"/>	X	
53.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	<input type="checkbox"/>	X	<input type="checkbox"/>	See comments from the biopharmaceutics team on p. 18

## REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

Craig M. Bertha, PhD, Acting CMC Lead  
 John Duan, PhD, Biopharmaceutics Primary Reviewer  
 Tapash Ghosh, PhD, Biopharmaceutics Team Leader  
 Eric Duffy, PhD, Division Director, DNDQA III, ONDQA

*{See appended electronic signature page}*

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4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
-----

CRAIG M BERTHA  
08/21/2014

JOHN Z DUAN  
08/21/2014

TAPASH K GHOSH  
08/25/2014

ERIC P DUFFY  
09/02/2014



### Overall Manufacturing Inspection Recommendation

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Assigned To



**Christina Capacci Daniel**

This was done on

**Jun 23, 2015**

(34 days ago)

Status

**Complete**

This task is waiting on

2 Tasks

Last Update

Jun 23, 2015

Submitted On

Nov 6, 2014

Reference Number

2918413

#### Inspection Management Form

As of 9:20 AM

##### Inspection Management Form

NDA 206038-Orig1-New - Proprietary Name/NDA - Request for Review(3)

VERTEX PHARMACEUTICALS INC | 1000513211 | TCM TABLETS, PROMPT RELEASE | Approve Facility - 2015-07-05

(b) (4) TCM TABLETS, PROMPT RELEASE | Approve Facility -

(b) (4) | CSN NON-STERILE API BY CHEMICAL SYNTHESIS |

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility -

(b) (4) TCM TABLETS, PROMPT RELEASE | Approve Facility -

(b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility

(b) (4) TCM TABLETS, PROMPT RELEASE | Approve Facility -

(b) (4) TCM TABLETS, PROMPT RELEASE | Approve Facility -

(b) (4) CTL CONTROL TESTING LABORATORY | Approve

(b) (4) TCM TABLETS, PROMPT RELEASE | Approve

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility -

#### Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

Overall Application Re-evaluation Date

7/5/15



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